Computer Assisted Thermal Complexation Studies of Vanadium with Benzodiazepine Drugs

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Received: 12 February 2019;

Accepted: 22 June 2019;

Published online: 30 August 2019;

AJC-19550

The complexing tendency of vanadium with nifoxipam and lorazepam were carried out by pH metric titration technique in aqueous acid media at different temperatures (298, 308 and 318 K) and an ionic strength of 0.2 M. The degree of complexation was investigated at different pH values. Potentiometric measurement of hydrogen ion concentration was also studied with the degree of complex formation. The proton-ligand and metal-ligand stability constants were resolved by modified Calvin-Bjerrum pH titration technique (Irving and Rossitti) using computer programming. The important thermodynamic parameters such as Gibb's free energy change (ΔG), entropy change (ΔS) and enthalpy change (ΔH) for the complexation reactions were calculated. The formation of metal complexes was found to be spontaneous, exothermic and conducive in nature at lower temperatures.

Keywords: Benzodiazepine drugs, Vanadium metal, Thermodynamic parameters.

INTRODUCTION

Derivatives of 1,4- benzodiazepine are being used in medicine as tranquilizer and sedative hypnotic agents [1-3]. Present work determines the formation constants of metal complexes derived from 1,4-benzodiazepines. Hitherto work has done on the synthesis and physico-chemical studies of transition metal complexes of benzodiazepines [4,5]. X-ray study of 1,4-benzodiazepine (parazepam) revealed that it acts as an anionic bidentate ligand, being coordinated to the metal centre through N-4 atom and the *ortho*-carbon atom phenyl ring [6].

Benzodiazepines are used as depressants to produce sedation, induce sleep, relieve anxiety, muscle spasms and prevent seizures. In general, benzodiazepines act as hypnotics in high doses, anxiolytics in moderate doses and sedatives in low doses. These are among the most widely prescribed medications [7]. In living systems, 1,4-benzodiazepines can interact with metal ions and their therapeutic action may thus be affected by metal complexation [8]. The chemistry of 1,4-benzodiazepines has mainly focused on synthetic aspects and complexes with copper [9,10], gold [11], platinum and palladium [12]. A synthetic and spectroscopic study on group II B metal complexes of 1,4-benzodiazepine has also been reported [13]. Several methods for

the analysis of benzodiazepine have been reported including HPLC ion spray mass spectrometry [14,15], tandem mass spectrometry [16,17], polarography [18,19], liquid chromatography [20,21], potentiometry [22,23] and voltammetry [24]. Literature survey revealed that the available complex formation constants were determined in various aqueous-organic solvent systems because many drug compounds and their metal complexes are sparingly soluble in water. The study of complex formation constants in aqueous-organic medium is useful in interpreting the role of solvents in complex formation reactions.

The stability constants of complexes of 1,5- benzodiazepine, 1,6-benzodiazepine and 4,6-benzodiazepine with iron(II), cobalt(II) and nickel(II) and complexes of 1,5- and 4,6- benzodiazepine with copper(II) and cadmium(II) were evaluated [25]. For comparative aspiration, the data of 1,6-benzodiazepine complexes with iron(II) as well as those of analogous complexes of 1,10-phenanthroline [26,27] which is an efficient complexing agent, isomeric with benzodiazepines.

In both +5 and +4 oxidation states, vanadium complexes of rather high stability with ligand able to displace oxygen (partially or fully) from VO^{2+} and VO^{2+} oxocations [28-30]. With increasing pH, oxo coordination is restored and normal VO(IV) and $\text{VO}_2(\text{V})$ complexes are formed with metal bonding

to one or two hydroxamic functions of the ligand [31]. In the present study, the complex formation constants of complexes formed by benzodiazepines with vanadium metal ions are reported. The complex systems studied are vanadium-nifoxipam and vanadium-lorazepam. The effect of temperature on the complex formation constants was evaluated. The current study delineates the result of formation constants of vanadium metal ion with benzodiazepines by potentiometer method at a fixed ionic strength and temperature $25 \pm 1^\circ\text{C}$ in an aqueous medium.

EXPERIMENTAL

All analytical grade reagents were purchased from Merck and Aldrich. Stock solutions of $(0.001 \text{ mol dm}^{-3})$ of nifoxipam and lorazepam were prepared by dissolving an accurately weighed amount in ethanol. Sodium perchlorate, an inert electrolyte $(1.0 \text{ mol dm}^{-3})$ and standard solution of vanadium salt $(0.010 \text{ mol dm}^{-3})$ were prepared by dissolving the required amount of each salt in double distilled water. The solutions were stored in the dark and under refrigeration to minimize the risk of decomposition.

Potentiometric titration: Potentiometric measurements were carried out using an Elico LI-120 pH-meter equipped with a combined glass electrode. The pH-meter was standardized with phthalate and phosphate buffers before titrations. The electrode was activated by storing it in 0.10 mol dm^{-3} HCl for 24 h and then immersing it in distilled water for another 24 h. The electrode was cleaned before performing a titration by rinsing it with distilled water. The three different types of mixtures *viz.* (i) free acid; (ii) free acid and ligand; and (iii) free acid, ligand and metal ion were prepared and titrated potentiometrically at different temperatures against standard $0.002 \text{ mol dm}^{-3}$ NaOH in double distilled water:

The total volume of each mixture was adjusted to 40 mL and the ionic strength of the solutions was maintained constant

at 0.2 M by adding an appropriate amount of stock solution of electrolyte. Equilibrium pH values were determined at every incremental addition of standard NaOH to the solutions. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded until table values, within ± 0.002 pH units were obtained.

RESULTS AND DISCUSSION

The results attained were examined through a computer program using titration data and stability constant values were calculated. The potentiometric titration curves obtained for three mixtures (i) to (iii) are displayed in Fig. 1 and the data is arranged in Table-1.

Determination of proton-ligand stability constant and metal-ligand stability constant of benzodiazepine-V(V) complexes: The dissociation constant (pK_a) is one of the substantial properties of benzodiazepine molecules, on account of its relation to physiology activity, solubility and rate of absorption [32]. Furthermore, it has a paramount value in preparative chemistry, since ionization constants divulge the conditions under which the substance can be isolated in maximal.

From the titration curves (acid *vs.* NaOH) in absence and presence of benzodiazepines at constant ionic strength, the acid dissociation constant of the complexes were calculated. With the help of Calvin-Bjerrum pH-titration [33], which is amended by Irving and Rossotti [34] the proton-ligand equilibrium constant for benzodiazepine were determined under experimental conditions. Considering the titration curves shown in Fig. 2, the average number of protons linked with the ligand ($\bar{\eta}_A$) at different pH values was calculated by deploying the acid and ligand. Metal-ligand and proton-ligand stability constants are listed in Table-2.

The proton-ligand formations ($\bar{\eta}_A$) were calculated by Irving and Rossotti expression:

TABLE-1
THE η_A , η , pNX AND pLZ VALUES FOR V(V)-NIFOXIPAM (NX) AND V(V)-LORAZEPAM (LZ) SYSTEM AT 298 K

Vanadium(V)-NX							Vanadium(V)-LZ						
pH	KOH (mL)			η_A	η	pNX	pH	KOH (mL)			η_A	η	pLZ
	V_A	V_L	V_M					V_A	V_{L+A}	V_{M+L+A}			
4.6	3.389	3.393	3.401	1.999041	0.004796	4.901238	3.9	3.435	3.438	3.445	1.999282	0.004191	4.201186
4.8	3.390	3.394	3.402	1.999041	0.004796	5.101238	4.0	3.436	3.439	3.446	1.999282	0.004191	4.301186
4.9	3.391	3.395	3.403	1.999041	0.004795	5.201238	4.2	3.437	3.440	3.447	1.999282	0.004191	4.501186
5.2	3.392	3.397	3.405	1.998802	0.004796	5.501290	4.4	3.440	3.441	3.449	1.999761	0.004789	4.701082
5.4	3.393	3.399	3.406	1.998562	0.004197	5.701343	5.0	3.443	3.442	3.452	2.000239	0.005984	5.300978
5.6	3.395	3.401	3.407	1.998562	0.003597	5.901343	5.2	3.445	3.446	3.453	1.999761	0.004190	5.501082
5.8	3.397	3.403	3.409	1.998562	0.003597	6.101343	5.4	3.447	3.448	3.454	1.999761	0.003591	5.701082
6.0	3.399	3.405	3.412	1.998562	0.004196	6.301343	5.6	3.449	3.451	3.455	1.999521	0.002394	5.901134
6.2	3.401	3.407	3.415	1.998562	0.004795	6.501343	5.8	3.452	3.453	3.456	1.999761	0.001795	6.101082
6.4	3.403	3.409	3.417	1.998562	0.004795	6.701343	6.0	3.454	3.456	3.459	1.999521	0.001795	6.301134
6.6	3.412	3.419	3.425	1.998323	0.003596	6.901395	6.2	3.458	3.461	3.467	1.999282	0.003591	6.501186
6.8	3.429	3.435	3.442	1.998563	0.004193	7.101342	6.6	3.469	3.471	3.478	1.999521	0.004188	6.901134
7.0	3.445	3.461	3.472	1.996170	0.006593	7.301864	6.8	3.509	3.513	3.512	1.999044	-0.00060	7.101238
7.5	3.468	3.478	3.485	1.997607	0.004191	7.801550	7.0	3.514	3.522	3.527	1.998088	0.002990	7.301446
7.7	3.471	3.481	3.487	1.997608	0.003592	8.001550	7.2	3.516	3.526	3.531	1.997610	0.002990	7.501550
7.9	3.475	3.487	3.489	1.997129	0.001197	8.201655	7.8	3.518	3.528	3.536	1.997610	0.004784	8.101550
8.2	3.478	3.488	3.490	1.997608	0.001197	8.501550	8.0	3.52	3.531	3.539	1.997371	0.004784	8.301602
8.4	3.482	3.489	3.491	1.998326	0.001197	8.701394	8.2	3.521	3.532	3.541	1.997371	0.005382	8.501602
8.6	3.485	3.491	3.493	1.998565	0.001197	8.901342	8.4	3.522	3.533	3.542	1.997371	0.005382	8.701602
8.8	3.486	3.492	3.494	1.998565	0.001196	9.101342	8.8	3.523	3.534	3.543	1.997372	0.005382	9.101602
9.1	3.487	3.493	3.495	1.998565	0.001196	9.401342	9.4	3.524	3.535	3.545	1.997372	0.00598	9.701602

Fig. 1. pH metric titration curve pH vs. vol. of alkali for (a) LZ-V(V) & (b) NX-V(V) complex at 298 K

Fig. 2. Formation curve for (a) NX-V(V) & (b) LZ-V(V) complex plotting of η_A vs. pH at 298 KTABLE-2
PROTON-LIGAND AND METAL-LIGAND STABILITY CONSTANTS OF VANADIUM(V)-BENZODIAZEPINE COMPLEXES

Ligand	pK ₁			pK ₂			System	Temp. (K)	log K ₁	log K ₂
	298 K	308 K	318 K	298 K	308 K	318 K				
NX	9.35	8.29	7.82	4.61	4.37	3.98	V(V)-NX	298	7.06	3.69
LZ	9.39	8.87	8.51	4.54	4.09	3.89		308	6.81	3.37
								318	6.21	2.91
							V(V)-LZ	298	6.69	3.32
								308	6.3	3.03
								318	5.91	2.95

NX = Nifoxipam, LZ = Lorazepam

$$\bar{\eta}_A = \gamma - \frac{(V_L - V_A)(N^0 + E^0)}{(V_{\text{total}} + V_A)T_L^0} \quad (1)$$

where, V_A and V_L are the volumes of alkali (mL) needed to reach the same pH in ligand and acid titration curves, respectively, T_L^0 is the total ligand concentration in 40 mL solution, γ is the total number of free protons linked to ligand molecule, N^0 is the normality of the alkali, E^0 is the initial concentra-

tion of free acid and V_{total} is the total volume (mL) of titration solution.

The average number of metal ion linked with the ligand ($\bar{\eta}$) at different pH values was determined from the ligand and metal ion titration curve shown in Fig. 3 using the following equations:

$$\bar{\eta}_A = \frac{(V_M - V_L)(N^0 + E^0)}{(V_{\text{total}} + V_L)\bar{\eta}_A T_M^0} \quad (2)$$

Fig. 3. Formation curve for (a) NX-V(V) & (b) LZ-V(V) complex plotting of η vs. pH at 298 K

$$pL = \log_{10} \left(\frac{\sum_{n=0}^{n=i} \beta_n^H \left(\frac{1}{\text{anti log pH}} \right) \cdot \frac{V_{\text{total}} + V_M}{V_{\text{total}}}}{T_L^0 - \bar{\eta} T_M^0} \right) \quad (3)$$

where T^0_m is the total concentration of metal present in the solution, V_M is the volume (mL) of metal ions present in the solution and β_n^H is the overall proton ligand stability constant. At different pH values, the value of ($\bar{\eta}$) and pL for metal ion were computed. The plots of ($\bar{\eta}$) vs. pL values for the solution containing molar ratio 1:1 (metal:ligand) are displayed in Fig. 4. A plot of η_A against pL in Fig. 5 revealed that the number of species could be formed from ligand-metal interaction by the number of maxima. Here, the ligand undertaken for current study contains a hydroxyl group which is capable of donating a proton and the remaining anion can behave as a complexing agent. The amino group of benzodiazepine is responsible for complexation through nitrogen atom with metal ion. The pK_1 value (9.62) and pK_2 (4.97) at 293 K can be estimated.

Now, it is obvious that there is a competition between the metal ion and the protons for capturing the ligand due to which there would be a change in pH of solution during complexation. Eventually, the complexation reaction can be studied potentiometrically. There is no tendency to form hydroxo complexes, as during the titration no precipitates were formed [35].

Thermodynamic parameters: Thermodynamic parameters *viz.* Gibb's free energy change (ΔG) for formation of complexes were computed using eqn. 4. Furthermore, enthalpy (ΔH) was attained from the slope of the plot $\log K_i$ against $1/T$ (Fig. 6) using the graphical representation of Van't Hoff equation (eqn. 5). From the ΔG and ΔH values, one can obtain the entropy change (ΔS) using eqn. 6. All the thermodynamic parameters of complexes are shown in Table-3.

$$\Delta G = -2.303RT \log K \quad (4)$$

$$\Delta H = \frac{2.303RT_1T_2}{(T_2 - T_1)} \log K \quad (5)$$

$$\Delta S = \frac{(\Delta G - \Delta H)}{T} \quad (6)$$

Fig. 4. Formation curve for (a) NX-V(V) & (b) LZ-V(V) complex plotting of pL vs. η at 298 K

Fig. 5. Formation curve for (a) NX-V(V) & (b) LZ-V(V) complex plotting of pL vs. η_A at 298 K Fig. 6. van't Hoff plot $\log K_i$ against $1/T$ for (a) NX-V(V) & (b) LZ-V(V) complexTABLE-3
THERMODYNAMIC PARAMETERS OF BENZODIAZEPINE COMPLEXES FORMATION WITH VANADIUM(V) METAL ION

System	Temp. (K)	ΔG (kJ/mol)		ΔH (kJ/mol)		ΔS (kJ/mol)	
		ΔG_1	ΔG_2	ΔH_1	ΔH_2	ΔS_1	ΔS_2
V-NX	298	-4843.15	-3235.37	-149169	-99649.3	484.3151	323.5366
	308	-4753.81	-3010.58	-146417	-92725.7	475.3811	291.2830
	318	-4525.26	-2646.90	-139378	-81524.6	452.5260	248.0431
V-LZ	298	-4709.76	-2973.53	-145060	-91584.9	470.9756	297.3535
	308	-4560.92	-2747.04	-140476	-84608.8	456.0916	265.7849
	318	-4402.56	-2680.73	-135599	-82566.6	440.2561	251.2134

The negative ΔG values signify that both the complexation process and the dissociation of the ligand are spontaneous [36]. The negative values of enthalpy change (ΔH) and decrease in the metal-ligand stability constant ($\log K_i$) with increase in temperature for the complexation indicates that entire complexation reactions are favourable at lower temperature and exothermic in nature. It also revealed that the metal-ligand binding process is enthalpy driven and metal-ligand bonds are quite strong [37]. The positive values of entropy change (ΔS) for

the complexation process signifies that the complex formation is entropically favourable [38].

Conclusion

According to data obtained from the titration curves, it is perceived that the deviation for all compositions consisting acid and ligand, acid, ligand and metal commenced from pH = 3.9 and 4.6. The value of $\log K_i$ varies little which imply that the complex formation is evolving simultaneously between

vanadium and benzodiazepines ligands. Metal ion solution used in the current study was very diluting which ceases the possibility of emergence of polynuclear complexes or hydrolysis of vanadium (V) metal ion. The formation of metal complexes is sustained by the decrease in pH for the metal titration curves relative to ligand titration curve. It is clear from the data the negative values of ΔH , ΔG and positive ΔS are in favour of the complex formation and revealed that the reactions are exothermic in nature. After going through all the complexation, it is found that there is a decrease in proton ligand stability constant and metal-ligand stability constant values with increase in temperature. Therefore, at higher temperature the protons can liberate easily.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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