

Binary Complexes of Oxovanadium (IV) with Vitamin B₆ Compounds and Glycinehydroxamate

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Abstract: Several oxovanadium (IV) complexes of pyridoxamine (PM), pyridoxol (P), pyridoxal (PL), and glycinehydroxamate (GX) were obtained as a result of potentiometric data analysis using SUPERQUAD at I = 0.15 M NaCl and T = 25°C. Protonated, unprotonated and hydroxospecies were detected in solutions. No polymeric species of oxovanadium(IV) were found under the experimental conditions used. Differential pulse polarography (DPP) was used to study the reduction properties of VO²⁺ complex species. Electronic spectra of the systems were discussed. Structures of some complex species of the vanadyl ions were suggested based on the knowledge of the ligating atoms provided by the ligands as well as the assumption that the metal ion can acquire at least an octahedral geometry. The uptake of these species in biological systems was also discussed.

INTRODUCTION

Vanadium is an essential trace element for different organisms. Our body contains about 23 mg of vanadium distributed in many parts of the body and some of it is stored in fat tissues [1]. Many reports reveal that different vanadium compounds reduce cholesterol levels in humans [2]. These compounds may also help in treating atherosclerosis and heart disease [3]. Other reports have shown that some vanadium compounds exhibit antitumoral effect [4,5]. It has also been found that vanadium compounds reduce the growth of human prostate cancer cells in tissue cultures, and also lower the bone and liver cancer in animals [3]. One of the most important physiological response of vanadium is its insulin-mimetic property [6-9]. Vanadium compounds enhance glucose transport and oxidation. They also increase glycogen synthesis in liver and inhibit gluconeogenesis [10].

It is also known that vanadium is required as an essential cofactor in certain haloperoxidases and nitrogenases of some red and brown algae [11]. On the other hand, vanadate compounds even at low concentration, inhibit certain enzymes such as ion transport ATP-ase, phosphatase and ribonuclease [12]. Although the uptake of vanadium in humans is about 10-60 µg/day, yet its essentiality as an ultratrace element has not been proven [13].

To avoid complexity of biochemical processes, chemists usually deal with model systems in order to understand the behaviour of chemical species in solutions. These models allow chemists to establish a relationship between structural, equilibrium, and kinetic features of well defined chemical systems and to apply the results to a more complicated biological systems.

Most of vanadium compounds that have insulin-mimetic properties have vanadium in the oxidation state (IV). Examples of these are: vanadyle sulfate [6], bis(pyrrrolidine-N-carbodithioato)oxovanadium(IV) [14], bis(cysteine methylester)-oxovanadium(IV), [15], bis(acetylacetonato)oxovanadium(IV) [16], bis-(picolinato)oxovanadium(IV), [5]. Although clinical tests of oral administration of vanadate compounds reduces blood sugar, yet this process is associated with toxic symptoms such as weight loss, poor appetite, vomiting and diarrhea. Continuous effort is devoted to prepare vanadium compounds of high potency for blood sugar and less toxicity [17]. Although the mechanism that describes the role of vanadium compounds as therapeutic agents in reducing blood sugar is not clear, yet its inhibiting ability on the protein tyrosine phosphatases can not be neglected [18].

The main goal of this investigation is to understand the chemical properties and behaviour of oxovanadium(IV) complexes involving low molecular weight biological ligands in solutions and to apply such knowledge in future to relevant biological systems. The selected ligands were vitamin B₆ compounds and glycinehydroxamate which have no reported toxic characters compared to other used ligands.

EXPERIMENTAL

Materials

Reagent grade glycinehydroxamate, pyridoxamine dihydrochloride, pyridoxol hydrochloride, and pyridoxal hydrochloride were Sigma chemicals (>98%). They were used without further purification. Highly pure VOSO₄ (Aldrich) was used in this work.

Preparation of Solutions

A stock solution of VO²⁺ (0.02M) and glycinehydroxamate(0.02M) were prepared in identical concentration of

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HCl. The stock solutions of the vitamin B₆ ligands were freshly prepared before titrations. The stock solutions of the ligands were stored at ~4 °C. The stock solution of VO²⁺ was standardized by complexometric EDTA titration using CuY-PAN or dithizone as an indicator. The appropriate concentration of the ligands and metal ions (1.0 – 3.0) × 10⁻³ M were prepared, keeping the ionic strength of solution constant at *I* = 0.15 M NaCl in a 25.0 ml measuring flasks.

The determination of binary formation constants of vanadium metal ion with vitamin B₆ compounds, pyridoxamine (PM), pyridoxol (P), and pyridoxal (PL), and glycinehydroxamate (GX) was achieved by potentiometric titrimetry.

Potentiometric titrations were carried out by Metrohm Titrator, model 670 Titroprocessor, equipped with Metrohm glass and calomel electrodes. The pH meter was calibrated by three standard buffers (4.00, 7.00, 10.00) as well as by titrating standard HCl solution (0.10 M) against standard NaOH, carbonate free (0.097 M) at *I* = 0.15 M NaCl and at *T* = (25 ± 0.01)°C. The calculated pH values were different from the measured values by only ~ 0.016 pH unit. This was attributed to the glass junction-potential and the activity coefficient of the H⁺ ions.

The prepared solutions of different systems were transferred to a titration cell thermostated at (25 ± 0.01)°C by using Julabo circulator. Highly purified nitrogen gas is purged through the titrated solution before and during titration. Titration with 0.097 M NaOH carbonate free at ionic strength of 0.15 M NaCl was done till pH ~11. Although the equilibration time was found to be less than 5 seconds yet the pH readings were taken after 40 seconds by adjusting the titrator time to a 40 s time interval after each addition of the titrant. The data is then collected by an online personal computer.

Spectrophotometric Analysis A Cary 500 spectrophotometer was used to collect the spectral data for GX-V(IV), PM-V(IV), PL-V(IV) and P-V(IV) systems. Solutions of VO²⁺ (1.0 – 3.0) × 10⁻⁴ M and the ligands (1.0 – 3.0) × 10⁻³ M in 100 ml volumetric flask at the ionic strength of 0.15 M NaCl were prepared. The pH of solutions were adjusted by the addition of small amount of NaOH or HCl as appropriate.

Polarographic measurements were done by using Metrohm Polarecord E 506. The polarograph was provided with a dropping mercury indicator electrode, saturated Ag/AgCl reference electrode and a counter platinum-wire

electrode. The settings of the polarographs were as follows: the voltage range varied, depending on the system under consideration, between 0.0 and – 2.0 volt. The pulse amplitude was 40 mV, the drop time was one second, the recorder speed was 0.5 mm/s. The experiment was performed at room temperature (~ 23°C). The pH values were in the range of 2.0 to 11.0 and were obtained by a Radiometer pH meter type 84 provided with a Russell combination electrode (calibrated as previously mentioned). The concentrations of the ligands were each 5.0 × 10⁻³ M and that of VO²⁺ was 1.0 × 10⁻³ M. All solutions were deoxygenated by purging with pure humidified nitrogen gas through them before taking the differential pulse polarograms (DPP) and above the surface during the run.

RESULTS AND DISCUSSION

Equilibrium Study

Table 1 shows the sets of solutions used in the potentiometric titrations of VO²⁺ and that of the ligands: pyridoxol (P), pyridoxal (PL), pyridoxamine (PM) and glycinehydroxamate (GX). The precipitation pH's are only noticed in case of PL-V(IV), and PM-V(IV) systems at pH > 5.0.

The inflection points in the graphs of pH vs *a*, Fig. 1(a, b, c, and d), (where *a* is the number of moles of base per total number of moles of hydrogen ions; both from the ligands and added acid) indicated complex formation of different stoichiometries. The pH vs *a* graphs shifts to the left in all systems as the ligand: metal ratios (at constant metal ion concentration) increases. This may be attributed to the absence of higher complex species of the form 3:1: rH⁺ (*r* = number of hydrogen ions).

Several equilibrium models were tested by using SUPERQUAD program [19], keeping invariant the protonation constants of the ligands. The best set of formation constants was determined by selecting the model resulted from obtaining the best values of the statistical parameters provided by the program, Table 2. In addition, the model which gave calculated pH identical to the experimental pH was accepted as shown in the distribution curves of different complex species as a function of pH, Figs. 2(a, b, c, and d) and/or correlating the calculated and experimental titration volume obtained from the adopted equilibrium model, Figs. 3(a, b, c, and d). In both cases HYSS2003 program was used [20].

Table 1. Concentration in Molarity of the Reactants Used in the pH-Metric Study at Ionic Strength of 0.15 M NaCl and T= 25°C

VO ²⁺ × 10 ³ M	GX × 10 ³ M	PM × 10 ³ M	P × 10 ³ M	PL × 10 ³ M
1.0	1.0	1.0	1.0	1.0
2.0	2.0	2.0	2.0	2.0
0.8	1.6	1.6	1.6	1.6
1.0	2.0	2.0	2.0	2.0
1.5	3.0	3.0	3.0	3.0
0.8	2.4	2.4	2.4	2.4
1.0	3.0	3.0	3.0	3.0

Duplicate runs were done for each experiment.

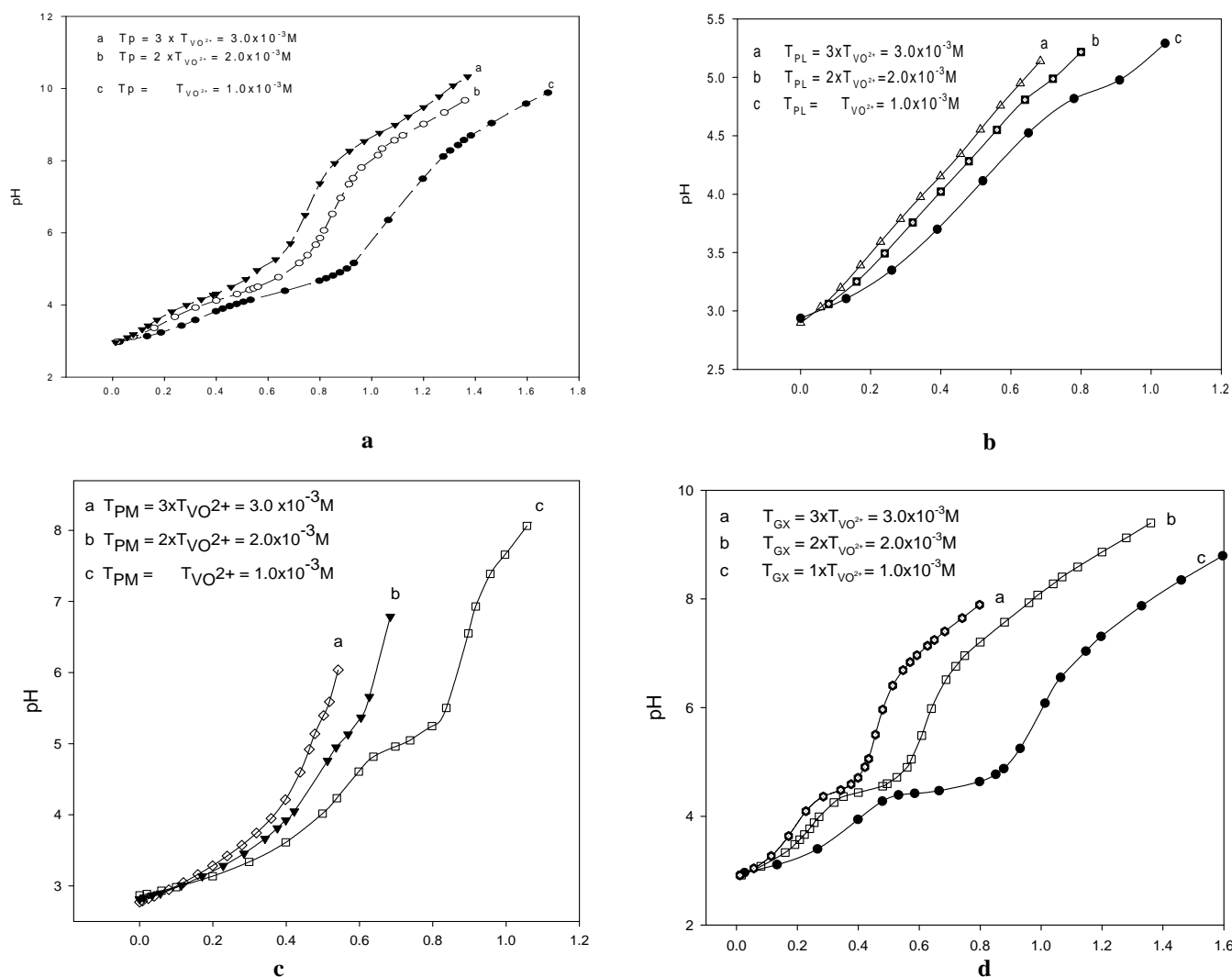


Fig. (1). The variation of pH as function of *a* for: a) P-V(IV), b) PL-V(IV), c) PM-V(IV), d) GX-V(IV).

Table 2. Summary of the Protonation Constants and Overall Formation Constants Encountered in the VO^{2+} -GX and Vitamin B₆ Compounds Systems, where *p*, *q*, and *r* are the Stoichiometric Coefficients for the Species ($L_p V_q H_r$)

System	Stoichiometric Coefficients			Species Charge	Log β (±σ)	pH Range Used	(χ ² , σ and n) [*]	Ref.
	p	q	r					
GX-H	1	0	1	0	9.55			[23]
	1	0	2	+	17.15			
P-H	1	0	1	0	8.96			[23]
	1	0	2	+	13.81			
PL-H	1	0	1	0	8.48			[24]
	1	0	2	+	12.57			
PM-H	1	0	1	0	10.41			[25]
	1	0	2	+	18.56			
	1	0	3	2+	22.06			

(Table 2). Contd.....

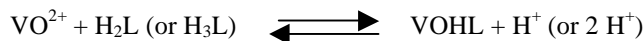
System	Stoichiometric Coefficients			Species Charge	Log β (±σ)	pH Range Used	(χ ² , σ and n)*	Ref.
	p	q	r					
V-OH	0	1	-1	+	-5.44±0.08			This work
	0	1	-2	0	-9.22±0.06			
H-OH	0	0	-1		-13.76			[26]
GX-V**	1	1	1	2+	15.09±0.06	3.1~ 9.0	36.5, 3.1, 399	This work
	1	1	0	+	10.87±0.05			
	1	1	-1	0	4.08±0.06			
	1	1	-2	-	-4.10±0.05			
	1	1	-3	2-	-13.34±0.07			
	2	1	1	+	23.90±0.10			
	2	1	0	0	16.30±0.10			
P-V**	1	1	1	2+	12.55±0.07	3.0 ~ 9.9	66.3, 4.4, 398	This work
	1	1	0	+	8.48±0.03			
	1	1	-2	-	-5.60±0.08			
	1	1	-3	2-	-15.07±0.08			
	2	1	1	+	20.81±0.08			
	2	1	0	0	14.20±0.20			
PL-V**	1	1	1	2+	11.98±0.03	3.0 ~ 5.4	16.9, 1.3, 237	This work
	1	1	-3	2-	-8.45±0.09			
	2	1	1	+	18.82±0.08			
PM-V**	1	1	2	3+	22.00±0.10	2.8 ~ 5.2	24.0, 1.0, 159	This work
	1	1	1	2+	18.80±0.10			
	1	1	-3	2-	-2.23 ±0.08			
	2	1	1	+	31.26±0.10			
	2	1	2	2+	36.48±0.09			

*χ², σ, and n are chi squared, sigma, and number of titration points.

**The equilibrium reaction is: p L + q VO²⁺ + r H⁺ = L_p(VO²⁺)_qH_r, where L stands for ligand in the deprotonated forms.

The affinity of VO²⁺ to oxygen ligating sites of the ligands is shown by the common presence of three species 1:1:1, 1:1:-3 and 2:1:1 (L:V:rH⁺; L stands for ligand) although the ligands are different in structure and in the location of the ligating atoms, Fig. (4).

The formation of 1:1:1 species resulted likely from the following reaction:



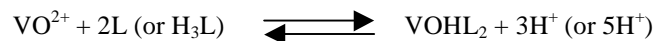
where L stands for GX, P, PL, or PM. Since $\Delta G^\circ = -RT \ln \beta$ then

$$\log \beta_{111} = \log \beta_{201(\text{or } 301)} + (2.303 RT)^{-1} \{ (G^\circ_{\text{V}} - G^\circ_{\text{H}}) + (G^\circ_{201(\text{or } 301)} - G^\circ_{111}) \}$$

(where the G^o's are the standard free energy of the involved species). The graph of log β₁₁₁ vs log β_{201(or 301)} should be linear with unit slope if the second term on the right of eq. 1 is constant. However the slope was not one (~0.74) indicating that the second term is not constant and since the term

(G^o_V - G^o_H) is constant one should expect that the term (G^o_{201(or 301)} - G^o₁₁₁) varies with log β_{201(or 301)}.

The formation of 2:1:1 complex species may result from the following reaction



An equation similar to eq.1 is obtained

$$\log \beta_{211} = 2 \log \beta_{201(\text{or } 301)} + (2.303 RT)^{-1} \{ (G^\circ_{\text{V}} - G^\circ_{\text{H}}) + (G^\circ_{201(\text{or } 301)} - G^\circ_{211}) \}$$

The plot of log β₂₁₁ vs log β_{201(or 301)} should be linear with slope = 2 if the second term on the right of eq.2 is constant. However this was not the case, a linear relation was obtained with slope under 2 (~ 1.3) which also indicates the linear dependence of (G^o_{201(or 301)} - G^o₂₁₁) on log β_{201(or 301)}.

The ligating atoms are mainly oxygen and nitrogen. The nitrogen ligating atoms are either of aromatic (pyridinic) or aliphatic (amino group) nature and may be excluded from

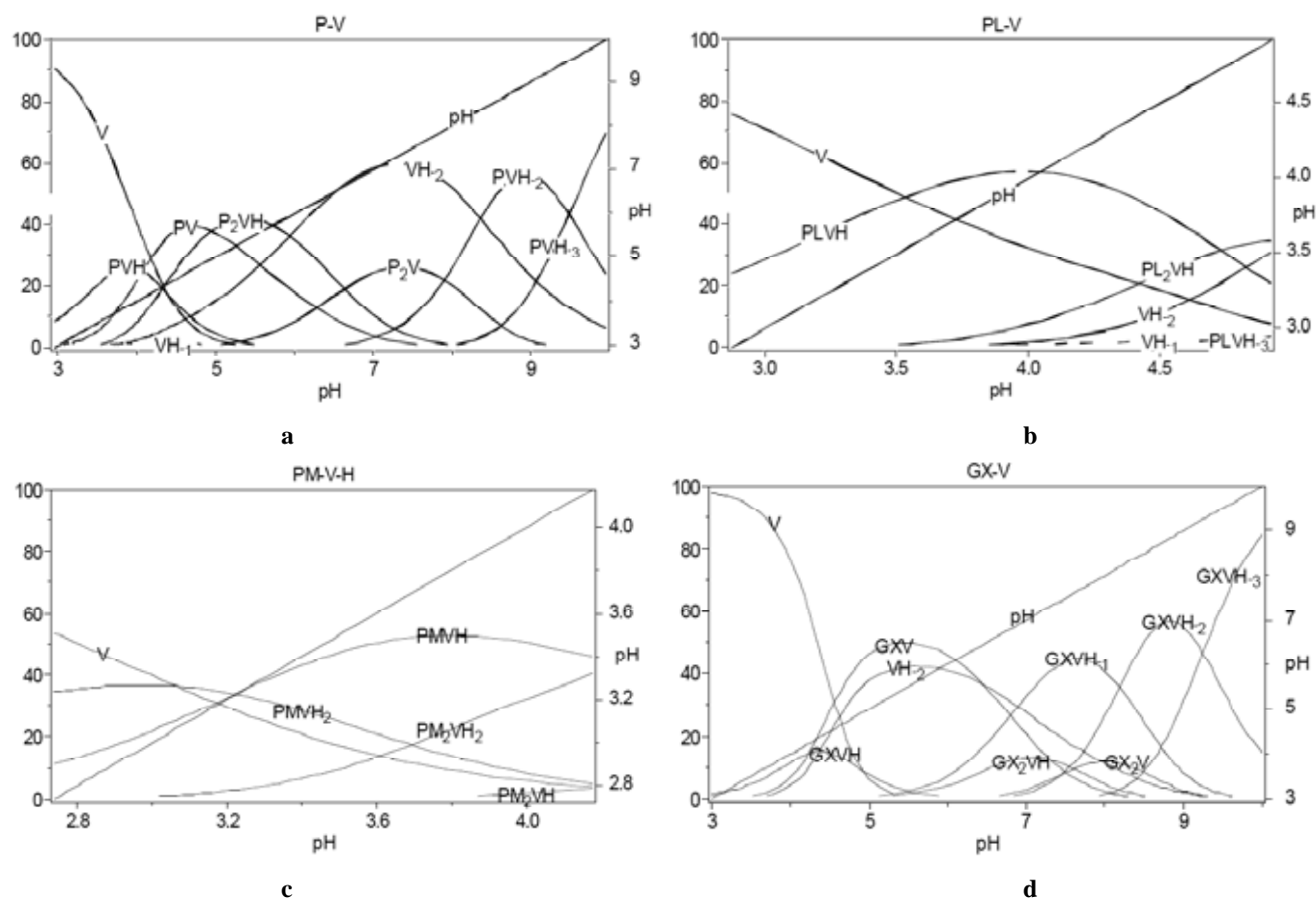


Fig. (2). The distribution of different complex species as function of pH and the corresponding calculated and experimental pH for: **a**) P-V(IV), **b**) PL-V(IV), **c**) PM-V(IV), **d**) GX-V(IV). The initial concentration of the ligands were 2.0×10^{-3} M and that of the VO^{2+} 1.0×10^{-3} M.

ligation with VO^{2+} in preference to the more electronegative oxygen ligating atoms in most cases. The presence of the 1:1:-3 in all systems reflects this tendency where VO^{2+} are complexed in addition with OH^- specially above pH 7.0 in case of GX-V(IV) and P-V(IV) systems and less than pH 7.0 in case of PL-V(IV) and PM-V(IV) systems. Although the inclusion of polymeric complexes in all suggested equilibrium models were not successful, they may not be excluded in PL-V(IV) and PM-V(IV) systems due to the occurrence of early precipitation.

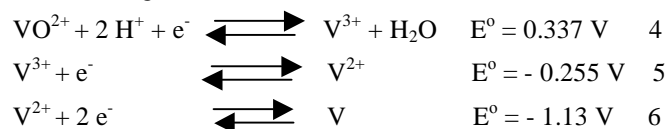
Polarographic Study

The DPP of VO^{2+} at different pH values in the range of ~3-5 resulted in a single peak with E_{max} (the potential at maximum differential Faradaic current (δ_i)) of -0.896 V with respect to Ag/AgCl (0.242 V) reference electrode. The peak is splitted at only pH = 4.0 to two overlapped peaks at -0.864 V and at -0.916 V. The peak is slightly shifted to -0.880 V from -0.896 V as the pH increased (supplementary materials).

The E_{max} was attributed to the reduction of VO^{2+} to metallic V. This conclusion was obtained by calculating E^0 of the following half-reaction



from the knowledge of the standard electrode potentials of the following half-reactions [21]:



and by considering the hydrogen ion concentration ($\sim 10^{-4}$ M), V(IV) concentration (1.0×10^{-3} M), the standard electrode potential of the reference electrode (0.242 V) and the magnitude of the pulse amplitude used (0.04 V), one can arrive at a calculated value of $E_{\text{max}}(\text{calc.}) = -0.876$ V. The calculated value is different from the experimental value by ~ 0.02 V. The difference may be due to the employment of concentration rather than activity of the species in the above calculation.

The half-peak width is found to be 0.144 V, which is large if compared with the value obtained from a four electron reduction process, assuming reversibility [22].

The split in $E_{\text{max},v}$ at pH ≈ 4.0 may indicate the stepwise reduction of V(IV) to another lower oxidation state species rather than to elemental vanadium.

The $E_{\text{max},v}$ of VO^{2+} is lost above pH ≈ 5 as a result of the precipitation of white hydrolyzed species of the metal ions.

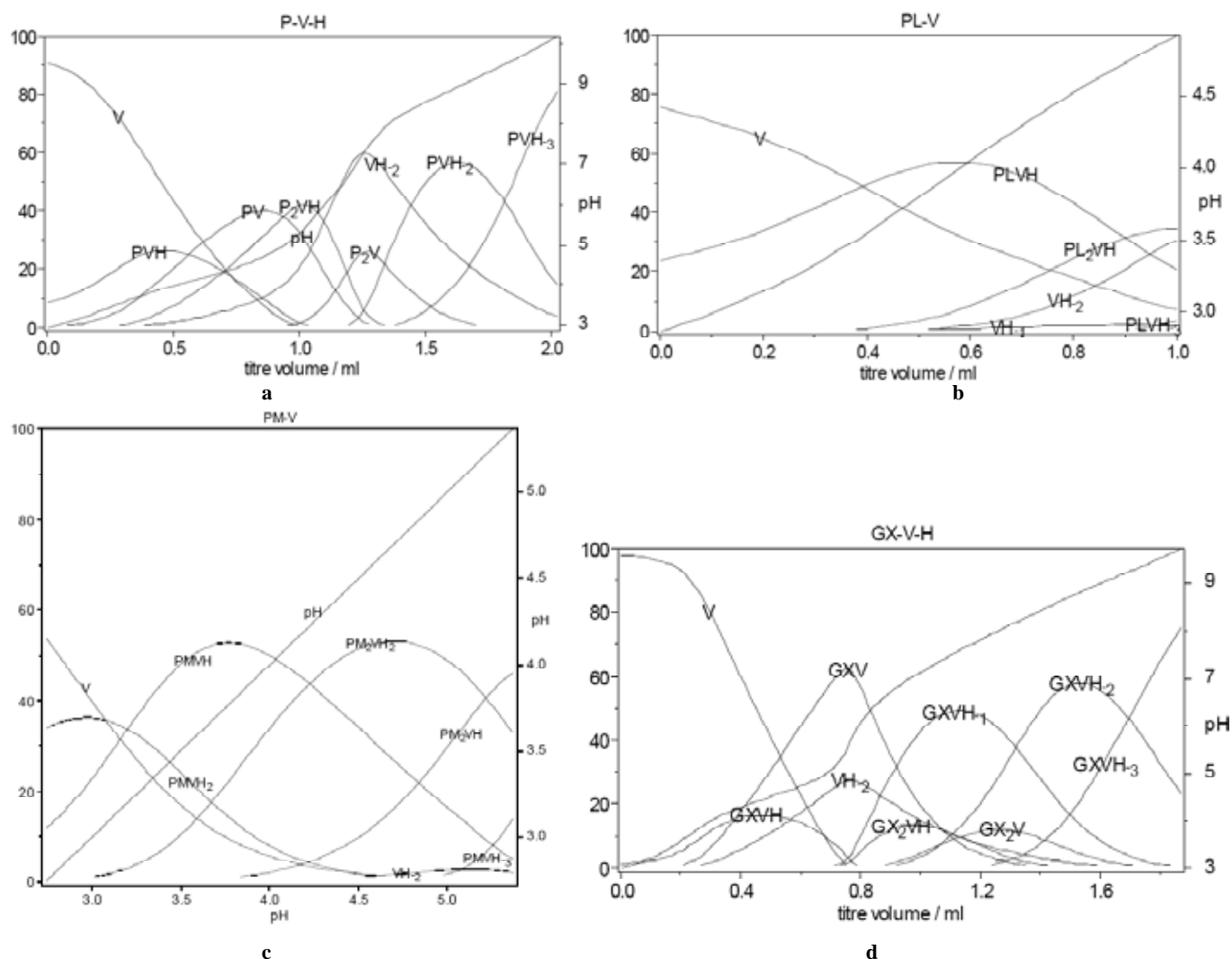


Fig. (3). The distribution of different complex species as function of calculated and experimental titration volume for: **a)** P-V(IV), **b)** PL-V(IV), **c)** PM-V(IV), **d)** GX-V(IV). The initial concentration of the ligands were 2.0×10^{-3} M and that of the VO^{2+} 1.0×10^{-3} M.

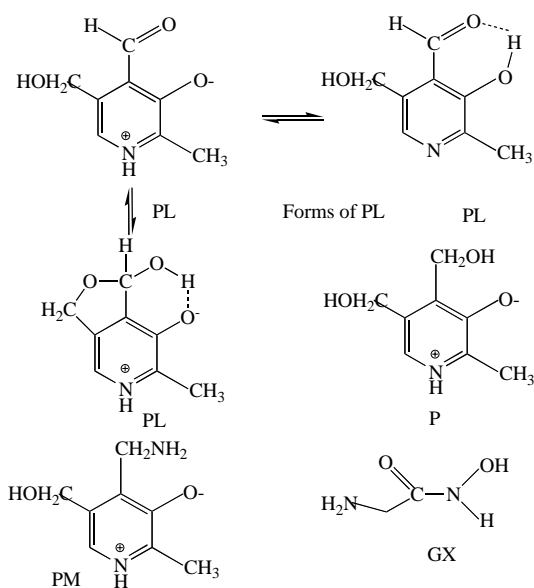


Fig. (4). The structural formulas of the ligands PL, P, PM and GX.

The DPP of GX-V(IV) system almost resembles that of VO^{2+} with $E_{\text{max,GX-V}}$ shifted slightly to ~ -0.9 volt in the pH range ~ 3.0 - 4.0 , Fig. (5). The intensity of the peak (δ_i) decreased as the pH of the medium increased above pH ~ 3.4 . A behavior which is rationalized as due to the formation of VO^{2+} complexes with GX characterized by a decrease in the amount of free VO^{2+} in solution. A broad $E_{\text{max,GX-V}}$ was observed with regular shifts toward more positive potentials in the pH range ~ 4 -5. It may be explained as a result of the increase in the positive character of the metal ion either by the delocalization of electron density from the VO^{2+} toward the ligand or to the removal of oxygen of the VO^{2+} on complex formation with GX. However, at pH values >5 there is regular shift in $E_{\text{max,GX-V}}$ toward more negative potentials due the stabilization of the metal ions oxidation state by further complex formation. The DPP peaks are accompanied with color changes from yellow, to green, to orange, and finally to red wine. It should be mentioned that the solution of GX alone did not show any color changes or any reduction peaks in the range of 0.0 to -1.2 volt. Another $E_{\text{max,GX-V}}$ appeared around 0.0 volt, which may indicate the complex formation with another lower stepwise oxidation state of vanadium or,

in other words, they may indicate the reduction of VO^{2+} to a lower oxidation state which was stabilized by GX complex formation.

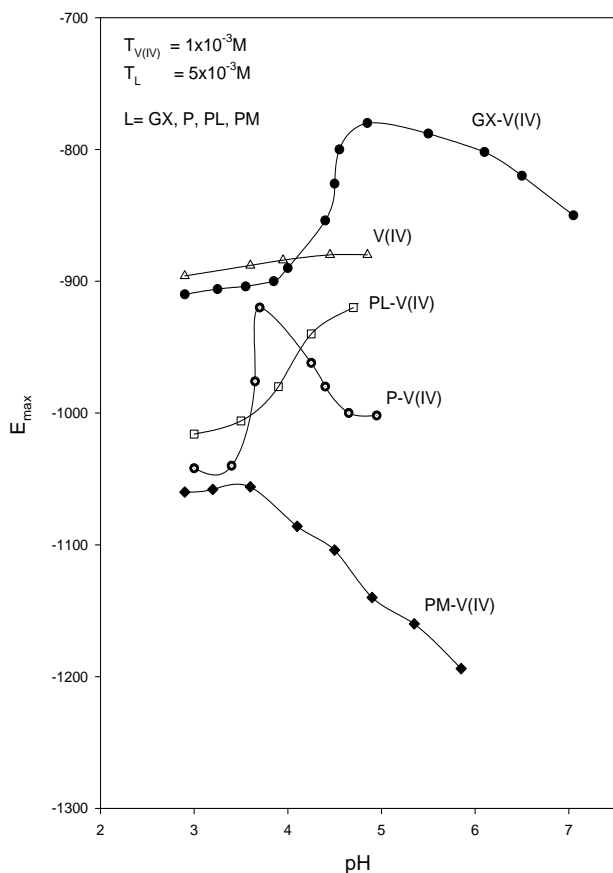


Fig. (5). The variation of E_{\max} of V(IV) as function of pH in the absence and presence of the ligands.

The DPP of vitamin B₆ compounds in absence of the VO^{2+} have apparently two E_{\max} or more in the potential range 0.0 to -1.2 volt, one probably for the reduction property of the aromatic system and the others for the reduction properties of the functional groups. Of course, one should expect that these E_{\max} will complicate the DPP of vitamin B₆ complexes with VO^{2+} . Actually, these E_{\max} 's were sensitive to complex formation with vitamin B₆ compounds. Generally, they were shifted to more negative potentials as a result of the stabilization of the oxidation states of vanadium on complex formation. However, the E_{\max} of the VO^{2+} in presence of vitamin B₆ are quite isolated from those of vitamin B₆ compounds (see the supplementary materials).

The $E_{\max, \text{P-V}}$ of the VO^{2+} in presence of pyridoxol are similar to those of VO^{2+} alone with large negative shift with respect to VO^{2+} alone at pH values below ~ 3.4 . However, in the narrow pH range of ~ 3.4 - 3.7 there are more shifts toward positive potentials, Fig. (5), which may be interpreted, as in the case of GX-V(IV), either to the removal of the oxy-

gen from the VO^{2+} or to the transfer of electron density from the VO^{2+} toward the ligand species on complex formation. The transfer of electron density from the VO^{2+} to the ligand reflects the type of bonding between pyridoxol and VO^{2+} . At pH values > 3.7 there are large shifts to more negative potentials due to the stabilization of the oxidation states of the metal ions by further complex formation.

The $E_{\max, \text{PL-V}}$ of VO^{2+} in presence of PL is similar to that of P-V(IV) system at pH values < 3.7 with a large shift to negative potential with respect to that of vanadyl ions alone, Fig. (5). The shift is accompanied by gradual decrease in the current intensity, δ_i , an indication of the decrease in the free VO^{2+} as complex formation increases by the increase in pH. Besides, a large shift toward less negative potentials at pH values > 3.7 was observed. Similarly, they were explained as result of increase in the positive character of the metal ions either by the removal of the oxygen of the vanadyl ions or increase in the electron density transfer toward the ligand. Due to the early precipitation at pH ~ 5.0 no further negative shift of the $E_{\max, \text{PL-V}}$ was observed.

The $E_{\max, \text{PM-V}}$ of VO^{2+} in presence of PM is similar to that of P-V(IV) system at pH values < 3.6 with large shift to negative potentials with respect to vanadyl ions alone. The shift is accompanied by a decrease in δ_i as pH increased up to the value of 3.6 as free vanadyl ions decreased as a result of complex formation. The formation of higher complexes as pH values increased was characterized by large negative shift in $E_{\max, \text{PM-V}}$. There was no prior shift toward less negative potentials as pH increased, Fig. (5).

Spectral Study

The VO^{2+} spectrum in the near UV-Vis region consists of three bands at ~ 770 , ~ 625 , and ~ 240 nm. The first two bands are of very low intensity (the molar absorptivity, ϵ , is $\sim 10 \text{ dm}^3/(\text{mol cm})$ or less) while the last one has high intensity. Upon the addition of GX to the vanadyl ion solution, the bands at 770 and 625 nm shifted to shorter wavelength

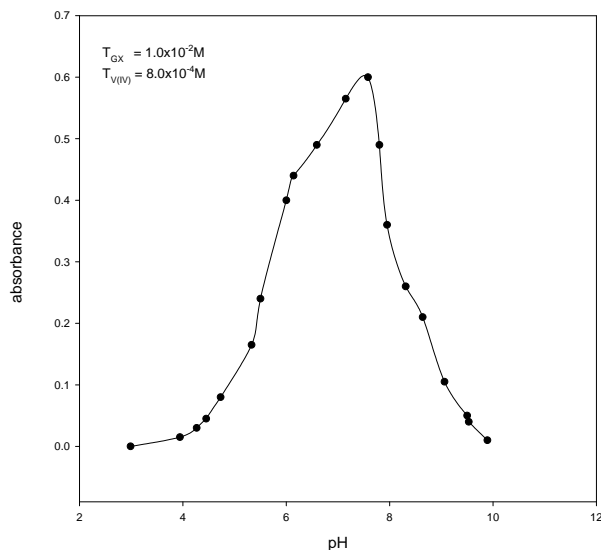


Fig. (6). The variation of absorbance at $\lambda = 485 \text{ nm}$ of V(IV) in presence of GX as function of pH.

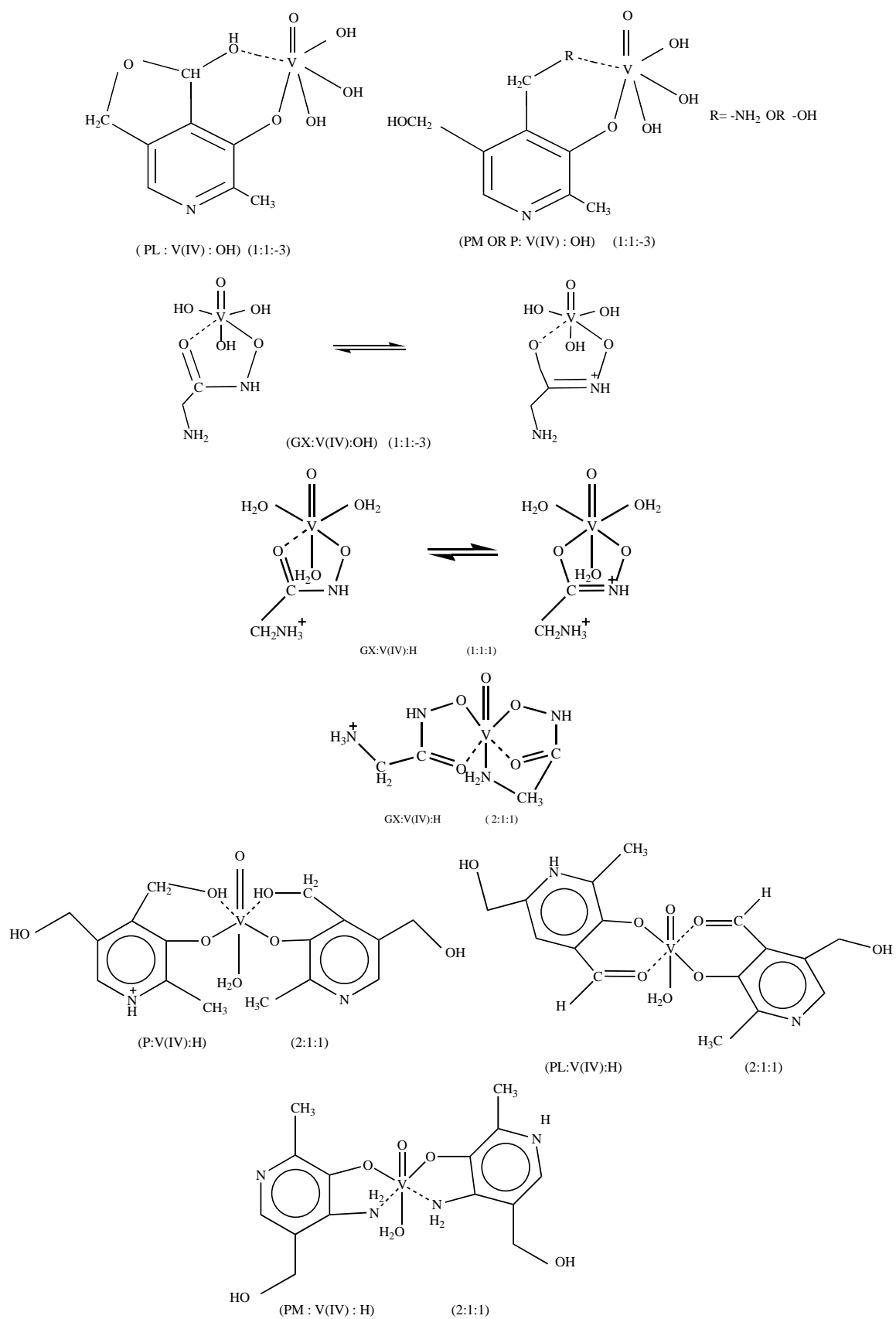


Fig. (7). Predicted structural formulas for some of the metal complexes of vitamin B₆ compounds and glycinehydroxamate.

(λ) with a maximum at 485 nm. The absorbance as function of pH at $\lambda = 485$ nm follows the pattern shown in Fig. (6), with a maximum $\epsilon = \sim 750 \text{ dm}^3/(\text{mol cm})$. The change in absorbance as a function of pH is an indication of the formation of several complexes. The behavior is similar to that of $E_{\text{max,GX-V}}$ vs pH, Fig. (6).

The spectra of the vanadyl ions in the visible region were shifted to near UV in the presence of vitamin B₆ compounds where the latter absorbances are strongly interfering with that of the metal ions complexes. The strong interference made it difficult to follow up spectrophotometrically the interaction between the vanadyl ions and the vitamin B₆ compounds.

CONCLUSIONS

The usefulness of metal complexes to be biomimetic lies in the fact that they should be able to cross biological membranes. There are two mechanisms either by passive diffusion or by active transport. Since the latter is usually less favorable, passive diffusion is usually the choice. In such case biomimetic complexes should be of low molecular weight, neutrally charged, with moderate stability, and not easily reduced by the medium. They are also preferable to have both lipophilic and hydrophilic character. In addition, they should be thermodynamically and hydrolytically stable in aqueous media.

If the complexes in this work are examined according to the criteria mentioned above one find out that most of the complexes are charged, Table 2, and very few are neutral shown only by GX-V(IV) and P-V(IV) systems. Most of the vanadyl complexes encountered in this work are moderately stable in aqueous solutions in a wide pH range except PM-V(IV) and PL-V(IV) systems which showed early precipitation above pH 5. Moreover, most of them are not easily reduced up to pH ~ 3.7 and above pH ~ 4 in most cases as indicated by the polarographic study, Fig. (5). One should expect that these ligands will stabilize the vanadyl ions in different biological media. However, there is a narrow pH range of ~ 3.7 - 4.5 where these complexes are not stable to reduction relative to those mentioned in more acidic medium (less than pH 3.7) and higher than pH 4.0 except those of PM-V(IV) system.

The predicted structures, based on the found stoichiometries, are shown in Fig. (7) where the ligands are acting as bidentate in most cases and sometimes tridentate in case of GX-V(IV) system.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

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