Synthesis, structures, and insulin-like activity of oxidovanadium(V) complexes derived from 2-chloro-N'-(3-ethoxy-2-hydroxybenzylidene)benzohydrazide

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ABSTRACT

Three new oxidovanadium(V) complexes, \([\text{VOLL}']\) (L = 2-chloro-N'-(3-ethoxy-2-hydroxybenzylidene)benzohydrazide, \(L' = \) acetohydroxamate for 1, methylmaltolate for 2, and ethylmaltolate for 3), have been prepared. The complexes have been characterized by physicochemical methods and single-crystal X-ray determination. Vanadium in each complex is coordinated by the NOO donor set of L, the OO donor set of \(L'\), and one oxido, forming octahedral coordination. The complexes were administered intragastrically to both normal and alloxan-diabetic mice for two weeks. The biological activities show that the complexes at doses of 10.0 and 20.0 mg V·kg\(^{-1}\) can significantly decrease the blood glucose level in alloxan-diabetic mice, but the blood glucose level in the treated normal mice was not altered.
1. Introduction

Vanadyl complexes have interesting biological activities, such as antimicrobial [1, 2], anticancer [3–5], and insulin-mimetic [6–9]. Since the 1980s, inorganic vanadium salts and vanadium complexes with various ligands have been reported to possess potent insulin-mimetic activity. Studies indicated that vanadium compounds improve not only hyperglycemia in human subjects and animal models of type I diabetes but also glucose homeostasis in type II diabetes [10, 11]. However, inorganic vanadium salts are considered as less active and more toxic. In order to reduce the side effects of inorganic vanadium salts, vanadium complexes have received particular attention and demonstrated to be effective [12–14]. Schiff bases play an important role in the development of coordination chemistry related to their biological properties. Several vanadium complexes derived from Schiff bases normalize blood glucose level with high efficiency and low toxicity, even at low concentrations [15, 16]. Schiff bases with hydrazones are interesting due to their biological properties [17–21]. In addition, vanadium complexes with maltol ligands such as bis(maltolato)oxovanadium(IV) (BMOV) and bis(ethylmaltolato)oxovanadium(IV) (BEOV) possess effective insulin enhancing activity [22–24]. In the present work, aroylhydrazone and maltol ligands were combined for the first time by coordinating to V ions. Three oxidovanadium complexes, [VOLL1] (1), [VOLL2] (2), and [VOLL3] (3), where L is the dianionic form of 2-chloro-N′-(3-ethoxy-2-hydroxybenzylidene)benzohydrazide (H2L), and L1, L2, and L3 are the monoanionic form of acetohydroxamic acid (HL1), methylmaltol (HL2), and ethylmaltol (HL3), respectively (scheme 1), have been prepared and studied for insulin-like activity to both normal and alloxan-diabetic mice.

2. Experimental

2.1. General methods and materials

Starting materials, reagents, and solvents were purchased from commercial suppliers with AR grade and used without purification. Elemental analyses were performed on a Perkin-Elmer 240C elemental analyzer. IR spectra were recorded on a Jasco FT/IR-4000 spectrometer as KBr pellets from 4000 to 400 cm⁻¹. UV–vis spectra were recorded on a Perkin-Elmer Lambda 900 spectrometer. ¹H NMR spectra were recorded on a Bruker spectrometer at 300 MHz. HRMS data were obtained with ESI (electrospray ionization) mode. H₂L was prepared according to the literature method [25].

2.2. Synthesis of the complexes

Complexes 1, 2, and 3 were prepared by the method described here. A methanolic solution (30 mL) of VO(acac)₂ (0.27 g, 1.0 mmol) was added to a methanolic solution (20 mL) of H₂L (0.32 g, 1.0 mmol) and the bidentate ligands (1.0 mmol each), with stirring. The mixtures were stirred at room temperature for 30 min to give deep brown solution. The resulting solution was allowed to stand in air for a few days until three-quarters of the solvent evaporated. Brown block-shaped single crystals of the complexes, suitable for X-ray single-crystal diffraction, were formed at the bottom of the vessel. The crystals were

Scheme 1. The ligands.
isolated by filtration, washed three times with cold methanol, and dried in air. Yields: 2.56 g, 56% (1); 3.71 g, 73% (2); 3.56 g, 68% (3).

1. Anal. Calcd for C_{18}H_{17}ClN_{3}O_{6}V: C, 47.2; H, 3.7; N, 9.1%. IR data (cm\(^{-1}\)): 3210 (m), 1612 (vs), 1528 (w), 1447 (s), 1391 (w), 1346 (s), 1283 (m), 1248 (m), 1215 (w), 1178 (w), 1097 (m), 1009 (w), 970 (m), 892 (w), 735 (m), 668 (w), 587 (s), 497 (w), 435 (w). UV in acetonitrile (\(\lambda\), \(\varepsilon\)): 275 nm, 2.86 \times 10^4 L\cdot mol^{-1}\cdot cm^{-1}; 350 nm, 1.26 \times 10^4 L\cdot mol^{-1}\cdot cm^{-1}; 435 (w). 1H NMR (300 MHz, d\textsubscript{6}-dMSO): \(\delta\) 13.97 (s, 1H, N\(\ H\)), 9.06 (s, 1H, C\(\ H\)=N), 7.73 (d, 1H, ar\(\ H\)), 7.57–7.40 (m, 3H, ar\(\ H\)), 7.33 (d, 1H, ar\(\ H\)), 7.21 (d, 1H, ar\(\ H\)), 6.92 (t, 1H, ar\(\ H\)), 4.09 (q, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 2.11 (s, 3H, C\(\ H\)\textsubscript{3}C(O)NHO), 1.34 (t, 3H, OCH\textsubscript{2}CH\textsubscript{3}).

2. Anal. Calcd for C_{22}H_{18}ClN_{2}O_{7}V: C, 51.9; H, 3.6; N, 5.5%. IR data (cm\(^{-1}\)): 1602 (vs), 1556 (w), 1511 (w), 1439 (s), 1259 (vs), 1200 (s), 1099 (w), 973 (m), 895 (w), 841 (w), 771 (m), 730 (m), 648 (w), 612 (w), 538 (w), 475 (m), 446 (w). UV in acetonitrile (\(\lambda\), \(\varepsilon\)): 280 nm, 3.02 \times 10^4 L\cdot mol^{-1}\cdot cm^{-1}; 353 nm, 9.15 \times 10^3 L\cdot mol^{-1}\cdot cm^{-1}; 475 nm, 7.12 \times 10^3 L\cdot mol^{-1}\cdot cm^{-1}. 1H NMR (300 MHz, d\textsubscript{6}-dMSO): \(\delta\) 9.19 (s, 1H, maltol-C\(\ H\)), 8.45 (d, 1H, C\(\ H\)=N), 7.70 (d, 1H, ar\(\ H\)), 7.50 (m, 2H, ar\(\ H\)), 7.42 (m, 2H, ar\(\ H\)), 7.28 (d, 1H, ar\(\ H\)), 7.02 (t, 1H, ar\(\ H\)), 6.74 (d, 1H, maltol-C\(\ H\)), 4.09 (q, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 3.36 (s, 3H, maltol-C\(\ H\)\textsubscript{3}), 1.29 (t, 3H, OCH\textsubscript{2}CH\textsubscript{3}).

3. Anal. Calcd for C_{23}H_{20}ClN_{2}O_{7}V: C, 52.8; H, 3.9; N, 5.4%. IR data (cm\(^{-1}\)): 1603 (vs), 1545 (m), 1443 (s), 1349 (s), 1256 (s), 1183 (m), 1147 (w), 1094 (m), 978 (s), 940 (w), 892 (w), 839 (w), 738 (m), 645 (w), 603 (w), 527 (w), 480 (w), 446 (w). UV in acetonitrile (\(\lambda\), \(\varepsilon\)): 280 nm, 2.39 \times 10^4 L\cdot mol^{-1}\cdot cm^{-1}; 353 nm, 2.39 \times 10^4 L\cdot mol^{-1}\cdot cm^{-1}; 475 nm, 7.25 \times 10^3 L\cdot mol^{-1}\cdot cm^{-1}. 1H NMR (300 MHz, d\textsubscript{6}-dMSO): \(\delta\) 9.19 (s, 1H, ethylmaltol-C\(\ H\)), 8.48 (d, 1H, C\(\ H\)=N), 7.72 (d, 1H, ar\(\ H\)), 7.51 (m, 2H, Ar\(\ H\)), 7.42 (m, 2H, Ar\(\ H\)), 7.28 (d, 1H, Ar\(\ H\)), 7.02 (t, 1H, Ar\(\ H\)), 6.74 (d, 1H, ethylmaltol-C\(\ H\)), 4.08 (q, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 2.96 (q, 2H, CH\textsubscript{2}CH\textsubscript{3}), 1.32–1.26 (m, 6H, CH\textsubscript{3}).

2.3. X-ray crystallography

Diffraction intensities for the complexes were collected at 298(2) K using a Bruker SMART 1000 CCD area-detector diffractometer with MoK\(\alpha\) radiation (\(\lambda = 0.7073\) Å). The collected data were reduced with SAINT [26], and multi-scan absorption correction was performed using SAINT [27]. Structures of the complexes were solved by direct methods and refined against \(F^2\) by full-matrix least-squares using SHELXL [28]. All of the non-hydrogen atoms were refined anisotropically. The amino H in 1 was located from a difference Fourier map and refined isotropically, with N–H distance restrained to 0.90(1) Å. The remaining hydrogens were placed in calculated positions and constrained to ride on their parent atoms. Crystallographic data for the complexes are summarized in table 1. Selected bond lengths and angles are given in table 2.

2.4. Glucose-lowering assay

Male Kunming mice, weighing about 25–32 g, were obtained from the Experimental Animal Center, Shandong Lukang Pharmaceutical Co., Ltd. of China, and maintained on a light/dark cycle. All animals were allowed free access to food and water. Temperature and relative humidity were maintained at 24 °C and 50%. Mice were acclimatized for seven days prior to induction of diabetes. Diabetes was induced by a single intra-peritoneal injection of freshly prepared alloxan (200 mg·kg\(^{-1}\) body weight) in 0.9% saline. The control mice were injected with an equal volume of vehicle. After seven days, blood was collected from the tail vein and serum samples were analyzed for blood glucose. Animals showing fasting (12 h) blood glucose higher than 11.1 mmol·L\(^{-1}\) were considered to be diabetic and used for the study.

The experimental animals were randomly divided into six groups with six mice each according to the blood glucose. Group 1, normal control group: normal mice treated with 0.5% carboxymethyl cellulose (CMC). Groups 2–4, treated normal group: normal mice treated with 20 mg V·kg\(^{-1}\) vanadium complexes. Group 5, diabetic control group: alloxan diabetic mice treated with 0.5% CMC. Groups 6–11, treated diabetic group: alloxan diabetic mice treated with vanadium complexes at dose of 10 and
20 mg V·kg⁻¹ ig. The complexes were administered as suspensions in 0.5% CMC. The substances were administered intragastrically once a day at the volume of 10 mL·kg⁻¹ for two weeks.

Throughout the experimental period, the body weight of mice was monitored daily. Blood samples were obtained from the tail vein of the mice and blood glucose levels were determined with an Accu-Chek blood glucose monitor (Roche Diagnostics GmbH, Mannheim, Germany).

3. Results and discussion

3.1. Chemistry

The aroylhydrazone, 2-chloro-N’-(3-ethoxy-2-hydroxybenzylidene)benzohydrazide, was readily prepared by condensation of 3-ethoxysalicylaldehyde with 2-chlorobenzohydrazide in methanol. The complexes were prepared by reaction of equimolar quantities of the aroylhydrazone and VO(acac)₂ with acetohydroxamic acid, methylmaltol, and ethylmaltol, respectively, in methanol. Crystals of the complexes are stable in open air at room temperature. Elemental analyses are in agreement with the chemical formulas proposed for the compounds. It should be pointed out that the vanadium in the starting materials is V(IV), but it appears to be V(V) in the complexes, indicating that it was oxidized by air during the reaction.

3.2. Structure description of the complexes

Figures 1, 2, and 3 give perspective views of 1, 2, and 3, respectively, together with the atom labeling system. Structures of the complexes are very similar except for the bidentate co-ligands. The V ions in the complexes are octahedral, with the phenolate O, imino N, and enolate O of the aroylhydrazone ligand, and the hydroxy O of bidentate ligands defining the equatorial plane, and with one oxido O and the carbonyl O of the bidentate ligands at the axial positions. The V ions deviate from the least-squares planes defined by the equatorial atoms by 0.276(1) Å for 1, 0.293(1) Å for 2, and 0.296(1) Å for 3. The

| Table 1. Crystal data for 1–3. |
|--------------------------------|
| 1                           | 2                                   | 3                          |
| Formula                      | C₁₈H₁₇C₁N₃O₆V                       | C₂₂H₁₈C₁N₂O₇V               | C₂₃H₂₀C₁N₂O₇V               |
| FW                          | 457.74                              | 508.77                      | 522.80                      |
| Crystal shape/color          | Block/brown                         | Block/brown                 | Block/brown                 |
| Crystal size/mm              | 0.23 × 0.23 × 0.18                   | 0.27 × 0.27 × 0.24          | 0.20 × 0.20 × 0.17          |
| Crystal system               | Monoclinic                          | Triclinic                   | Monoclinic                  |
| Space group                  | P₂₁/n                               | P-1                         | P₂₁/c                       |
| a (Å)                       | 9.3293(9)                           | 8.587(2)                    | 13.116(2)                   |
| b (Å)                       | 12.443(1)                           | 10.220(2)                   | 14.438(2)                   |
| c (Å)                       | 17.006(2)                           | 13.069(3)                   | 12.949(2)                   |
| α (°)                       | 90                                  | 90.798(2)                   | 90                          |
| β (°)                       | 90.403(2)                           | 100.318(2)                  | 108.504(2)                  |
| γ (°)                       | 90                                  | 104.087(2)                  | 90                          |
| V (Å³)                      | 1974.0(3)                           | 1092.4(4)                   | 2325.3(6)                   |
| Z                           | 4                                   | 2                           | 4                           |
| λ (MoKα) (Å)                | 0.71073                             | 0.71073                     | 0.71073                     |
| T (K)                       | 298(2)                              | 298(2)                      | 298(2)                      |
| μ (MoKα) (cm⁻¹)             | 0.679                               | 0.624                       | 0.589                       |
| T_Min                       | 0.8595                              | 0.8496                      | 0.8914                      |
| T_Mag                       | 0.8876                              | 0.8698                      | 0.9066                      |
| Reflections/parameters      | 18,406/285                          | 10,421/300                  | 16,322/327                  |
| Unique reflections          | 3484                                | 4018                        | 4127                        |
| Observed reflections [I ≥ 2σ(I)] | 2097                             | 2498                        | 2340                        |
| Restraints                  | 17                                  | 0                           | 4                           |
| Goodness of fit on F²       | 1.184                               | 0.997                       | 1.016                       |
| R₁, wR₁, [I ≥ 2σ(I)]        | 0.0828, 0.1784                      | 0.0676, 0.1620              | 0.0693, 0.1221              |
| R₁, wR₁, (all data)         | 0.1464, 0.1986                      | 0.1204, 0.1939              | 0.1421, 0.1498              |
The V–O oxido distances in the three complexes are in the middle of the range 1.57–1.61 Å observed for five-coordinate oxidovanadium complexes [21, 29–33]. However, the V1–O1 (phenolate) distance of 1 (1.883(5) Å) is shorter than those of 2 (1.585(3) Å) and 3 (1.584(3) Å). The V–O oxido distances in the three complexes are in the middle of the range 1.57–1.61 Å observed for five-coordinate oxidovanadium complexes [21, 29–33]. However, the V1–O1 (phenolate) distance of 1

**Table 2.** Selected bond lengths (Å) and angles (°) for 1–3.

|   | 1       | 2       | 3       |
|---|---------|---------|---------|
| V1–O1 | 1.883(5) | V1–O2 | 1.940(5) |
| V1–O4 | 1.569(6) | V1–O5 | 2.196(6) |
| V1–O6 | 1.845(5) | V1–N1 | 2.072(7) |
| O4–V1–O6 | 95.7(3) | O4–V1–O1 | 99.6(3) |
| O6–V1–O1 | 104.2(2) | O4–V1–O2 | 96.9(3) |
| O6–V1–O2 | 91.3(2) | O1–V1–O2 | 156.0(2) |
| O4–V1–N1 | 101.5(3) | O6–V1–N1 | 159.2(3) |
| O1–V1–N1 | 84.4(2) | O2–V1–N1 | 75.2(2) |
| O4–V1–O5 | 171.7(3) | O1–V1–O5 | 82.9(2) |
| O6–V1–O5 | 76.0(2) | N1–V1–O5 | 86.6(2) |
| O2–V1–O5 | 83.2(2) |            |        |
| V1–O1 | 1.842(3) | V1–O2 | 1.945(3) |
| V1–O4 | 1.585(3) | V1–O5 | 2.297(3) |
| V1–O6 | 1.861(3) | V1–N1 | 2.066(3) |
| O4–V1–O1 | 100.18(16) | O4–V1–O6 | 99.40(14) |
| O1–V1–O6 | 105.25(13) | O4–V1–O2 | 98.88(15) |
| O1–V1–O2 | 153.42(14) | O6–V1–O2 | 89.65(12) |
| O4–V1–N1 | 96.20(14) | O1–V1–N1 | 84.84(13) |
| O6–V1–N1 | 159.50(14) | O2–V1–N1 | 74.81(13) |
| O4–V1–O5 | 175.57(15) | O1–V1–O5 | 83.55(13) |
| O6–V1–O5 | 77.20(12) | O2–V1–O5 | 78.38(12) |
| N1–V1–O5 | 86.47(12) |            |        |

**Figure 1.** Molecular structure of 1 showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and hydrogens are shown as small spheres of arbitrary radii.
(1.883(5) Å) is longer than those of 2 (1.842(3) Å) and 3 (1.854(3) Å). As for the distances of the remaining bonds, they are similar to each other in the three complexes. In general, the V–O(phenolate), the V–O(enolate), and the V–N(imine) bond lengths in the complexes are comparable with the bond lengths observed in vanadium complexes with aroylhydrazone ligands [34–36]. Distortion of the octahedral coordination can be observed from the coordinate bond angles for the perpendicular angles, ranging from 75.2(2) to 104.2(2)° for 1, from 74.8(1) to 105.2(1)° for 2, and from 74.6(1) to 106.2(1)° for 3, and from 156.0(2) to 171.7(3)° for 1, from 153.4(1) to 175.6(1)° for 2, and from 152.5(1) to 176.6(1)° for 3, for the diagonal angles. The dihedral angles between the benzene rings of the aroylhydrazone ligands are 56.9(4)° for 1, 10.7(3)° for 2, and 15.0(5)° for 3.
3.3. IR and UV–vis spectra

The medium and broad absorption at 3443 cm−1 in the spectrum of the aroylhydrazone substantiates the presence of phenol group, which is absent in the complexes. The sharp bands indicative of N–H vibrations are located at 3175 and 3210 cm−1, respectively, in the spectra of H2L and 1. The intense band indicative of the C=O vibration at 1663 cm−1 in the spectrum of the aroylhydrazone is absent in the complexes, indicating the enolization of the amide functionality and subsequent proton replacement by V. The strong absorption bands at 1612, 1602, and 1603 cm−1 for 1, 2, and 3, respectively, are assigned to the azomethine ν(C=N) [37], which are shifted to lower wavenumbers when compared with that of the free aroylhydrazone (1620 cm−1). The absorptions at 970, 973, and 978 cm−1 can be assigned to the V=O vibration [35].

Electronic spectra of the complexes were recorded at 10−5 mol·L−1 in acetonitrile from 200 to 800 nm. In the UV–vis region, the complexes show bands at approximately 350 nm and weak bands centered at 450 nm for 1 and 475 nm for 2 and 3. The weak bands are attributed to intramolecular charge transfer transitions from the pπ orbital on the nitrogen and oxygen to the empty d orbitals of the metal [38]. The intense bands observed at 215 and 280 nm for the complexes are assigned to intraligand π–π* transitions [38].

3.4. Effects of complex on blood glucose in both normal and alloxan-diabetic mice

The complexes were administered intragastrically to both normal and alloxan-diabetic mice for two weeks. The results (table 3) showed that the complexes had blood glucose-lowering effect at doses of 10.0 and 20.0 mg V·kg−1, which can significantly decrease the blood glucose level in alloxan-diabetic mice, but the blood glucose level in the treated normal mice (20.0 mg V·kg−1 ig for two weeks) was not altered as compared with the untreated normal mice (p > 0.05). The alloxan-diabetic mice exhibited significant hyperglycemia. After two-week administration with the complexes, the blood glucose level was decreased compared with the diabetic control group (p < 0.05). It is obvious that the order of the glucose-lowering effect of the complexes is 2 ≈ 3 > 1. During the experiment, the mean body weight in alloxan–diabetic mice was lower than normal mice. Two-week administration of the complexes had no effect on the body weight in the diabetic group, compared with the diabetic control group (table 4). The results agree with the conclusion that vanadium complexes with Schiff base ligands bearing Cl possess increased anti-diabetic properties [39]. In general, the glucose-lowering abilities of the complexes are similar to vanadium complexes reported [39, 40].

Table 3. Effects of the vanadium complexes on blood glucose levels in both normal and diabetic mice.

| Group            | Dose (mg V·kg−1) | 0     | 1st week | 2nd week | 3rd week |
|------------------|------------------|-------|----------|----------|----------|
| normal mice      | CMC              | 5 ± 1 | 6 ± 1    | 6 ± 1    | 5 ± 1    |
| normal mice + 1  | 20.00            | 6 ± 2 | 6 ± 2    | 7 ± 2    | 7 ± 2    |
| normal mice + 2  | 20.00            | 6 ± 1 | 6 ± 2    | 6 ± 1    | 6 ± 1    |
| normal mice + 3  | 20.00            | 6 ± 1 | 5 ± 1    | 6 ± 2    | 6 ± 1    |
| alloxan mice     | CMC              | 16 ± 3a | 16 ± 2a | 16 ± 2a  | 15 ± 2a  |
| alloxan mice + 1 | 20.00            | 15 ± 2a | 7 ± 1b  | 7 ± 1b   | 8.4 ± 0.9b |
| alloxan mice + 2 | 10.00            | 15 ± 2a | 8 ± 1b   | 10 ± 2b  | 11 ± 1b  |
| alloxan mice + 2 | 20.00            | 14 ± 2a | 6.1 ± 0.9b | 6 ± 1b  | 7 ± 2b   |
| alloxan mice + 2 | 10.00            | 15 ± 2a | 7 ± 1b   | 8 ± 1b   | 9 ± 2b   |
| alloxan mice + 3 | 20.00            | 15 ± 2a | 6 ± 1b   | 7 ± 2b   | 8 ± 2b   |
| alloxan mice + 3 | 10.00            | 15 ± 2a | 7.5 ± 0.7b | 8 ± 2b   | 9 ± 3b   |

Data were expressed as mean ± standard deviations for six mice in each group.

*p < 0.05 or less vs. normal mice.

*p < 0.05 or less vs. alloxan-diabetic mice (Dunnett’s test).
4. Conclusion

The present study reports synthesis, characterization, and crystal structures of three new oxidovanadium(V) complexes derived from 2-chloro-N′-(3-ethoxy-2-hydroxybenzylidene)benzohydrazide and similar bidentate ligands. Methylmaltol, ethylmaltol, and acetohydroxamic acid as co-ligands readily coordinate to V through the carbonyl and deprotonated phenol groups. The complexes have effective insulin-like activity on alloxan-diabetic mice.

Supplementary material

CCDC 1061753 (1), 1061754 (2) and 1061755 (3) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44) 1223-336-033; or E-mail: deposit@ccdc.cam.ac.uk.

Disclosure statement

No potential conflict of interest was reported by the authors.

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