

Short communication

Vanadium Complex Derived from *N'*-(3-Bromo-5-chloro-2-hydroxybenzylidene)-3-methylbenzohydrazide: Synthesis, Crystal Structure and Biological Activity

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Received: 20-01-2016

Abstract

Reaction of VO(acac)₂ with *N'*-(3-bromo-5-chloro-2-hydroxybenzylidene)-3-methylbenzohydrazide (H₂L) in methanol afforded a new mononuclear vanadium(V) complex, [VOL(OMe)(MeOH)]. Structure of the complex has been characterized by physico-chemical methods and single-crystal X-ray diffraction. The complex crystallizes as the monoclinic space group *P*2₁/*c*, with unit cell dimensions *a* = 13.1345(10) Å, *b* = 18.6279(14) Å, *c* = 7.8983(8) Å, β = 90.248(2)°, *V* = 1932.4(3) Å³, *Z* = 4, *R*₁ = 0.0963, *wR*₂ = 0.2213, *S* = 1.113. X-ray analysis indicated that the V atom in the complex is in octahedral coordination. The insulin-like activity of the complex was studied, which can stimulate glucose uptake with 2-DOG uptake value of 0.81 nmol / 3 min.

Keywords: Hydrazone ligand; Vanadium complex; Crystal structure; Insulin-like activity

1. Introduction

Transition metal complexes with various ligands have been received much attention because they have interesting biological activities. The increasing interest in the coordination chemistry of vanadium is derived from its well-established chemical and biological functions.¹ Vanadium is recognized as an essential trace element for different organisms.² The element is present in vanadium-containing enzymes such as nitrogenase and haloperoxidases.³ Due to structural similarity between vanadates and phosphate and being able to be transported into cells through the anion channel of the plasma membranes,⁴ many vanadium compounds have been shown to increase glucose transport into cells and its oxidation *via* glycolysis.⁵ Oxovanadium(IV) sulphate has been demonstrated to possess oral insulin-like activity similar to that of the vanadates, with lowered toxicity.⁶ Oxovanadium(IV) salts,

however, are known to be poorly absorbed and less bioavailable compared to vanadates.⁷ Therefore, a number of low molecular weight vanadium complexes have been prepared and studied on their insulin-like activity in an attempt to improve the bioavailability of vanadium.⁸ In general, these complexes exhibit insulin-like activity and are effective at lower doses with demonstrable lower toxicities than the vanadium salts.⁹ In addition, such vanadium complexes normalized glucose and lipid values without an increase in insulin levels, and improved glucose tolerance. Considering hydrazone ligands are bioactive species,¹⁰ and compounds bearing one or more halide atoms on the aromatic rings can improve biological activities,¹¹ in the present paper, we report the synthesis, characterization and insulin-like activity of a new vanadium complex, [VOL(OMe)(MeOH)], where L is the dianionic form of the hydrazone ligand *N'*-(3-bromo-5-chloro-2-hydroxybenzylidene)-3-methylbenzohydrazide (H₂L).

2. Experimental

2.1. General Methods and Materials

VO(acac)₂, 3-bromo-5-chlorosalicylaldehyde and 3-methylbenzohydrazide were purchased from Lancaster and used as received. All other reagents were of analytical reagent grade. Elemental analyses of C, H and N were carried out in a 2400 Series-II CHN analyzer. FT-IR spectra were obtained on a Jasco FT/IR-4000 spectrometer with samples prepared as KBr pellets. Molar conductance was measured with a Shanghai DDS-11A conductometer. In vitro insulin-mimic activity was determined according to the literature method.⁸

2.2. Synthesis of the Complex

3-Bromo-5-chlorosalicylaldehyde (0.23 g, 1.0 mmol) and 3-methylbenzohydrazide (0.15 g, 1.0 mmol) were dissolved and mixed in methanol (20 mL). The mixture was stirred at room temperature for 10 min to give a colorless solution. To the solution was added dropwise a methanol solution (20 mL) containing VO(acac)₂ (0.26 g, 1.0 mmol). The color changed to brown immediately. The brown mixture was stirred at room temperature for 30 min and filtered. The filtrate was kept at ambient temperature. Single crystals of the complex, suitable for X-ray diffraction, were grown from the filtrate upon slow evaporation within a few days. The crystals were isolated by filtration, washed with methanol and dried in air. Yield 45%. Characteristic IR data (cm⁻¹): 3445w, 1612s, 1497s, 1428m, 1382m, 1355m, 1283w, 1045s, 965m, 927w, 898w, 820w, 712w, 641m, 553w, 470w. Anal. Calcd for C₁₇H₁₇BrClN₂O₅V: C 41.20, H 3.46, N 5.65 %; found: C 41.03, H 3.52, N 5.78 %.

2.3. X-ray Crystallography

Single-crystal X-ray diffraction data for the complex were collected on a Bruker Smart 1000 CCD diffractometer at 298(2) K with Mo K α radiation ($\lambda = 0.71073$ Å) by Ω scan mode. The program SAINT was used for integration of the diffraction profiles.¹² The structure was solved by direct methods using the SHELXS program of the SHELXTL package and refined by full-matrix least-squares methods with SHELXL (semi-empirical absorption corrections were applied using the SADABS program).¹³ The positions of the non-hydrogen atoms were located in difference Fourier syntheses and least-squares refinement cycles, and finally refined anisotropically. The methanol hydrogen atom was located from the electronic density map and refined isotropically, with O–H distance restrained to 0.85(1) Å. The remaining hydrogen atoms of the complex were placed theoretically onto the specific atoms and refined isotropically as riding atoms. Crystallographic data and experimental details for structural analyses are summarized in Table 1. Selected bond lengths and angles for the complex are listed in Table 2.

Table 1. Crystallographic information for the complex

Formula	C ₁₇ H ₁₇ BrClN ₂ O ₅ V
Formula weight	495.63
Crystal shape/color	Block/brown
Crystal system	Monoclinic
Space group	<i>P2₁/c</i>
<i>a</i> (Å)	13.1345(10)
<i>b</i> (Å)	18.6279(14)
<i>c</i> (Å)	7.8983(8)
β (°)	90.248(2)
<i>V</i> (Å ³)	1932.4(3)
<i>Z</i>	4
<i>D</i> _{calc} (g cm ⁻³)	1.704
μ (Mo K α) (mm ⁻¹)	2.750
<i>F</i> (000)	992
Measured reflections	6361
Unique reflections	3084
Observed reflections (<i>I</i> \geq 2 σ (<i>I</i>))	2289
Parameters	250
Goodness of fit on <i>F</i> ²	1.113
<i>R</i> ₁ , <i>wR</i> ₂ [<i>I</i> \geq 2 σ (<i>I</i>)] ^a	0.0844, 0.1851
<i>R</i> ₁ , <i>wR</i> ₂ (all data) ^a	0.1130, 0.2095
Largest different peak and hole (e Å ⁻³)	0.817, -0.645

$$^a R_1 = F_o - F_c/F_o, wR_2 = [\sum w(F_o^2 - F_c^2)/\sum w(F_o^2)]^{1/2}$$

Table 2. Selected bond lengths (Å) and angles (°) for the complex with estimated standard deviations (e.s.d.s) in parentheses

Bond distances (Å)			
V1–O1	1.880(6)	V1–O2	1.958(6)
V1–O3	1.576(8)	V1–O4	1.757(6)
V1–O5	2.332(8)	V1–N1	2.134(7)
Bond angles (°)			
O3–V1–O4	103.2(3)	O3–V1–O1	98.4(3)
O4–V1–O1	100.3(3)	O3–V1–O2	98.3(3)
O4–V1–O2	96.5(3)	O1–V1–O2	153.0(3)
O3–V1–N1	94.6(3)	O4–V1–N1	160.9(3)
O1–V1–N1	83.6(3)	O2–V1–N1	74.0(2)
O3–V1–O5	174.8(3)	O4–V1–O5	81.6(3)
O1–V1–O5	82.6(3)	O2–V1–O5	79.0(3)
N1–V1–O5	80.4(3)		

3. Results and Discussion

3.1. Synthesis and Characterization

The hydrazone ligand was prepared by reaction of 3-bromo-5-chlorosalicylaldehyde and 3-methylbenzohydrazide in methanol. The ligand was not isolated and purified, and was immediately used to prepare the vanadium complex with VO(acac)₂. It should be pointed out that the vanadium in the starting materials is in V(IV) oxidation state, but it appears to be V(V) in the product, indicating that it was oxidized by air during the reaction procedures. Elemental analysis of the complex is in accordance with

the molecular structure proposed by the X-ray analysis. The complex show typical C=N absorption at 1612 cm^{-1} , and typical V=O absorption at 965 cm^{-1} .¹⁴ The bands due to $\nu(\text{V}-\text{N})$ and $\nu(\text{V}-\text{O})$ observed occurred at $470\text{--}560\text{ cm}^{-1}$. The complex is stable in air at room temperature, and did not decompose when heated up to $250\text{ }^\circ\text{C}$. The molar conductivity of the complex measured in acetonitrile at a concentration of 10^{-3} M is $22\ \Omega^{-1}\text{ cm}^2\text{ mol}^{-1}$, indicating its non-electrolytic nature in solution.¹⁵

3. 2. Structure Description of the Complex

The molecular structure of the complex is shown in Figure 1. The V atom is in an octahedral coordination, and is

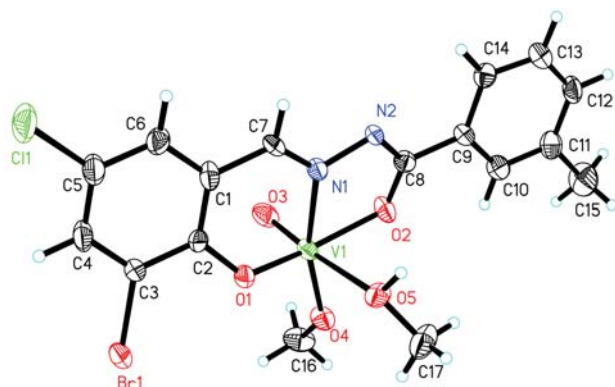


Figure 1. A perspective view of the molecular structure of the complex. Thermal ellipsoids are drawn at the 30% probability level.

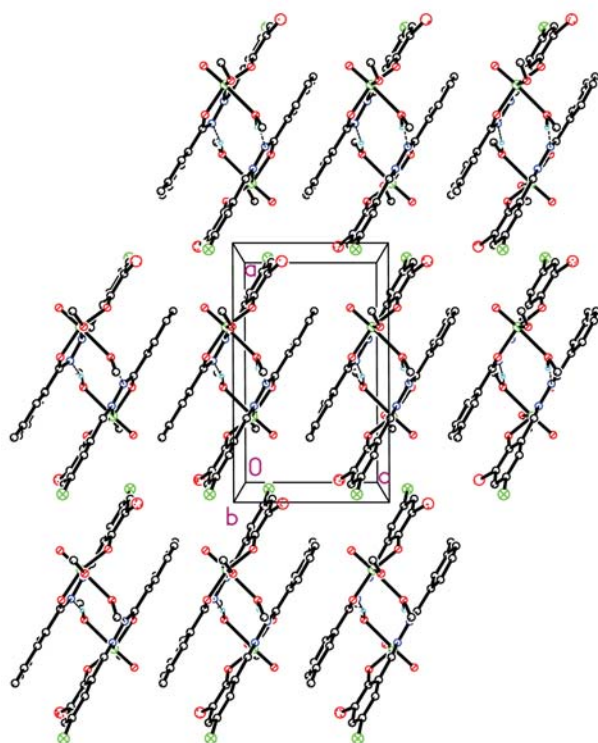


Figure 2. A perspective view of the dimeric structure of the complex.

coordinated by one hydrazone ligand, one oxo oxygen atom, one deprotonated methanol molecule and one neutral methanol molecule. The hydrazone ligand coordinates to the V atom *via* the phenolate oxygen, imino nitrogen, and enalate oxygen. As expected, the neutral methanol ligand is situated at the opposite position of the oxo oxygen. Thus, the bond of V1–O5 is much longer than that of V1–O3. The V atom is situated $0.298(2)\text{ \AA}$ from the least-squares plane defined by the equatorial donor atoms, O1, N1, O2 and O4. The distances related to the remaining V–O [$1.757(6)\text{--}1.959(6)\text{ \AA}$] and V–N [$2.134(7)\text{ \AA}$] bonds are comparable to those observed in similar vanadium(V) complexes.¹⁶

In the crystal packing (Figure 2), two adjacent molecules are linked *via* O5–H5...N2 hydrogen bond [O5–H5 = $0.85(1)\text{ \AA}$, H5...N2ⁱ = $2.02(4)\text{ \AA}$, O5...N2ⁱ = $2.836(9)\text{ \AA}$, O5–H5...N2ⁱ = $161(12)^\circ$; symmetry code for i: $1 - x, -y, 1 - z$].

3. 3. Insulin-like Activity

The presence of the complex in the incubation medium stimulated glucose uptake, with 2-DOG uptake value of $0.81\text{ nmol} / 3\text{ min}$. However, both insulin (IN) and [VO(acac)₂] are more effective than the present complex in enhancing glucose uptake by adipocytes, with 2-DOG uptake values of 1.70 and $1.51\text{ nmol} / 3\text{ min}$, respectively. Further study indicated that the complex inhibited glycerol release by adipocytes in a similar way as that observed with insulin. The results in the present work are similar to that of the vanadium complexes with thiosemicarbazone ligands reported by Beraldo and coworkers.^{8c}

4. Supplementary Material

CCDC–1435661 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/const/retrieving.html> or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.

5. Acknowledgments

This work was financially supported by the Program for Young Teachers Scientific Research in Qiqihar University (2012k-M05), and the Education Office of Heilongjiang Province (Project No. 12531757).

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Povzetek

Pri reakciji VO(acac)₂ z N¹-(3-bromo-5-kloro-2-hidroksibenziliden)-3-metilbenzohidrazida (H₂L) v metanolu smo izolirali nov enojederni vanadijev(V) kompleks, [VOL(OMe)(MeOH)]. Struktura kompleksa je bila določena z fizikalno-kemijskimi metodami in monokristalno rentgensko difrakcijo. Spojina kristalizira v monoklinski prostorski skupini P2₁/c z dimenzijami osnovne celice a = 13.1345(10) Å, b = 18.6279(14) Å, c = 7.8983(8) Å, β = 90.248(2)°, V = 1932.4(3) Å³, Z = 4, R₁ = 0.0963, wR₂ = 0.2213, S = 1.113. Rentgenska strukturalna analiza je razkrila, da ima vanadijev atom oktaedrično koordinacijo. Inzulino sorodna aktivnost spojine je bila določena, in sicer stimulira vnos glukoze z vrednostmi 2-DOG vnosa 0,81 nmol/3 min.