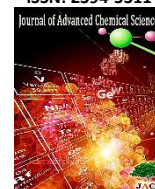




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journal homepage: www.jacsdirectory.com/jacsStudy of Zn²⁺- Famotidine Complexes by Polarography

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ABSTRACT

The complexes of famotidine and Zn²⁺ was investigated using D.C. polarography. The polarographic technique was used to determine the kinetic parameters (K_{on} , αn) and thermodynamic parameters such as enthalpy change (ΔH°), free energy change (ΔG°) and entropy change (ΔS°) of Zn²⁺ complexes with famotidine. The electrode processes were irreversible and diffusion controlled.

1. Introduction

Famotidine (Fig. 1) is pale yellowish-white, crystalline powder. It is sensitive to light, freely soluble in dimethylformamide and in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, practically insoluble in acetone, in alcohol, in chloroform, in ether and in ethyl acetate.

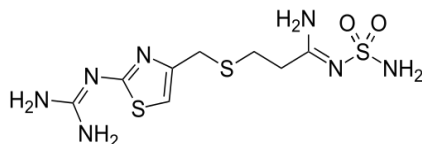


Fig. 1 3-[(2-(diaminomethyleneamino)thiazol-4-yl)methylthio]-N'-sulfamoylpropanimidamide

Famotidine, a competitive histamine H₂-receptor antagonist, is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions. Famotidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of famotidine include an increase in gastric bacterial flora such as nitrate-reducing organisms. Famotidine is given to surgery patients before operations to prevent postoperative nausea and to reduce the risk of aspiration pneumonitis. Famotidine is also given to some patients who take NSAIDs, to prevent peptic ulcers. It serves as an alternative to proton-pump inhibitors. Famotidine has also been used in combination with an H₁ antagonist to treat and prevent urticaria caused by an acute allergic reaction. It has been found to decrease the debilitating effects of chronic heart failure by blocking histamine [1-4].

Famotidine has been studied and determined by several procedures /techniques including spectrophotometric/spectrophotometry [5-8], Spectrofluorimetry [9], colorimetry [10], potentiometry [11-12], HPLC [13-15]. Many electrochemical procedures have been reported for the determination of famotidine. Famotidine has been determined in different samples by different techniques as Square wave adsorptive stripping voltammetric [15-17], Square wave voltammetry [18], DPP [19] and others [20,21]. Study of famotidine complexes have been done with some metals [22,23].

Here attempts have been made to study the electroreduction of various complexes of famotidine in various experimental conditions using direct current polarography.

Zinc is considered an essential element, because all living organisms need zinc. Because the amount of zinc present in nature varies widely, living organisms have natural processes that regulate their uptake of zinc. Zinc is essential for human health. Adequate daily intake of zinc is vital for the proper functioning of the immune system, digestion, reproduction, taste, smell, and many other natural processes.

There are 2–4 grams of zinc [24] distributed throughout the human body. Most zinc is in the brain, muscle, bones, kidney, and liver, with the highest concentrations in the prostate and parts of the eye [25]. Semen is particularly rich in zinc, which is a key factor in prostate gland function and reproductive organ growth [26]. In humans, zinc plays "ubiquitous biological roles" [27]. It interacts with "a wide range of organic ligands", and has roles in the metabolism of RNA and DNA, signal transduction, and gene expression. Famotidine – zinc complex was synthesized by Muhammad Amin et al [28]. Now this is the time to report famotidine – zinc complex behavior by D.C. polarography.

2. Experimental Methods

2.1 Apparatus

The digital D.C. polarograph (CL-357) of Elico Limited was used to record current-voltage data. This equipment has the three electrode assembly, dropping mercury electrode as working electrode, calomel as reference electrode and platinum electrode as counter electrode. The current responses and applied potential were recorded at scan rate 150 mV/min. Dropping mercury electrode had the characteristics $m = 2.422$ mg/sec, $t = 2.5$ sec and $h = 60$ cm.

The Elico digital pH meter model 111E was used to measure the pH of the analytes.

2.2 Proposed Procedure

The general procedure used to produce DC polarograms was as follows: An aliquot (10 mL) of experimental solution which contains drug (famotidine), metal solution, supporting electrolyte/ buffer, Triton-X-100 (maxima suppresser) and water was placed in a dry, clean polarographic cell and deoxygenated with nitrogen for 15 min. the current-voltage values were measured manually.

The negative potential was applied to the working electrode with 150 mV/min scan rate and 100 nA/div sensitivity of current measurement. After the background polarogram had been obtained, aliquots of the required amounts of Famotidine solution were added.

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2.3 Reagents

Famotidine was obtained from Panchseel Organics Ltd., Mumbai, Maharashtra, India. Famotidine was dissolved in water. All solutions were prepared freshly with triple distilled water and analytical reagent grade chemicals (MERCK).

Analytical grade salts of zinc sulphate $[\text{ZnSO}_4]$ of strength 2.5×10^{-2} M were used for present study. Aqueous buffers of different pH were prepared. pH was adjusted by 0.1 M HCl and 0.1 M NaOH. 1.0 M KNO_3 was used as supporting electrolyte for NiNO_3 , ZnSO_4 , PbNO_3 and 1.0 M acetate buffer (pH = 4.37) for $\text{Cd}(\text{CH}_3\text{COO})_2$. All solutions were prepared in triple distilled water. Triton X-100 (0.001%) was used to suppress polarographic maxima. The depolariser (metal) and ligand (drug) were taken in different ratio.

3. Results and Discussion

Pure zinc(II) shows a well-defined wave in 0.1 M KNO_3 at $E_{1/2} = -1.0$ volts vs S.C.E. shift in half wave potential of Zn(II) towards negative potential and decrease in the diffusion current with increase in the concentration of the famotidine confirms complex formation. Zinc undergoes $2e^-$ reduction with famotidine. System has been studied at different ligand concentrations in 40 % and 60 % methanol medium, at different pH and different temperatures.

The plots of $\log [i/(i_d - i)]$ vs $E_{d.e.}$ were linear with slope values much higher than expected for reversible reaction, which suggests that electrode reaction is irreversible. Kinetic parameters (K^0_{fh} , αn) are calculated by using Meites-Israel and Gaur-Bhargava methods at different experimental conditions. Polarographic characteristics and kinetic parameters are summarised in Table 1 to 4.

Table 1 Effect of ligand concentration on the half wave potential of Zn(II) in 40% Ethanol medium. (pH = 7.89; Triton-X-100 = 0.001%; Temperature = 298 ± 1 K)

Conc. (M)	$E_{1/2}$ (Volt)	$i_d \times 100$ nA	D ($\text{cm}^2 \text{sec}^{-1}$)	Slope (V)	αn (M.I.) (V)	αn (G.B.) (V)	K^0_{fh} (M.I.) (cm sec^{-1})	K^0_{fh} (G.B.) (cm sec^{-1})
1.32×10^{-3}	-1.167	14.0	12.627	0.0648	0.8360	0.9123	5.34×10^{-17}	2.25×10^{-18}
2.65×10^{-3}	-1.189	13.1	2.7639	0.0657	0.8243	0.8996	2.10×10^{-17}	8.73×10^{-19}
3.98×10^{-3}	-1.234	12.2	1.0654	0.0668	0.8105	0.8845	5.96×10^{-18}	2.32×10^{-19}
5.31×10^{-3}	-1.256	11.7	0.5511	0.0673	0.8048	0.8783	2.82×10^{-18}	1.06×10^{-19}
6.64×10^{-3}	-1.272	11.2	0.3232	0.0679	0.7981	0.8710	1.83×10^{-18}	6.79×10^{-20}
7.96×10^{-3}	-1.287	10.6	0.2010	0.0682	0.7943	0.8669	1.09×10^{-18}	3.97×10^{-20}
9.29×10^{-3}	-1.296	9.8	0.1262	0.0683	0.7928	0.8652	7.08×10^{-19}	2.53×10^{-20}
10.6×10^{-3}	-1.327	9.1	0.0833	0.0685	0.7910	0.8632	2.43×10^{-19}	8.05×10^{-21}

Table 2 Effect of ligand concentration on the half wave potential of Zn(II) in 60% ethanol medium. (pH = 7.89; Triton-X-100 = 0.001%; Temperature = 298 ± 1 K)

Conc. (M)	$E_{1/2}$ (Volt)	$i_d \times 100$ nA	D ($\text{cm}^2 \text{sec}^{-1}$)	Slope (V)	αn (M.I.) (V)	αn (G.B.) (V)	K^0_{fh} (M.I.) (cm sec^{-1})	K^0_{fh} (G.B.) (cm sec^{-1})
1.32×10^{-3}	-1.162	13.2	11.225	0.0634	0.8539	0.9319	2.63×10^{-17}	1.05×10^{-18}
2.65×10^{-3}	-1.176	12.5	2.5165	0.0649	0.8341	0.9102	1.94×10^{-17}	8.06×10^{-19}
3.98×10^{-3}	-1.215	11.8	0.9967	0.0658	0.8228	0.8979	5.87×10^{-18}	2.29×10^{-19}
5.31×10^{-3}	-1.238	11.3	0.5141	0.0668	0.8110	0.8850	3.57×10^{-18}	1.37×10^{-19}
6.64×10^{-3}	-1.261	10.6	0.2895	0.0672	0.8061	0.8798	1.64×10^{-18}	6.06×10^{-20}
7.96×10^{-3}	-1.277	9.9	0.1753	0.0682	0.7946	0.8671	1.37×10^{-18}	5.13×10^{-20}
9.29×10^{-3}	-1.284	9.3	0.1137	0.0693	0.7817	0.8531	1.69×10^{-18}	6.58×10^{-20}
10.6×10^{-3}	-1.311	8.7	0.0761	0.0693	0.7815	0.8529	6.16×10^{-19}	2.23×10^{-20}

Table 3 Effect of pH on zinc-famotidine system. (Famotidine Conc. = 3.32×10^{-3} ; Triton-X-100 = 0.001%; Temperature = 298 ± 1 K)

pH (± 0.01)	$E_{1/2}$ (Volt)	i_d μA	D ($\text{cm}^2 \text{sec}^{-1}$)	αn (M.I.) (V)	αn (G.B.) (V)	K^0_{fh} (M.I.) (cm sec^{-1})	K^0_{fh} (G.B.) (cm sec^{-1})
4.35	-1.133	15.7	2.5405	0.8408	0.9176	5.86×10^{-17}	2.68×10^{-18}
6.13	-1.175	14.1	2.0491	0.8229	0.8981	3.01×10^{-17}	1.31×10^{-18}
7.89	-1.213	12.5	1.6104	0.8146	0.8890	1.17×10^{-17}	4.72×10^{-19}
9.05	-1.286	11.8	1.4351	0.7930	0.8655	3.21×10^{-18}	1.16×10^{-19}
10.23	-1.324	10.9	1.2245	0.7883	0.8603	1.17×10^{-18}	3.88×10^{-20}

Table 4 Effect of temperature on zinc -famotidine system. (pH = 7.89; Famotidine Conc. = 3.32×10^{-3} ; Triton-X-100 = 0.001%)

Temp. ($^\circ\text{C}$)	$E_{1/2}$ (Volt)	i_d μA	D ($\text{cm}^2 \text{sec}^{-1}$)	αn (M.I.) (V)	αn (G.B.) (V)	K^0_{fh} (M.I.) (cm sec^{-1})	K^0_{fh} (G.B.) (cm sec^{-1})
20	-1.209	11.5	1.3632	0.7968	0.8695	2.83×10^{-17}	1.25×10^{-18}
25	-1.212	12.6	1.6364	0.8151	0.8896	1.19×10^{-17}	4.80×10^{-19}
30	-1.214	13.3	1.8233	0.8321	0.9081	5.27×10^{-18}	1.97×10^{-19}
35	-1.213	14.0	2.0203	0.8493	0.9269	2.54×10^{-18}	8.83×10^{-20}
40	-1.216	14.6	2.1972	0.8620	0.9408	1.32×10^{-18}	4.29×10^{-20}

Further, thermodynamic parameters (ΔH° , ΔH° , ΔG° , ΔS°) have been reported in Table 5. The value of slope of the plot ($\log K^0_{fh}$ vs $1/T$) comes out to be 6.122×10^3 .

Table 5 Thermodynamic parameters at different temperatures

Temp. ($^\circ\text{C}$)	ΔH° (J/Mole)	ΔH° (J/Mole)	ΔG° (J/Mole)	ΔS° (J/K)
20	11.7218×10^4	11.4782×10^4	11.0681×10^4	13.9986
25	11.7218×10^4	11.4741×10^4	11.4770×10^4	-0.09750
30	11.7218×10^4	11.4699×10^4	11.8798×10^4	-13.5269
35	11.7218×10^4	11.4658×10^4	12.2677×10^4	-26.0364
40	11.7218×10^4	11.4616×10^4	12.6432×10^4	-37.7517

4. Conclusion

From the values reported in table 1 to 4, it can be concluded that values of i_d and D decreases with increase in the concentration of complexing agent (drug). Further, values of K^0_{fh} i.e. formal forward rate constant, calculated by Meites-Israel and Gaur-Bhargava's methods, decreases with increasing concentration of drug which indicates decrease of reversibility means increase in irreversibility. Further, when complexation was carried out at different pH and different temperatures, values of K^0_{fh} decrease with increasing pH and temperature separately hence reversibility decreases or irreversibility increases with increasing pH and temperature.

The values of various quantities present in Table 5 show that activation free energy change (ΔG°) is positive at all the temperatures suggesting the non-spontaneous nature of electrode process. Negative value of ΔS° (excepting temperature 20°C) suggests that formation of activated state is accompanied by decrease of entropy but at 20°C temperature it accompanied by increase of entropy.

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