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**Complexation of Bis(acetylacetonate)oxovanadium(IV) with
D-penicillamine at neutral medium**

R.Hakimelahi^{1,2}, M.A. Seyed Sadjadi¹, H.Aghaie^{1*} and M.Aghaie³

1. Department of Chemistry, Science and Research Campus Islamic Azad University, Tehran, Iran

2. Department of Chemistry, Jahrom Branch, Islamic Azad University, Jahrom, Iran

3. Faculty of Chemistry, North Tehran Branch, Islamic Azad University, Tehran, Iran

ABSTRACT

Neutral bidentate N-O type complex of VO(II) has been synthesized through condensation of D-penicillamine, (D-H₂Pen), with Bis(acetylacetonate)-oxovanadium(IV), [VO(acac)₂], at neutral medium. The established Schiff base (NO type) complex was characterized on the basis of IR and mass spectroscopy techniques. Besides, D-H₂Pen binding behavior to [VO(acac)₂] has been studied in thermodynamic viewpoint using UV/Vis spectroscopy. The measurements were done in 5mM phosphate buffer, pH 7.0 and various temperatures. The optical absorption spectra of [VO(acac)₂] were analyzed in order to obtain binding constants and stoichiometries using SQUAD software. The results show that the best fitting corresponds to 1:2 metal to ligand, complex between [VO(acac)₂] and D-H₂Pen. The estimation of binding constant at various temperatures enabled us to calculate all of the thermodynamic parameters of binding using Van't Hoff equation.

Keywords: Penicillamine; Bis (acetylacetonate) oxovanadium (IV) ; Schiff base; SQUAD; Thermodynamic parameters.

* . Corresponding author: hn_Aghaie@yahoo.com

INTRODUCTION

Vanadium coordination chemistry and biochemistry have attracted increasing interest during the last few years[1]. This is mainly due to the discovery that vanadium is an essential element in biological systems. Vanadium, participates in enzymatic reactions such as halogenation of a variety of organic substrates by haloperoxidases[2], and nitrogen fixation by vanadium nitrogenases[3]. The use of (oxo)vanadium complexes in oxidation and oxo transfer catalysis[4] has been noted. The potential medicinal application such as the treatment of diabetes type I (insulin deficiency) and II (insulin resistance)[5] has further stimulated research into vanadium coordination compounds.

Many vanadium compounds have been synthesized, structurally characterized and tested for insulin mimetic activity, some of them have been found to enhance insulin action when administered orally such as Bis(maltolato)oxovanadium(IV) (BMOV)[6]. Studies to identify the target enzymes of insulin mimetic vanadium compounds ordinarily encounter a rich chemistry of multiple oxidation states, possible redox processes in the cell, and variable stability of coordination geometry and ligand composition. For vanadium to be useful as an orally available insulin mimetic agent (IMA) it must be able to cross biological membranes, both for the initial absorption process and for intracellular uptake for vanadium in a complex the metallocomplex must have no positive or negative charge, and a fair degree of resistance to hydrolysis. A high synthetic yield and known non-toxic metabolic products are advantageous. The lipophilicity of the complex must be balanced with its hydrophilicity. Moreover, the metal-ligand complex should possess adequate thermodynamic stability[7]. Several types of vanadyl complexes with different coordination modes such as $\text{VO}(\text{O}_4)$, $\text{VO}(\text{N}_4)$, $\text{VO}(\text{S}_4)$, $\text{VO}(\text{O}_2\text{N}_2)$, $\text{VO}(\text{S}_2\text{N}_2)$ and $\text{VO}(\text{O}_2\text{S}_2)$ have been developed [8]. In recent years, various vanadium complexes of dianionic schiff bases have been proposed for potential use as insulin mimetic agents. These ligands are of particular interest because they

provide coordination environments which efficiently stabilize different oxidation states of vanadium, while still providing active sites capable of binding other molecules[9]. These compounds also show a great catalytic reactivity towards organic substances, in particular the oxidation of organic substrates such as alkenes and sulfides. When chiral schiff bases are used as ligands, vanadyl complexes can effectively catalyze asymmetric oxidation of sulfides, disulfides and dithioacetates [10]. A $\text{VO}(\text{ONS})_2$ vanadium complex has been synthesized by using an indirect method[11]. We synthesized a schiff base vanadyl complex with direct reaction of $\text{VO}(\text{acac})_2$ and D-penicillamine.

EXPERIMENTAL

Materials

Vanadyl(IV)-acetylacetonate, $\text{VO}(\text{acac})_2$, (Aldrich) and D-penicillamine, $\text{C}_5\text{H}_{11}\text{NO}_2\text{S}$, (Fluka) were used as supplied. Sodium hydrophosphate, $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$, and potassium dihydrophosphate, KH_2PO_4 , were obtained from Merck and were used for making buffer pH 7.0. All other chemicals used were of analytical reagent grade.

Preparation of vanadyl schiff base complex [VOL₂]

$[\text{VO}(\text{acac})_2]$ (0.66 g, 2.5 mmol) was suspended in a mixture of dry dichloromethane (5 mL) and methanol (10 mL) and D-penicillamine (0.75 g, 5 mmol) was added. The mixture was stirred at room temperature for 4 h, upon standing the mixture was filtered, the solvent was evaporated and residue washed with acetone several times and dried in vacuum. (yield 80%, m.p 192°C)

Absorption spectra

The absorption spectra were recorded on Shimadzu 1650 spectrophotometer using 1 cm quartz cuvettes, with thermostat cell compartment that control the temperature around the cell. Spectrophotometer titrations were carried out by adding 50 μl aliquots portions of an 0.145 M D-penicillamine directly into a quartz cell containing 0.015 M $\text{VO}(\text{acac})_2$. The titration experiment was continued until the absorbance of the $\text{VO}(\text{acac})_2$ solution in the UV-Vis range

remained constant. The spectra were recorded with in range of 500 to 900 nm. The measurements were performed at 5mM phosphate buffer pH 7.0 with ionic strength 0.1 M (KCl) and 6 different temperature (20,25,30,35,40, and 45°C). At the same condition, the absorption spectra of vanadyl sulphate solution were recorded and titration with D-penicillamine has no change on the its absorbance spectra.

RESULTS AND DISCUSSION

Preparation of vanadyl schiff base complex

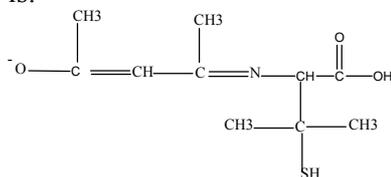
The reaction of $[\text{VO}(\text{acac})_2]$ with D-penicillamine (Scheme 1) yields green $[\text{VOL}_2]$. As confirmed by spectral data vanadyl ion is coordinated by prepared schiff base from reaction of acac^- and D- H_2Pen , through one oxygen and one nitrogen atom.

The IR data are in agreement with vanadyl schiff base (N-O) complex. eg. The single strong absorption about 966 cm^{-1} belongs to $\text{V}=\text{O}$, The broad absorption around $2600 - 3600\text{ cm}^{-1}$ due to $\nu(\text{O}-\text{H})$ belongs to carboxylic acid. The $\nu(\text{C}=\text{O})$ band appears at 1651 cm^{-1} and C-O stretching is about 1280 cm^{-1} . The characteristic $\nu(\text{C}=\text{N})$ mode appears at 1581 cm^{-1} , a shift to a lower wave number has took place because of the resonance of C=N.

The mass spectroscopy (m/z : 166, 129, 100, 85, 45, 44, 43) also confirms suggested structure of the complex (Scheme 2) formed according to the following equation (eq. 1),



That L is:



Thermodynamic studies

a. Formation constants

The value of Absorbance of λ_{max} and concentration range (0.01M-0.025M) indicates that the absorbance obeys Beer's law in the range of 500-900 nm. The general feature of $\text{VO}(\text{acac})_2$ spectra at various D- H_2Pen concentrations, was shown in Figure 1. In

order to analyze the spectral data of $\text{VO}(\text{acac})_2$ at various concentrations of D- H_2Pen in titration experiments, 50 wavelengths showing suitable absorbance variations upon addition of D- H_2Pen were selected from spectrum of $\text{VO}(\text{acac})_2$. The values of absorbance of these selected wavelengths at various D- H_2Pen concentration were analyzed in order to calculate equilibrium formation constants using SQUAD software. This program is designed to calculate the best values for the stability constants of the proposed equilibrium model by employing a non-linear least square approach. This program is completely general in scope, having the capability to refine stability constants for the general complex $\text{M}_m\text{M}'_l\text{H}_j\text{L}_n\text{L}'_q$, where $m, l, n, q \geq 0$ and J is positive for protons, negative (for hydroxyl ions) or zero. The algorithm employed in SQUAD program. Our input data for analysis of $\text{VO}(\text{acac})_2$ -D- H_2Pen system were absorbance at 50 different wavelength of 15 $\text{VO}(\text{acac})_2$ spectra. These 15 spectra correspond to 15 various concentrations of D- H_2Pen . The outputs are the logarithm of equilibrium formation constant, $\log k_{ij}$, for formation of $[\text{VOL}_2]$ (eq. 2) that L is a two functional schiff base (N-O donor) ligand as shown in eq. 1

$$K_{ij} = \frac{[\text{VOL}_2]}{[\text{VO}(\text{acac})_2][\text{D-H}_2\text{Pen}]} \quad (2)$$

The program also calculates the values of uncertainty in $\log k_{ij}$. The results show that the best fitting corresponds to 2 : 1 complex model at all studied temperatures with sum of squares of reduced error between 10^{-2} - 10^{-3} . The estimated equilibrium constants for the formation of 2 : 1 ligand to metal ratio between D- H_2Pen and $\text{VO}(\text{acac})_2$ at various temperatures are listed in Table 1.

b. Thermodynamic constants

The equilibrium of $\text{VO}(\text{acac})_2$:D- H_2Pen can be conveniently characterized by three familiar thermodynamic parameters: standard Gibbs free energy, ΔG° , enthalpy, ΔH° , and entropy, ΔS° , changes. The ΔG° can be calculated from equilibrium constant, K , of the reaction using the familiar relationship, $\Delta G^\circ = -RT \ln K$ in which R and T referring to the gas constant and the absolute temperature, respectively. If

heat capacity change of reaction is negligible, the van't Hoff equation(3) gives a linear plot of $\ln K$ versus $1/T$. The ΔH° can be calculated from the slope, $\Delta H^\circ/R$, and the ΔS° from the intercept, $\Delta S^\circ/R$ from eq.4.

$$\frac{d \ln K}{d(1/T)} = \frac{-\Delta H^\circ}{R} \quad (3)$$

$$\Delta S^\circ = \frac{(\Delta H^\circ - \Delta G^\circ)}{T} \quad (4)$$

The van't's Hoff plot for binding of $\text{VO}(\text{acac})_2$ to D- H_2Pen in the phosphate buffer is shown in Figure 2 and their calculated thermodynamic parameters are listed in Table 1.

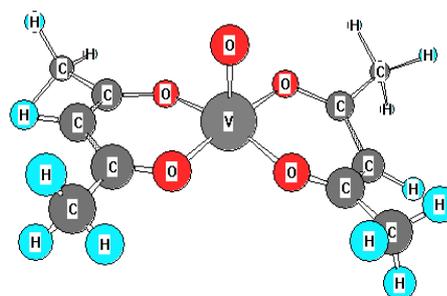
CONCLUSION

D-penicillamine is potentially tridentate ligand, but the pK_a for the $-\text{COOH}$, NH_3 and $\text{S}-\text{H}$ groups are 1.99-2.00, 8.0 and 10.6 respectively, so $\text{S}-\text{H}$ can't release H at $\text{pH}=7.00$ and the coordination of S is not possible[12]. $[\text{VO}(\text{acac})_2]$ is a coordination compound with four O-donor atoms, (as β -diketonate), vanadium atom has square pyramidal coordination with one terminal oxygen atom and four oxygen atoms from the ligand molecule. D- H_2Pen converts $[\text{VO}(\text{acac})_2]$ to a vanadyl schiff base (N-O) complex, because imino nitrogen atoms are often suitable donor atoms for the coordination of transition metal ions and many schiff base ligands have been used for the synthesis of vanadium complexes. In spite of spectral techniques, two other points, are in good agreement with the schiff base complex formation:

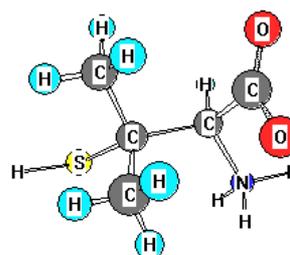
1. There is no reaction between vanadyl sulphate (VOSO_4) and D- H_2Pen at $\text{pH}=7.00$ that confirms the participation of acac^- in the reaction. (experimental part)
2. Exothermic feature of the reaction of $[\text{VOL}_2]$ formation, due to decreasing of entropy through converting two molecules to one molecule.

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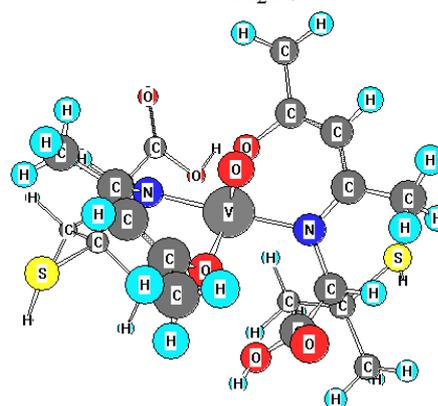


VO(acac)₂



D-H₂Pen

Scheme 1. Structure of $\text{VO}(\text{acac})_2$ and D- H_2Pen



Scheme 2. Vanadyl Schiff Base Complex $[\text{VOL}_2]$

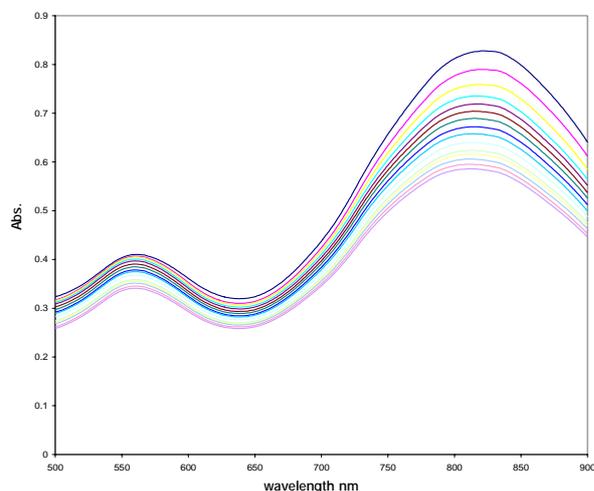


Figure 1. Absorption spectra of $\text{VO}(\text{acac})_2$ upon titration with D- H_2Pen in phosphate buffer, pH 7.0 and $I = 0.1 \text{ mol dm}^{-3}$ (KCl) at 25°C .

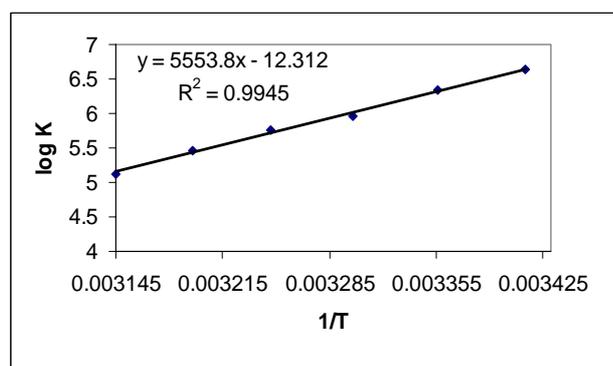


Figure 2. The Van't Hoff plot for binding of $\text{VO}(\text{acac})_2$ to D- H_2Pen in 5 mM phosphate buffer, pH 7.00 and $I = 0.1 \text{ mol dm}^{-3}$ (KCl) at various temperatures

$t/^\circ\text{C}$	$(K \pm \Delta K) \times 10^{-5}$	$\Delta G^\circ + \Delta \Delta G^\circ \text{ kJmol}^{-1}$	$\Delta H^\circ + \Delta \Delta H^\circ \text{ kJmol}^{-1}$	$\Delta S^\circ + \Delta \Delta S^\circ \text{ Jmol}^{-1} \text{K}^{-1}$
20	43.652 ± 0.000023	-37.251 ± 2.020	-106.339 ± 3.943	-235.795 ± 0.104
25	22.387 ± 0.000021	-36.232 ± 1.826	-106.339 ± 3.943	-235.258 ± 0.104
30	8.912 ± 0.000017	-34.519 ± 1.392	-106.339 ± 3.943	-237.030 ± 0.104
35	5.888 ± 0.000018	-34.027 ± 1.651	-106.339 ± 3.943	-234.779 ± 0.104
40	2.818 ± 0.000019	-32.662 ± 1.678	-106.339 ± 3.943	-235.390 ± 0.104
45	1.349 ± 0.000019	-31.235 ± 1.644	-106.339 ± 3.943	-236.176 ± 0.104

Table 1: Thermodynamic parameters for binding of $[\text{VO}(\text{acac})_2]$ to D- H_2Pen in 5 mM phosphate buffer, pH 7.00 and $I = 0.1 \text{ mol dm}^{-3}$ (KCl) at various temperatures.

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