Evaluation of Stability Constants of Mesalamine with Lanthanum (III) and Neodymium (III) by Potentiometry

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ABSTRACT

Potentiometry is one of the most convenient and successful technique employed for metal complex equilibrium measurements. The binary complexes of some transition metal (III) ions with Mesalamine were studied using potentiometric titrations. In the present work, the interactions of transition metal ions La(III) and Nd(III) with Mesalamine has been investigated in double distilled water mixture at 0.2 M ionic strength at temp 25 °C + 1.00C by potentiometrically. Proton ligand (pK) and metal-ligand (logK) stability constant were determined by using Calvin Bjerrum titration technique as modified by Irving & Rossoti.

Keywords: Potentiometry, Transition metals, Stability constant, Mesalamine

I. INTRODUCTION

Considerable research work has been done on the study of complexes in solution in last five decades. Rossotti and Rossotti1 have define a complex as a species formed by the association of two more simple species each capable of independent existence, when one of the simple species is a metal ion the resulting entity is known as metal complex.

The term ligand some time applied to the particular atom in the molecules by means of which the molecules is attached to the central metal atom or it may be applied to the molecules as whole some ligand are attached to the metal atom more than one doner atom in such a manner as to formed heterocyclic ring. This is known as chelation.

The stability of complex in a solution is governed by the nature of central atom and the ligands. Chelation as well as stability is governed by nature of metal. Nature of metal ion also plays an important role in chelation and stability of complexes. The extensive

work in co-ordination complexes have been made possible with the help of various experimental techniques and has led in number of empirical conclusions which have been detailed by Martell2.

Stability order of metal ions transition metal ions is found by Irving and Williams3 by comparing the ionic radius and second ionization potential of the metal ions because it is valid for most nitrogen and oxygen doner ligands.

The ligand Mesalamine is slightly soluble in cold water, ethanol, more soluble in hot water, soluble in hydrochloric acid. Mesalamine, also known as Mesalazine or 5-ASA. Mesalamine have been known for their strong complex forming ability. Now a day's Mesalamine is the recommended therapy for the induction and maintenance of remission of ulcerative colitis(UC).[4,5], Mesalamine is an anti-inflammatory drug used to treat inflammation of the digestive tract ulcerative colitis[6] and mild-to-moderate Crohn's disease.[7] The drug acts topically at the colonic mucosa to reduce mucosal inflammation,[5] yet

because the active drug is rapidly absorbed in the stomach and small intestine,[3] a number of oral formulations have been developed to deliver 5-ASA to the colon.[5,8]

The Mesalamine is β-hydroxy acid; as the name signifies, this compound contains both -NH$_2$ amine and –COOH acidic groups. The Literature survey reveals that no work has been reported on complex formation of Mesalamine with transition metal ions in aqueous medium. Therefore in order to understand the complex formation behavior of Mesalamine at ionic strength 0.2M NaClO$_4$ at constant temperature i.e. 25 °C $\pm$ 1.0^{0}C is studied.

The structure of Mesalamine is shown as below:
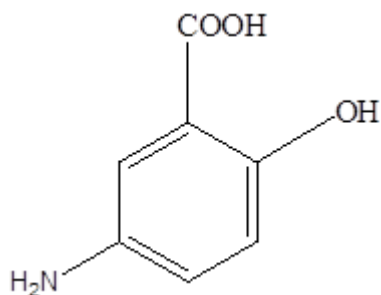
II. MATERIALS AND METHODS

Materials:

All the chemicals used were of high grade of purity (AR Grade). Ligand sample of Mesalamine in pure form was obtained from (HI- MIDIA) pharma industries and used as received. The ligand is soluble in water and its 0.1M concentration standard solution was prepared by dissolving the required quantity of ligand in double distilled water. NaClO$_4$ solution was prepared in carbon dioxide free double distilled water. Metal ions were used in the nitrate form (Indian Rare Earth). A carbonate free NaOH solution was prepared by dissolving the Anlar pellets in double distilled water and standardized against oxalic acid solution (0.2 M) and standard alkali solution was again used for standardization of HClO$_4$(0.2 M). The ionic strength was maintained at 0.2M by using NaClO$_4$ (B.D.H.). The ligand solution and acid solution were transferred into 100 ml beaker and titrated against NaOH solution. The titration was performed first without addition of metal and then in its presence.

Method:

The potentiometric titrations are performed by using a Welltronix model PM-300 digital pH meter in conjuction with a combined glass electrode consisting of glass and reference electrode. The combined glass electrode was activated by immersing 24 hours in 0.1 N hydrochloric acid and then 12 hours immersed in glass distilled water. The precautions suggested by Bates [9], Albert and Sergent [10] were adopted for smooth handling of electrode. The combined glass electrode was connected to pH meter. The metal ion solutions were prepared by dissolving metal nitrates (Indian Rare Earth) and standardized by EDTA [11].

By adopting standard procedure, all titrations were carried out under inert atmosphere by bubbling oxygen free nitrogen gas through an assembly. The buffer solution having the pH ranges 4.00 and 9.18 was used for the standardization of pH meter, before and after each titration. The ligand solution of Mesalamine was prepared in aqueous medium which was used for further titrations i.e. without and with the transition metals La(III) and Nd(III) maintaining ionic strength 0.2M NaClO$_4$ at constant temperature 25°C $\pm$ 1.0^{0}C. The titration curves were obtained by plotting experimental data, which were utilized to determine the proton ligand formation constants of ligand and their metals complexes. The relative stabilities of the complexes formed are investigated potentiometrically adopting Irving and Rossotti [12] pH –titration technique. Proton ligand (pK) and metal –ligand Stability constants (log K) are determined using the Microsoft office excel computer program.

Potentiometric procedure:

The experimental procedure involved potentiometric titrations of the solutions of:
1. Free HClO$_4$ (A)
2. Free HClO$_4$ + Ligand (A+L)
3. Free HClO$_4$ + Ligand +Metal ion (A+L+M)

The solutions were titrated against standard carbonate free sodium hydroxide at $25^0C \pm 1.0^0C$ using Irving – Rossotti pH titration techniques. The concentration of Perchloric acid(0.2M) and sodium perchlorate (1M) were kept constant for all sets. The water thermostat was used to maintain the temperature constant. The solutions were equilibrated in the thermostat for about 15 minute before titrations. The volume of every mixture was made up to 50 ml with double distilled water. The curves of pH versus ml-base solution were plotted (Figure-1 and 2) and Proton ligand (pK) and metal–ligand Stability constants (log K) are determined.

III. EXPERIMENTAL RESULTS AND DISCUSSION

The potentiometric titration curves of Mesalamine with transition metal ion is shown in fig.1 and fig.2. The pH of complex formation is much below than the pH of metal ion hydrolysis. These features of the pH metric studies confirm the formation of complexes by all the metal ions with Mesalamine The basicities of the ligand have been measured in term of their proton-ligand stability constant. Proton ligand stability constants (pK) of drugs were determined by point wise calculation method as suggested by Irving & Rossotti and are given in table 1. The formation constants for these complexes are given in table-2. It is found that in the ligand $\bar{n}H$ values ranges between 1 and 3 indicating the liberation of three protons during complexation. Therefore the drug gives three (pK).

The basicity of the ligand have been measured in terms of their proton-ligand stability constant. The interaction of metal ion with a base is similar to the neutralization reaction involving hydrogen ion. J.

Bjerrum [13] pointed out that the bases which have the strongest affinity for hydrogen ions form most stable complexes. This trend was observed in Mesalamine.The more basic ligands form more stable complexes. Similar linear relationship was shown by several workers [14-16] between the logK of a series of
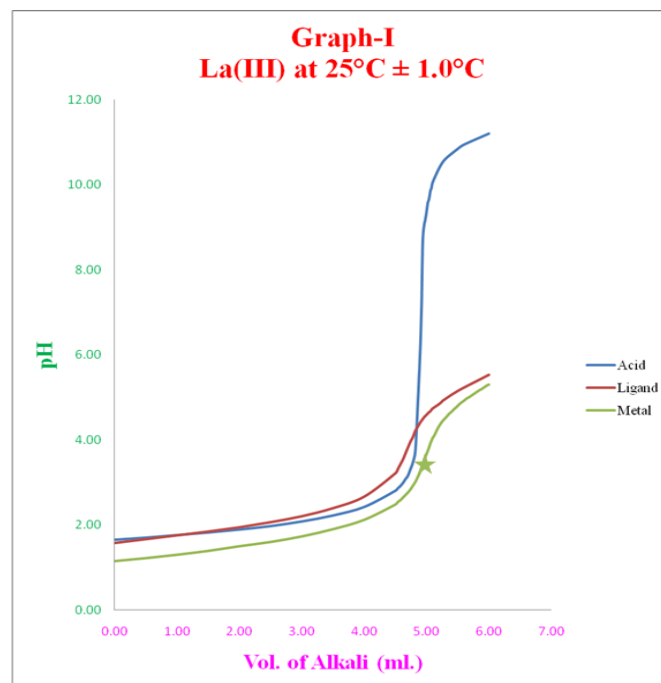
metal complexes derived from one metal ion with a set of similar ligands and their pK values.

Table 1. Proton ligand stability constants of Mesalamine at 0.2M ionic Strength

Medium – Water, Temperature- $25°C \pm 1.0^0C$.

Proton Ligand stability constants	Ionic Strengths 0.2M
pK_1^H	2.822
pK_2^H	6.194
pK_3^H	8.894

Table 2. Metal ligand stability constants of of Mesalamine at 0.2M ionic Strength.

Transition Metals	Metal Ligand stability constants		LogK$_1$/LogK$_2$	LogK$_1$-LogK$_2$
La(III)	$log\beta_2$	6.175	1.254	0.697
	$logK_1$	3.436		
	$logK_2$	2.739		
Nd(III)	$log\beta_2$	6.174	1.254	0.698
	$logK_1$	3.436		
	$logK_2$	2.738		

Figure 1. Representative titration curves for formation of La (III)- Mesalamine complexes at $25^e \pm 1.0^eC$ and 0.2M ionic strength in aqueous solution.
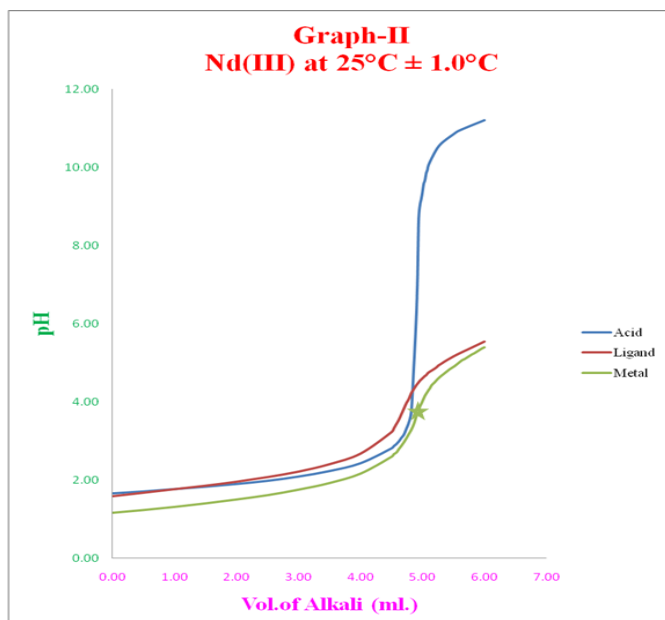
Figure 2. Representative titration curves for formation of Nd(III)- Mesalamine complexes at 25º ±1.0ºC and 0.2M ionic strength in aqueous solution.

IV. CONCLUSION

The metal ligand formation curve data for Mesalamine with transition metal ions indicate that the $\bar{n}$ value range between 0.653 to 1.488 and this suggests that metal ions form 1:1 complexes with ligand in solution. The logK values are evaluated by the computational techniques are in good agreement. The ratio of $LogK_1 / LogK_2$ is positive and greater than one in both cases. This implies that there is little or no steric hindrance to the addition of ligand molecule. The difference between $logK_1$ and $logK_2$ was 0.697 and 0.698 in both cases indicating the formation of 1:1 complexes.

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