

New vanadyl complexes with metformin derivatives as potential insulin mimetic agents

Rodica Olar · Andreea Dogaru · Dana Marinescu · Mihaela Badea

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Abstract Three new complexes with formula $[\text{VOL}_2] \cdot x\text{H}_2\text{O}$ [(1) HL: *N,N*-dimethylbiguanide, $x = 0.5$; (2) HL: 1-phenylbiguanide, $x = 0$; (3) HL: 1-(*o*-tolyl)biguanide, $x = 0.5$] were synthesised and characterised. The IR and UV–Vis spectral data indicate that these biguanide derivatives act as bidentate chelating anionic 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.

Keywords Biguanide derivative · Paracyanide · Thermal stability · Vanadyl(IV) complex

Introduction

A variety of vanadium chelate complexes have been shown to have insulin-mimetic properties in animal model and cell culture systems, thus these compounds have great potential for the pharmacotherapy of diabetes [1–17]. The first report of vanadium's insulin mimetic and antidiabetic potential in vivo was published by Poucheret et al. [18]. The study was performed on streptozotocin (STZ) diabetic rats treated with sodium orthovanadate. In cultured cells lines, vanadium compounds enhance insulin receptor activation and downstream signalling. In animal models of diabetes, vanadium compounds enhance insulin sensitivity resulting in decreased levels of plasma glucose.

One likely mechanism for the insulin-mimetic activity of vanadium compounds relates to their potent inhibition of PTP's. A variety of vanadium compounds have been shown to directly inhibit a wide range of PTP's, including PTP1B. A lot of paper revealed the superior insulin-mimetic activities for vanadium complexes compared to sodium orthovanadate [5, 7, 12, 13, 17].

Besides having chelating ability, the biguanide derivatives demonstrated so far a large spectrum of biological activities such antimicrobial [19], glucose lowering agents [20], analgesic, antimalarial [21] as well as antimetabolite for organisms that inhibit the metabolism of folic acid [22].

Having in view these aspects, new complexes of the type $[\text{VOL}_2] \cdot x\text{H}_2\text{O}$ with biguanide derivatives [1-phenylbiguanide and 1-(*o*-tolyl)biguanide] together with the known vanadyl complex of *N,N*-dimethylbiguanide were synthesised and characterised by elemental analysis as well as IR and UV–Vis spectroscopy. Considering the low solubility in water of complexes, developing proper drug delivery systems requires the thermal analysis amongst others [23]. As result, the thermal analysis (TG and DTA) of the complexes was performed 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, reagent grade and were used without further purification.

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

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 Bruker Tensor 37 spectrometer in the range 400–4,000 cm^{-1} .

Electronic spectra by diffuse reflectance technique, with Spectralon as standard, were recorded in the range 200–1,000 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 °C/min. The measurements were carried out in synthetic air atmosphere (flow rate 16.66 mL^3/min) using alumina crucibles.

Synthesis of complexes

All the complexes were obtained following the general procedure: to a solution of $\text{VO}(\text{SO}_4) \cdot 5\text{H}_2\text{O}$ (2.5 mmol) in distilled water (50 cm^3) was slowly added, under continuous stirring, a solution of biguanide derivative (5.0 mmol dissolved in 30 cm^3 of distilled water). The reaction mixture was then stirred at 50 °C for 2 h until a microcrystalline product was formed. The sparingly soluble product was filtered off, washed several times with ethanol and air-dried.

$\text{VO}(\text{DMBG})_2(\text{H}_2\text{O})_{0.5}$. *Analysis found*: V, 15.27; C, 28.82; H, 6.54; N, 42.27%; *requires for* $\text{VC}_8\text{H}_{21}\text{N}_{10}\text{O}_{1.5}$: V, 15.33; C, 28.92; H, 6.37; N, 42.16%. Reaction yield 80%.

$\text{VO}(\text{PhBG})_2$. *Analysis found*: V, 12.15; C, 45.68; H, 5.34; N, 33.37%; *requires for* $\text{VC}_{16}\text{H}_{22}\text{N}_{10}\text{O}$: V, 12.09; C, 45.60; H, 5.26; N, 33.24%. Reaction yield 72%.

$\text{VO}(\text{o-TBG})_2(\text{H}_2\text{O})_{0.5}$. *Analysis found*: V, 11.05; C, 47.48; H, 5.46; N, 30.87%; *requires for* $\text{VC}_{18}\text{H}_{25}\text{N}_{10}\text{O}_{1.5}$: V, 11.16; C, 47.37; H, 5.52; N, 30.69%. Reaction yield 90%.

The obtained complexes are sparingly soluble in water, methanol, ethanol, acetonitrile, partially soluble in dimethylformamide and soluble in dimethylsulphoxide.

Results and discussion

Physico-chemical characterization of complexes

Based on glucose lowering activity of *N,N*-dimethylbiguanide (Metformin, HDMBG), we selected two biguanide derivatives [1-phenylbiguanide (HPhBG) and 1-(*o*-tolyl)biguanide (*o*-HTBG)] as ligands to synthesize new vanadyl complexes as potential insulin-mimetic agents. Because the known complex of metformin with vanadyl ion [20] was not investigated regarding the thermal stability we included it in this study.

The major goal of this article was to evidence the thermal behaviour of complexes isolated from the reactions of these biguanide derivatives with $\text{VO}(\text{SO}_4) \cdot 5\text{H}_2\text{O}$. The complexes have been formulated on the basis of chemical analysis, IR and electronic spectra as follows:

$\text{VO}(\text{DMBG})_2(\text{H}_2\text{O})_{0.5}$	(1)	Or	$\text{VC}_8\text{H}_{21}\text{N}_{10}\text{O}_{1.5}$
$\text{VO}(\text{PhBG})_2$	(2)	Or	$\text{VC}_{16}\text{H}_{22}\text{N}_{10}\text{O}$
$\text{VO}(\text{o-TBG})_2(\text{H}_2\text{O})_{0.5}$	(3)	Or	$\text{VC}_{18}\text{H}_{25}\text{N}_{10}\text{O}_{1.5}$

The IR spectra of the complexes exhibit the characteristic patterns of ligands (Table 1).

In the IR spectra of complexes band assigned to imine stretching mode is shifted to higher wavenumbers whilst the band in the range 1,600–1,700 cm^{-1} , assigned to vibration mode $\nu(\text{C}=\text{N})$ is shifted to higher wavenumbers comparing with ligands spectra. These features indicate the coordination of biguanide derivatives through N^2 and N^4

Table 1 Selected absorption maxima (cm^{-1}) for complexes

HDMBG	(1)	HPhBG	(2)	<i>o</i> -HTBG	(3)	Assignments
	3,420m		–		3,435m	$\nu(\text{OH})$
3,371s	3,340m	3,345s	3,338s	3,467s	3,329s	$\nu_{\text{as}}(\text{NH}) (\text{NH}_2)$
3,296m	3,189m	3,278s	3,220s	3,434m	3,210s	$\nu_{\text{s}}(\text{NH}) (\text{NH}_2)$
3,173s	3,018m	3,025s	Covered	3,377s	Covered	$\nu(\text{NH})$
–	–	3,000m	Covered	3,110m	3,105m	$\nu(\text{CH})$ aromatic ring
1,635s	1,689s	1,655vs	1,683s	1,613vs	1,680s	$\nu(\text{C}=\text{N})$
–	–	1,520s	1,535s	1,532vs	1,537s	$\nu(\text{C}=\text{C})$
1,488m	1,492m	1,500s	1,495m	1,483s	1,492m	$\delta_{\text{as}}(\text{CH}_3)$
–	–	1,160w	1,161w	1,116w	1,117w	$\delta(\text{CH})$ aromatic ring
1,419w	1,410w	–	–	1,375s	1,383m	$\delta_{\text{s}}(\text{CH}_3)$
–	979s	–	975s	–	970s	$\nu(\text{V}=\text{O})$
–	–	737m	730m	750m	754m	$\gamma(\text{CH})$ aromatic ring

Table 2 Electronic data for complexes (nm)

Complex	Absorption maxima (nm)		
	${}^2B_2 \rightarrow {}^2A_1$	${}^2B_2 \rightarrow {}^2B_1$	${}^2B_2 \rightarrow {}^2E$
(1)	410	564	897
(2)	405	560	900
(3)	403	568	905

atoms. Furthermore, in the complexes spectra appear a new band around 975 cm^{-1} , which is characteristic for the stretching vibration of the V=O bond [24].

In the electronic spectra of complexes (Table 2) an intense band appears at about 400 nm accompanied by two bands with a lower intensity around 560 and 900 nm. This pattern is characteristic for a square-pyramidal stereochemistry of VO^{2+} ion. The bands from UV-Vis range are assigned to ${}^2B_2 \rightarrow {}^2A_1$ and ${}^2B_2 \rightarrow {}^2B_1$ spin allowed transitions, respectively, whilst that from NIR region is characteristic to ${}^2B_2 \rightarrow {}^2E$ transition [25].

On the basis of above data the proposed coordination for the complexes is as it follows (Fig. 1):

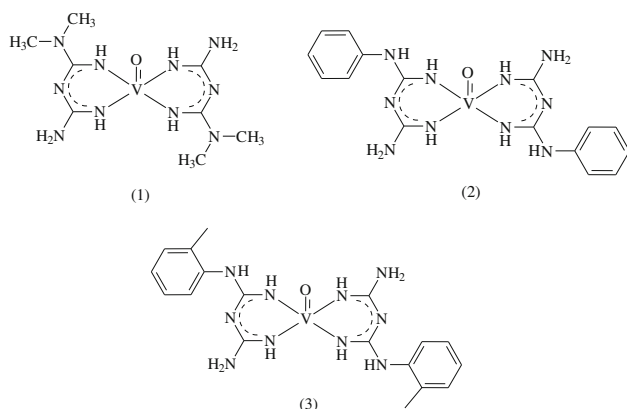
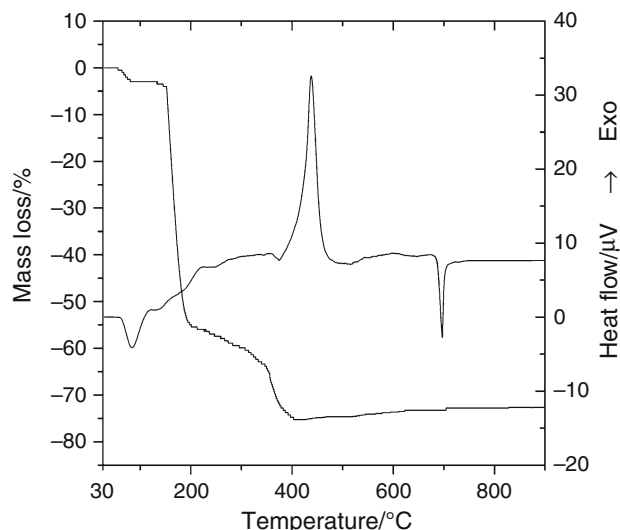
Thermal behaviour of complexes

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

Thermal decomposition of $\text{VO}(\text{DMBG})_2(\text{H}_2\text{O})_{0.5}$

The TG and DTA curves corresponding to the complex (1) heated in the 30–900 °C temperature range are presented in Fig. 2.

The thermal decomposition of $\text{VO}(\text{C}_{27}\text{H}_{31}\text{O}_{14})_2(\text{H}_2\text{O})_8$ (1) occurs in three, well-defined steps (Table 3). The first step, endothermic one, corresponds to the loss of all water molecules. The reaction proceeds with a maximum rate at 85 °C. The low temperature range corresponding to this transformation indicates the presence of crystallisation

**Fig. 1** The proposed coordination for complexes**Fig. 2** TG and DTA curves of $\text{VO}(\text{DMBG})_2(\text{H}_2\text{O})_{0.5}$

water [26]. The anhydrous compound is stable up to 140 °C when decomposition starts. According to TG curve, the rapid weight loss between 140 and 290 °C corresponds to the partial decomposition of *N,N*-dimethylbiguanide anion leading to an intermediate residue containing VO_2 and paracyanide $(\text{CN})_{2n}$. This behaviour seems to be a trend in thermal decomposition of complexes bearing biguanide derivatives [27–31]. This step is a complex one being an overlapping of at least two processes as DTA curve indicates. The intermediate isolated at 290 °C exhibits an IR spectrum with a structured band centred at $1,518\text{ cm}^{-1}$ assigned to $\nu(\text{C}=\text{N})$ (Fig. 3). The other strong bands centred at 995, 875, 623 and 518 cm^{-1} are assigned to the V=O stretching (the first one) and to V–O–V deformation modes (the last three) [32].

The third step, an exothermic one, corresponds to the oxidative degradation of the remaining paracyanide. The intermediate product, vanadium (IV) oxide shows gradual oxidation to V_2O_5 in the temperature range of 405–625 °C. The final thermal event is the V_2O_5 melting as DTA curve shows at about 682 °C. The smaller value observed comparing with the bulk particle (690 °C) can be due to the particles size. The powder XRD analysis of the final residue obtained after cooling reveals the structure of V_2O_5 as shcherbinaite modifications (ASTM 41-1426) (found/calcd. overall mass loss: 72.7/72.6%).

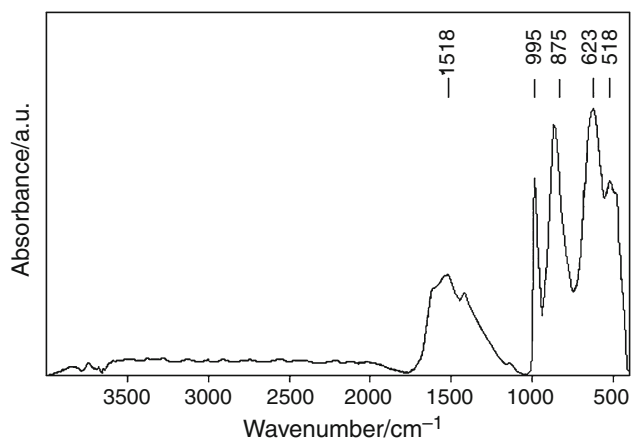
Thermal decomposition of $\text{VO}(\text{PhBG})_2$

The TG curve of complex $\text{VO}(\text{PhBG})_2$ (2) is almost stable up to 235 °C indicating the absence of any lattice or coordinated water molecule (Fig. 4; Table 3). The first mass loss step corresponds to the ligand side group release (Scheme 1). This step is a complex one being an overlap of

Table 3 Thermal behaviour data (in air atmosphere) for the complexes

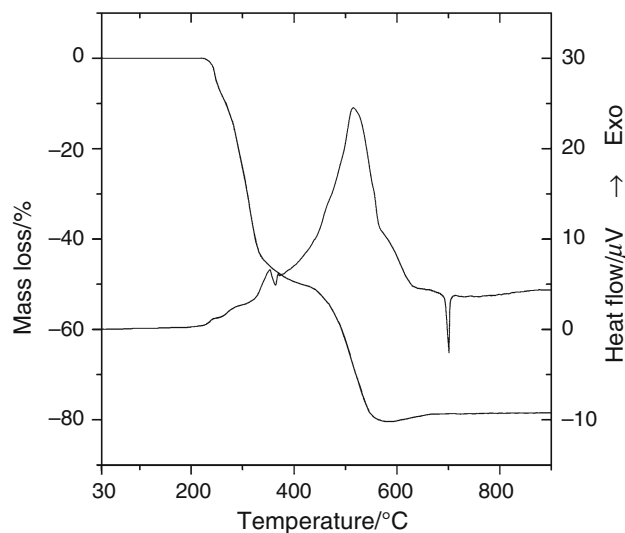
Complex	Step	Thermal effect	Temperature interval/°C	$\Delta m_{\text{exp}}/\%$	$\Delta m_{\text{calc}}/\%$
VO(DMBG) ₂ (H ₂ O) _{0.5} (1)	1.	Endothermic	55–105	2.8	2.7
	2.	Exothermic	140–290	56.4	56.6
	3.	Exothermic	290–405	16.0	15.7
	4.	Exothermic	405–625	+2.5	+2.4
	5.	Endothermic	682*	–	–
	Residue (V ₂ O ₅)				27.3
VO(PhBG) ₂ (2)	1.	Exothermic	235–430	50.6	50.4
	2.	Exothermic	430–570	29.7	29.9
	3.	Exothermic	570–630	+2.0	+1.9
	4.	Endothermic	685*	–	–
	Residue (V ₂ O ₅)				21.7
VO(o-TBG) ₂ (H ₂ O) _{0.5} (3)	1.	Endothermic	60–100	2.3	2.0
	2.	Exothermic	210–440	65.4	65.6
	3.	Exothermic	440–495	14.1	14.1
	4.	Exothermic	495–638	+1.8	+1.8
	5.	Endothermic	687*	–	–
	Residue (V ₂ O ₅)				20

* Melting point

**Fig. 3** IR spectrum for isolated intermediate of complex (1) at 290 °C

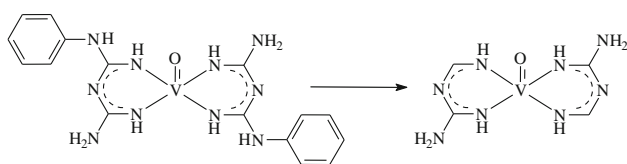
at least three processes as DTA curve indicates. Similar as for the previous discussed complex, the low thermal effect observed for this step indicate that there is an equilibrium between the bonds cleavage and the oxidative processes suggesting that at least a part of the volatile product are released without oxidation.

The proposed decomposition mechanism is sustained by the IR spectrum of intermediate isolated at 430 °C (Fig. 5b) which still contains the characteristic vibration bands for primary and secondary amine groups [$\nu_{\text{as}}(\text{NH}_2)$, 3410 s; $\nu_{\text{s}}(\text{NH}_2)$, 3175 s; $\nu(\text{NH})$, 3000 sh] as well as for carbon–nitrogen bonds [$\nu(\text{C}=\text{N})$, 1659 s; $\nu(\text{C}-\text{N})$, 1123 s]; the disappearance of the strong band characteristic to stretching

**Fig. 4** TG and DTA curves of VO(PhBG)₂

C=C vibration from the benzene ring (1,535 cm⁻¹ in complex, Fig. 5a) also sustains this assumption. The strong band around 1,300 cm⁻¹ was observed for other complexes with biguanide derivatives [33] and can be associated either with the formation of the chelate ring or with the activation of an IR band as result of the complex symmetry decreasing upon packing in the new network.

The second step, which is strong exothermic, corresponds to oxidative degradation of the remaining ligand leading to VO₂ oxide. The last two steps are similar with



Scheme 1

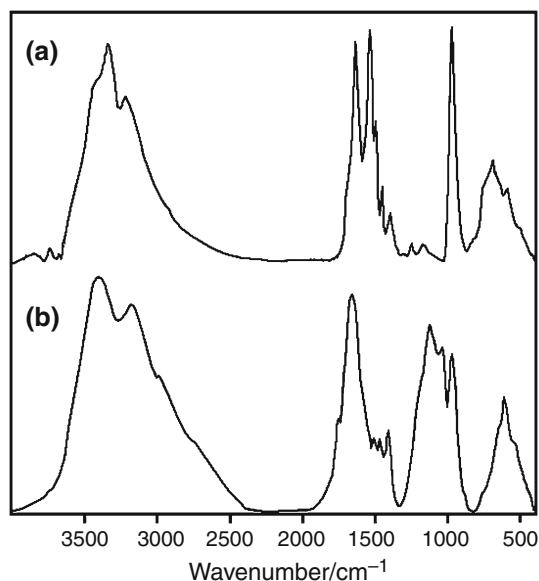


Fig. 5 IR spectra of complex (2) (a) and isolated intermediate at 430 °C (b)

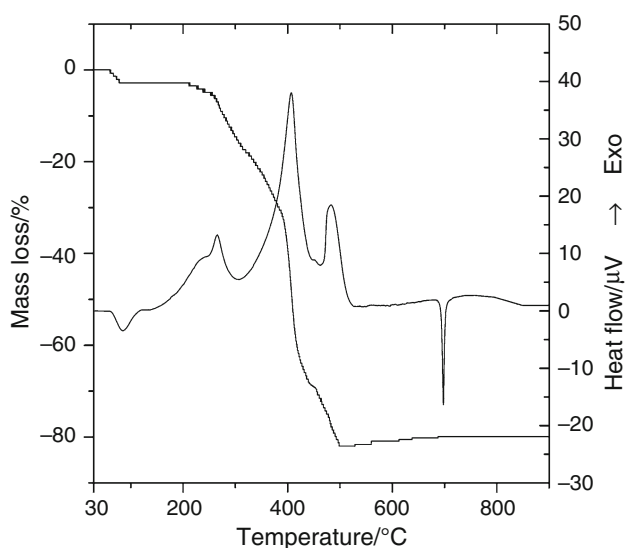


Fig. 6 TG and DTA curves of $\text{VO}(\text{o-TBG})_2(\text{H}_2\text{O})_{0.5}$

those observed for complex (1), VO_2 oxidation to V_2O_5 followed by the melting of final product (found/calcd. overall mass loss: 78.3/78.4%).

Thermal decomposition of $\text{VO}(\text{o-TBG})_2(\text{H}_2\text{O})_{0.5}$

The analysis of TG and DTA curves allowed us to establish the final formula of this compound (Fig. 6). Thus, the first endothermic mass loss in the temperature range 60–100 °C corresponds to the lattice water molecules release. The anhydrous compound is stable over a large temperature range (100–210 °C) and then it decomposes in a similar way with compound (1).

Conclusions

The new complexes of oxovanadium (IV) with biguanide derivatives that belong to a class of coordination compounds of current interest for their insulin-mimetic properties have been synthesised and characterised. Spectral data indicate a square pyramidal stereochemistry for complexes and a chelate coordination mode for biguanide derivatives.

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 that the intermediate steps correspond to the oxidative degradation of ligands. The residue in all cases was shcherbinaite modifications of V_2O_5 as indicated by powder X-ray diffraction.

These complexes seem to be more stable in the case of aromatic side groups present in ligands.

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