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COMPARATIVE STUDY OF STABILITY CONSTANT OF ANTIBACTERIAL DRUGS WITH RARE EARTH METAL IONS

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ABSTRACT

In the present work, the stability constant of antibacterial drugs oxytetracycline hydrochloride (OTC), cefotaxime sodium (CFO) and ceftriaxone sodium (CFT) complexes with rare earth metal ions La (III), Ce (III), Nd (III), Sm (III), Gd (III), Tb (III) and Dy (III) have been investigated using pH metric titration technique in 20% (v/v) ethanol-water mixture at 25^{o}C and at an ionic strength of 0.1 M $NaClO_4$. The method of Calvin and Bjerrum as adopted by Irving and Rossotti has been employed to determine metal-ligand stability constant (log K) values. It is observed that rare earth metal (Lanthanide) ions forms 1 : 1 and 1 : 2 complexes.

Key words: pH metry, Stability constant, Rare earth metal, Antibacterial drugs.

INTRODUCTION

Drugs have various functional groups present in its structure, which can bind to metal ions present in human body. Metal complexes of drugs are found to be more potent than parent drugs. Chemistry of drugs attracts many researchers because of its application in medicinal study. The stability of metal complexes with medicinal drugs play a major role in the biological and chemical activity. Metal complexes are widely used in various fields, such as biological processes, pharmaceuticals, separation techniques, analytical processes etc. Most of the f-block elements form complexes. There are different kinds of ligand used for

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complexation. For the present investigation, antibacterial drugs OTC, CFO and CFT have been selected as ligand. They are used to treat many infections, common and rare. Literature survey reveals that a very few researchers have done such type of work using rare earth metal ions and antibacterial drug as a ligand[1-6]. Therefore, it was decided to study stabilitry constant of binary complexes of antibacterial drugs with rare earth metal ions La (III), Ce (III), Nd (III), Sm (III), Gd (III), Tb (III) and Dy (III) using pH metry.

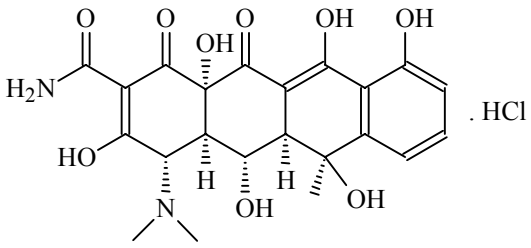

Fig. 1: Oxytetracycline hydrochloride (molecular formula $C_{22}H_{25}N_2O_9Cl$)

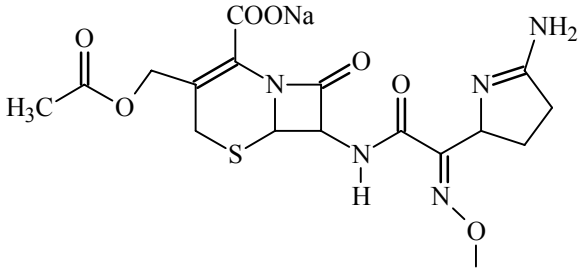

Fig. 2: Cefotaxime sodium (molecular formula $C_{16}H_{16}N_5O_7NaS_2$)

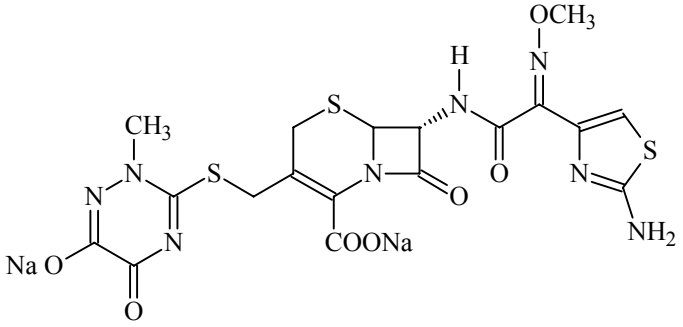

Fig. 3: Ceftriaxone sodium (molecular formula $C_{18}H_{16}N_8O_7Na_2S_3$)

EXPERIMENTAL

Materials and solution

The ligand OTC is soluble in ethanol while CFO and CFT are soluble in double distilled water. NaOH, $NaClO_4$, $HClO_4$ and metal salts were of AR grade. The solutions used in the potentiometric titration were prepared in double distilled water. The NaOH solution was standardized against oxalic acid solution (0.1 M) and standard alkali solution was again used for standardization of $HClO_4$. The metal salt solutions were also standardized using EDTA titration. All the measurements were made at 25°C in 20% ethanol-water mixture at 0.1 M $NaClO_4$ strength. Thermostat model SL-131 (Adar Dutt and Co (India) Pvt. Ltd. Mumbai) was used to maintain the temperature constant. The pH measurements were made using a digital pH meter model Elico L1-120 in conjunction with a glass and reference calomel electrode (reading accuracy ± 0.01) The pH-meter was adjusted with buffer of pH 4.00, 7.00 and 9.18.

Potentiometric procedure

For evaluating the protonation constant of the ligand and the formation constant of the complexes in 20% ethanol-water mixture with different metal ions; following three sets of solutions were prepared.

(A) $HClO_4$ (A)

(B) $HClO_4$ + Drug (A + L)

(C) $HClO_4$ + Drug + Metal (A + L + M)

The above mentioned sets were prepared by keeping M : L ratio, the concentration of perchloric acid and sodium perchlorate (0.1 M) were kept constant for all sets. The volume of every mixture was made upto 50 mL with double distilled water. The test solutions were magnetically stirred, NaOH was added stepwise and pH reading was recorded until stable values, within ± 0.002 pH units.

Table 1: Proton-ligand stability constant of antibacterial drugs at 0.1 M ionic strength in 20% (v/v) ethanol-water medium

Ligands (drugs)	Proton-ligand stability constant	
	pK_1	pK_2
OTC	---	4.3162
CFO	3.1563	10.763
CFT	4.0932	10.740

Table 2: Metal-ligand stability constant of rare earth metal ions with antibacterial drugs at 0.1 M ionic strength in 20% (v/v) ethanol-water medium

Ligands (Drugs)	Metal-ligand stability constant	La (III)	Ce (III)	Nd (III)	Sm (III)	Gd (III)	Tb (III)	Dy (III)
OTC	$\log K_1$	4.323	4.431	4.531	4.614	4.460	4.568	4.705
	$\log K_2$	3.350	3.426	3.730	3.959	3.858	4.094	4.149
	$\log \beta$	7.673	7.857	8.261	8.573	8.318	8.662	8.854
CFO	$\log K_1$	6.891	7.470	8.144	8.455	7.314	7.588	8.297
	$\log K_2$	5.658	6.236	6.807	7.187	6.249	6.631	7.208
	$\log \beta$	12.549	13.706	14.951	15.642	13.563	14.219	15.505
CFT	$\log K_1$	4.668	4.811	4.938	5.749	5.541	5.745	5.837
	$\log K_2$	3.776	4.041	4.103	4.820	4.673	4.710	4.773
	$\log \beta$	8.444	8.852	9.041	10.569	10.214	10.455	10.61

RESULTS AND DISCUSSION

Titration curves were obtained for different sets. During titration, no precipate was formed indicating that there is no tendency to form hydroxo complexes. The stability constants of the formed complexes were investigated in the pH range of 4-6. The mean value, the average number of protons associated with the ligand $\bar{n}_A$, at different pH values were calculated. The pKa values were determined from $\bar{n}_A$. Similarly $\bar{n}$ i.e metal ligand formation number, which can be defined as average number of ligand molecules coordinated to the metal ions, were also obtained using Irving and Rossotti method. The $\bar{n}$ values obtained between 0.2 to 0.8 indicates 1 : 1 complexation and when $\bar{n}$ lies in between 1.2 to 1.8, it indicates 1 : 2 complexation. The values of proton ligand stability constants (pKa) and metal ligand stability constant (log k) are represented in Tables 1 and 2, respectively. For the present investigation, we have studied the stability constants of trivalent lanthanide metal ions. Since we got $\bar{n}_A$ between 0.2 to 0.8 and 1.2 to 1.8 indicating 1 : 1 and 1 : 2 complex formation. In complexation data analysis, three types of equilibria should be considered i.e. protonation of ligand, hydrolysis of metal ions and three component equilibria given below -

$$pM^{n+} + qH^{+} + rL \rightleftharpoons [MpHqLr]^{n+} \; ; \; \beta qpr \qquad \ldots(1)$$

In our case we have considered q = 0 i.e. the formation of pure ML_n complexes. During the titrations, it was observed that the metal titration curves were displaced to the

right hand side of the ligand titration curves, indicating proton release upon complex formation of metal ion with the ligand[7].

The order of stability constants for all the three ligands OTC, CFO and CFT were as follows -

$La^{3+} < Ce^{3+} < Nd^{3+} < Sm^{3+} < Gd^{3+} < Tb^{3+} < Dy^{3+}$ and shows a break at gadolinium.

The ratio of log K_1/ log K_2 is positive and greater than one in all cases. This implies that there is little or no steric hindrance to the addition of secondary ligand molecule.

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