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Complexation of Vanadium(IV) with Hydroxamate Chelators and Their Stability Relation with pH

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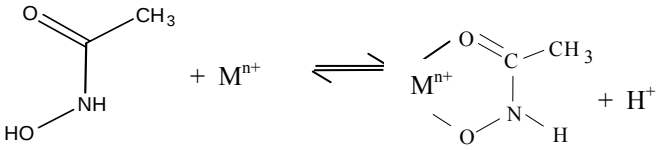
Hydroxamic acids, RCONHOH, form highly stable complexes with vanadium(IV) in 1:1, 1:2 and 1:3 molar ratios. The stability constants of the complexes were determined through spectrophotometric and potentiometric methods at various pH and found to be comparable. Acetohydroxamate, benzohydroxamate and salicylhydroxamate were selected for the study. Using the spectrophotometric method, graphical calculations were applied to confirm the results. Potentiometric method associated with computer calculation program BEST was also applied to check the reproducibility of the results.

Keywords: Oxovanadium(IV), Hydroxamates, Spectrophotomery, Potentiometry, Complex stability, Graphical methods

INTRODUCTION

Hydroxamic acids have been used as therapeutic agents in chelation therapy and as metalloenzyme inhibitors [1-3]. Other medical applications of the hydroxamates which utilize their affinity for high charge density metal ions include the possible use of their metal complexes as imaging agents [4]. Simple hydroxamate analogues (acetohydroxamic, benzohydroxamic and salicylhydroxamic acids) (Fig. 1) can undergo two deprotonation processes and act as either hydroxamato^{-} or hydroxamato^{2-} ligands, which behave as monodentate as well as bidentate ligands [5]. Among numerous siderophore structures, the hydroxamates are of interest due to their ability to form stable transition metal complexes through the formation of a five membered chelate ring as shown in Scheme 1 [6]. Catechols and N-hydroxylated (such as L-Glutathion) ligands which can be considered as biological sequestering agents for a large class of metal ions, are particularly effective in stabilizing high oxidation state for elements such as vanadium and molybdenum [5,7-14].



Scheme 1

These ligands can utilize the capability of free vanadium ions to activate glucose uptake and glucose metabolism in rats adipocytes *in vitro* by 4-5 folds and to lower blood glucose levels in hyperglycemic rats *in vivo* by 5-7 folds [15]. They form an intense ultra violet-absorbing complex upon associating with vanadium(IV) at 1 to 3 molar stoichiometry [16].

In both +5 and +4 oxidation states, vanadium can form complexes of rather high stability with ligands able to displace, partly or fully, oxygen from the stable VO^{2+} and VO_2^{+} oxo-cations [5,7]. In highly acidic media, reversible oxygen displacement occurs from the metal ion to yield

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nonoxo V(IV) or V(V) complexes, which exhibit distinct EPR and ^{51}V NMR spectral features, respectively. In these species, the bare vanadium ions are coordinated to the three hydroxamic functions of the ligand. With increasing pH, oxo-coordination is restored and normal VO(IV) and VO_2(V) complexes are formed with metal bonding to one or two hydroxamic functions of the ligand [17].

VO^{2+} complexes have extensive clinical applications. A new turning point appeared in 1985, when a scientist claimed that oral administration of vanadate to Type-I diabetic rats lowered the high levels of blood glucose to normal values. Unlike insulin, which is not absorbed orally, vanadate as a low-molecular weight substance and a phosphate analog can permeate plasma membranes and intestinal wall with relative ease [18].

In vivo studies of bis(maltolato) oxo-vanadium(IV) proves that it is at least three times more effective than non-complexed vanadyl sulfate [17,19]. The ligand is effective in yielding nonoxo complexes of vanadium(IV). An intensely red colored specie formed in acidic aqueous solution is supposed to contain bare V(IV) coordinated by the three hydroxamate functions of the ligands. One of the three hydroxamate moieties of this complex is then displaced by an oxygen with pK = 2.85 [19], resulting in the formation of a normal VO(IV) complex displaying a light blue color.

The aim of the present study is to have an insight into vanadium complexation with the simple hydroxamte analogues, acetohydroxamic acid (AHA), benzohydroxamic acid (BHA) and salicylhydroxamic acid (SHA) (Fig. 1).

EXPERIMENTAL

All reagents used were of A. R. grade. For all solutions, CO_2 free distilled deionized water was used. Equal Volumes of 0.01 M $VOSO_4.5H_2O$ solution were mixed with equimolar

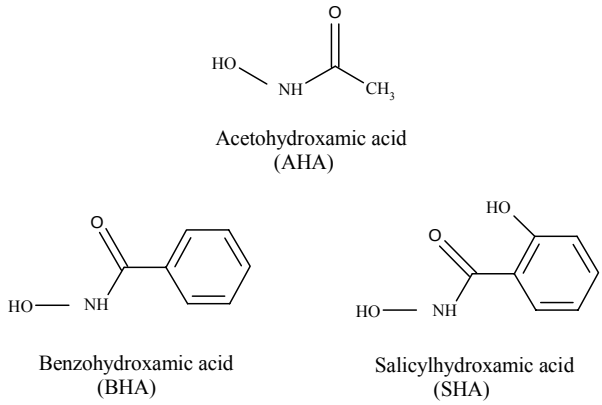


Fig. 1. Structure of ligands.

ligands. Temperature was maintained at 35 °C by circulating water from the thermostat to the reaction cell. Aliquots of standard 0.20 M NaOH solution were added with the help of a micro-pipette with continuous stirring by a magnetic stirrer and the pH variation was measured by an Orion S. A model 720 pH meter having a resolution of ± 0.001 pH unit. Spectral characteristics of all complexes were determined by mixing metal and ligand in 1:15 ratio. On the selected wavelength for complex, the absorbances were measured for 0.01 M V(IV) mixed with variable ratio of the ligands from 0.01 M to 0.1 M, using a Shimadzu-UV 160 model spectrophotometer.

RESULTS AND DISCUSSION

For spectral study of each complex at various pH and mole ratios, suitable wavelengths were selected and the molar extinction coefficients were determined (Table 1). The concentrations of the remaining ligand, the remaining

Table 1. Spectral Characteristics of V(IV)-Hydroxamic Acid Complexes

Hydroxamate analog	Wavelength selected (nm)	Molar extinction coefficient (M^{-1} cm^{-1})	pH
AHA	400	200	5.0
BHA	455	550	8.5
SHA	600	220	3.5

Table 2. Vanadium(IV)-Hydroxamate Complexes at Selected Wavelengths by Spectrophotometric Method: pH = 5.0, T = 35 ^{o}C, [M] = 0.01mmoles, [L] = 0.01M, β_1= [ML] /[M]$_r$[L]$_r$, β_2= [ML$_2$]/[M]$_r$[L]$_r^2$, β_3 = [ML$_3$]/[M]$_r$[L]$_r^3$

mmoles of ligand	Stability constants for V(IV)-AHA			Stability constants for V(IV)-BHA			Stability constants for V(IV)-SHA		
	β_1	β_2	β_3	β_1	β_2	β_3	β_1	β_2	β_3
0.05	2.9×10^3	4.9×10^5	9.0×10^9	0.000	0.000	0.000	3.6×10^2	5.3×10^5	1.1×10^9
0.10	2.9×10^3	4.9×10^5	8.9×10^9	5.3×10^2	4.4×10^5	5.9×10^8	4.1×10^2	3.7×10^5	5.8×10^8
0.15	3.0×10^3	5.0×10^5	9.0×10^9	7.6×10^2	4.6×10^5	5.1×10^8	3.3×10^2	2.2×10^5	2.8×10^8
0.20	3.1×10^3	5.2×10^5	9.1×10^9	1.0×10^3	5.1×10^5	4.6×10^8	2.8×10^2	1.5×10^5	1.9×10^8
0.25	3.0×10^3	$5.0.\times10^5$	9.0×10^9	1.5×10^3	5.5×10^5	3.6×10^8	2.3×10^2	9.5×10^4	8.3×10^7
0.30	3.2×10^3	5.2×10^5	9.1×10^9	2.2×10^3	4.4×10^5	1.2×10^8	1.4×10^2	2.7×10^4	8.0×10^6

metal and the complex produced were calculated for variable M:L ratios at various pH.

Using equations of stability constant:

$$\beta = [ML_n]/[M]_r\,[L]_r^n \qquad (1)$$

where [ML$_n$] = concentration of complex, [M]$_r$ = concentration of the remaining metal, [L]$_r$ = concentration of the remaining ligand and β = overall stability constant. The β values were calculated by simple method using different 'n' values from 1-3. These β values were calculated at pH 5, which was found to be very sitable due to pK values of the selected hydroxamates. Consistency was found in those β values which were calculated at low pH when 'n' is taken as 1, indicating that the average value of β in this pH range is the stability constant for a 1:1 complex, so that it is β_1. Average β_2 and β_3 were also calculated for each V(IV) hydroxamate complex in the same manner (Table 2). The same procedure was followed with buffer solutions in the pH range 2.5-6. It was found that, at low pH upto 3, the ML form may be present in solution, while at pH 3.5 to 4.5, the ML$_2$ and abve this pH the ML$_3$ complexes are the dominant spicies in solution (Table 3). The final β values of the V(IV) complexes with AHA, BHA, and SHA complexes are summerized in Table 4. For further confirmation of the above β values, a graphical method was also applied and for this purpose equation (1) was modified in the logarithmic form as follows:

$$\log [complex]/[M]_r = \log\beta_n + n\log[L]_r \qquad (2)$$

According to equation (2), a plot of log [complex]/[M]r *vs* log [L]r will result in a stright line with a slope of 'n' and an intercept of β_n. If n = 1, the intercept gives a value of β_1 (Fig. 2A). At pH = 5 and low ligand concentrations, the slope of the plot of log [ML$_n$]/[M]$_r$ *vs* log [L]$_r$ is equal to 1. The intercept of this line is equal to log β_1. While, at slightly higher ligand concentrations, slope is 2 and log β_2 is then obtained from the intercept of this line. When very high ligand concentrations were used, slope of the line equals to 3 and the intercept may give log β_3 (Fig. 2 B). At pH 8, when the same metod was applied, the slope becomes

Table 3. Calculated Stability Constants for Vanadium (IV)-AHA Complex at Different pH by Spectrophotometric Method

S. No.	pH	log β_1	log β_2	log β_3
1	3.0	2.5	4.1	6.2
2	5.0	3.2	5.5	9.7
3	8.0	2.2	4.2	8.3

Table 4. Average Stability Constant Values for V(IV)-Hydroxamate Complexes by pectrophotometric Method

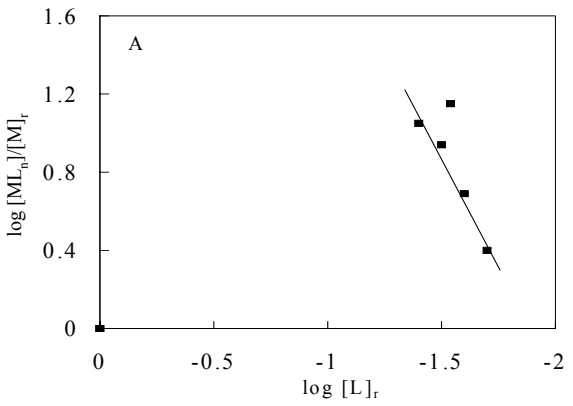
Comple×es	β_1	β_2	β_3
V(IV)-AHA	$(3.0\pm0.1)\times10^3$	$(5.0\pm0.15)\times10^5$	$(9.0\pm0.2)\times10^9$
V(IV)-BHA	$(1.2\pm0.5)\times10^3$	$(4.8\pm0.5)\times10^5$	$(4.0\pm0.52)\times10^9$
V(IV)-SHA	$(2.9\pm0.5)\times10^2$	$(2.3\pm0.7)\times10^5$	$(3.7\pm0.75)\times10^8$

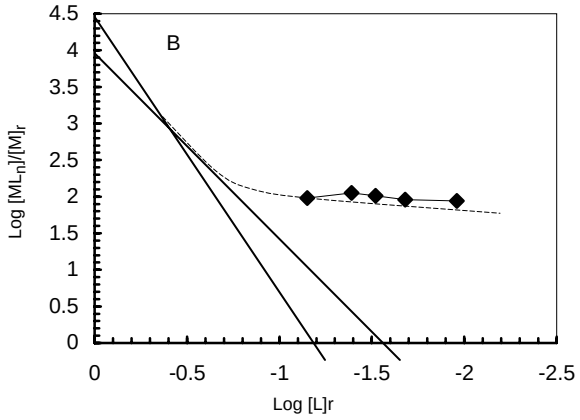
equal 2 at initial on low concentration of the ligand. However, as the ligand concentration increased, this metod became invalied. The reason may be that, at high pH, the vanadyl oxygen is restored [17] and, thus, the metal has a tendency to make a square pyramid complex with a 1:2 metal to ligand ratio. The complete complexation occurs at very low concentration of the ligand, and after that the remaining ligand concentration in the solution begins to increase (Fig 2C). The ratio of complex with the remaining ligand became almost constant and, therefore, no metal ion is left in solution. The same calculations were applied to evaluate the β values of BHA and SHA complexes of vanadyl ions (Table 5).

The stability constant or β values for these species were re-evaluated by potentiometric method and by using theoretically calculated values from the potentiometric curves (Table 5).

Table 5. Comparison of log β Values of Vanadium(IV) Complexes With Hydroxamate Analogues Calculated from Different Methods

Ligand	Ratio	BEST	Spectrophoto-metry	Graphical method
AHA	1:1	7.20	4.10	*
	1:2	10.10	5.30	*
	1:3	11.50	10.40	*
BHA	1:1	2.87	*	*
	1:2	5.56	5.50	5.20
	1:3	8.75	8.50	*
SHA	1:1	2.96	3.00	*
	1:2	6.16	5.50	*
	1:3	8.54	8.20	*





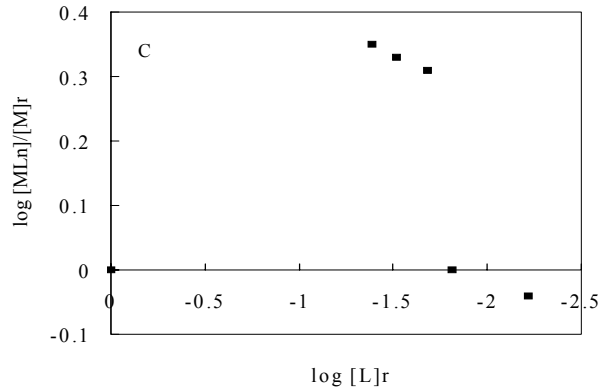


Fig. 2. Slope ratio method plots at λ_{max} = 400 nm for V(IV)-AHA complex at (A) pH = 3, (B) pH = 5 and (C) pH = 8.

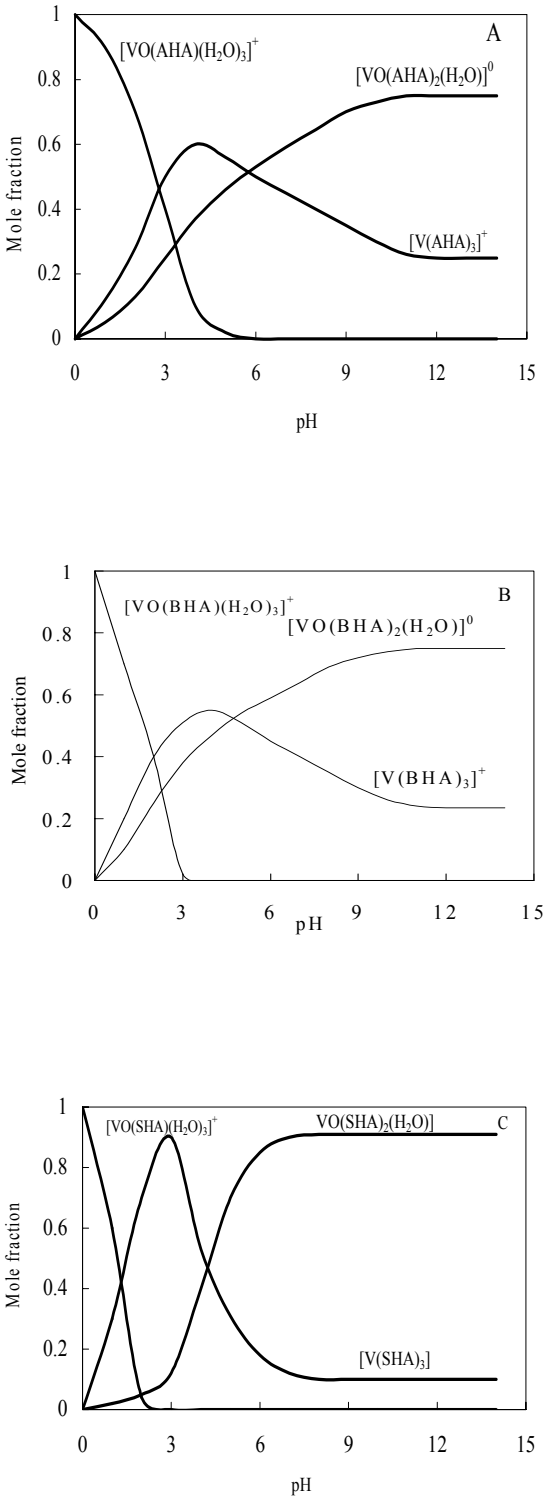


Fig. 3. Species distribution diagrams for (A) V(IV)-AHA, (B) V(IV)-BHA and (C) V(IV)-SHA complexes.

These values were subjected to computer program BEST for refining upto the least σ-fit value [21]. The results obtained from both methods showed that V(IV)AHA complexes are more stable at higher pH values. Using these β values, the species distribution diagrams at different pH for Vanadium(IV)–AHA, Vanadium(IV)–BHA, and Vanadium(IV)–SHA, calculated from the same computer software, were also determined (Fig. 3). It was found that , in the case of V(IV)-AHA, all metal ions were complexed after pH 3 where 60% was 1:3 bidentate with no axial oxygen, and 20% was 1:2 bidentate. However, at pH = 10, 80% of 1:2 with axial oxygen and a water molecule and 20% 1:3 were observed (Fig. 3 A).

In the case of V(IV)-BHA, the dominating specie was 1:3 at pH = 3 with an extent of 50% while the 1:2 complex with axial oxygen was about 30%. At pH 9 and higher, some 80% 1:2 complex and 20% 1:3 specie are existed in solution (Fig. 3 B). In V(IV)-SHA system, the 1:2 complex was predominant even at very high pH, which may be due to the tridentate property of the ligand at such high pH values. At pH = 3, the 1:3 complex with no axial oxygen is predominant with an extent of 90% (Fig. 3 C).

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