基于 4-氟-N′-(3-乙氧基-2-羟基苯亚甲基)苯甲酰肼的甲基麦芽酚和乙基麦芽酚配位的氧钒(V)配合物的合成、晶体结构及其类胰岛素活性

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摘要: 制备了一个芳酰腙化合物 4-氟-N′-(3-乙氧基-2-羟基苯亚甲基)苯甲酰肼(H_2L)。利用 H_2L 和 $VO(acac)_2$ 分别与甲基麦芽酚(mat)和乙基麦芽酚(Emat)在甲醇中反应,得到了 2 个配合物[VO(L)(mat)] (**1**)和[VO(L)(Emat)] (**2**)。通过元素分析、红外光谱、紫外可见光谱和核磁共振氢谱表征了这些化合物的结构。通过单晶 X 射线衍射进一步确定了化合物的结构。芳酰腙配体以二价阴离子的方式通过酚羟基氧、亚胺基氮和烯醇氧原子与钒原子进行配位。在每个配合物中,钒都采取八面体配位构型。将配合物通过灌胃对正常的大鼠和四氧嘧啶糖尿病大鼠给药 2 周时间,结果表明这两个配合物在剂量为 10.0 和 20.0 $mg_V\cdot kg^{-1}$ 时可以显著降低四氧嘧啶糖尿病大鼠的血糖值,而对于正常大鼠的血糖值却没有改变。

关键词: 钒配合物;芳酰腙;晶体结构;类胰岛素活性
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Syntheses, Crystal Structures and Insulin-like Activity of Maltolato- and Ethylmaltolato-Coordinated Oxovanadium(V) Complexes Derived from 4-Fluoro-N′-(3-ethoxy-2-hydroxybenzylidene)benzohydrazide

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Abstract: A new aroylhydrazone compound 4-fluoro-N′-(3-ethoxy-2-hydroxybenzylidene)benzohydrazide (H_2L) was prepared. Reaction of H_2L and $VO(acac)_2$ with maltol(mat) and ethylmaltol(Emat), respectively, in methanol afforded the complexes [VO(L)(mat)] (**1**) and [VO(L)(Emat)] (**2**). Both H_2L and the oxovanadium complexes were characterized by elemental analysis, IR, UV-Vis and ^1H NMR spectra. The structures of the compounds were further confirmed by single crystal X-ray diffraction. The aroylhydrazone ligand, in its dianionic form, coordinated to the V atoms through the phenolate oxygen, imino nitrogen and enolate oxygen. The maltol and ethylmaltol ligands coordinated to the V atoms through the carbonyl oxygen and deprotonated hydroxyl oxygen. The V atom in each complex is in octahedral coordination. The complexes were administered intragastrically to both normal and alloxan-diabetic mice for two weeks. The biological activity results show that the complexes at doses of 10.0 and 20.0 $mg_V\cdot kg^{-1}$, can significantly decrease the blood glucose level in alloxan-diabetic mice, but the blood glucose level in the treated normal mice was not altered. CCDC: 1522005, $H_2L\cdot H_2O$; 1005095, **1**; 1005096, **2**.

Keywords: aroylhydrazone; oxovanadium(V) complex; crystal structure; insulin-like activity

Inorganic vanadium salts and vanadium complexes with various ligands have been reported to possess insulin-mimetic activities[1-4]. 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[5-6]. However, the inorganic vanadium salts are considered as less active and more toxic. In order to reduce the side effects of inorganic vanadium salts, vanadium complexes with various organic ligands have received particular attention and demonstrated to be effective[7-9]. Among the complexes, bis(maltolato)oxovanadium (Ⅳ) (BMOV) [10], synthesized by simple metathesis of vanadyl sulfate trihydrate and maltol (3-hydroxy-2-methyl-4-pyrone), has important and interesting insulin-enhancing activity[11]. Yet, there are some side effects of BMOV, principally diarrhea[12]. Schiff bases play important role in biological chemistry. Several vanadium complexes derived from Schiff bases have shown to normalize blood glucose level with high efficiency and low toxicity, even at low concentration[13-14]. Schiff bases with hydrazone type are of particular interest due to their biological properties[15-18]. In view of the increasing importance of vanadium complexes with hydrazone type Schiff bases, we report herein the synthesis, characterization, and insulin-enhancing activities of a maltolato-coordinated and an ethylmaltolato-coordinated oxovanadium(Ⅴ) complexes derived from the aroylhydrazone compound 4-fluoro-N' -(3-ethoxy-2-hydroxybenzylidene)benzohydrazide (H₂L; Scheme 1).
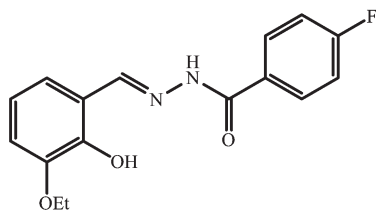
Scheme 1　Structure of aroylhydrazone H₂L

1　Experimental

1.1　Materials and measurement

Starting materials, reagents and solvents were purchased from commercial suppliers with AR grade, and were 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 in 4 000~200 cm⁻¹ region. UV-Vis spectra were recorded on a Perkin-Elmer Lambda 900 spectrometer. ¹H NMR spectra for H₂L and the complexes were recorded on a Bruker spectrometer at 300 MHz. X-ray diffraction was carried out on a Bruker SMART 1000 CCD diffractometer. High-resolution mass spectrum was recorded with ESI (electrospray ionization) on a Thermo Scientific LTQ Orbitrap XL in the positive mode.

1.2　Synthesis of H₂L

3-Ethoxy-2-hydroxybenzaldehyde (1.66 g, 0.01 mol) and 4-fluorobenzohydrazide (1.54 g, 0.01 mol) were reacted in 30 mL of methanol. The mixture was stirred at room temperature for 1 h to give a clear colorless solution. The solution was allowed to stand in air for a few days, which gained colorless block-shaped crystals of H₂L·H₂O. The crystals were isolated by filtration, washed three times with cold methanol and dried in air. Yield: 65%. Anal. Calcd. for C₁₆H₁₇ FN₂O₄(%): C, 60.0 H, 5.3; N, 8.7. Found(%): C, 59.8; H, 5.4; N, 8.9. HRMS (ESI): m/z Calcd. for C₁₆H₁₅ FN₂O₃ 303.1139; Found: 303.1139. ¹H NMR (300 MHz, DMSO-d₆): δ 12.09 (s, 1H, O*H*), 10.91 (s, 1H, N*H*), 8.65 (s, 1H, C*H*=N), 8.03 (q, 2H, Ar*H*), 7.39 (t, 2H, Ar*H*), 7.15 (d, 1H, Ar*H*), 7.03 (d, 1H, Ar*H*), 6.85 (t, 1H, Ar*H*), 4.08, (q, 2H, C*H*₂), 1.36 (t, 3H, C*H*₃).

1.3　Syntheses of the complexes

The two complexes were prepared by the same method as described. Equimolar quantities (1.0 mmol each) of VO(acac)₂ (0.27 g) and H₂L (0.30 g) dissolved in methanol (30 mL) were added to a methanolic solution (20 mL) of maltol for **1** and ethylmaltol for **2**, respectively. The mixture was stirred at room temperature for 30 min to give a brown solution. The resulting solution was allowed to stand in air for a few days. Brown block-shaped crystals of the complex were isolated by filtration, washed three times with cold methanol and dried in air.

Complex **1**: Yield: 63%. Anal. Calcd. for C₂₂H₁₈ FN₂O₇V(%): C, 53.7; H, 3.7; N, 5.7. Found(%): C, 53.9; H, 3.6; N, 5.6. ¹H NMR (300 MHz, DMSO-d₆): δ 9.17

(s, 1H, OCH=CH), 8.45 (s, 1H, CH=N), 7.92~7.87 (m, 2H, ArH), 7.43~7.26 (m, 4H, ArH), 7.00 (t, 1H, ArH), 6.70 (d, 1H, OCH=CH), 4.08 (q, 2H, CH$_2$), 2.65 (s, 3H, CH$_3$), 1.30 (t, 3H, CH$_3$).

　　Complex **2**: Yield: 70%. Anal. Calcd. for C$_{23}$H$_{20}$FN$_2$O$_7$V(%): C, 54.6; H, 4.0; N, 5.5. Found(%): C, 54.5; H, 4.1; N, 5.7. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 9.17 (s, 1H, OCH=CH), 8.47 (s, 1H, CH=N), 7.92~7.87 (m, 2H, ArH), 7.43~7.25 (m, 4H, ArH), 7.00 (t, 1H, ArH), 6.70 (d, 1H, OCH=CH), 4.07 (q, 2H, CH$_2$), 3.03 (q, 2H, CH$_2$), 1.35~1.25 (m, 6H, CH$_3$).

1.4　X-ray crystallography

　　Diffraction intensities for H$_2$L and the complexes were collected at 298(2) K using a Bruker SMART 1000 CCD area-detector diffractometer with Mo Kα radiation (λ=0.071 073 nm). Collected data were reduced with SAINT[19], and multi-scan absorption correction was performed using SADABS[20]. Structures of the compounds were solved by direct methods and refined against F^2 by full-matrix least-squares method using SHELXTL[21]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms attached to N and O atoms in H$_2$L were located from a difference Fourier map and refined isotropically, with N-H and O-H distances restrained to 0.090(1) and 0.085(1) nm, respectively. The remaining hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. Crystallographic data for H$_2$L·H$_2$O and the complexes are summarized in Table 1. Selected bond lengths and angles are given in Table 2.

　　CCDC: 1522005, H$_2$L·H$_2$O; 1005095, **1**; 1005096, **2**.

1.5　Glucose-lowering assay

　　Male Kunming mice, weighing 25~32 g, were obtained from 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

Table 1　Crystallographic and experimental data for H$_2$L·H$_2$O and the complexes

Compound	H$_2$L·H$_2$O	*1*	*2*
Formula	C$_{16}$H$_{17}$FN$_2$O$_4$	C$_{17}$H$_{15}$BrN$_3$O$_6$V	C$_{17}$H$_{15}$BrN$_3$O$_6$V
Molecular weight	320.3	488.2	488.2
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	P2$_1$/c	P$\bar{1}$	P$\bar{1}$
a / nm	0.937 0(1)	0.778 89(7)	0.778 89(7)
b / nm	1.308 5(1)	0.869 61(8)	0.869 61(8)
c / nm	1.240 4(1)	1.524 2(1)	1.524 2(1)
α / (°)	90	94.078(3)	94.078(3)
β / (°)	96.367(2)	98.547(3)	98.547(3)
γ / (°)	90	110.424(3)	110.424(3)
V / nm^3	1.511 4(2)	0.948 3(2)	0.948 3(2)
Z	4	2	2
D$_c$ / (g·cm^{-3})	1.408	1.710	1.710
μ (Mo Kα) /mm^{-1}	0.110	2.670	2.670
F(000)	672	488	488
Independent reflections	2 667	3 490	3 490
Observed reflections [I≥2σ(I)]	1 815	3 004	3 004
Parameters	219	258	258
Restraints	4	1	1
Goodness-of-fit on F^2	1.040	1.053	1.053
R$_1$, wR$_2$ [I≥2σ(I)]*	0.040 6, 0.086 3	0.040 1, 0.095 4	0.040 1, 0.095 4
R$_1$, wR$_2$ (all data)*	0.076 3, 0.100 5	0.048 4, 0.100 7	

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

Table 2 Selected bond lengths (nm) and angles (°) for H₂L·H₂O and the complexes

		H₂L			
C7-N1	1.270(2)	N1-N2	1.383(2)	N2-C8	1.342(2)
C8-O3	1.224(2)				
		1			
V1-O1	0.184 6(5)	V1-O2	0.192 3(5)	V1-O3	0.226 7(6)
V1-O4	0.185 5(5)	V1-O6	0.157 2(6)	V1-N1	0.205 2(7)
O6-V1-O1	99.6(3)	O6-V1-O4	99.9(3)	O1-V1-O4	102.6(2)
O6-V1-O2	99.8(3)	O1-V1-O2	152.1(2)	O4-V1-O2	93.6(2)
O6-V1-N1	95.8(3)	O1-V1-N1	83.4(3)	O4-V1-N1	161.9(2)
O2-V1-N1	74.9(2)	O6-V1-O3	176.8(3)	O1-V1-O3	81.6(2)
O4-V1-O3	76.8(2)	O2-V1-O3	80.1(2)	N1-V1-O3	87.3(2)
		2			
V1-O1	0.185 2(4)	V1-O2	0.193 1(3)	V1-O3	0.226 5(4)
V1-O4	0.187 0(3)	V1-O6	0.157 9(3)	V1-N1	0.207 1(4)
O6-V1-O1	99.11(17)	O6-V1-O4	99.40(17)	O1-V1-O4	102.91(15)
O6-V1-O2	100.17(17)	O1-V1-O2	152.23(16)	O4-V1-O2	93.45(14)
O6-V1-N1	95.14(17)	O1-V1-N1	83.65(16)	O4-V1-N1	162.82(16)
O2-V1-N1	74.89(16)	O6-V1-O3	176.71(16)	O1-V1-O3	80.97(14)
O4-V1-O3	77.41(15)	O2-V1-O3	80.91(15)	N1-V1-O3	88.14(15)

and relative humidity were maintained at 24 ℃ 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 eight groups with four mice each according to the blood glucose. Group 1, normal control group: normal mice treated with 0.5% carboxymethyl cellulose (CMC). Groups 2 and 3, treated normal group: normal mice treated with 20 mg$_V$·kg^{-1} vanadium complexes. Group 4, diabetic control group: alloxan diabetic mice treated with 0.5% CMC. Groups 5~8, treated diabetic group: alloxan diabetic mice treated with vanadium complexes at doses of 10 and 20 mg$_V$·kg^{-1} by intragastrical administration. 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).

2 Results and discussion

2.1 Crystal structure description of H₂L·H₂O

Fig.1 gives a perspective view of H₂L·H₂O together with the atomic labeling system. The asymmetric unit of the compound contains an aroylhydrazone molecule and a lattice water molecule. The aroylhydrazone molecule adopts E configuration with respect to the methylidene unit. The distance of the C7-N1 methylidene bond (0.127 0(2) nm) confirms it as a typical double bond. The shorter distance of the C8-N2 bond (0.134 2(2) nm) and the longer distance of the C8-O3 bond (0.122 4(2) nm) for the -C(O)-NH- unit than

Table 3　Hydrogen bond parameters for $H_2L \cdot H_2O$

D–H⋯A	d(D-H) / nm	d(H⋯A) / nm	d(D⋯A) / nm	∠D–H⋯A / (°)
O1–H1⋯N1	0.082	0.202	0.273 1(2)	144
O1–H1⋯O4[i]	0.082	0.262	0.305 8(2)	115
O4–H4B⋯O3ii	0.085(1)	0.187(1)	0.272 0(2)	169(2)
O4–H4A⋯O1[iii]	0.085(1)	0.219(1)	0.295 1(2)	150(2)
N2–H2⋯O4[iv]	0.090(1)	0.208(1)	0.297 2(2)	174(2)

Symmetry codes: [i] −1+x, −1+y, z; [ii] 1+x, 1+y, z; [iii] 1−x, 1−y, 1−z; [iv] 1−x, −1/2+y, 3/2−z.

usual, suggest the presence of conjugation effect in the molecule. The bond lengths in the compound are within normal values[18]. The dihedral angle between the two benzene rings is 23.9(3)°. In the crystal structure of the compound, adjacent two aroylhydrazone molecules are linked through two water molecules via intermolecular hydrogen bonds, to form a dimer (Table 3, Fig.2).
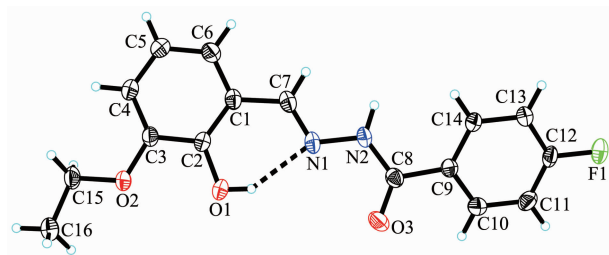
Thermal ellipsoids for non-hydrogen atoms are drawn at the 30% probability level; Hydrogen bond is shown as a dashed line; Water molecule is omitted for clarity

Fig.1　Perspective view of the molecular structure of $H_2L \cdot H_2O$ with the atom labeling scheme
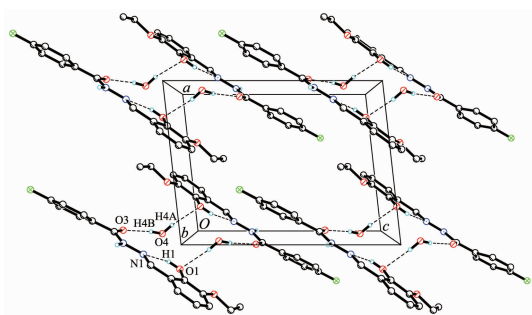

Hydrogen bonds are shown as dashed lines

Fig.2　Molecular packing diagram of $H_2L \cdot H_2O$

2.2　Crystal structures description of the complexes

The molecular structures of complexes **1** and **2** are shown in Fig.3 and 4, respectively. X-ray crystall-ography reveals that both complexes are structurally similar, except for the secondary ligands, viz. maltolate for **1** and ethylmaltolate for **2**. In each complex, the aroylhydrazone ligand coordinates to the V atom through phenolate O, imino N, and enolate O atoms. The V atoms in both complexes are in octahedral
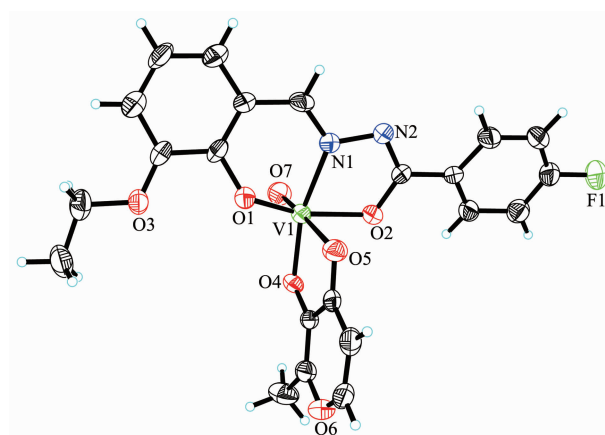
Thermal ellipsoids for non-hydrogen atoms are drawn at the 30% probability level

Fig.3　Perspective view of the molecular structure of complex **1** with the atom labeling scheme
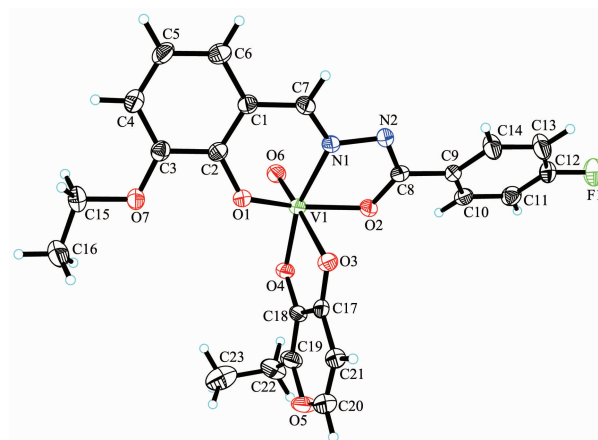
Thermal ellipsoids for non-hydrogen atoms are drawn at the 30% probability level

Fig.4　Perspective view of the molecular structure of complex **2** with the atom labeling scheme

coordination, with the three donor atoms of the aroylhydrazone ligand and the deprotonated hydroxyl O atom of the maltolate (or ethylmaltolate) ligand defining the equatorial plane, and with one oxo O atom and carbonyl O atom of the maltolate (or ethylmaltolate) ligand occupying the axial positions. The distances between atoms V1 and O6 are 0.157~ 0.158 nm, indicating that they are typical V=O bonds. The coordinate bond lengths in the complexes are comparable to each other, and also similar to those observed in mononuclear oxovanadium complexes with octahedral coordination[22-24]. Distortion of the octahedral coordination can be observed from coordination bond angles, ranging from 74.9(2)° to 102.9(2)° for the perpendicular angles, and from 152.1(2)° to 176.8(3)° for the diagonal angles. The displacement of V atoms from the equatorial planes towarding the axial oxo O atoms are 0.029 6(2) nm for **1** and 0.028 6(2) nm for **2**. The dihedral angles between the two benzene rings are 36.6(3)° for **1** and 46.8(3)° for **2**.

The coordination of H_2L to V atoms results the change of related bonds. The bond length of C7-N1 in H_2L is 0.127 nm, which is shorter than C7-N1 bonds (0.128 ~0.130 nm) in the complexes. The same phenomenon is observed for N1-N2 bonds in H_2L and the complexes. The N2-C8 bond in H_2L is much longer than those in the complexes, and the C8-O2 bond in H_2L is much shorter than those in the complexes, which indicates the change of N-C-O groups from carbonyl in H_2L to enolate during coordination.

2.3 IR and UV-Vis spectra

The weak and broad absorption bands centered at 3 383 cm^{-1} in the spectrum of H_2L substantiates indicate the presence of phenol group, which is absent in the complexes. The sharp band indicative of N-H vibration is located at 3 234 cm^{-1} in the spectrum of H_2L. The typical strong ν(C=O) (1 652 cm^{-1}) and the sharp ν(N-H) absorption bands of the free hydrazone ligand are absent in the complexes, indicating enolisation of the amide functionality and subsequent proton replacement by V atoms. The strong absorption bands at 1 605 cm^{-1} for H_2L and 1 610 cm^{-1} for the complexes are assigned to azomethine ν(C=N)[25]. Typical absorption at 980 cm^{-1} can be assigned to V=O vibration[26].

Electronic spectra of H_2L and the complexes were recorded in methanol and acetonitrile (10 μmol· L^{-1}), respectively, in the range of 200~600 nm. In the UV-Vis region the complexes show bands centered at 350 nm and weak bands at 466 nm. The weak bands are attributed to intramolecular charge transfer transitions from the p_π orbital on the nitrogen and oxygen to the empty d orbitals of the metal[27]. The intense bands observed at 280 nm for the complexes and 299 nm for H_2L are assigned to intraligand π-π* transitions[27].

2.4 Effects of the complexes 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 4) showed that the complexes

Table 4 Effect of the vanadium complexes on blood glucose levels in both normal and diabetic mice

Group	Dose / (mg$_V$·kg^{-1})	Blood glucose* / (mmol·L^{-1})			
		Beginning	1st week	2nd week	3rd week
Normal mice	CMC	5.8±0.6	6.1±1.2	6.0±1.1	5.9±1.0
Normal mice+**1**	20.00	5.9±1.0	6.0±0.9	5.9±1.3	5.8±1.2
Normal mice+**2**	20.00	6.0±0.8	6.0±1.1	6.1±0.9	6.0±1.4
Alloxan mice	CMC	16.1±1.9	15.7±2.0	15.9±2.1	15.0±1.6
Alloxan mice+**1**	20.00	14.0±1.7	6.3±1.2	6.7±1.5	7.8±2.0
Alloxan mice+**1**	10.00	15.0±1.4	7.3±0.8	8.1±1.2	8.7±1.7
Alloxan mice+**2**	20.00	14.2±1.3	6.1±0.7	6.5±1.0	7.9±1.4
Alloxan mice+**2**	10.00	14.9±1.7	7.1±1.1	8.0±1.5	8.5±1.5

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

Table 5　Effects of the complexes on body weight of both normal and diabetic mice

Group	Dose / (mg$_V$·kg^{-1})	Body weight[*] / g			
		Beginning	1st week	2nd week	3rd week
Normal mice	CMC	30.5±2.1	32.9±2.5	34.5±3.0	36.6±3.2
Normal mice+**1**	20.00	30.1±1.8	32.5±2.0	34.6±2.6	37.1±2.9
Normal mice+**2**	20.00	30.6±2.0	32.7±2.2	34.9±2.7	37.5±3.0
Alloxan mice	CMC	27.3±1.1	28.0±1.2	29.1±1.5	30.0±2.2
Alloxan mice+**1**	20.00	27.5±1.3	28.7±1.5	30.1±2.1	32.4±3.1
Alloxan mice+**1**	10.00	27.1±1.5	28.3±1.8	29.4±2.0	31.0±2.7
Alloxan mice+**2**	20.00	28.0±1.2	29.1±1.5	30.2±1.8	32.6±2.5
Alloxan mice+**2**	10.00	27.5±1.3	28.6±1.9	30.1±2.0	31.3±2.9

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

had blood glucose-lowering effect at doses of 10.0 and 20.0 mg$_V$·kg^{-1}, which can signicantly decrease the blood glucose level in alloxan-diabetic mice. The blood glucose level in the treated normal mice (20.0 mg$_V$·kg^{-1} by intragastrical administration for two weeks) was not altered as compared with the untreated normal mice. The alloxan-diabetic mice exhibited significant hyperglycemia. After two-week administra-tion with the complexes, the blood glucose level was decreased compared with the diabetic control group. It is obvious that the glucose-lowering effect of the complexes is similar to each other. During the experiment, the mean body weight in alloxan-diabetic mice was lower than normal mice. Two-week admin-istration of the complexes had no effect on the body weight in the diabetic group, compared with the diabetic control group (Table 5).

3　Conclusions

A new aroylhydrazone and its maltolato- and ethylmaltolato-coordinated oxovanadium(Ⅴ) complexes were synthesized, characterization and their crystal structures were analyzed. The aroylhydrazone coor-dinates to V atoms through phenolate oxygen, imino nitrogen and enolate oxygen. The complexes have effective insulin-like activity on alloxan-diabetic mice.

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