

OXOVANADIUM(IV) AND (V) COMPLEXES WITH
NATURALLY-OCCURRING MOLECULES

by

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Abstract

Complexes with naturally-occurring ligating moieties were prepared and studied as part of an overall process to understand the coordination chemistry of vanadium. Bis(kojato)oxovanadium(IV), VO(ka)_2 , bis(3-oxy-1,2-dimethyl-4-pyridinonato)-oxovanadium(IV), VO(dpp)_2 , bis(2-hydroxymethyl-5-oxy-1-methyl-4-pyridinonato)-oxovanadium(IV), VO(hmp)_2 , bis[2-(2'-oxyphenyl)-2-oxazolinato]oxovanadium(IV), VO(oz)_2 , bis[2-(2'-oxyphenyl)-2-thiazolinato]oxovanadium(IV), $\text{VO(thz)}_2 \cdot 0.5\text{H}_2\text{O}$ and bis(benzohydroxamato) oxovanadium(IV), VO(bz)_2 were prepared and characterized. In addition, two oxovanadium(V) complexes, bis(benzohydroxamato)methoxo-oxovanadium(V), $\text{VO(OCH}_3\text{)(bz)}_2$ and bis(benzohydroxamato)ethoxo-oxovanadium(V), $\text{VO(OC}_2\text{H}_5\text{)(bz)}_2$ were also prepared from VO(bz)_2 . All eight complexes were prepared in one step processes, in particular VO(dpp)_2 and VO(hmp)_2 which were prepared directly from maltol and kojic acid, respectively, using vanadyl and methylamine in a one-pot synthesis method.

All oxovanadium complexes were characterized by infrared spectroscopy, mass spectrometry, elemental analyses and room temperature magnetic susceptibility measurements, and whenever possible, by UV-Visible spectrophotometry. ^1H and ^{51}V NMR were also used to characterize the two oxovanadium(V) complexes, $\text{VO(OCH}_3\text{)(bz)}_2$ and $\text{VO(OC}_2\text{H}_5\text{)(bz)}_2$. Single crystal X-ray diffraction studies of VO(oz)_2 and VO(thz)_2 were also performed by the departmental facility.

Characterization of the oxovanadium(IV) complexes revealed them to be 5-coordinate square pyramidal bis(ligand)oxovanadium(IV) complexes with each ligand binding in a bidentate fashion to the central vanadium atom. $\text{VO(OCH}_3\text{)(bz)}_2$ and $\text{VO(OC}_2\text{H}_5\text{)(bz)}_2$ were found to be 6-coordinate bis(ligand)oxovanadium(V) complexes. Comparison of the infrared stretching frequencies of the vanadium-oxo bond revealed that the strength of the vanadium-oxo bond in the eight complexes was consistent with bond

strength observed in other oxovanadium complexes. Single crystal X-ray diffraction studies of $\text{VO}(\text{oz})_2$ and $\text{VO}(\text{thz})_2$ showed them to be isostructural. The bidentate ligands are bonded to the vanadium center through the phenolate oxygen and the oxazoline or thiazoline ring nitrogen. The two complexes are both regular square pyramids with the bidentate ligands coordinated in a trans fashion. The vanadium atoms in these complexes are elevated by approximately 0.6 Å from the basal square planes defined by the four ligand O and N donors. The average V=O bond length is 1.6 Å.

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LIST OF ABBREVIATIONS

<u>Abbreviation</u>	<u>Meaning</u>
a	length of the unit cell along the a axis
Å	angstrom
α	interaxial angle between unit cell edges b and c
b	length of the unit cell along the b axis
β	interaxial angle between unit cell edges a and c
BM	Bohr magneton
c	length of the unit cell along the c axis
°C	degrees Celsius
cm ⁻¹	wave number
δ	chemical shift
D _{calc}	calculated density
deg	degrees
ϵ	molar extinction coefficient
EI	electron-impact ionization
EIMS	electron-impact ionization mass spectrometry
+FAB	positive ion fast atom bombardment
+FABMS	positive ion fast atom bombardment mass spectrometry
fw	formula weight
g	grams
γ	interaxial angle between unit cell edges a and b
⁶⁷ Ga	gallium-67
¹ H	proton
Hbz	benzohydroxamic acid
H ₃ DFB	deferriferrioxamine B

Hdpp	3-hydroxy-1,2-dimethyl-4-pyridinone
Hhmp	2-hydroxymethyl-5-hydroxy-1-methyl-4-pyridinone
Hka	kojic acid, 2-hydroxymethyl-5-hydroxy- γ -pyrone
Hoz	2-(2'-hydroxyphenyl)-2-oxazoline
Hthz	2-(2'-hydroxyphenyl)-2-thiazoline
Hz	hertz
I.P.	intraperitoneal
IR	infrared
J _{ab}	NMR coupling constant between hydrogens a and b
K	degrees Kelvin
kg	kilograms
L	liter
LL	bidentate ligand
λ	wavelength, nm
maltol	3-hydroxy-2-methyl-4-pyrone
mL	milliliter
mmol	millimole
ν_{x-y}	vibrational stretching mode
nm	nanometer, 10 ⁻⁹ m
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot
R	agreement factor
R _w	weighted agreement factor
STZ	streptozotocin
T	temperature
UV-Vis	ultraviolet-visible
VO(bz) ₂	bis(benzohydroxamato)oxovanadium(IV)

VO(bz) ₂ Cl	bis(benzohydroxamato)chlorooxovanadium(V)
VO(dpp) ₂	bis(3-oxy-1,2-dimethyl-4-pyridinonato)oxovanadium(IV)
VO(hmp) ₂	bis(2-hydroxymethyl-5-oxy-1-methyl-4-pyridinonato) oxovanadium(IV)
VO(H ₂ O)(C ₂ O ₄) ₂	aquobis(oxalato)oxovanadium(IV)
VO(ka) ₂	bis(kojato)oxovanadium(IV)
VO(ma) ₂	bis(maltolato)oxovanadium(IV)
VO(OCH ₃)(bz) ₂	bis(benzohydroxamato)methoxooxovanadium(V)
VO(OC ₂ H ₅)(bz) ₂	bis(benzohydroxamato)ethoxooxovanadium(V)
VO(OiPr)(ox) ₂	isopropoxobis(8-hydroxyquinolinato)oxovanadium(V)
VO(OR)(bz) ₂	bis(benzohydroxamato)alkoxooxovanadium(V)
VO(oz) ₂	bis[2-(2'-oxyphenyl)-2-oxazolinato]oxovanadium(IV)
VO(thz) ₂	bis[2-(2'-oxyphenyl)-2-thiazolinato]oxovanadium(IV)
ω	weighting factor
W _{1/2}	peak width at half peak height
Z	number of molecules in the unit cell (excluding solvent molecules of crystallization)

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To my parents and my sisters who always support me with their love.

Chapter 1. General Introduction

Vanadium is a widely distributed first row transition metal and is the nineteenth most abundant element in the earth's crust. Research into the chemistry and biological importance of vanadium has been in progress since its discovery by N. G. Sefstrom in 1831,¹ however, interest in vanadium intensified after the discovery of the inhibitory actions of orthovanadate ion (VO_4^{3-}) in sodium-potassium pump in 1977² and the discovery of the insulin mimicking properties of vanadate in 1980.^{3,4} Much progress concerning the chemistry and biological relevance of vanadium has been made during the past decade. It is known that the biological role of vanadium encompasses stimulatory, regulatory and inhibitory functions.¹ Vanadium has also been recognized as an endogenous component present in trace quantities in tissues of higher animals and is suspected to be essential for growth and development in many organisms. Whether vanadium is essential for humans remains unclear, although mounting evidence increasingly suggests that vanadium is most likely an essential trace element.^{5,6,7} Research into this suggestion has led to numerous studies which have examined the behaviour of vanadium within the human body. For example, the binding of V(IV) and V(V) to human serum transferrin has been well documented.⁸ In addition, the discovery of vanadate as a possible insulin mimicking agent has also stimulated research into the synthesis of new vanadium compounds and the study of their properties *in vivo*. Vanadium is of course found in numerous other biological systems besides humans. Recently, vanadium has been recognized as a part of the catalytically active center in the nitrogenase system of a special strain of *Azotobacter chroococcum*⁹ and in the vanadate(V)-dependent haloperoxidases of several marine algae.¹⁰ However, much work is still required before the precise functions of vanadium in these and other biological systems can be fully understood.

Although much effort has been expended studying the behaviour and function of

vanadium in naturally-occurring systems, there is also much interest in studying the properties of synthetic vanadium compounds and their possible applications. For example, the discovery of the insulin mimicking properties of vanadate has accelerated the search for vanadium compounds which could replace insulin in the treatment of diabetes.^{3,4} Diabetes is a condition in which the level of glucose in the blood plasma of mammals is abnormally high.¹¹ Present diabetic treatment often involves twice daily injections of insulin, a hormone which regulates the utilization and storage of basic human nutrients. Since insulin is not orally active, there is tremendous interest in developing an orally active vanadium compound as a replacement for insulin.

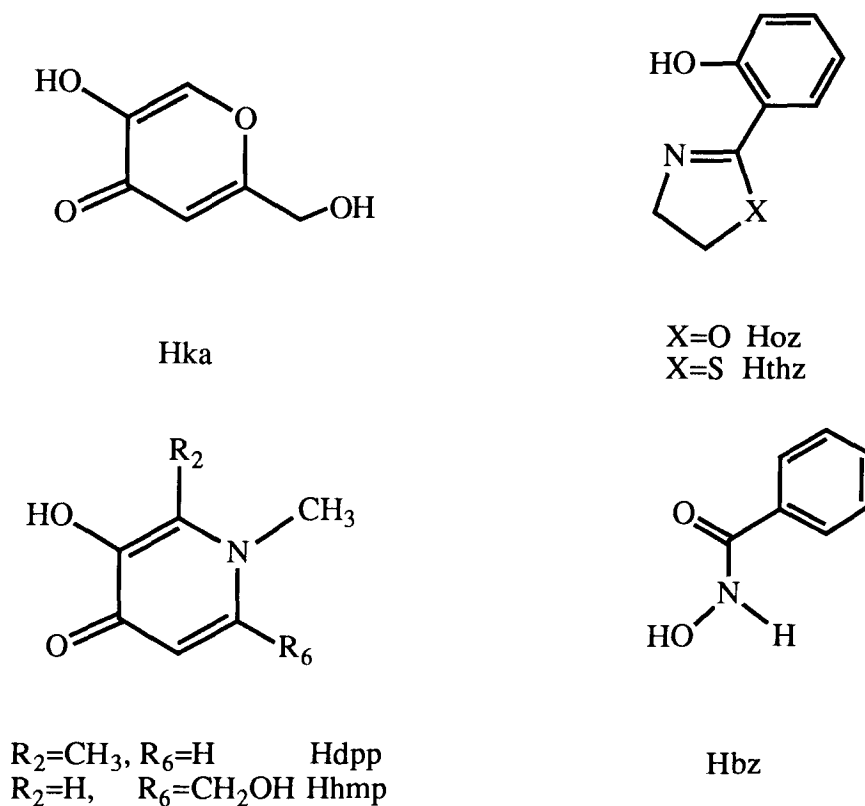


Figure 1.1. Ligand precursors chosen for the bis(ligand)oxovanadium(IV) complexes.

In order to better understand the biological role of vanadium, the relevant coordination chemistry of vanadium needs to be thoroughly investigated. Vanadium exists in a number of oxidation states, but only oxidation states +3, +4 and +5 are important in biological systems.¹² Compounds of oxovanadium(IV) are of particular interest to us because oxovanadium(IV) compounds are less toxic in the rabbit, rat, mouse, and guinea pig than vanadate(V) compounds, and, furthermore, several studies have indicated that the insulin-like actions of vanadate are also found with the vanadyl form and that the formation of vanadyl from vanadate *in vitro* coincided with the appearance of effects that are similar to those observed with insulin.¹³

The VO^{2+} moiety is known to bond effectively to electronegative donor atoms such as fluorine, chlorine, oxygen and nitrogen. Complexes with fluorine and oxygen donor atoms are known to be especially stable.¹⁴ Examples of the VO^{2+} moiety bonding to sulfur and phosphorus atoms are also known.¹⁴ In this study of the coordination chemistry of vanadium, potential bidentate ligands with oxygen-oxygen or oxygen-nitrogen donor atoms were chosen to coordinate to the VO^{2+} moiety. It was our desire to utilize naturally-occurring compounds or ligating moieties as a basis for choosing potential ligands of interest. The ligands in this study of the coordination behaviour of oxovanadium(IV) are illustrated in Figure 1.1.

The coordination of oxovanadium(IV) with benzohydroxamic acid (Hbz), 2-(2'-hydroxyphenyl)-2-oxazoline (Hoz) and 2-(2'-hydroxyphenyl)-2-thiazoline (Hthz) were studied because the ligating moieties of these ligands can be found in certain classes of microbial iron chelators (i.e. the siderophores). For example, the binding groups in the siderophore mycobactin consists of two hydroxamic acid residues and a 2-(2'-hydroxyphenyl)-2-oxazoline residue. Two examples of siderophores (mycobactins and deferriferrioxamine B) containing the 2-(2'-hydroxyphenyl)-2-oxazoline residue and the hydroxamic acid residues are shown in Figure 1.2.^{15,16,17} It is of interest to determine how the ligating moieties in these ligands would bind to oxovanadium(IV).

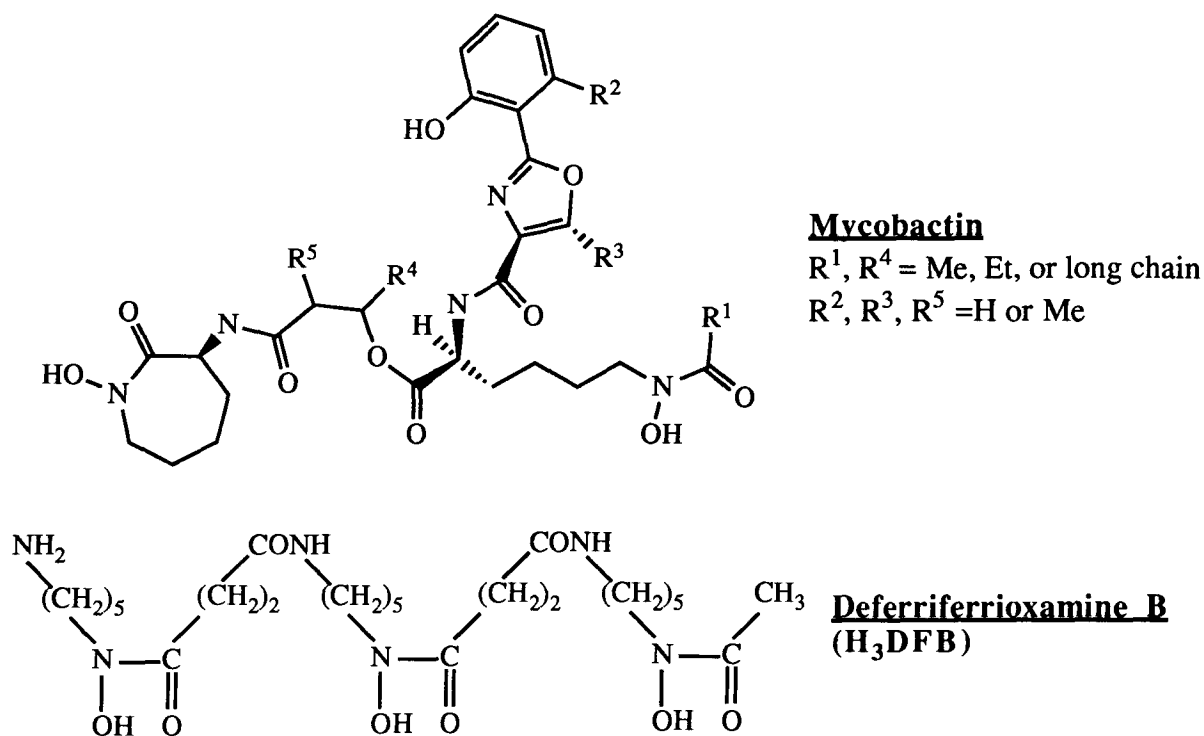


Figure 1.2. Structure of the siderophores mycobactin and deferriferrioxamine B (H₃DFB)

Over the past several years, the coordination of the α -hydroxyketone moiety with various metal centers has been investigated in this lab. Initial investigation focused on ligands containing the α -hydroxyketone moiety derived from 3-hydroxy-4-pyrones and 1-alkyl-3-hydroxy-4-pyridinones. Aluminium, gallium, indium, rhenium, and technetium complexes with these pyrone and pyridinone ligands have been prepared and studied.^{17,18} Coordination of these ligands to Al, Ga, and In resulted in 6-coordinate tris(ligand) metal complexes. For Tc and Re, 6-coordinate bis(ligand) complexes containing a metal oxo bond were formed. As a continuation of this work, the coordination of the α -hydroxyketone moiety to oxovanadium(IV) was studied. Kojic acid (Hka), a naturally-occurring compound which contains the α -hydroxyketone moiety was chosen as one of the potential ligands for this study. In addition, 3-hydroxy-1,2-dimethyl-4-pyridinone (Hdpp)

and 2-hydroxymethyl-5-hydroxy-1-methyl-4-pyridinone (Hhmp), which also contain the α -hydroxyketone unit, also were chosen as potential ligands for coordination with oxovanadium(IV).

A unique combination of biologically relevant properties (water solubility, hydrolytic stability and lipophilicity) has made pyrone and pyridinone complexes particularly interesting with respect to their possible medical application. For example, the tris(maltolato)aluminium complex has been used widely in the study of Al neurotoxicity.¹⁹ Another example is the ^{67}Ga complex tris(1-p-methoxyphenyl-2-methyl-3-oxy-4-pyridinonato)gallium(III), which is a potential heart imaging agent.²⁰ These pyrone and pyridinone ligands are non-toxic, naturally-occurring or easily synthesized and the properties of their complexes can be altered by changing the substituents on the ligands. With such favorable ligand properties, oxovanadium(IV) complexes of these ligands may prove to have interesting potential medical applications considering the insulin mimicking properties of some vanadium compounds.

Coordination of six different bidentate ligands to oxovanadium(IV) were studied. For each ligand, 5-coordinate bis(ligand) complexes with a VO^{2+} core were synthesized and characterized. The characterization of these complexes involved the use of infrared spectroscopy, mass spectrometry, elemental analyses, magnetic susceptibility measurements and ultraviolet-visible spectrophotometry when possible. X-ray crystallographic analyses of bis[2-(2'-oxyphenyl)-2-oxazolinato]oxovanadium(IV), $\text{VO}(\text{oz})_2$, and bis[2-(2'-oxyphenyl)-2-thiazolinato]oxovanadium(IV), $\text{VO}(\text{thz})_2$, were also obtained. Besides the oxovanadium(IV) complexes, two V(V) derivatives of $\text{VO}(\text{bz})_2$, $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$ which are 6-coordinate oxovanadium(V) complexes were also synthesized. In addition to the techniques used to characterized the six oxovanadium(IV) complexes, ^1H and ^{51}V NMR were also used to study $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$. The preparation and characterization of the eight vanadium complexes are summarized in Chapter 2. It is the belief that by studying the

coordination of vanadium with ligating moieties of biological or medical significance, a better understanding of the general roles or behaviour of vanadium in nature can be achieved. As a secondary objective, some of these oxovanadium complexes could also be evaluated as potential replacement for insulin in the treatment of diabetes (see Appendix B).

Chapter 2. Experimental Details

2.1 Synthesis Material and Methods

All chemicals were reagent grade and were used as received without further purification: kojic acid (2-hydroxymethyl-5-hydroxy- γ -pyrone), maltol (3-hydroxy-2-methyl-4-pyrone) and benzohydroxamic acid (Hbz, Sigma), $\text{VOSO}_4 \cdot 5\text{H}_2\text{O}$ and $\text{VOSO}_4 \cdot 3\text{H}_2\text{O}$ (Aldrich), $\text{NaOAc} \cdot 3\text{H}_2\text{O}$ (Fisher). 2-(2'-Hydroxyphenyl)-2-oxazoline (Hoz)²¹, and 2-(2'-hydroxyphenyl)-2-thiazoline (Hthz)²² were prepared according to the literature and were used without further purification. Water was deionized (Barnstead D8902 and D8904 cartridges) and distilled (Corning MP-1 Megapure still). The yields are for analytically pure compounds and they are calculated based on vanadium. The melting points were measured with a Mel-Temp apparatus; however, all the vanadium complexes were non-volatile, charring and decomposing above 120°C. Room temperature (293.5 K) magnetic susceptibilities were measured on a Johnson Matthey magnetic susceptibility balance, using $\text{Hg}[\text{Co}(\text{NCS})_4]$ as the susceptibility standard. Diamagnetic corrections were estimated by using Pascal's constants²³.

Bis(kojato)oxovanadium(IV), VO(ka)₂. VOSO₄·5H₂O (2.50 g, 9.88 mmol) was dissolved in 10 mL hot water and the solution was degassed with Ar for 10 minutes. The solution was then added to 10 mL of a degassed aqueous solution of kojic acid (2.88 g, 20.3 mmol) and NaOAc·3H₂O (2.97 g, 21.8 mmol). After refluxing under Ar overnight, a blue solid was collected by vacuum filtration using a Schlenk filtering funnel and dried overnight *in vacuo*. The yield was 2.69 g (78%). The solid state magnetic moment was 1.76 BM.

Bis(3-oxy-1,2-dimethyl-4-pyridinonato)oxovanadium(IV), VO(dpp)₂. To a solution of maltol (2.10 g, 16.7 mmol) and VOSO₄·5H₂O (2.01 g, 8.0 mmol) in 20 mL hot water was added 20 mL 40% methylamine in water (26 mmol) and the pH of the solution was decreased from 11.7 to 9.9 by addition of 2 N H₂SO₄. The solution was refluxed for 8 hours. A gray blue solid was collected by filtration and washed several times with hot water. The yield was 2.56 g (94%). The solid state magnetic moment was 1.77 BM.

Bis(2-hydroxymethyl-5-oxy-1-methyl-4-pyridinonato)oxovanadium(IV), VO(hmp)₂. To a solution of kojic acid (2.80 g, 19.7 mmol) in 40 mL hot water was added 20 mL 40% methylamine in water (26 mmol) and VOSO₄·5H₂O (2.47 g, 9.8 mmol) in 20 mL hot water. The pH of the solution was decreased from 12.8 to 11.0 by addition of 2 N H₂SO₄. The solution was refluxed under Ar for 8 hours. A blue solid was collected by filtration and washed several times with hot water. The yield was 2.45 g (67%). The solid state magnetic moment was 1.74 BM.

Bis[2-(2'-oxyphenyl)-2-oxazolinato]oxovanadium(IV), VO(oz)₂. To a solution of Hoz (0.31 g, 1.90 mmol) and NaOAc·3H₂O (0.27 g, 1.95 mmol) in CH₃OH (10 mL) was added VOSO₄·3H₂O (0.20 g, 0.92 mmol) in 11 mL of CH₃OH:H₂O (10:1) solution. A gray-blue solid immediately precipitated and was collected by filtration. Recrystallization of the

solid from CH_2Cl_2 yielded large blue crystals. The yield was 0.27 g (75%). The solid state magnetic moment was 1.84 BM.

Bis[2-(2'-oxyphenyl)-2-thiazolinato]oxovanadium(IV), $\text{VO}(\text{thz})_2 \cdot 0.5 \text{H}_2\text{O}$. The preparation was as for $\text{VO}(\text{oz})_2$. $\text{VOSO}_4 \cdot 3\text{H}_2\text{O}$ (0.20 g, 0.92 mmol), Hthz (0.34 g, 1.90 mmol) and $\text{NaOAc} \cdot 3\text{H}_2\text{O}$ (0.27 g, 1.95 mmol) were employed. Recrystallization from CH_2Cl_2 yielded large yellow-green crystals. The yield was 0.32 g (82%). The solid state magnetic moment was 1.80 BM.

Bis(benzohydroxamato)oxovanadium(IV), $\text{VO}(\text{bz})_2$. $\text{VOSO}_4 \cdot 3\text{H}_2\text{O}$ (0.20 g, 0.92 mmol) in 10 mL water was added dropwise to a solution of benzohydroxamic acid (0.26 g, 1.90 mmol) in 20 mL hot water. A purple solid precipitated. The pH of the suspension was raised from 1.7 to 7.4 by the slow addition of 0.5 N NaOH. The suspension was then stirred for 1.5 hours. The purple solid was collected by filtration yielding 0.22 g (71%) of the product. The solid state magnetic moment was 1.72 BM.

Bis(benzohydroxamato)methoxooxovanadium(V), $\text{VO}(\text{OCH}_3)(\text{bz})_2$. $\text{VO}(\text{bz})_2$ (0.11 g, 0.32 mmol) was dissolved in 10 mL $\sim 35^\circ\text{C}$ methanol and then stirred for 2 hours. A brick-red microcrystalline solid precipitated after the addition of 10 mL water. The product was collected by filtration and washed several times with water. The yield was 0.065 g (54%).

Bis(benzohydroxamato)ethoxooxovanadium(V), $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$. $\text{VO}(\text{bz})_2$ (0.10 g, 0.30 mmol) was dissolved in 10 mL hot ethanol and stirred for 2 hours. A golden-red solid precipitated upon slow evaporation of solvent. The product was collected by filtration and washed several times with water. The yield was 0.058 g (52%).

2.2. Characterization

The bis(ligand)oxovanadium(IV) complexes were characterized by infrared (IR) spectroscopy, positive ion fast atom bombardment mass spectrometry (+FABMS) or electron-impact ionization mass spectrometry (EIMS), UV-visible spectrophotometry (UV-Vis), elemental analyses, and in some cases, X-ray crystallography. In addition to the above methods, the six-coordinate bis(ligand)alkoxooxovanadium(V) complexes were also characterized by ^1H NMR and ^{51}V NMR.

IR spectra were recorded as KBr disk in the range $4000\text{--}400\text{ cm}^{-1}$ on a Perkin-Elmer PE783 spectrophotometer and were referenced to polystyrene. The mass spectra were obtained with an AEI MS9 (FABMS) spectrometer, or a Kratos MS50 (EIMS) instrument by the UBC mass spectrometry service. Elemental analyses were performed by Mr. Peter Borda of the Microanalytical Laboratory of this department. ^1H NMR spectra, recorded on a Varian XL-300 instrument, are reported in ppm downfield of tetramethylsilane (TMS) as the internal standard. ^{51}V NMR spectra were recorded on a Varian XL-300 instrument and are referenced to external VOCl_3 . The UV-Vis spectra were recorded from 900-200 nm with a Shimadzu UV-2100 spectrophotometer. Both crystal structures reported in this thesis were determined with a Rigaku AFC6S diffractometer by Dr. Steven J. Rettig of the UBC Structural Chemistry Laboratory.

2.2.1 Infrared Spectroscopy

The relevant IR data is summarized in Table 2.2.1. All compounds exhibit a strong V=O stretching frequency in the region from 960 to 995 cm^{-1} .

Table 2.2.1 Characteristic IR absorptions (cm^{-1}).

All bands are sharp and strong except where noted.*

Assignment	VO(ka) ₂	VO(dpp) ₂	VO(hmp) ₂
	1610	1605	1610(m)
$\nu_{\text{C=O}}$ and	1550	1550	1560(m)
$\nu_{\text{C=C(ring)}}$	1500	1490	1510
	1470	1450	1450
		1430(w)	
$\nu_{\text{V=O}}$	980	965	970
$\nu_{\text{C-N(ring)}}$	----	----	1300

Assignment	VO(oz) ₂	VO(thz) ₂
$\nu_{\text{C=N}}$	1620	1600
$\nu_{\text{C=C(aromatic)}}$	1595(w)	1570
		1540
$\nu_{\text{V=O}}$	990	980

Assignment	VO(bz) ₂	VO(OCH ₃)(bz) ₂	VO(OC ₂ H ₅)(bz) ₂
	1600	1600	1600
$\nu_{\text{C=O}}$ and	1570	1520(b)	1550(b)
$\nu_{\text{C=C(aromatic)}}$	1510		1520(b)
	1480	1480	1490
	1440	1440	1450
$\nu_{\text{V=O}}$	995	960	970
$\nu_{\text{N-H}}$	3200(b)	3200(b)	3200(b)

* w, weak; m, medium; b, broad.

2.2.2. Elemental Analyses

Satisfactory elemental analyses were obtained for all complexes (refer to Table 2.2.2). Prior to analysis, each sample was purified by recrystallization when possible and dried at ~65°C *in vacuo* for at least 24 hours.

Table 2.2.2 Results of elemental analyses of the vanadium complexes
(Calculated[Found])

Compound	Formula	%C	%H	%N
VO(ka) ₂	C ₁₂ H ₁₀ O ₉ V	41.28[41.06]	2.89[2.89]	----
VO(dpp) ₂	C ₁₄ H ₁₆ N ₂ O ₅ V	48.99[48.56]	4.70[4.65]	8.16[8.38]
VO(hmp) ₂	C ₁₄ H ₁₆ N ₂ O ₇ V	44.81[45.00]	4.30[4.39]	7.47[7.47]
VO(oz) ₂	C ₁₈ H ₁₆ N ₂ O ₅ V	55.25[55.12]	4.12[4.17]	7.16[7.08]
VO(thz) ₂ ·0.5H ₂ O	C ₁₈ H ₁₇ N ₂ O _{3.5} S ₂ V	50.00[50.42]	3.98[3.83]	6.48[6.47]
VO(bz) ₂	C ₁₄ H ₁₂ N ₂ O ₅ V	49.57[49.37]	3.57[3.66]	8.26[8.02]
VO(OCH ₃)(bz) ₂	C ₁₅ H ₁₅ N ₂ O ₆ V	48.66[48.46]	4.08[4.03]	7.57[7.54]
VO(OC ₂ H ₅)(bz) ₂	C ₁₆ H ₁₇ N ₂ O ₆ V	50.01[50.32]	4.46[4.54]	7.29[7.16]

2.2.3. ¹H NMR Spectroscopy

¹H NMR spectral data of the two vanadium(V) complexes are listed in Table 2.2.3. Both spectra exhibit a doublet and two triplets for the phenyl hydrogens and characteristic signals for the alkoxy hydrogens.

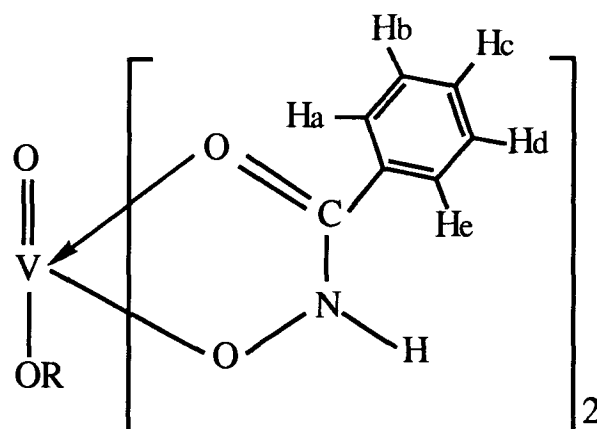


Figure 2.2.3. $\text{VO}(\text{OR})(\text{bz})_2$ complexes atom labelling used in NMR data.

Table 2.2.3. ^1H NMR chemical shifts (δ) for the $\text{VO}(\text{OR})(\text{bz})_2$ complexes (ppm).^a

Refer to Figure 2.2.3. for atom labelling.

	$\text{VO}(\text{OCH}_3)(\text{bz})_2$	$\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$
$\text{H}_{a,e}$ (d)	7.73(2H, $J=7.1$ Hz)	7.78(2H, $J=7.2$ Hz)
$\text{H}_{b,d}$ (t)	7.40(2H, $J=7.5$ Hz)	7.43(2H, $J=7.5$ Hz)
H_c (t)	7.49(1H, $J=7.5$ Hz)	7.52(1H, $J=7.4$ Hz)
CH_3^f (s)	3.34(3H)	----
CH_2^g (q)	----	3.60(2H, $J=7.1$ Hz)
CH_3^h (t)	----	1.17(3H, $J=7.1$ Hz)

^a in CD_3OD

Abbreviations: s=singlet d=doublet t=triplet q=quartet

2.2.4. Variable Temperature ^1H NMR Spectroscopy

The variable low temperature ^1H NMR spectra for $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$ in CD_3OD were recorded over the range -80°C to 25°C . The low temperature ^1H NMR spectra did not differ significantly from the spectrum obtained at room temperature except for a slight broadening of the signals.

2.2.5. ^{51}V NMR Spectroscopy

^{51}V NMR data for $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$, recorded in CH_2Cl_2 and $\text{C}_2\text{H}_5\text{OH}$ respectively, are given in Table 2.2.5. Both complexes yielded one sharp single resonance, as expected for single species.

Table 2.2.5. ^{51}V NMR chemical shifts (δ) for the $\text{VO}(\text{OR})(\text{bz})_2$ complexes (ppm).

complex	chemical shift.(ppm)	line width ($W_{1/2}$, Hz)
$\text{VO}(\text{OCH}_3)(\text{bz})_2^{\text{a}}$	-425	222
$\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2^{\text{b}}$	-411	543

^a in CH_2Cl_2 , ^b in $\text{C}_2\text{H}_5\text{OH}$

2.2.6. Mass Spectrometry

The mass spectra of the complexes showed the HVOL_2^+ , and/or VOL_2^+ fragments when recorded in the positive ion FAB mode, or the VOL_2^+ , VOL^+ , and L^+ fragments in the EI mode. The results are listed in Table 2.2.6.1. for positive ion FAB mode and in Table 2.2.6.2. for the EI mode.

Table 2.2.6.1. FAB mass spectral data (m/z) of the vanadium complexes.

	HVOL_2^+	VOL_2^+
VO(ka)_2	350*	349
VO(bz)_2	340	339*
VO(dpp)_2	344*	343
VO(hmp)_2	376*	375
$\text{VO(OCH}_3\text{)(bz)}_2$		339
$\text{VO(OC}_2\text{H}_5\text{)(bz)}_2$		339

* indicates the base peak.

Table 2.2.6.2. EI mass spectral data (m/z) of the vanadium complexes.

The relative intensities of the peaks are included in the parentheses.

	VOL_2^+	VOL^+	L^+
VO(oz)_2	391(100)	229(17.9)	163(88.9)
VO(thz)_2	423(100)	245(11.4)	179(5.2)

2.2.7. UV-Vis Spectrophotometry.

The UV-Visible spectral data which were obtained at room temperature are summarized in Table 2.2.7. Data for VO(dpp)₂, VO(hmp)₂ and VO(bz)₂ were not obtained either due to their very limited solubility in various solvents or due to the reaction of the complexes with the solvents.

Table 2.2.7. UV-Vis spectral data, λ , nm (ϵ , M⁻¹cm⁻¹).

complex	solvent	λ_{\max} (ϵ)			
		I	II	III	other
VO(ka) ₂	H ₂ O	842(30)	612(15)	----	223(34200)
VO(oz) ₂	CH ₂ Cl ₂	597(47)	543(45)	409(sh*, 111)	331(12000) 239(63700)
VO(thz) ₂	CH ₂ Cl ₂	595(53)	537(66)	437(sh, 179)	346(11200) 242(56500)
VO(OCH ₃)(bz) ₂	CH ₃ OH	----	----	----	441(2000) 222(22200) 203(25600)
VO(OC ₂ H ₅)(bz) ₂	C ₂ H ₅ OH	----	----	----	446(2400) 222(25600) 204(29700)

* sh=shoulder

2.2.8. X-ray Crystallographic Analyses

The solid state structures of VO(oz)₂ and VO(thz)₂ were established by single crystal X-ray diffraction studies at 21°C. Single crystals of the bis(ligand)oxovanadium(IV) complexes were grown by slow evaporation from saturated methylene chloride solution. Crystallographic data, final atomic coordinates and equivalent isotropic thermal parameters B_{eq} for VO(oz)₂ and VO(thz)₂ are given in Appendix A as Tables A1, A2 and A3. The complete list of bond lengths and bond angles are summarized in Tables A4 and A5 in Appendix A.

Chapter 3. Results and Discussion

The coordination chemistry of oxovanadium(IV) was studied with kojic acid (Hka), 3-hydroxy-1,2-dimethyl-4-pyridinone (Hdpp), 2-hydroxymethyl-5-hydroxy-1-methyl-4-pyridinone (Hhmp), 2-(2'-hydroxyphenyl)-2-oxazoline (Hoz), 2-(2'-hydroxyphenyl)-2-thiazoline (Hthz) and benzohydroxamic acid (Hbz) as potential ligands for binding to the VO^{2+} moiety. The ligands used in this study were chosen because they all possess qualities which are desirable for bonding to oxovanadium(IV). All of these

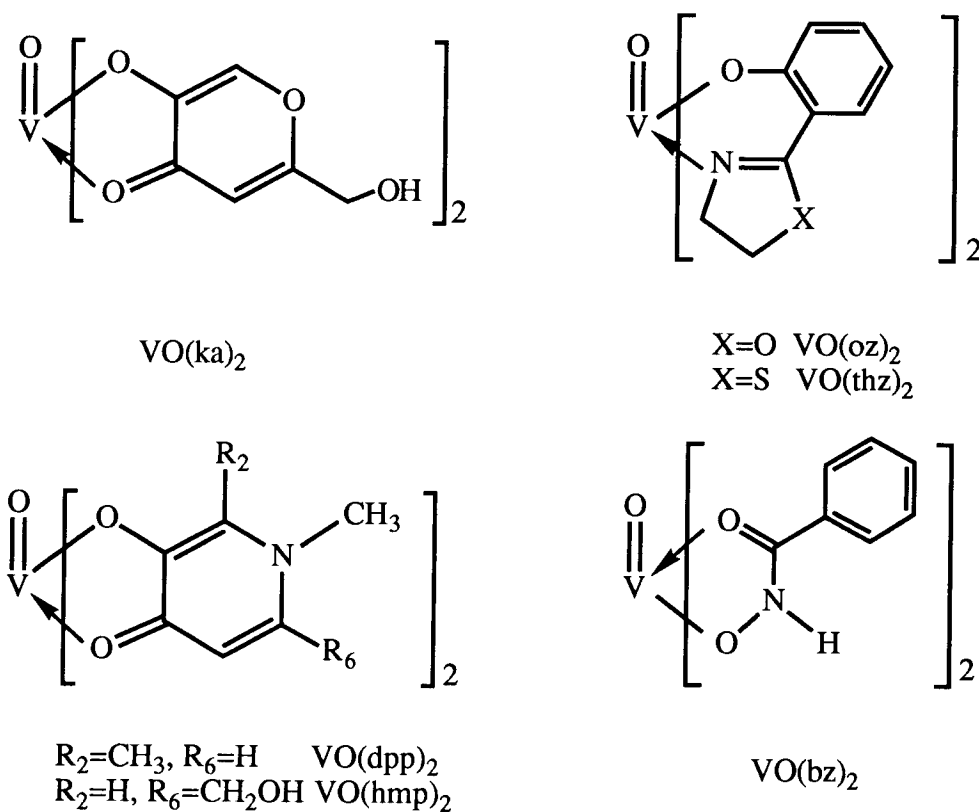


Figure 3.1. Bis(ligand)oxovanadium(IV) complexes.

potential ligands when deprotonated behave as bidentate Lewis bases.^{24,25} The VO^{2+} cation is classified as a hard Lewis acid,²⁶ therefore, according to hard soft acid base theory,²⁶ the VO^{2+} cation should bind favorably to donor atoms which are hard Lewis bases. In the case of Hka, Hdpp, Hhmp and Hbz, the deprotonated hydroxy oxygen and the carbonyl oxygen act as donor atoms, each donating an electron pair to the oxovanadium(IV) center. For Hoz and Hthz, the donor atoms are the deprotonated hydroxy oxygen and the oxazoline or thiazoline ring nitrogen. The hydroxy oxygen, the carbonyl oxygen and the ring nitrogen within these ligands can be classified as relatively hard bases.²⁵ Binding of the hard Lewis acid, VO^{2+} , to the hard Lewis base donor atoms resulted in bis(ligand) metal complexes of neutral charge. Each ligand binds to the central vanadium atom to form 5 or 6-membered chelate rings (refer to Figure 3.1.). The chelate effect contributes to the overall thermodynamic stability of these bis(ligand) oxovanadium(IV) complexes.

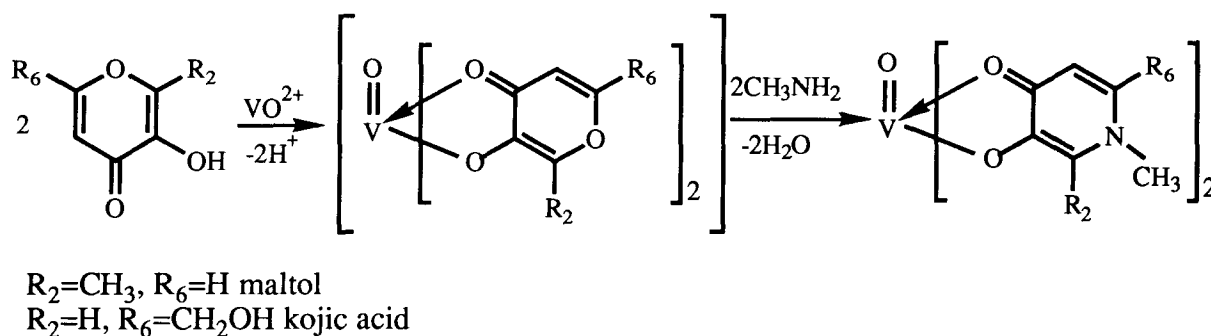


Figure 3.2. Scheme for the one-pot synthesis of bis(3-oxy-4-pyridinonato)oxovanadium(IV) complexes

The synthesis of oxovanadium(IV) complexes with the {O, O} or {O, N} bidentate monobasic ligands were straightforward and gave relatively high yields (67%-94%). The ratio of ligand precursor to VO^{2+} used was 2:1 with a slight excess of ligand precursor

used to force the reaction to completion. In the synthesis of VO(dpp)_2 and VO(hmp)_2 , a one pot synthetic method was utilized.²⁷ The synthesis involves the conversion of the metal coordinated pyrone precursor to the corresponding coordinated pyridinone metal complex. The traditional method of synthesis for 3-hydroxy-4-pyridinone involves the amination of the analogous 3-hydroxy-4-pyrone.²⁷ To carry out this conversion, protected pyrone precursors are usually utilized in a multistep process. The overall conversion is time consuming and rigorous. On the other hand, one pot synthesis of VO(dpp)_2 and VO(hmp)_2 took only a single step and gave yields of 94% and 67%, respectively. The one pot synthetic process begins by the *in situ* formation of the metal-pyrone complex. This is then followed by the insertion of a primary amine into the pyrone ring to form the appropriate pyridinonate complex. Figure 3.2. outlines the synthetic scheme for the one-pot synthesis of the oxovanadium pyridinonate complexes.

Recrystallization of the oxovanadium(IV) complexes was not always possible due to the limited solubility of some of these complexes in common solvents or due to the oxidation of the complex by oxygen within the solvent. For example, purple VO(bz)_2 dissolves in methanol to give a light orange solution which quickly changes colour to dark red. Addition of water to this solution yields microcrystalline $\text{VO(OCH}_3\text{)(bz)}_2$, an oxovanadium(V) species. Dissolving VO(bz)_2 in ethanol produces similar results; the oxovanadium(V) complex, $\text{VO(OC}_2\text{H}_5\text{)(bz)}_2$ was obtained.

All the oxovanadium(IV) complexes were found to be air stable and exhibit a magnetic moment at room temperature in the solid state. Vanadium(IV) has an electron configuration of $[\text{Ar}]3d^1$ and hence has a single unpaired electron. Assuming that the magnetic moment has contribution from only the spin angular momentum of the unpaired electron, the spin only formula predicts a magnetic moments of 1.73 for a d^1 system. The six oxovanadium(IV) complexes possess solid state magnetic moment of 1.72 to 1.84 BM at room temperature. The observed magnetic moment for the six oxovanadium(IV) complexes is within the range of values commonly found for many vanadium(IV)

complexes and indicates the presence of a single unpaired electron.²⁸ $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$ are oxovanadium(V) species with an electron configuration of $[\text{Ar}]3d^0$. The two oxovanadium(V) complexes showed no solid state magnetic moment since they possess no unpaired electron.

Infrared measurements for each of the oxovanadium complexes are summarized in Chapter 2, Table 2.2.1. The infrared spectral pattern of the ligands is preserved in these complexes with a general bathochromatic shift upon coordination to the oxovanadium center. In the infrared spectra of the eight oxovanadium complexes, the absorption associated with the characteristic $\text{V}=\text{O}$ stretching frequency is of particular interest. The stretching frequencies of the $\text{V}=\text{O}$ bond in oxovanadium complexes are generally observed around 930 cm^{-1} to 1030 cm^{-1} .¹⁴ For the eight oxovanadium complexes synthesized in this study, $\nu_{\text{V}=\text{O}}$ was observed to range from 965 to 995 cm^{-1} .

The oxovanadium(V) complexes, $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$, showed $\nu_{\text{V}=\text{O}}$ at 960 cm^{-1} and 970 cm^{-1} respectively. The $\nu_{\text{V}=\text{O}}$ for $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$ were 35 cm^{-1} and 25 cm^{-1} lower than $\nu_{\text{V}=\text{O}}$ in the oxovanadium(IV) complex $\text{VO}(\text{bz})_2$ (995 cm^{-1}). This indicates that the vanadium oxo bond in the $\text{VO}(\text{OR})(\text{bz})_2$ complexes is weaker than the vanadium oxo bond in $\text{VO}(\text{bz})_2$. This may be explained as follows.

The $\text{V}=\text{O}$ bond is a multiple covalent bond involving $p\pi$ - $d\pi$ electron donation from the oxygen to the vanadium center which has empty acceptor orbital.²⁹ This electron donation through the π bond is superimposed upon a σ bond. Changes in the electron accepting ability of the vanadium center causes changes in the strength of the vanadium oxo bond, which is reflected in changes in the $\text{V}=\text{O}$ stretching frequency. Coordinated ligands which donate electron density to the vanadium center will increase the electron density in the vanadium d orbitals. This increased electron density in the vanadium d orbitals reduces the electron accepting ability of the vanadium atom, therefore reducing the $\text{V}=\text{O}$ $p\pi$ - $d\pi$ electron donation. The degree of reduction in the $\text{V}=\text{O}$ $p\pi$ - $d\pi$ electron

donation depends on the electron donating ability of the ligands. It is not unreasonable to assume that the total electron accepting ability of a metal ion in a particular valence state is certain.³⁰ When a V^{4+} complex oxidises to a V^{5+} complex, the vanadium ion increases its electrophilicity. At this stage, when a monodentate negative group reaches the coordination zone, it may or may not exactly counterbalance the increased electrophilicity of V^{5+} . If the donor property of the new ligand is greater than the increased acceptor property of the metal ion, there will be an overall accumulation of increased electron density around the vanadium ion. This would greatly affect V=O bond, the stretching frequency of which would certainly be lowered. This is what is found in the complexes $VO(bz)_2$ and $VO(OR)(bz)_2$ (R=methyl or ethyl).

Analyses for carbon, hydrogen and, when appropriate, nitrogen were carried out for each oxovanadium complex. The results are summarized in Table 2.2.2. The data are consistent with the formulation of bis(ligand) oxovanadium complexes. With the exception of $VO(thz)_2$, no solvate water was observed in these complexes. Attempts to remove the solvated water in $VO(thz)_2$ by drying at approximately 65°C *in vacuo* (< 0.3 Torr) for a minimum of 24 hours were not successful.

The eight synthesized oxovanadium complexes were examined by mass spectrometry. The data are summarized in Chapter 2, Tables 2.2.6.1 and 2.2.6.2. The mass spectra of $VO(oz)_2$ and $VO(thz)_2$ were obtained using electron impact ionization (EI) while the mass spectra of the other complexes were obtained using positive ion fast atom bombardment (+FAB). The spectra of $VO(oz)_2$ and $VO(thz)_2$ showed strong signals corresponding to VOL_2^+ , VOL^+ and L^+ fragments. For $VO(ka)_2$, $VO(bz)_2$, $VO(dpp)_2$ and $VO(hmp)_2$, the mass spectra revealed very strong signals corresponding to $HVOL_2^+$ and VOL_2^+ fragments. The results for these complexes are consistent for a VOL_2 formulation. In the case of $VO(OCH_3)(bz)_2$ and $VO(OC_2H_5)(bz)_2$ complexes, $VO(OR)(bz)_2^+$ and $HVO(OR)(bz)_2^+$ fragments were not the dominant fragments. The base peak in the observed mass spectra corresponds instead to VOL_2^+ . The alkoxy group was lost during

the fragmentation process in the mass spectrometer. This would suggest that the alkoxy group is bonded less strongly to the vanadium(V) center compared to the other oxygen donor atoms within the complexes.

^1H NMR data for $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$ were recorded in CH_3OD and are presented in Table 2.2.3. The assignments and integrations of the ^1H signals are consistent with the coordination of two bidentate ligands to the oxovanadium core. ^1H signals due to the phenyl ring hydrogens of the two benzohydroxamate ligands suggest that the phenyl rings of the two ligands are in the same chemical environment. Low temperature ^1H NMR of both complexes were carried out and the spectra at different temperatures show only slight broadening of the signals. No emergence of any additional ^1H resonances was observed even at -80°C .

Six isomers are possible for the $\text{VO}(\text{OR})(\text{bz})_2$ complexes. These possible isomers are illustrated in Figure 3.3. Isomers I and II have the alkoxy group trans to the $\text{V}=\text{O}$ bond whereas isomers III to VI have the alkoxy group cis to the $\text{V}=\text{O}$ bond. At room temperature, the ^1H NMR spectra shows the hydrogens on the two phenyl rings associated with the two benzohydroxamate ligands to be in the same chemical environment. This would suggest that the oxovanadium complex has assumed a trans configuration where the hydrogens in the two phenyl rings are chemically equivalent (I or II). However, fast exchange of the two benzohydroxamate ligands in a cis configuration (III to VI) would also show equivalent phenyl ring hydrogens. If such an exchange process is occurring, lowering the temperature might slow down the rate of exchange and allow the observation of two sets of inequivalent hydrogens on each of the benzohydroxamate ligands. However, variable temperature ^1H NMR experiments (as low as -80°C) did not produce any significant changes in the ^1H NMR spectra. This may suggest that the oxovanadium complexes are indeed in a trans configuration. However, the possibility of the complexes in a cis configuration can not be ruled out on the basis of the results from the variable

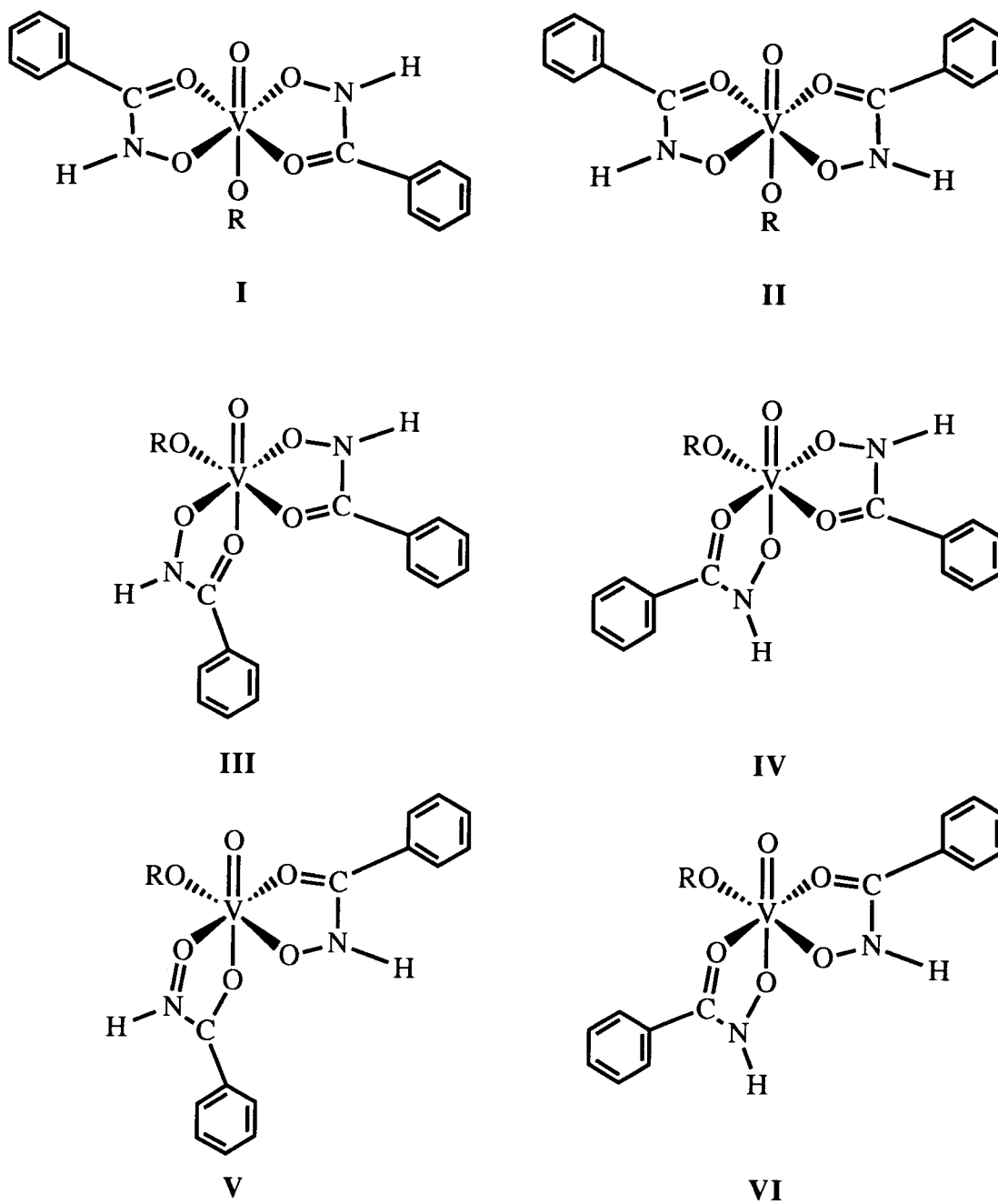


Figure 3.3. Six possible isomers for $\text{VO}(\text{OR})(\text{bz})_2$ complexes.

temperature ^1H NMR experiments. It may be that the rate of exchange of the benzohydroxamate ligands is faster than the NMR time scale; then the stereochemistry at the vanadium metal center would not be elucidated using ^1H NMR.

A crystal structure of bis(benzohydroxamato)chlorooxovanadium(V), $\text{VOCl}(\text{bz})_2$ (Figure 3.4.) was reported by Raymond et al.³¹ In this crystal structure, the oxovanadium(V) complex assumes a cis configuration corresponding to the stereoisomer III in Figure 3.3 with the chlorine atom cis to the vanadium oxo bond. Similar structures

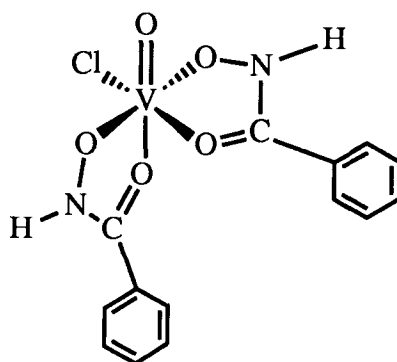


Figure 3.4. Structure of bis(benzohydroxamato)chlorooxovanadium(V) complex.³¹

have been observed in aquobis(oxalato)oxovanadium(IV), $\text{VO}(\text{H}_2\text{O})(\text{C}_2\text{O}_4)_2$ ³² and isopropoxobis(8-hydroxyquinolino)oxovanadium(V), $\text{VO}(\text{OiPr})(\text{ox})_2$.³³ These oxovanadium(V) complexes exhibit the trans influence which refers to the ability of one ligand to lengthen (and apparently weaken) the bond to the ligand trans to it.³⁴ It was predicted that a multiply bonded ligand (e.g. $\text{V}=\text{O}$) will preferentially weaken other ligand bonds in the trans position.³⁴ Thus, ligands that tend to form strong bonds will preferentially occupy a position cis to the vanadium oxo bond.³¹ In 6-coordinate oxovanadium complexes with both bidentate and monodentate ligands, it is likely that one

donor atom of the bidentate ligand would occupy the trans position with the monodentate ligand occupying the cis position. This could be attributed to the chelate effect of the bidentate ligand, since the extra thermodynamic stability caused by the positive enthalpy change after chelation might overcome the trans influence from the vanadium oxo group.²⁴ The trans influence of the oxo group within $\text{VO}(\text{bz})_2\text{Cl}$, $\text{VO}(\text{H}_2\text{O})(\text{C}_2\text{O}_4)_2$ and $\text{VO}(\text{OiPr})(\text{ox})_2$ causes the chlorine, the water and the isopropoxy group to assume a position cis relative to the vanadium oxo bond. In our example, $\text{VO}(\text{OR})(\text{bz})_2$, it is suspected that the trans influence of the oxo group would also cause the alkoxy group to take up a cis position relative to the oxo bond. However, we have been unable to obtain evidence which supports this conclusion in the $\text{VO}(\text{OR})(\text{bz})_2$ complexes. Hence, in the absence of any concrete evidence in solid state or in solution, the possibility of the alkoxy group being trans to the oxo group cannot be entirely ruled out.

Single crystal X-ray diffraction studies of $\text{VO}(\text{oz})_2$ and $\text{VO}(\text{thz})_2$ were performed. The analyses show unequivocally that the complexes are indeed the expected bis(ligand) oxovanadium(IV) complexes. The crystal structure of $\text{VO}(\text{oz})_2$ was found to be isostructural with $\text{VO}(\text{thz})_2$. Computer generated ORTEP diagrams of $\text{VO}(\text{oz})_2$ and $\text{VO}(\text{thz})_2$ are presented in Figures 3.5. and 3.6.. Selected bond lengths and bond angles are summarized in Tables 3.1. and 3.2. respectively. X-ray diffraction studies revealed both $\text{VO}(\text{oz})_2$ and $\text{VO}(\text{thz})_2$ to be 5-coordinate square pyramidal oxovanadium(IV) complexes, with the oxo group in the axial position. This structure is common for many oxovanadium(IV) complexes.¹⁰ The 2-(2'-oxyphenyl)-2-oxazolate and 2-(2'-oxyphenyl)-2-thiazolate ligands are coordinated to the vanadium center via the phenolate oxygen and the oxazoline or thiazoline ring nitrogen. The two oxazolate or thiazolate ligands are found to be trans to one another and cis to the oxo group.

The vanadium oxo bond lengths in $\text{VO}(\text{oz})_2$ and $\text{VO}(\text{thz})_2$ are observed to be 1.594(1) Å and 1.591(3) Å, respectively, and are typical for V=O bond lengths in oxovanadium(IV) complexes (1.52 Å-1.68 Å).²⁹ Within the six-membered chelate ring

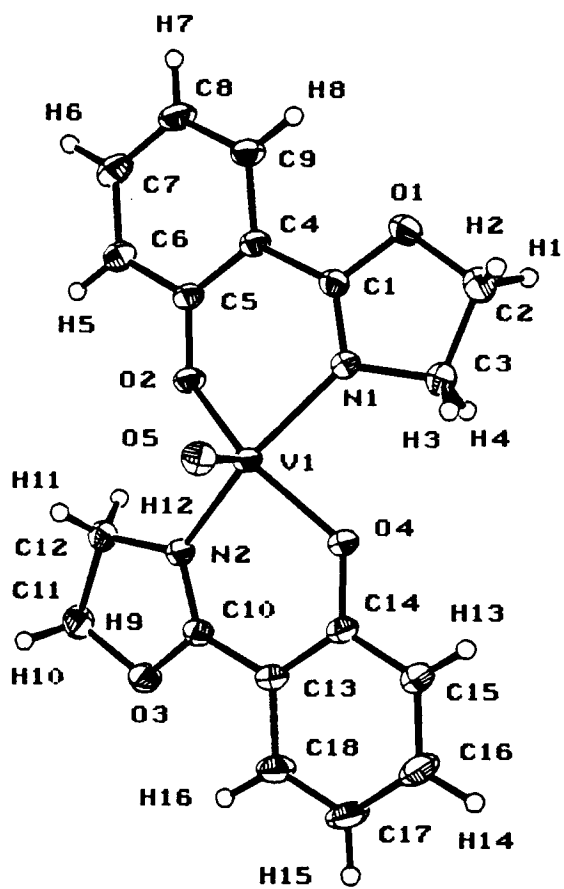


Figure 3.5. ORTEP view of the VO(ox)₂ unit.

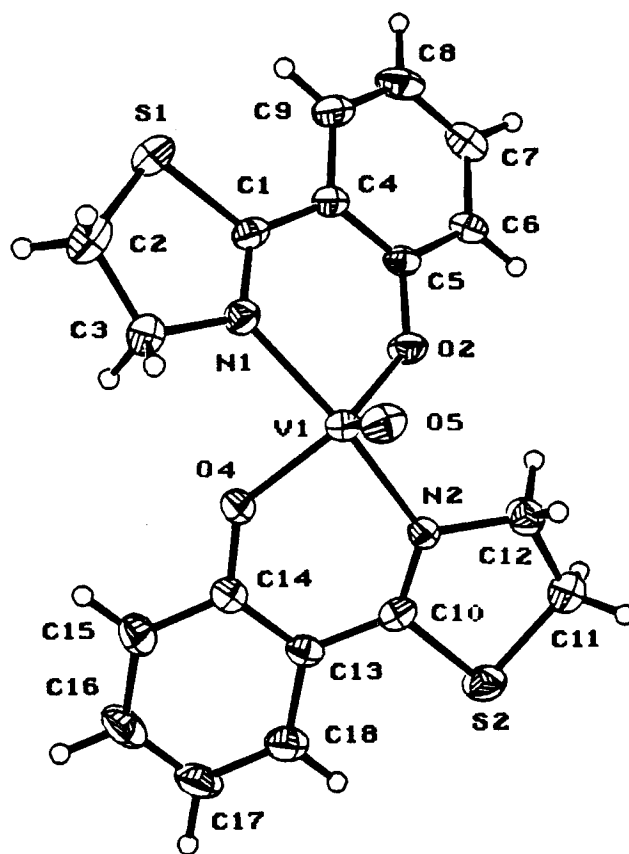


Figure 3.6. ORTEP view of the VO(thz)₂ unit.

Table 3.1. Selected Bond Lengths (Å) for VO(oz)₂ and VO(thz)₂ with Estimated Standard Deviations in Parentheses

VO(oz) ₂		VO(thz) ₂	
Atoms	Distance	Atoms	Distance
V(1)-O(2)	1.931(1)	V(1)-O(2)	1.903(3)
V(1)-O(4)	1.926(1)	V(1)-O(4)	1.900(3)
V(1)-O(5)	1.594(1)	V(1)-O(5)	1.591(3)
V(1)-N(1)	2.068(1)	V(1)-N(1)	2.083(3)
V(1)-N(2)	2.061(1)	V(1)-N(2)	2.083(3)
O(1)-C(1)	1.347(2)	S(1)-C(1)	1.757(4)
O(1)-C(2)	1.460(2)	S(1)-C(2)	1.790(5)
O(2)-C(5)	1.315(2)	O(2)-C(5)	1.330(4)
O(3)-C(10)	1.346(2)	S(2)-C(10)	1.761(4)
O(3)-C(11)	1.458(2)	S(2)-C(11)	1.788(5)
O(4)-C(14)	1.319(2)	O(4)-C(14)	1.328(4)
N(1)-C(1)	1.284(2)	N(1)-C(1)	1.295(5)
N(1)-C(3)	1.472(2)	N(1)-C(3)	1.479(5)
N(2)-C(10)	1.287(2)	N(2)-C(10)	1.291(4)
N(2)-C(12)	1.472(2)	N(2)-C(12)	1.474(5)

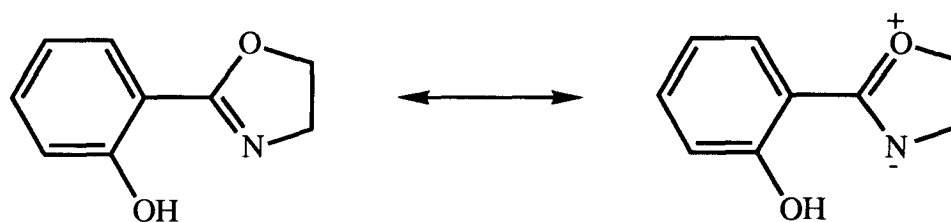
Table 3.2. Selected Bond Angles (deg) for VO(oz)₂ and VO(thz)₂ with Estimated Standard Deviations in Parentheses.

Atoms	Angle	
	VO(oz) ₂	VO(thz) ₂
O(2)-V(1)-O(5)	108.41(5)	115.2(1)
O(4)-V(1)-O(5)	108.81(5)	114.9(1)
O(5)-V(1)-N(1)	104.73(6)	99.1(1)
O(5)-V(1)-N(2)	103.79(5)	99.4(1)
O(2)-V(1)-N(1)	85.28(5)	86.8(1)
O(2)-V(1)-N(2)	85.25(5)	86.4(1)
O(4)-V(1)-N(1)	85.23(5)	85.5(1)
O(4)-V(1)-N(2)	86.21(5)	85.7(1)
O(2)-V(1)-O(4)	142.79(5)	129.9(1)
N(1)-V(1)-N(2)	151.47(5)	161.4(1)

formed by the coordination of the phenolate oxygen and the ring nitrogen to the vanadium center, the average vanadium phenolate oxygen bond length is 1.928(1) Å and 1.901(3) Å for VO(oz)₂ and VO(thz)₂ respectively. The average vanadium ring nitrogen bond length is 2.064(1) Å for the oxazolate complex and is 2.083(3) Å for the thiazolate complex. The V-O and V-N bond lengths fall in the range of V-O and V-N bond lengths observed for many oxovanadium Schiff base complexes.³⁵ The average V-O bond length in both complexes are shorter than the observed V-N bond lengths. In the complexes M(oz)₃ (M=Al³⁺, Ga³⁺ and In³⁺), the M-O bonds were also found to be shorter than the M-N bonds.¹⁷

Examination of one of the oxazoline rings in $\text{VO}(\text{oz})_2$ (Figure 3.5.) shows the C(1)-O(1) bond length of 1.347(2) Å to be significantly shorter than the C(2)-O(1) bond length of 1.460(2) Å. Also the C(1)-N(1) bond length (1.284(2) Å) is shorter than the C(3)-N(1) bond length (1.472(2) Å). The average bond length of a carbon oxygen single bond is 1.45 Å while a typical carbon oxygen double bond has a bond length of about 1.25 Å. A typical carbon nitrogen single bond has bond length of about 1.47 Å.³⁶ Comparison of the observed C-N and C-O bond lengths with typically observed bond lengths suggests that some of the C-N and C-O bonds exhibit double bond character. This can be rationalized using resonance structures (see Scheme I).^{17,37}

For the complex $\text{VO}(\text{thz})_2$, similar double bond character was observed for the C-N bonds of the thiazoline rings. However, very little double bond character, if any was observed for the C-S bonds in the thiazoline rings. Hence no resonance structures like the ones in Scheme I can be given for the thiazoline rings of the $\text{VO}(\text{thz})_2$ complex.



Scheme I

In the structure of both $\text{VO}(\text{oz})_2$ and $\text{VO}(\text{thz})_2$, the vanadium atom is displaced toward the oxo group and away from the least-square basal plane defined by the four ligating atoms, N1, N2, O2 and O4 (refer to Figures 3.5. and 3.6.). This displacement of the vanadium atom is observed in many oxovanadium(IV) complexes. The displacement of the vanadium atom was observed to be 0.57 Å in $\text{VO}(\text{oz})_2$ and 0.60 Å in $\text{VO}(\text{thz})_2$. These observed displacements are close to those commonly observed in other similar

oxovanadium(IV) complexes.^{35,38}

Ultraviolet-visible spectra of $\text{VO}(\text{ka})_2$, $\text{VO}(\text{oz})_2$, $\text{VO}(\text{thz})_2$, $\text{VO}(\text{OCH}_3)(\text{bz})_2$ and $\text{VO}(\text{OC}_2\text{H}_5)(\text{bz})_2$ were recorded in appropriate solvents. A summary of the observed absorbances for the oxovanadium(IV) complexes are listed in Chapter 2, Table 2.2.7. Oxovanadium(IV) complexes typically exhibit three d-d or ligand field bands in the UV-Visible spectra.^{14,39,40,41,42,43} These three bands, band I, band II, and band III are observed in the regions of 900 to 625 nm, 690 to 520 nm and 470 to 330 nm respectively. The extinction coefficient of the observed bands range from 5 to $100 \text{ M}^{-1}\text{cm}^{-1}$. Band III whose absorbance is of the highest energy is frequently obscured by the strong charge transfer bands in the ultraviolet region of the spectra. When band III is observable, it often appears as a shoulder on one of the charge transfer bands so that its maximum position is known with the least accuracy among the three bands.⁴⁰ Oxovanadium(IV) complexes commonly exhibit coordination numbers of 5 or 6 with observed coordination geometries of square pyramid or distorted octahedron.¹⁰ However, due to the presence of a dominant axial field, the energy level diagrams associated with each coordination geometry do not differ very much from each other.⁴² Hence, the bands of both 5-coordinate and 6-coordinate oxovanadium(IV) complexes can be assigned on the basis of the same energy level scheme.⁴²

Ballhausen and Gray have proposed a energy level diagram for $\text{VO}(\text{H}_2\text{O})_5^{2+}$.⁴¹ The orbital transformation scheme for the C_{4v} species $\text{VO}(\text{H}_2\text{O})_5^{2+}$ defines: (i) a strong σ -bond of a_1 symmetry between the $(3d_{z^2}+4s)$ hybrid on vanadium and the sp_σ oxygen hybrid; (ii) two e symmetry π -bonds lying between the vanadium d_{xz} and d_{yz} orbitals and the $2p_x$ and $2p_y$ orbitals of oxygen; (iii) formation of four σ -bonds between the sp_σ hybrids (on the equivalent water oxygens) and the vanadium $(4s-3d_{z^2})$ (a_1 symmetry), $4p_x$ and $4p_y$ (e symmetry), and $3d_{x^2-y^2}$ (b_1 symmetry) orbitals; (iv) the sixth ligand forming a σ -bond with the $4p_z$ vanadium orbital; and (v) a nonbonding b_2 symmetry $3d_{xy}$ orbital of vanadium.⁴⁰ Figure 3.6. illustrates the proposed energy level diagram.³⁸

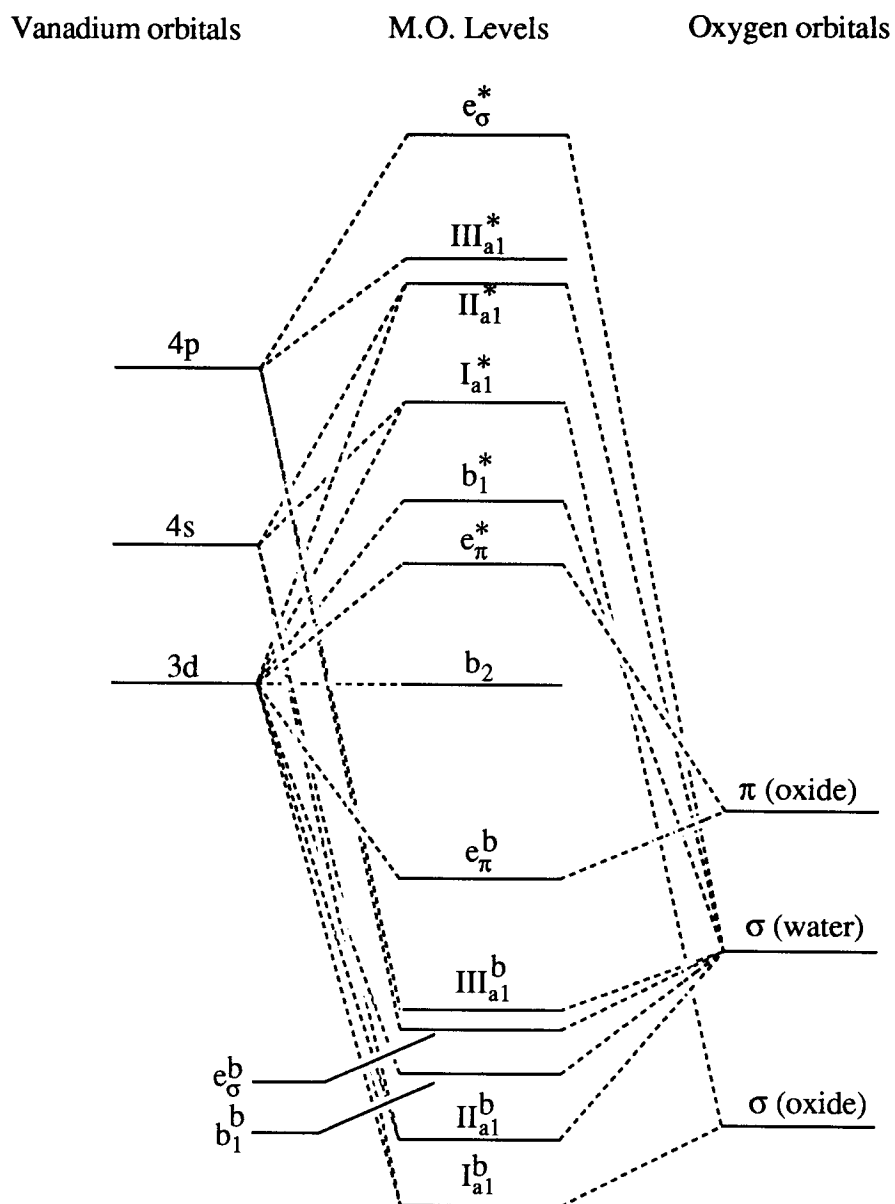


Figure 3.6. Molecular orbital scheme for $[\text{VO}(\text{H}_2\text{O})_5]^{2+}$ (C_{4v} symmetry) according to Ballhausen and Gray⁴¹

With reference to the energy level diagram in Figure 3.7., the three observed bands were assigned by Ballhausen and Gray as follows: (a) band **I**, electronic transition from b_2 to e_π^* or $2B_2$ to $2E(I)$ (b) band **II**, electronic transitions from b_2 to b_1^* or $2B_2$ to $2B_1$ (c) band **III**, electronic transitions from b_2 to Ia_1^* or $2B_2$ to $2A_1$.⁴¹ The second transition maximum yields the value of $10Dq$ directly.³⁹ The intense higher energy bands that are observed out to 200 nm are assumed to be charge transfer in origin.^{39,40,41} Even though in some cases, distortion from C_{4v} symmetry occurred (especially where LL is a bidentate ligand in common complexes of the type $VO(LL)_2$), the three observed bands were assigned in the same way as that for C_{4v} species by the comparison of the energies and intensities with the C_{4v} species.⁴¹ However, it should be noted that there is still no real agreement on the ordering of the energy levels.³⁹

In our study, the UV-Visible spectrum of the complex $VO(ka)_2$ shows only two bands in the region of 330-900 nm. The lowest energy band observed at 842 nm is assigned to the b_2 to e_π^* transition while the band observed at 612 nm is assigned to the b_2 to b_1^* transition. The band corresponding to the higher energy b_2 to Ia_1^* transition (or band **III**) is obscured by the low energy tail of the intense charge transfer band in the UV region of the spectra. In the case of $VO(oz)_2$ and $VO(thz)_2$, the higher energy band **III** which could be assigned to b_2 to Ia_1^* transition was observed as a shoulder of the charge transfer band at 409 nm and 437 nm, respectively. In addition, band **I** for these complexes was observed at approximately 595 nm, which falls slightly out of the region where band **I** is commonly observed for previously reported oxovanadium(IV) complexes.

The intensity of band **I** is commonly observed to be greater than the intensity (i.e. extinction coefficient) of band **II** for many oxovanadium(IV) complexes. For $VO(ka)_2$, band **I** is observed to have an extinction coefficient of 30 while band **II** has an extinction coefficient of 15. These observed intensities and extinction coefficients are consistent with the fact that the b_2 to e_π^* transition is partially allowed (allowed xy)⁴⁰ while the

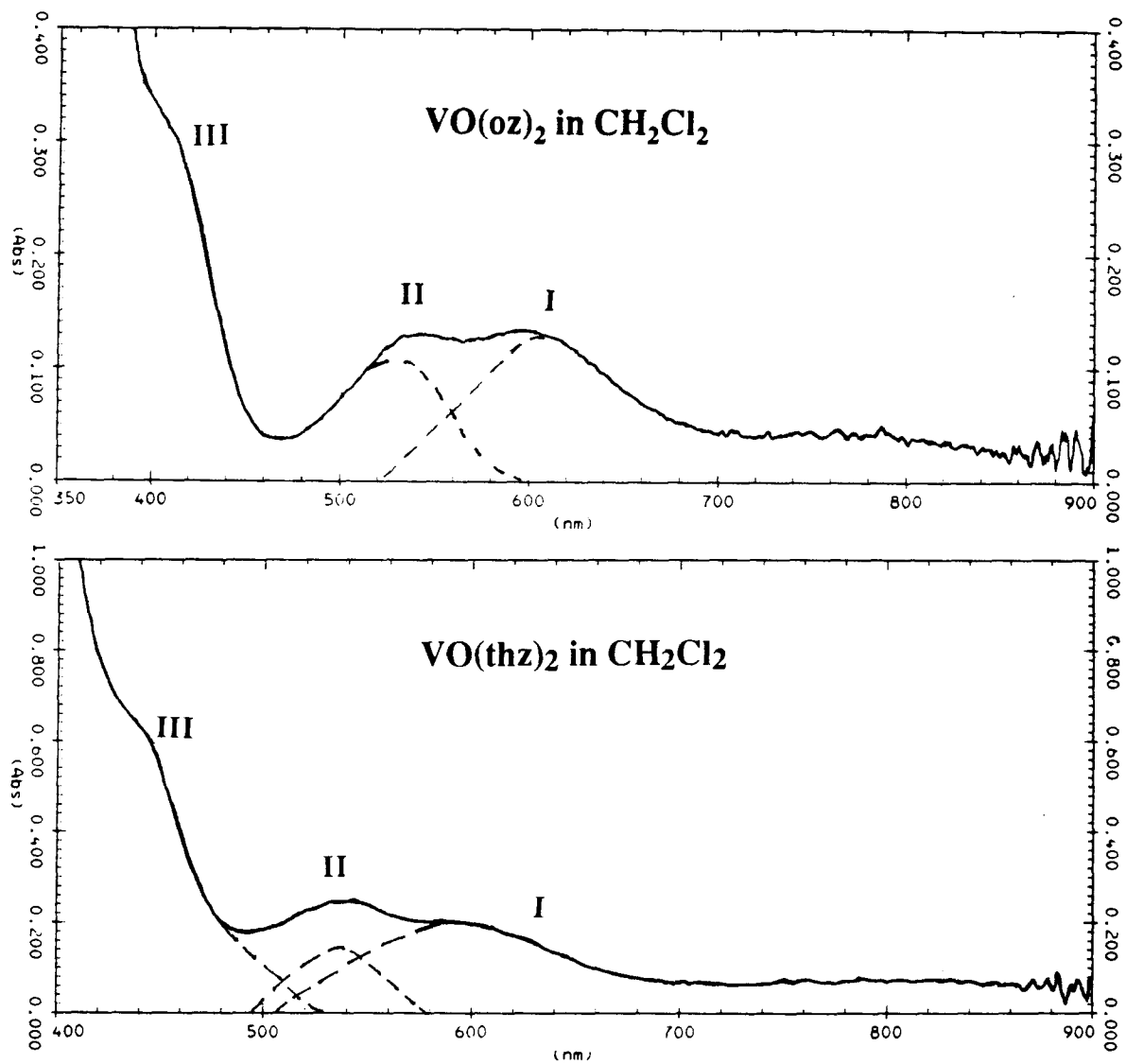


Figure 3.8. Potential “intensity stealing” effect in UV-Vis spectrophotometric study of VO(oz)_2 and VO(thz)_2 .

transitions corresponding to the other bands are totally forbidden. However, this phenomenon of band I having a greater intensity than band II is not found in $\text{VO}(\text{oz})_2$ and $\text{VO}(\text{thz})_2$. This is particularly true for $\text{VO}(\text{thz})_2$ where the intensity of band II is abnormally higher than band I. The greater intensity of band II is probably due to the "intensity stealing" effect of band II. Figure 3.8. illustrates the intensity stealing effect of band II.

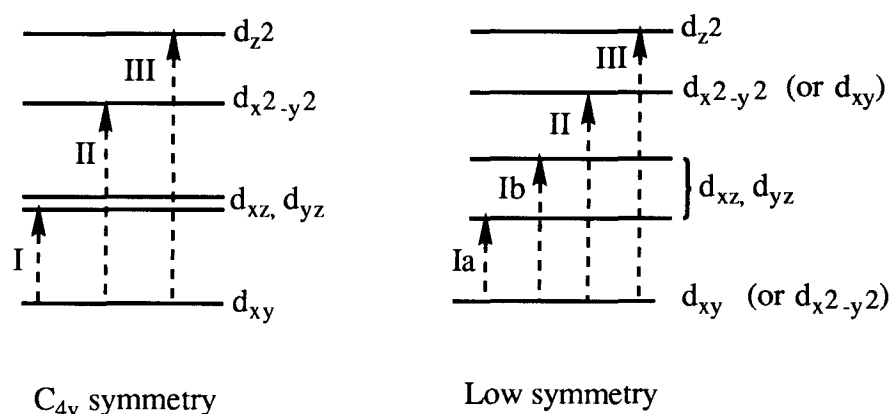


Figure 3.9. Splitting of the vanadium d levels (b_2 , e and b_1 considered mainly as V orbitals)

It should be noted that for some oxovanadium(IV) complexes, four distinct bands are observed in the UV-Visible spectra. This is attributed to a lowering of the symmetry of the complexes. A lowering of symmetry would result in the lifting of the degeneracy of the e_π^* orbital. This would change the molecular orbital diagram to that shown in Figure 3.9.¹⁴ With this lowering of symmetry, four bands are expected in the UV-Visible spectrum. Low symmetry oxovanadium(IV) complexes involving tartrate, lactate, mandelate or malate groups have UV-Visible spectra showing four well defined absorption bands in the region of 1000 to 380 nm.⁴³ For the oxovanadium(IV) complexes investigated in our study, the highest possible symmetry of the VOL_2 complex (L is a

bidentate ligand) is C_2 . The symmetry of $VO(oz)_2$ and $VO(thz)_2$, in the solid state, was shown by single crystal X-ray diffraction studies to be C_2 (refer to Figure 3.5. and 3.6.). However, the complexes studied in this thesis all showed less than four bands. It is assumed that the splitting of the e_π^* level caused by the lowering of symmetry is simply too small to be observed experimentally.⁴⁰

Vanadium(V) has a d^0 configuration and as such does not exhibit d-d transition. The two oxovanadium(V) complexes, $VO(OCH_3)(bz)_2$ and $VO(OC_2H_5)(bz)_2$ do not show d-d transitions in the UV-Vis spectra. Only high intensity ligand to metal charge transfer bands, which are allowed transitions, are observed in the UV portion of the optical spectra. UV-Visible spectra of freshly prepared solutions of $VO(bz)_2$ in methanol or ethanol show no d-d transition bands. This is because the reaction of $VO(bz)_2$ with solvent molecules (methanol or ethanol) produces $VO(OCH_3)(bz)_2$ or $VO(OC_2H_5)(bz)_2$ extremely rapidly.

In conclusion, some new oxovanadium complexes have been prepared and the relevant coordination chemistry observed in these complexes is consistent with that expected from examining the literature. Naturally-occurring ligating moieties were used to coordinate to VO^{2+} because of the potential application of their oxovanadium complexes in the treatment of diabetes. An evaluation of $VO(ka)_2$ as a potential insulin mimicking agent has been performed and preliminary data are presented in the appendix B.

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Appendix A

Table A1 Selected Crystallographic Data for VO(oz)₂ and VO(thz)₂.

complex	VO(oz) ₂	VO(thz) ₂
formula	C ₁₈ H ₁₆ N ₂ O ₅ V	C ₁₈ H ₁₆ N ₂ O ₃ S ₂ V
fw	391.28	423.40
crystal system	triclinic	orthorhombic
space group	P $\bar{1}$	Pbca
a, Å	10.408(1)	12.331(2)
b, Å	11.282(1)	26.090(2)
c, Å	7.666(1)	11.125(2)
α , deg	103.78(1)	----
β , deg	109.64(1)	----
γ , deg	84.75(1)	----
V, Å ³	823.3(2)	3579.3(9)
Z	2	8
D _{calc} , g/cm ³	1.578	1.571
T, °C	21	21
radiation (λ , Å)	Mo K α (0.71069)	Mo K α (0.71069)
μ (MoK α) cm ⁻¹	6.14	7.80
transmission factor	0.92-1.00	0.82-1.00
R	0.034	0.035
R _w	0.035	0.030

Table A2 Final atomic coordinates (fractional) and B_{eq} (\AA^2) for $\text{VO}(\text{oz})_2$.

Atom	x	y	z	B_{eq}
V(1)	0.27964(3)	0.46204(2)	0.12244(4)	2.351(8)
O(1)	0.2143(1)	0.7491(1)	0.5528(2)	3.41(4)
O(2)	0.4605(1)	0.5193(1)	0.2775(1)	2.79(3)
O(3)	0.4041(1)	0.1095(1)	-0.1073(2)	3.42(4)
O(4)	0.1376(1)	0.3577(1)	0.1060(2)	3.05(4)
O(5)	0.2300(1)	0.5241(1)	-0.0560(2)	3.16(4)
N(1)	0.2157(1)	0.5813(1)	0.3285(2)	2.62(4)
N(2)	0.3771(1)	0.3041(1)	0.0311(2)	2.55(4)
C(1)	0.2793(1)	0.6769(1)	0.4406(2)	2.50(5)
C(2)	0.0801(2)	0.6965(2)	0.5014(3)	4.18(7)
C(3)	0.0860(2)	0.5753(2)	0.3635(3)	3.45(6)
C(4)	0.4150(1)	0.7131(1)	0.4626(2)	2.52(5)
C(5)	0.5005(1)	0.6279(1)	0.3840(2)	2.45(5)
C(6)	0.6357(2)	0.6628(2)	0.4224(2)	3.12(5)
C(7)	0.6814(2)	0.7763(2)	0.5293(3)	3.84(7)
C(8)	0.5959(2)	0.8606(2)	0.6204(3)	3.80(6)
C(9)	0.4645(2)	0.8287(1)	0.5705(2)	3.27(6)
C(10)	0.3223(2)	0.1989(1)	-0.0510(2)	2.57(5)
C(11)	0.5362(2)	0.1640(2)	-0.0636(3)	3.44(6)
C(12)	0.5210(2)	0.2953(2)	0.0397(2)	2.90(5)
C(13)	0.1823(2)	0.1673(1)	-0.0884(2)	2.72(5)
C(14)	0.0972(2)	0.2502(1)	-0.0059(2)	2.60(5)
C(15)	-0.0380(2)	0.2150(2)	-0.0460(3)	3.29(6)

C(16)	-0.0859(2)	0.1052(2)	-0.1638(3)	4.28(7)
C(17)	-0.0022(2)	0.0242(2)	-0.2450(3)	4.57(7)
C(18)	0.1306(2)	0.0548(2)	-0.2070(3)	3.71(6)

Table A3. Final atomic coordinates (fractional) and B_{eq} (\AA^2) for VO(thz)₂.

Atom	x	y	z	B_{eq}
V(1)	0.44725(6)	0.35945(2)	0.40706(6)	2.89(3)
S(1)	0.53110(11)	0.47063(5)	0.71884(11)	4.95(7)
S(2)	0.27819(10)	0.22705(5)	0.19962(12)	4.57(7)
O(2)	0.3157(2)	0.39716(10)	0.4207(3)	3.6(1)
O(4)	0.4955(2)	0.30099(10)	0.4937(2)	3.5(1)
O(5)	0.5296(2)	0.38000(10)	0.3081(2)	3.9(1)
N(1)	0.5023(3)	0.40147(13)	0.5541(3)	3.2(2)
N(2)	0.3596(2)	0.30771(12)	0.3027(3)	2.9(2)
C(1)	0.4587(3)	0.44201(15)	0.6006(4)	3.1(2)
C(2)	0.6426(4)	0.4276(2)	0.6984(4)	4.9(3)
C(3)	0.6046(4)	0.3859(2)	0.6131(4)	4.3(2)
C(4)	0.3560(3)	0.46407(15)	0.5638(4)	3.0(2)
C(5)	0.2891(3)	0.4402(2)	0.4778(4)	3.0(2)
C(6)	0.1880(4)	0.4621(2)	0.4510(4)	3.5(2)
C(7)	0.1551(4)	0.5065(2)	0.5064(5)	4.4(3)
C(8)	0.2201(4)	0.5304(2)	0.5904(5)	5.1(3)
C(9)	0.3193(4)	0.5097(2)	0.6170(4)	4.1(2)
C(10)	0.3619(3)	0.2582(2)	0.3049(4)	3.1(2)
C(11)	0.2258(4)	0.2873(2)	0.1495(4)	5.0(3)

C(12)	0.2914(3)	0.3290(2)	0.2060(4)	4.0(2)
C(13)	0.4290(2)	0.22764(15)	0.3840(4)	3.1(2)
C(14)	0.4925(3)	0.2508(2)	0.4746(4)	3.1(2)
C(15)	0.5560(4)	0.2194(2)	0.5486(4)	4.3(2)
C(16)	0.5585(4)	0.1673(2)	0.5324(5)	5.2(3)
C(17)	0.4972(4)	0.1444(2)	0.4440(5)	5.2(3)
C(18)	0.4330(4)	0.1737(2)	0.3714(4)	4.4(3)

Table A4. Bond Lengths (Å) for VO(oz)₂ and VO(thz)₂ with Estimated Standard Deviations in Parentheses

VO(oz) ₂		VO(thz) ₂	
Atoms	Distance	Atoms	Distance
V(1)-O(2)	1.931(1)	V(1)-O(2)	1.903(3)
V(1)-O(4)	1.926(1)	V(1)-O(4)	1.900(3)
V(1)-O(5)	1.594(1)	V(1)-O(5)	1.591(3)
V(1)-N(1)	2.068(1)	V(1)-N(1)	2.083(3)
V(1)-N(2)	2.061(1)	V(1)-N(2)	2.083(3)
O(1)-C(1)	1.347(2)	S(1)-C(1)	1.757(4)
O(1)-C(2)	1.460(2)	S(1)-C(2)	1.790(5)
O(2)-C(5)	1.315(2)	O(2)-C(5)	1.330(4)
O(3)-C(10)	1.346(2)	S(2)-C(10)	1.761(4)
O(3)-C(11)	1.458(2)	S(2)-C(11)	1.788(5)
O(4)-C(14)	1.319(2)	O(4)-C(14)	1.328(4)
N(1)-C(1)	1.284(2)	N(1)-C(1)	1.295(5)

N(1)-C(3)	1.472(2)	N(1)-C(3)	1.479(5)
N(2)-C(10)	1.287(2)	N(2)-C(10)	1.291(4)
N(2)-C(12)	1.472(2)	N(2)-C(12)	1.474(5)
C(1)-C(4)	1.451(2)	C(1)-C(4)	1.450(5)
C(2)-C(3)	1.526(3)	C(2)-C(3)	1.518(6)
C(4)-C(5)	1.415(2)	C(4)-C(5)	1.410(5)
C(4)-C(9)	1.405(2)	C(4)-C(9)	1.404(5)
C(5)-C(6)	1.411(2)	C(5)-C(6)	1.404(5)
C(6)-C(7)	1.374(2)	C(6)-C(7)	1.372(6)
C(7)-C(8)	1.391(3)	C(7)-C(8)	1.380(6)
C(8)-C(9)	1.372(2)	C(8)-C(9)	1.370(6)
C(10)-C(13)	1.448(2)	C(10)-C(13)	1.447(5)
C(11)-C(12)	1.526(2)	C(11)-C(12)	1.495(6)
C(13)-C(14)	1.414(2)	C(13)-C(14)	1.411(5)
C(13)-C(18)	1.405(2)	C(13)-C(18)	1.417(5)
C(14)-C(15)	1.409(2)	C(14)-C(15)	1.400(5)
C(15)-C(16)	1.370(2)	C(15)-C(16)	1.373(6)
C(16)-C(17)	1.389(3)	C(16)-C(17)	1.377(6)
C(17)-C(18)	1.372(3)	C(17)-C(18)	1.365(6)

Table A5. Bond Angles (deg) for VO(oz)₂ and VO(thz)₂ with Estimated Standard Deviations in Parentheses.

VO(oz) ₂		VO(thz) ₂	
Atoms	Angle	Atoms	Angle

O(2)-V(1)-O(5)	108.41(5)	O(2)-V(1)-O(5)	115.2(1)
O(4)-V(1)-O(5)	108.81(5)	O(4)-V(1)-O(5)	114.9(1)
O(5)-V(1)-N(1)	104.73(6)	O(5)-V(1)-N(1)	99.1(1)
O(5)-V(1)-N(2)	103.79(5)	O(5)-V(1)-N(2)	99.4(1)
O(2)-V(1)-N(1)	85.28(5)	O(2)-V(1)-N(1)	86.8(1)
O(2)-V(1)-N(2)	85.25(5)	O(2)-V(1)-N(2)	86.4(1)
O(4)-V(1)-N(1)	85.23(5)	O(4)-V(1)-N(1)	85.5(1)
O(4)-V(1)-N(2)	86.21(5)	O(4)-V(1)-N(2)	85.7(1)
O(2)-V(1)-O(4)	142.79(5)	O(2)-V(1)-O(4)	129.9(1)
N(1)-V(1)-N(2)	151.47(5)	N(1)-V(1)-N(2)	161.4(1)
C(1)-O(1)-C(2)	106.7(1)	C(1)-S(1)-C(2)	91.6(2)
V(1)-O(2)-C(5)	129.80(9)	V(1)-O(2)-C(5)	133.2(3)
C(10)-O(3)-C(11)	107.0(1)	C(10)-S(2)-C(11)	90.7(2)
V(1)-O(4)-C(14)	130.4(1)	V(1)-O(4)-C(14)	134.6(3)
V(1)-N(1)-C(1)	125.6(1)	V(1)-N(1)-C(1)	127.5
V(1)-N(1)-C(3)	125.9(1)	V(1)-N(1)-C(3)	118.8(3)
C(1)-N(1)-C(3)	108.4(1)	C(1)-N(1)-C(3)	113.7(4)
V(1)-N(2)-C(10)	126.4(1)	V(1)-N(2)-C(10)	128.7(3)
V(1)-N(2)-C(12)	125.0(1)	V(1)-N(2)-C(12)	117.3(3)
C(10)-N(2)-C(12)	108.6(1)	C(10)-N(2)-C(12)	113.9(4)
O(1)-C(1)-N(1)	116.4(1)	S(1)-C(1)-N(1)	115.8(3)
O(1)-C(1)-C(4)	116.9(1)	S(1)-C(1)-C(4)	119.1(3)
N(1)-C(1)-C(4)	126.7(1)	N(1)-C(1)-C(4)	125.1(4)
O(1)-C(2)-C(3)	104.3(1)	S(1)-C(2)-C(3)	107.0(3)
N(1)-C(3)-C(2)	103.4(1)	N(1)-C(3)-C(2)	110.1(4)
C(1)-C(4)-C(5)	119.3(1)	C(1)-C(4)-C(5)	121.8(4)

C(1)-C(4)-C(9)	120.4(1)	C(1)-C(4)-C(9)	120.0(4)
C(5)-C(4)-C(9)	120.2(1)	C(5)-C(4)-C(9)	118.2(4)
O(2)-C(5)-C(4)	123.7(1)	O(2)-C(5)-C(4)	123.6(4)
O(2)-C(5)-C(6)	118.7(1)	O(2)-C(5)-C(6)	117.6(4)
C(4)-C(5)-C(6)	117.6(1)	C(4)-C(5)-C(6)	118.9(4)
C(5)-C(6)-C(7)	120.9(2)	C(5)-C(6)-C(7)	120.8(4)
C(6)-C(7)-C(8)	121.2(2)	C(6)-C(7)-C(8)	120.9(4)
C(7)-C(8)-C(9)	119.4(2)	C(7)-C(8)-C(9)	119.1(4)
C(4)-C(9)-C(8)	120.7(2)	C(4)-C(9)-C(8)	122.1(4)
O(3)-C(10)-N(2)	116.2(1)	S(2)-C(10)-N(2)	115.8(3)
O(3)-C(10)-C(13)	117.0(1)	S(2)-C(10)-C(13)	119.0(3)
N(2)-C(10)-C(13)	126.7(1)	N(2)-C(10)-C(13)	125.2(4)
O(3)-C(11)-C(12)	104.4(1)	S(2)-C(11)-C(12)	108.3(3)
N(2)-C(12)-C(11)	103.5(1)	N(2)-C(12)-C(11)	109.9(4)
C(10)-C(13)-C(14)	119.9(1)	C(10)-C(13)-C(14)	121.0(4)
C(10)-C(13)-C(18)	120.2(1)	C(10)-C(13)-C(18)	120.5(4)
C(14)-C(13)-C(18)	119.9(1)	C(14)-C(13)-C(18)	118.5(4)
O(4)-C(14)-C(13)	123.7(1)	O(4)-C(14)-C(13)	123.5(4)
O(4)-C(14)-C(15)	118.6(1)	O(4)-C(14)-C(15)	117.7(4)
C(13)-C(14)-C(15)	117.8(1)	C(13)-C(14)-C(15)	118.7(4)
C(14)-C(15)-C(16)	121.0(2)	C(14)-C(15)-C(16)	120.9(5)
C(15)-C(16)-C(17)	121.1(2)	C(15)-C(16)-C(17)	120.8(5)
C(16)-C(17)-C(18)	119.4(2)	C(16)-C(17)-C(18)	119.9(4)
C(13)-C(18)-C(17)	120.8(2)	C(13)-C(18)-C(17)	121.2(4)

Appendix B

Millions of people suffer from a mammalian condition known as diabetes. People suffering from diabetes have an abnormally high level of glucose in their blood plasma.¹ Diabetes can be life-threatening and can lead to a number of medical complications such as atherosclerosis, microangiopathy, kidney disorders, renal failure, cardiac disease, diabetic retinopathy and other ocular disorders including blindness.² There are a variety of ways to control diabetes but the primary method is the daily administering of insulin. Insulin is a hormone that is normally produced naturally in the pancreas and is primarily responsible for signaling the utilization or storage of basic nutrients. In general, insulin activates the enzymes that are involved in intracellular utilization and storage of basic nutrients such as glucose, amino acids and fatty acids.³ It is also involved in the inhibition of processes which breakdown glycogens, fats and proteins. In diabetic individuals, there is insufficient insulin present in the body or the body is tolerant to insulin, resulting in the body requiring an abnormally high dose of insulin to cause the desired effect. The use of insulin in treating diabetics involves the daily injection of the hormone. Insulin must be injected since it is not orally active and is known to decompose before or during passage through the gastrointestinal tract.

In 1980, it was discovered that vanadate simulated the action of insulin in glucose oxidation in rat adipocytes.^{4,5} The years following this discovery revealed that vanadate was able to mimic nearly all or most of the documented actions of insulin. Interest in the insulin mimicking action of vanadate rose even higher when McNeill et al reported that vanadate, administered to diabetic rats through drinking water caused a decrease in elevated blood glucose.⁶ Unfortunately, vanadate has the disadvantage of being poorly absorbed from the gastrointestinal tract. An even greater disadvantage of vanadate is that it must be administered at near toxic levels before any insulin mimicking effects are observed. Nevertheless, the work by McNeill et al showed that it may be possible to

utilize orally active vanadium compounds as a substitute for insulin. There has been interest in the insulin-mimetic effects of both vanadate and vanadyl since Sakurai et. al. showed that vanadate is reduced in vivo to vanadyl.⁷

Recently, our group in collaboration with Dr. McNeill of the Faculty of Pharmaceutical Sciences at UBC has been studying the feasibility of using bis(maltolato)oxovanadium(IV) as an insulin mimicking agent.² As a continuation of this work, the feasibility of bis(kojato)oxovanadium(IV) as an insulin mimic was also investigated.

Bis(kojato)oxovanadium(IV), VO(ka)₂, was prepared according to the procedure described in Chapter 2. Initial investigations into the feasibility of using VO(ka)₂ as insulin mimicking agent involved laboratory rats that were made diabetic by the injection of streptozotocin (STZ). VO(ka)₂ was administered by intraperitoneal injection as a suspension in 1% methyl cellulose or orally administered by gavage. Of the diabetic rats which were given 0.063 mmol/kg of VO(ka)₂ by injection, 60% showed decrease blood glucose levels within 24 hours. Of the diabetic rats which were given 0.55 mmol/kg of VO(ka)₂ by gavage, 57% showed reduced blood glucose level within 24 hours. Similar experiments were also carried out using bis(maltolato)oxovanadium(IV), VO(ma)₂. In experiments involving the administering of VO(ma)₂ by injection and by oral gavage, 50% of the rats showed reduced blood glucose level within 24 hours. A higher percentage of rats responding to the oxovanadium compound was observed with VO(ka)₂ compared to VO(ma)₂ in both cases when the oxovanadium compound was administered either by injection or by oral gavage. The results of the studies using VO(ka)₂ and VO(ma)₂ are summarized in Table B1.

A drinking water pilot study with VO(ka)₂ was also performed on 10 diabetic rats. Administration of VO(ka)₂ was done using aqueous solutions in the concentration range of 1.43 to 3.58 mM. The rats received doses in the range of 0.41 to 0.91 mmol/kg. On average, a reduced blood glucose level was observed in the diabetic rats. This is

Table B1 Comparison of the plasma glucose levels (mmol/L) between the acute time course experiments for bis(maltolato)oxovanadium(IV) (n=8) and bis(kojato)oxovanadium(IV) (n=10)

TIME (Hrs)	Bis(maltolato)oxovanadium(IV)				Bis(kojato)oxovanadium(IV)			
	I.P. Injection		Oral Gavage		I.P. Injection		Oral Gavage	
	(0.063 mmol/kg)		(0.55 mmol/kg)		(0.063 mmol/kg)		(0.55 mmol/kg)	
	DTR	DTN	DTR	DTN	DTR	DTN	DTR	DTN
	(50%)	(50%)	(50%)	(50%)	(60%)	(40%)	(57%)	(43%)
0	17.51	19.42	18.09	19.31	17.94	20.86	15.75	23.08
	±0.8	±0.15	±0.72	±0.35	±0.41	±0.28	±0.55	±1.27
1	14.77	18.82	14.55	18.05	14.75	18.55	12.5	21.18
	±2.0	±0.8	±1.96	±0.46	±0.44	±0.42	±1.46	±1.45
2	12.65	18.51	13.13	17.57	10.17	16.62	10.1	21.51
	±2.33	±0.79	±2.04	±0.5	±0.47	±0.65	±0.99	±1.72
4	10.6	17.94	11.68	16.92	9.26	17.37	7.96	20.57
	±2.39	±0.85	±2.07	±0.35	±0.32	±0.23	±0.26	±1.07
6	10.28	18.08	9.47	16.43	8.73	16.62	6.6	18.2
	±1.76	±0.48	±2.58	±0.43	±0.17	±0.35	±0.35	±0.89
8	9.08	17.77	9.27	15.02	7.4	15.49	6.87	19.06
	±1.06	±0.59	±2.27	±1.13	±0.12	±0.65	±0.33	±0.96
12	9.38	19.07	7.01	17.17	10.37	18.24	6.01	18.81
	±0.96	±0.37	±0.57	±0.6	±0.46	±0.45	±0.25	±0.33
24	7.15	19.01	6.31	18.07	13.28	18.77	6.74	25.0
	±1.51	±0.21	±0.57	±0.74	±0.83	±0.49	±0.05	±0.4

DTR-Diabetic Treated Responders

DTN-Diabetic Treated Non-responder

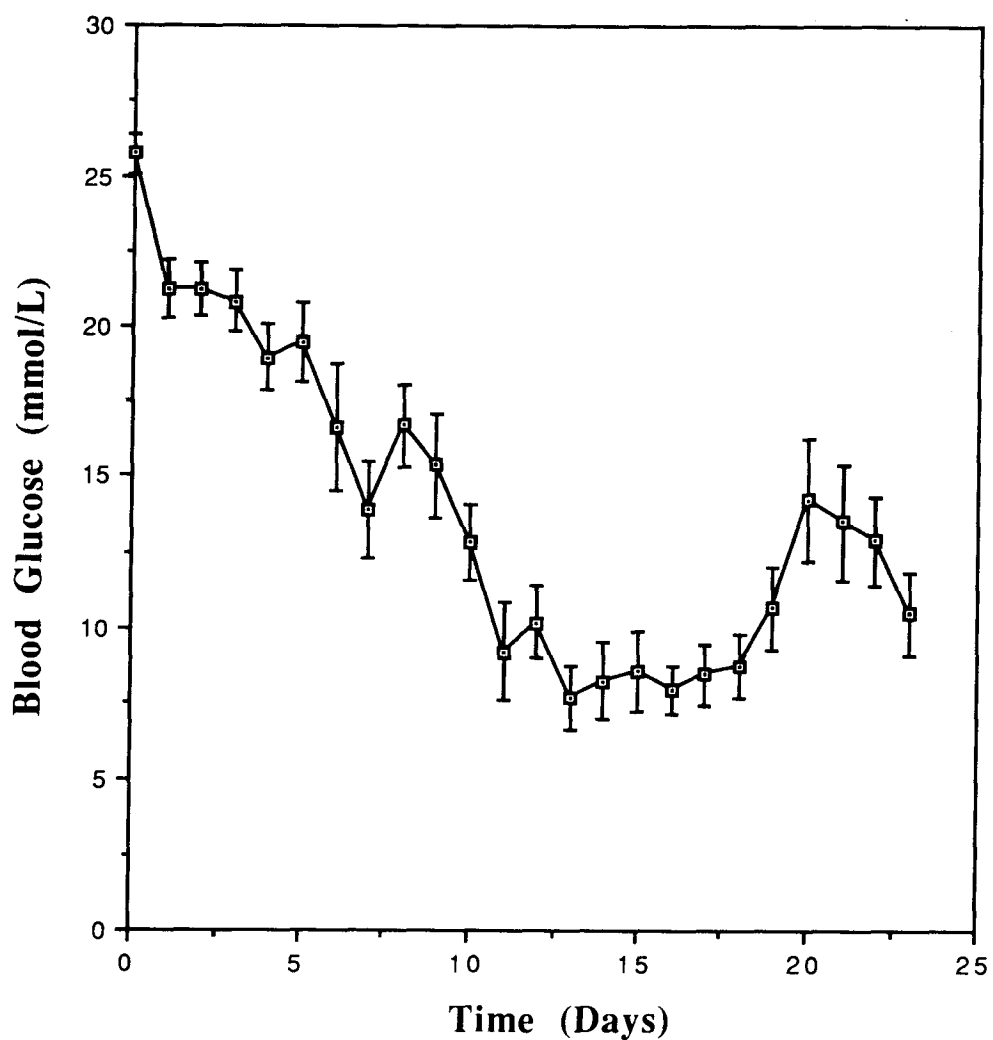


Figure B1. Daily average blood glucose levels for the ten STZ-diabetic rats following chronic administration of $\text{VO}(\text{ka})_2$ in the drinking water. Time 0 is the day of treatment started.

illustrated in Figure B1.

Initial studies into the feasibility of VO(ka)₂ as an orally active insulin mimicking agent have given promising results. It appears that VO(ka)₂ gives the same, if not, better performance than VO(ma)₂ in reducing blood glucose level in diabetic rats. The results from these preliminary experiments justify more in depth studies into the possibility of using VO(ka)₂ as an insulin mimicking agent.

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