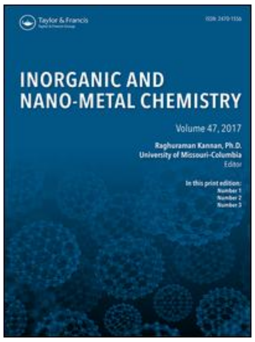

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Synthesis, Crystal Structure, and Insulin-like Activity of [*N'*-(2-Hydroxy-3-methoxybenzylidene)-2-methoxybenzohydrazonato](1,10-phenanthroline)oxovanadium(IV) Methanol Solvate

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Abstract

The aroylhydrazone Schiff base ligand *N'*-(2-hydroxy-3-methoxybenzylidene)-2-methoxybenzohydrazide (H_2L) reacts with $VO(acac)_2$ and 1,10-phenanthroline (Phen) in methanol gave the complex [*N'*-(2-hydroxy-3-methoxybenzylidene)-2-methoxybenzohydrazonato](1,10-phenanthroline)oxovanadium(IV) methanol solvate, $[V^{IV}OL(Phen)]\cdot CH_3OH$. The structure of the complex was characterized by elemental analyses and IR spectroscopic method in the solid state. Single crystal X-ray analysis was also performed. The complex crystallized in triclinic space group *P*-1, with unit cell dimensions $a = 9.220(3)$ Å, $b = 9.382(3)$ Å, $c = 16.593(5)$ Å, $\alpha = 73.900(5)°$, $\beta = 78.618(6)°$, $\gamma = 84.959(6)°$, V = 1351.1(7) Å^3, Z = 2, $R_1 = 0.0837$, $wR_2 = 0.0751$. The V atom in the complex is six-coordinated in an octahedral geometry. Thermal stability of the complex was determined. The insulin-like activity of the complex has been determined.

Keywords

Vanadium complex, crystal structure, aroylhydrazone, thermal property, insulin-like activity

Introduction

The presence of vanadium(IV) and vanadium(V) compounds in many vanadium-dependent enzymes, for instance, nitrogenases and haloperoxidases,[1-3] as well as insulin mimicking,[4,5] have stimulated the search for structural and functional models based on vanadium complexes. Moreover, oxovanadium complexes have been attracted tremendous attention for their versatile catalytic properties in organic synthesis.[6-8] In recent years, the remarkable biological activity of aroylhydrazones and the dependence of their mode of chelation with transition metal ions in living systems have been of significant interest.[9-14] 1,10-Phenanthroline (Phen) is a well-known bidentate ligand, which has been usually used as co-ligands in the preparation of metal complexes.[15] Recently, we have reported some aroylhydrazone compounds.[16,17] As a further study on the coordination of aroylhydrazone to vanadium ions, in this paper, a new oxovanadium complex, [*N′*-(2-hydroxy-3-methoxybenzylidene)-2-methoxybenzohydrazonato](1,10-phenanthroline)oxovanadium(IV) methanol solvate, $[V^{IV}OL(Phen)]\cdot CH_3OH$, was synthesized and characterized.

Experimental

Materials and Methods

3-Methoxysalicylaldehyde, 2-methoxybenzohydrazide, 1,10-phenanthroline and vanadium(IV) oxide acetylacetonate ($[VO(acac)_2]$) were purchased from Merck and Fluka, and used as received. The aroylhydrazone Schiff base ligand *N′*-(2-hydroxy-3-methoxybenzylidene)-2-methoxybenzohydrazide (H_2L) was prepared in a 93% yield by condensation reactions of 3-methoxysalicylaldehyde with 2-methoxybenzohydrazide in methanolic media, according to the literature method.[16,17] All other chemicals and solvents used in this work were of analytical grade available commercially and were used without further purification. Elemental analyses (carbon, hydrogen and nitrogen) of the compounds were obtained from a Carlo ERBA Model EA 1108 analyzer. Infrared spectra were collected by using KBr pellets on a Jasco-5300 FT-IR spectrophotometer. Solution electrical conductivity was measured with a DDS-11A conductivity meter. Thermal analysis of the complex was carried out by heating at a rate of 10°C per minute on a Perkin Elmer TGA-4000 thermo balance.

Synthesis of the Complex

$[VO(acac)_2]$ (0.01 mmol, 2.65 g) dissolved in methanol (30 mL) was added dropwise to a stirred methanolic solution (30 mL) of H_2L (0.01 mol, 3.00 g) and 1,10-phenanthroline (0.05 mmol, 0.09 g). The mixture was gently refluxed for 2 h, then most of the solvent was evaporated by distillation. After cooling, the resulting brown solid was filtered off, washed with cold absolute methanol, and dried in a vacuum containing anhydrous $CaCl_2$. Yield: 0.20 g (69%). IR data (cm^{--1}, KBr): 3449 (m), 1616 (s), 1525 (m), 1440 (m), 1375 (m), 1303 (w), 1244 (m), 1107 (m), 1028 (w), 963 (s), 846 (w), 735 (m), 676 (w), 598 (w), 493 (w), 435 (w). Dark brown block-like single crystals of the complex, suitable for single crystal X-ray diffraction, were obtained by slow evaporation of a methanol solution containing the complex. Anal. Calcd. for $C_{29}H_{26}N_4O_6V$ (%): C, 60.32; H, 4.54; N, 9.70. Found: C, 60.50; H, 4.67; N, 9.59.

X-Ray Crystallography

A suitable X-ray quality crystal of the complex was pick up under a microscope and investigated in a diffraction experiment at 298(2) K on a Bruker Apex II diffractometer with monochromated Mo

Kα radiation (λ = 0.71073 Å) obtained from a graded multilayer X-ray optics. The structure was solved by direct methods with SHELXS-97,[18] and refined with full-matrix least-squares techniques on F^2 with SHELXL-97.[18] The C-bonded hydrogen atoms were calculated in an idealized geometry, riding on their parent atoms, with distances restrained to 0.93--0.96 Å. The crystal data and refinement parameters are listed in Table 1.

Cell Culture and Viable Cell Counts

C2C12 mouse skeletal muscle cells were cultured in Dulbecco modified Eagle's medium with 4 mmol·L^{-1} *L*-glutamine. C2C12 cells were sub-cultured in log phase to 70% confluence and seeded at a density of 5000 cells per well into 96-well culture plates. After three days culture myotube formation was induced by replacing the fetal bovine serum in the medium with 10% horse serum. All experiments were done in 5 days when more than 75% of the cells were differentiated morphologically. The cells were suspended in a trypan blue (0.1% w/w) phosphate buffered saline solution and the ratio of stained to nonstained cells was determined after 5 min of incubation time. Viable cell counts were performed using a hemocytometer.

Glucose Uptake Determination

Cells were incubated in glucose and serum-free media after 3 hours prior to glucose uptake. On the 5th day, the medium was removed and replaced with 50 mL modified Dulbecco modified Eagle's medium without phenol red, supplemented with 8 mmol·L^{-1} glucose and 0.1% bovine serum albumin containing either the complex at concentration of 0.10 g·L^{-1} or the positive controls, insulin, at 1 mmol·L^{-1} were added to the 96-well plate. The plate was then incubated for 2 h at

37°C and 5% CO_2. After incubation, 4 mL media was removed from each well and transferred to a new 96-well plate to which 196 mL deionized water was added in each well. A total of 50 mL of this diluted medium was transferred to a new 96-well plate and 50 mL of the prepared glucose assay reagent was added per well and incubated for 30 min at 37°C. Absorbance was taken at 570 nm on a 96-well plate reader. The glucose concentration per well was calculated from a standard curve. Glucose utilization was determined by subtracting the glucose concentration left in the medium of the relevant wells following incubation to media not exposed to cells during incubation.

Results and Discussion

Synthesis and Characterization

The reaction of $VO(acac)_2$ with the tridentate aroylhydrazone Schiff base ligand *N'*-(2-hydroxy-3-methoxybenzylidene)-2-methoxybenzohydrazide and 1,10-phenanthroline in methanol afforded the neutral oxovanadium(IV) complex (Scheme 1). Elemental analyses of the complex are consistent with the general molecular formula proposed by single crystal X-ray determination. The complex is soluble in common organic solvents such as dimethylsulphoxide, dimethylformamide, methanol, and ethanol. In absolute methanolic solution, it is electrically non-conducting.

IR Spectra

The infrared spectra of the free aroylhydrazone Schiff base ligand and the complex gave information about the coordination. The free ligand displays a broad band centered at 3415 cm^{-1}

and a weak and sharp band at 3223 cm^{-1}. These bands are possibly due to the O--H and N--H stretches. However, the sharp band is absence in the spectrum of the complex. The absence of the ν(C = O) band, presents in H_2L at 1651 cm^{-1}, indicates the enolization of the amide functionality upon coordination to the V atom. Strong band observed at 1616 cm^{-1} for the complex can be attributed to the stretching vibrations of the azomethine group, $\nu_{C = N}$.[19] The spectrum of the complex displays typical and intense band at 963 cm^{-1} which can be assigned to the stretches of the V = O bond.[20]

Description of the Crystal Structure of the Complex

The molecular structure and atom numbering scheme for the complex is depicted in Figure 1. Selected bond lengths and angles are given in Table 2. The complex contains a neutral mononuclear oxovanadium complex and a methanol molecule of crystallization. The coordination geometry around the vanadium atom can be described as distorted octahedral with the tridentate aroylhydrazone ligand coordinated in a meridional fashion, forming five- and six-membered chelate rings with bite angles of 76.48(19)° (N(1)--V(1)--O(2)) and 88.2(2)° (N(1)--V(1)--O(1)), typical for this type of ligand system.[21,22] The aroylhydrazone Schiff base ligand coordinates in its dianionic enolate form, which is consistent with the observed C(8)--O(2) and C(8)--N(2) bond lengths of 1.278(6) and 1.311(7) Å. The three donor atoms of the aroylhydrazone ligands and N4 atom of 1,10-phenanthroline ligand define the equatorial plane of the octahedral coordination. The two axial positions of the octahedral coordination are occupied by the N(3) atom of 1,10-phenanthroline ligand and one oxo group. The N(3) atom in the complex coordinates to the V atom at rather elongated distance of 2.354(5) Å, due to the *trans* influence of the oxo group. This is accompanied by a significant displacement of the V atom from the equatorial plane towards the oxo group by 0.352(2) Å.

In the crystal structure of the complex, methanol molecules are linked to the vanadium complex molecules through intermolecular O(6)--H(6)···N(2) hydrogen bond [O(6)--H(6) = 0.82 Å, H(6)···N(2)^{ii} = 2.30(2) Å, O(6)···N(2)^{ii} = 2.906(8) Å, O(6)--H(6)···N(2)^{ii} = 131(3)°; symmetry code for ii: x, y, $1 + z$] (Figure 2).

Thermal Property

The thermogravimetric analysis of the complexes was carried out in the temperature range 50--1000°C at a heating rate of 10°C min^{-1}. The TG and DTA curves of the complex are given following degradation scheme (Figure 3). The complex is stable up to 83°C. Above this temperature, the TG curve show three steps of weigh losses. The first step of decomposition in the temperature range 83--104°C involved the removal of the lattice methanol molecule. The second step of decomposition in the temperature range 231--494°C involved the removal of the 1,10-phenanthroline ligand. With further elevation in temperature, a rapid weigh loss in the temperature range 494--538°C was observed. The decomposition of the final stage weight loss may be ascribed to the dissociation of the aroylhydrazone Schiff base ligand, and the formation of the final product V_2O_5.

Insulin-Like Activty

The glucose uptake by C2C12 muscle cells following exposure to the vanadium complex was studied. Insulin-like activity indicated that the complex can significantly stimulate cell glucose utilization with percentage in glucose utilization of 163. As a comparison, the percentage in glucose utilization of insulin is 145. It is excited that the insulin-like activity of the complex is more active than insulin.

Acknowledgments

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Supplementary Material

CCDC 906161 contains the supplementary crystallographic data for the complex. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk.

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Table 1. Crystallographic data for the complex

Chemical formula	$C_{29}H_{26}N_4O_6V$
Formula weight	577.48
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions	
a (Å)	9.220(3)
b (Å)	9.382(3)
c (Å)	16.593(5)
α (°)	73.900(5)
β (°)	78.618(6)
γ (°)	84.959(6)
V ($Å^3$)	1351.1(7)
Z	2
ρ (g cm^{-3})	1.419
μ (mm^{-1})	0.418
T_{min}, T_{max}	0.8955, 0.9100
Reflections collected	9275
Reflections unique	4487

Reflections observed [$I > 2\sigma(I)$]	1904
Parameters	365
R_1, wR_2 [$I > 2\sigma(I)$]	0.0751, 0.0837
R_1, wR_2 (all data)	0.1059, 0.2081
Goodness-of-fit on F^2	0.973
Largest difference in peak and hole (e Å^{-3})	0.308, --0.332

Table 2. Selected bond lengths (Å) and angles (°) for the complex

V(1)--O(1)	1.953(4)	V(1)--O(2)	1.999(4)
V(1)--O(5)	1.610(4)	V(1)--N(1)	2.026(5)
V(1)--N(3)	2.354(5)	V(1)--N(4)	2.133(5)
O(5)--V(1)--O(1)	101.1(2)	O(5)--V(1)--O(2)	101.4(2)
O(1)--V(1)--O(2)	155.44(18)	O(5)--V(1)--N(1)	105.0(2)
O(1)--V(1)--N(1)	88.2(2)	O(2)--V(1)--N(1)	76.48(19)
O(5)--V(1)--N(4)	93.6(2)	O(1)--V(1)--N(4)	97.38(18)
O(2)--V(1)--N(4)	90.96(18)	N(1)--V(1)--N(4)	159.1(2)
O(5)--V(1)--N(3)	165.7(2)	O(1)--V(1)--N(3)	79.87(19)
O(2)--V(1)--N(3)	80.82(19)	N(1)--V(1)--N(3)	89.3(2)
N(4)--V(1)--N(3)	72.1(2)		

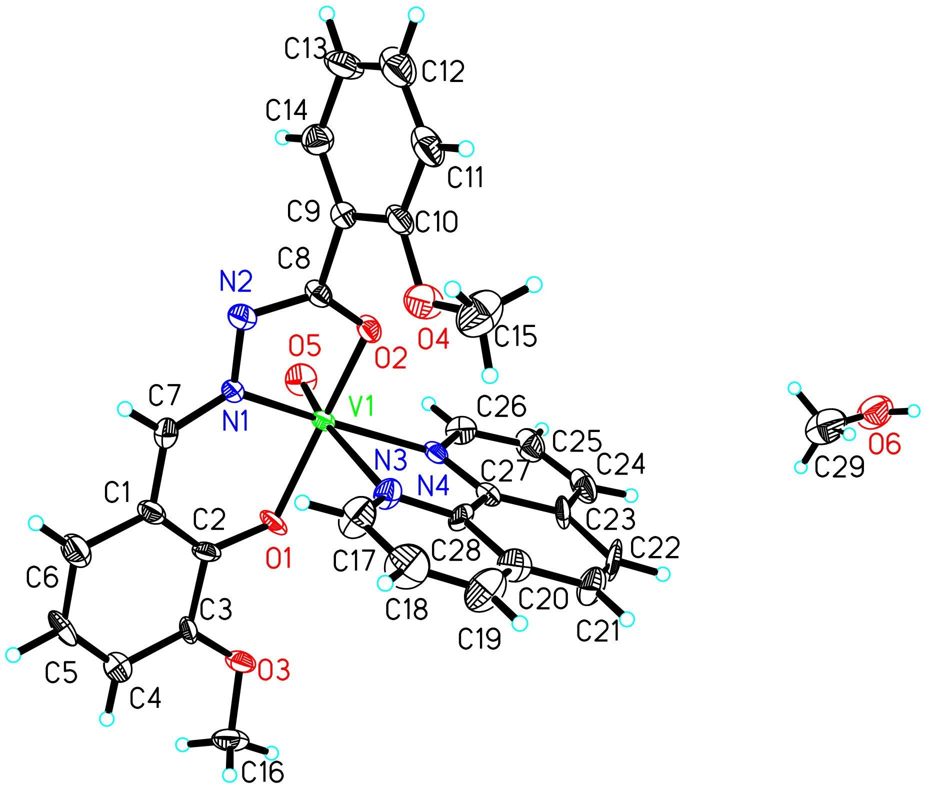


Figure 1. Structure of the complex with the atom labeling scheme. All non-hydrogen atoms are represented at 30% probability thermal ellipsoids.

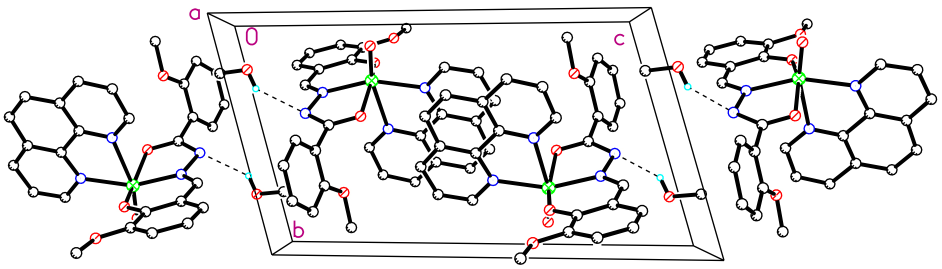


Figure 2. Molecular packing diagram of the complex, viewed down the *a* axis. Hydrogen bonds are drawn as dashed lines.

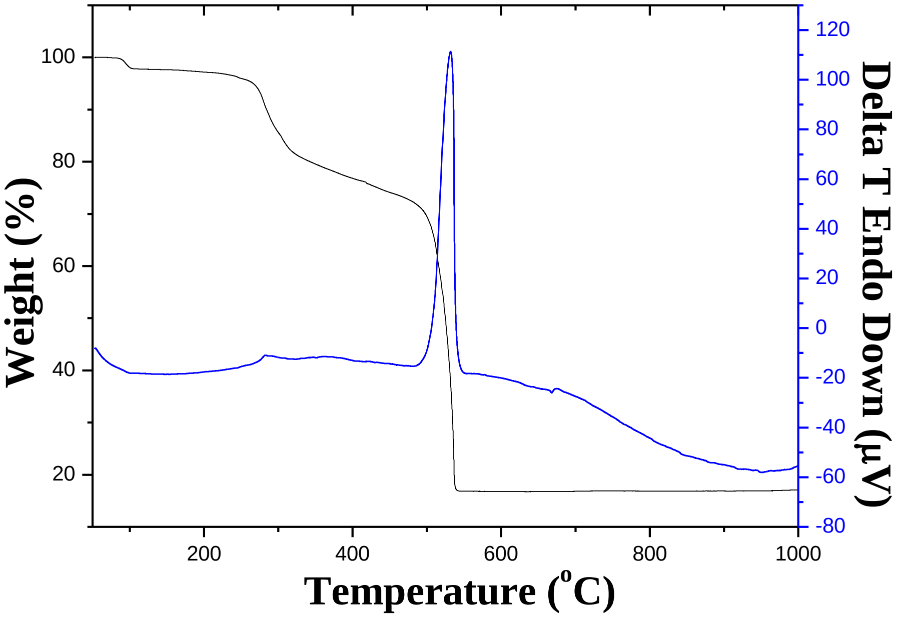
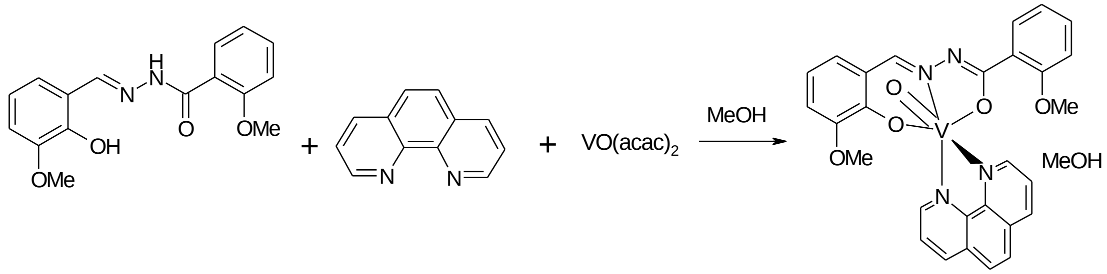


Figure 3. DT-TGA curves of the complex.



Scheme 1. The synthesis of the complex.