Chinese Journal of Chemistry, **2004**, *22*, 761—763 **Article**

Synthesis, Characterization and the Effect of Glucose-lowering of Guanidino Acid Oxovanadium(IV) Complexes

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Two guanidino acid oxovanadium(IV) complexes have been synthesized. Preliminary tests *in vivo* have shown that the two title complexes all display lowering glucose activity *in vivo* to STZ-rats. The effect of glucose-lowering of guanidino acetic acid oxovanadium(IV) complex *in vivo* is higher than that of guanidino propanoic acid oxovanadium(IV) complex.

Keywords oxovanadium, guanidino acetic acid, guanidino propanoic acid, lowering glucose activity

Introduction

The main abnormality in insulin-dependent diabetes mellitus is heperglycemia due to deficiency of insulin. At present severe diabetes can be controlled only by daily injections of insulin, so the development of compounds that cause insulin replacement or insulin mimetics on oral administration would be very helpful.

The finding in 1985 that vanadate (+5 oxidation state of vanadium) has an *in vivo* insulin-like effect stimulating research on insulin-mimetic vanadium.[1] The insulin-mimetic properties of uncomplexed inorganic vanadate and vanadyl, as well as vanadyl complexes, and the peroxovanadates have been reported.[2] Vanadate and vanadyl are poorly absorbed from the gastrointestinal tract into the blood and the necessary dosage is close to the toxic level.[3] It became evident that manipulation of the chemical form of the vanadium is necessary to allow for a less toxic, more easily absorbed agent that could be administered in a lower dose.[4-9]

We have observed that a number of oxovanadium(IV) complexes display strong insulin-mimetic activity *in vivo*. Reported here are the synthesis and effect of the glucose-lowering of the guanidino acid oxovanadium (IV) complexes.

Experimental

Physical and chemical measurements

Infrared spectra were recorded as KBr disks in the range of 4000—400 cm^{-1} on a Magna FT-IR 560 spectrometer. ^{51}V NMR spectra of the complexes were recorded on a Varian Unity-400 instrument at 400 MHz. V was determined by ICP emission spectrometry. C, N and H were determined by using a PE-2400 analyser.

Syntheses of oxovanadium(IV) guanidino acid

Guanidino acetic acid diethylenetriamine oxovanadium(IV), VO(detm)(gaa) (1) *S*-Ethylthiourea hydrobromic acid (9.20 g, 50 mmol) was dissolved in *ca.* 20 mL of 10% NaOH. Glycine (3.75 g, 50 mmol) in *ca.* 40 mL of hot water was added, with stirring under ice bath to the solution to yield a colorless solution. Then the colorless crystals were got in refrigerator for 24 h, washed with alcohol and diethyl ether, and dried over night *in vacuo*.

$VOSO_4 \cdot 3H_2O$ (1.00 g, 5 mmol) was dissolved in *ca.* 30 mL of water. Diethylenetriamine (0.60 g, 5 mmol) in *ca.* 30 mL of alcohol was added, with stirring under N_2 to the solution to yield a brown solution. Then guanidino acetic acid (1.20 g, 10 mmol) was added at heating and under N_2 atmosphere. The solution was stirred for 4 h and the green solid was collected by vacuum filtration, washed with alcohol and acetone, and dried over night *in vacuo*. The yield was 1.40 g (75.5% based on V). Anal. calcd for $C_{10}H_{25}N_9O_5V$: C 29.81, H 6.02, N 30.83, V 13.62; found C 29.68, H 5.92, N 30.71, V 13.51.

Guanidino propanoic acid diethylenetriamine oxovanadium(IV), VO(detm)(gpa) (2) *S*-Ethylthiourea hydrobromic acid (9.20 g, 50 mmol) was dissolved in *ca.* 20 mL of 10% NaOH. Alanine (4.45 g, 50 mmol) in *ca.* 40 mL of hot water was added, with stirring under ice bath, to the solution to yield a colorless solution. Then colorless crystals were got in refrigerator for 24 h, washed with alcohol and diethyl ether,

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and dried over night *in vacuo*.

$VOSO_4 \cdot 3H_2O$ (1.00 g, 5 mmol) was dissolved in *ca.* 30 mL of water. Diethylenetramine (0.60 g, 5 mmol) in *ca.* 30 of mL alcohol was added, with stirring under N_2 atmosphere to the solution to yield a brown solution. Then guanidino propanoic acid (1.30 g, 10 mmol) was added at heating and under N_2 atmosphere. The solution was stirred for 4 h and the green solid was collected by vacuum filtration, washed with alcohol and acetone, and dried over night *in vacuo*. The yield was 1.60 g (80.7% based on V). Anal. calcd for $C_{12}H_{29}N_9O_5V$: C 32.99, H 6.59, N 28.69, V 11.97; found C 32.81, H 6.46, N 28.57, V 12.06.

Lowering glucose activity

Materials and methods Male Wistar rats weighing 180—220 g were housed in cages on a 12 h light : dark schedule and were cared for in accordance with the principles and guidelines. The animals were acclimatized for 7—10 d, and then diabetes was induced by a single intravenous injection of STZ (60 mg•kg^{-1} in 0.9% NaCl, 1 mL•kg^{-1}). Diabetes was confirmed 3 d after STZ injection by tail-vein blood-glucose determination, with blood-glucose levels over 13 mmol•L^{-1} being taken as diabetic. On seven days post-STZ, the animals were divided into treatment groups: gum arabic alone, $NaVO_3$, VO(detm)(gaa) and VO(detm)(gpa). All drugs were administered as suspensions in 3% gum arabic. Animals were not fasted prior to drug administration. Blood was collected for glucose analysis immediately prior to drug administration and at selected time up to 72 h after drug administration. Blood was collected from the tail vein into heparinized capillary tubes and centrifuged 10000 g×15 min. The plasma was separated and analyzed immediately for glucose levels.

Oral gavage of STZ-diabetic rats Fourty diabetic rats were treated with gum arabic, $NaVO_3$, VO(detm)(gaa) or VO(detm)(gpa). All drug candidates were administered as suspensions in 3% gum arabic by oral gavage in a volume of 10.0 mL•kg^{-1} at a dose of 0.60 mmol•kg^{-1}. The control groups (gum arabic) received an equivalent volume of 3% gum arabic alone.

Results and discussion

IR and ^{51}V NMR characterization of the title complexes

The main IR and ^{51}V NMR spectral data and their assignments are summarized in Table 1. For guanidino acid oxovanadium complex **1**, ν(C=N) and ν(C=O) stretching vibration absorptions appear at near 1669.22 and 1625.27 cm^{-1}, and near 3387.33, 1154.95 and 968.71 cm^{-1} are assigned to ν(C=N—H), ν(C=N) and ν(V=O) stretching vibration absorptions, respectively. For complex **2**, the corresponding stretching vibration absorptions appear at near 1624.32, 1521.46, 3430.99, 1091.77 and 966.05 cm^{-1}.

Table 1 IR and ^{51}V NMR spectral data of the title complexes

Complex		VO(detm) (gaa) (**1**)	VO(detm) (gpa) (**2**)
IR/cm^{-1}	$\nu_{C=N-H}$	3387.33	3430.99
	$\nu_{C=N\ or\ C=O}$	1669.22	1624.32
		1625.27	1521.46
	$\nu_{C=N}$	1154.95	1091.77
	$\nu_{V=O}$	968.71	966.05
^{51}V NMR/δ		25.8	25.5

The ^{51}V NMR spectra of complexes give only a single peak, showing that the coordination pattern of vanadium atom with guanidino acid is single in complexes. In the oxovanadium complexes, oxovanadium cation coordinates with the three nitrogen atoms and the two O^- anions, respectively. The probable structures of the two complexes could be as follows (Figure 1).

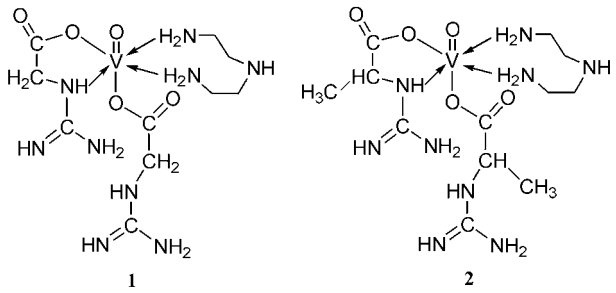

Figure 1 The structure of the complexes.

Lowering glucose activities of guanidino acid oxovanadium(IV) *in vivo*

It can be seen from Table 2 and Figure 2 that the two complexes display lowering glucose activities to

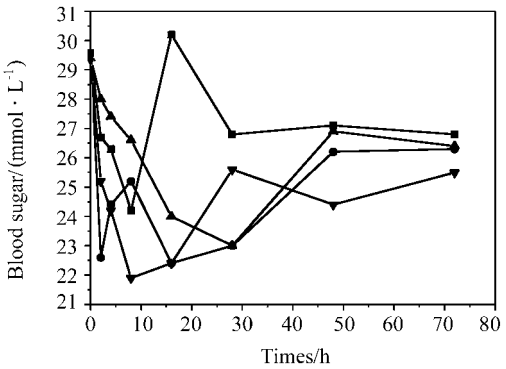

Figure 2 Plasma glucose levels for gum arabic (■, n=10), $NaVO_3$ (●, n = 10), VO(detm)(gaa) (▲, n = 10), and VO(detm)(gpa) (▼, n=10) following acute oral gavage administration in STZ-rats at a dose of 0.6 mmol•kg^{-1}.

Table 2 Lowering glucose activities of guanidino acid oxovanadium(IV) *in vivo*

Complex	Dose/(mmol V)	Plasma glucose/(mmol•L^{-1})							
		0 h	2 h	4 h	8 h	16 h	28 h	48 h	72 h
Control	0	29.6±2.7	26.7±2.5	26.3±4.1	24.2±4.2	30.2±2.4	26.8±3.2	27.1±2.3	26.8±1.8
$NaVO_3$	3.1	29.5±2.6	22.6±7.2	24.4±6.6	25.2±6.1	22.4±5.0	23.0±3.5	26.2±3.0	26.3±2.5
VO(detm)(gaa) (**1**)	3.2	29.3±3.2	25.2±3.5	24.2±2.7	21.9±4.2	22.4±5.7	25.6±3.5	24.4±3.8	25.5±3.5
VO(detm)(gpa) (**2**)	3.2	29.4±2.4	28.0±2.7	27.4±2.3	26.6±5.7	24.0±7.9	23.0±6.7	26.9±2.6	26.4±3.6

STZ-rats. The lowering glucose activities of guanidino acetic acid oxovanadium(IV) complex *in vivo* are higher than that of the guanidino propanoic acid oxovanadium(IV) complex.

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References

1 Heyliger, C. E.; Tahiliani, A. G.; McNeill, J. H. *Science* **1985**, *227*, 1474.
2 Thompson, K. H.; McNeill, J. H.; Orvig, C. *Chem. Rev.* **1999**, *99*, 2561.
3 McNeill, J. H.; Yuen, V. G.; Hoveyda, H. R.; Orvig, C. *J. Med. Chem.* **1992**, *35*, 1489.
4 Rehder, D. *Coord. Chem. Rev.* **1999**, *182*, 297.
5 Rehder, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 148.
6 Meyerovitch, J.; Farfel, Z.; Sack, J.; Shechter, Y. *J. Biol. Chem.* **1987**, *262*, 6658.
7 Mittag, T. W.; Guo, W. B.; Taniguchi, T. *Biochem. Pharmacol.* **1993**, *45*, 1311.
8 Zhang, A.; Gao, Z. Y.; Gilon, P.; Nenquin, M.; Drews, G.; Henquin, J. C. *J. Biol. Chem.* **1991**, *266*, 21649.
9 Liu, J.-F.; Liu, J.-T.; Ma, J.-F.; Chen, Y.-G.; Li, C. *Chem. Res. Chin. Univ.* **2002**, *18*, 246.

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