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pH-metric study of substituted thiopyrimidine complexes in mixed solvent media

M. P. Wadekar*, A. S. Shrirao and R. R. Tayade

Applied Chemistry Division, Govt. Vidarbha Institute of Science and Humanities, Amravati, Maharashtra, India

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ABSTRACT

The solution studies the proton-ligand stability constant pK and metal-ligand stability constants logk of binary (1 : 1) complexes of Ni(II), Cu(II) and Zn(II) with substituted thiopyrimidine drugs have been studied at 0.1M ionic strength in 70 % DMF-water mixture by Bjerrum method as adopted by Calvin and Wilson. It is observed that Ni(II), Cu(II) and Zn(II) metal ions form 1:1 and 1:2 complexes with ligands (L_1& L_2).The data obtained were used to estimate and compare the values of proton-ligand stability constant (pK) and metal-ligand stability constants (logk). From estimated data (pK and logk), the effects of substituents were studied.

Keywords: Substituted thiopyrimidine drugs, stability constant, pH-metry.

INTRODUCTION

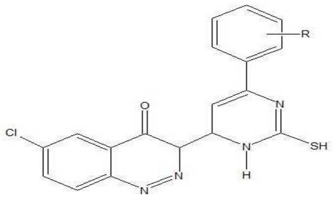
Pyrimidine moiety is an important class of nitrogen containing heterocycles [1] and is widely used as a key building block for pharmaceutical agents. Its derivatives exhibit antibacterial, antifungal[2], analgesic[3], calcium antagonist[4], anti-inflammatory[5] and anti-tumor activity[6]. In addition, several marine natural products with interesting biological activities containing pyrimidine core have recently been isolated[7].

Recently, there has been considerable interest in the study of binary and ternary complexes by pH-metric method[8-10] using biomolecules (drugs). Drugs have various functional groups present in its structure, which can bind to metal ions present in human body[11]. Metal complexes of drug are found to be more potent than parent drugs[12]. Chemistry of drugs attracts many researchers because of its applications in medicinal chemistry. Interesting results have been reported earlier on complex formation reactions of drug- transition metal ion complexes[13-15]. Coordination compounds play very important role in numerous chemical, biological and biochemical activities e.g. Chlorophyll, a magnesium complex essential for photosynthesis in plants; Haemoglobin, an iron complex, which carries oxygen to living organism cells; Coenzyme-Vitamin B_{12}, a cobalt complex which serves as a prosthetic group in metabolic activities of living organisms. The application of coordination chemistry is varied in the field of biological, biochemistry, medicine, agriculture, organometallic chemistry, solid state chemistry, catalysis and molecular receptors and devices. The metal ion complexes as a catalyst are invariably involved in various industrial processes.

Stability constant is well known tool for solution chemist, biochemist, and chemist. In general it help for determination the properties of metal-ligand reactions in water and biological system[16] . In the study of coordination compound in solution, first and foremost requirement is the knowledge of stability constant of complex. Reliable information of stability constant is of great importance in analytical and separation procedure. To remove undesirable and harmful metals from living organism, chelating agents are very much useful in biological systems. This gives importance to the study of determination of stability constant of metal complexes.

The complexes have been extensively studied in solution as well as in solid state by many workers, due to it's remarkable properties and high stability. Though vast amount of work has been done on stability constant of metal complexes. Many workers study the effect of transition metal on a stability of complex by pH metrically[17-19]. Also there is a investigation of stability constant of ligand with lanthanide metals[20-23].

In the present work, effect of metal ions such as Ni(II), Cu(II) and Zn(II) on the properties of complexes of substituted thiopyrimidines in 70% DMF+water mixture at 309K has studied. The ligands used are



L_1: R = -H

L_2: R = -2-Chloro

L_1: 6-chloro-3-(2-mercapto-6-phenyl-3,4-dihydropyrimidin-4-yl)cinnolin-4(3H)one
L_2: 6-chloro-3-(6-(2-chlorophenyl)-2-mercapto-3,4-dihydropyrimidi-4-yl) cinnolin-4(3H) one

EXPERIMENTAL SECTION

All chemicals used are of AR grade. The ligands (L_1) & (L_2) were synthesized in the laboratory by reported protocol. The stock solutions of the ligand was prepared by dissolving required amount of ligand in a of 70% (DMF+water) mixture.

Metal ions used (divalent metal ion in nitrates forms)
Ni(II), Cu(II) and Zn(II).
Stock solution
1M KNO_3 solution, 0.1M HNO_3 solution, 0.1M NaOH and 0.01M Transition metal ions solution are prepared in double distilled water . 0.01 M ligand (L_1 and L_2) solution in 70% (DMF –water) mixture.

- **Calvin –Bjerrum titration methods**

All pH-metric titrations and pH-measurements were carried out with EQIP-TRONIC DIGITAL pH meter model EQ-610 (accuracy ±0.05 units) with a glass and calomel electrodes assembly. at $(36\pm0.1)^0$c in 70% (DMF-water) mixture and at an inert atmosphere by bubbling nitrogen gas .

General procedure :
Types of Titrations
i) Free acid HNO_3(0.01 M)
ii) Free acid HNO_3(0.01 M) and ligand (20 x 10^{-4}M)
iii)Free acid HNO_3 (0.01 M) and ligand (20 x 10^{-4}) and metal ion (4 x 10^{-4}M) against standard 0.1N NaOH solution.

The ionic strength of all the solutions was maintained constant 1M by adding appropriate amount of KNO_3 solution. All the titrations were carried out in 70% (DMF-water) mixture and the reading were recorded for each 0.2 ml addition. The graph of volume of alkali added (NaOH) against pH were plotted.

CALCULATION

Titration curves are used to estimate the values of $\bar{n}_A$ (proton -ligand formation number) which are presented in Table-1 to 2. Formation curve are constructed between $\bar{n}_A$ and pH. The pH values at 0.5 $\bar{n}_A$ represent the pK values (proton-ligand dissociation constants) of respective ligand. Proton ligand dissociation constants (pK) are evaluated and presented in Table-3, which are calculated by half integral and verified by pointwise calculations method.

RESULTS AND DISCUSSION

The ligands involved in the present work may be considered as a monobasic acid having only one dissociable H^+ ion from thiolic -SH group and it can therefore, be represented as HL. The dissociating equillibria can be shown as.

$$HL \rightleftharpoons H^+ + L^-$$

By the law of mass action, we have,

$$k = \frac{[H^+][L^-]}{[HL]} \quad \text{……… (1)}$$

where, the quantities in bracket denote the activities of the species at equilibrium.

Calculation of Proton-Ligand Stability Constant ($\bar{n}_A$)

The plots between volume of NaOH and pH of the solution were used to determine the proton ligand stability constant (representing the replacement of H^+ ions from functional group of ligand with respect to pH value). The horizontal difference (V_2-V_1) was measured accurately between the titration curves of free acid and acid + ligand. It was used to calculate the formation number $\bar{n}_A$ at various pH values and fixed ionic strength $\mu = 0.1M$ using Irving and Rossotti's equation[1,2]

$$\bar{n}_A = \gamma - \frac{(V_2 - V_1)(N + E^0)}{(V^0 + V_1)T_L^0} \quad \text{…………. (2)}$$

where, V^0 is the initial volume of the solution. E^0 and TL^0 are initial concentrations of the mineral acid and ligand respectively. V_1 and V_2 are the volumes of alkali of normality N during the acid and ligand titration at given pH. γ is the replaceable proton from the ligand.

The data of $\bar{n}_A$ obtained at various pH along with the horizontal difference for some representative systems are represented in Table 1 to 2.

The metal–ligand formation number ($\bar{n}$) is estimated by Irving-Rossotti's equation.

$$\bar{n} = \frac{(V_3 - V_2)(N + E^0)}{(V^0 + V_2)\, n_A\, T_M^0} \quad \text{……… (3)}$$

where the notations have the same meaning as given in earlier equation. The horizontal difference (V_3-V_2) between the metal complex (A+M+L) and reagent (A+L) curve is used to evaluate the value of $\bar{n}$ using Irving Rossotti's equation.

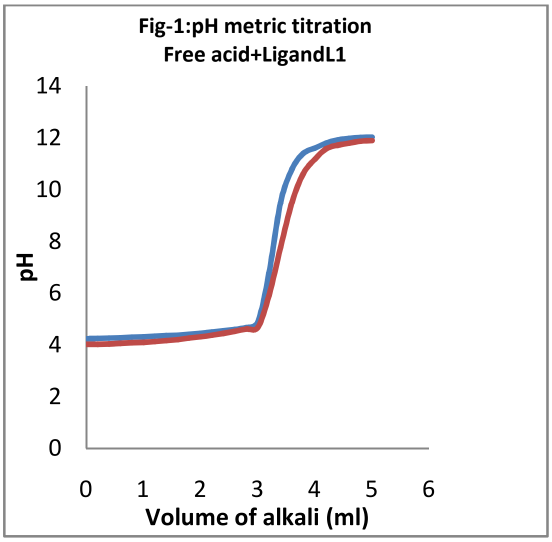


Fig-1:pH metric titration
Free acid+LigandL1

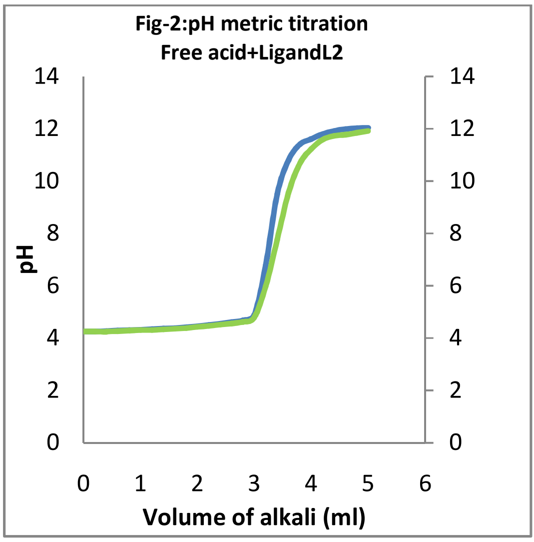


Fig-2:pH metric titration
Free acid+LigandL2

Table –1: Determination of $\overline{n}_A$ Values of L_1

pH	V_1	V_2	V_2-V_1	$\overline{n}_A$
5.00	3.02	3.07	0.05	0.8216
5.50	3.08	3.14	0.06	0.7863
6.00	3.14	3.21	0.07	0.7512
6.50	3.17	3.26	0.09	0.6805
7.00	3.22	3.32	0.10	0.6456
7.50	3.26	3.37	0.11	0.6108
8.00	3.29	3.42	0.13	0.5405
8.50	3.33	3.48	0.15	0.4705
9.00	3.36	3.54	0.18	0.3653
9.50	3.40	3.60	0.20	0.2958
10.00	3.45	3.67	0.22	0.2267
10.50	3.54	3.77	0.23	0.1941
11.00	3.65	3.91	0.26	0.0925
11.50	3.88	4.15	0.27	0.0651

Table – 2: Determination of $\overline{n}_A$ Values of L_2

pH	V_1	V_2	V_2-V_1	$\overline{n}_A$
5.00	3.02	3.06	0.04	0.8572
5.50	3.08	3.14	0.06	0.7863
6.00	3.14	3.20	0.06	0.7868
6.50	3.17	3.26	0.09	0.6805
7.00	3.22	3.32	0.10	0.6456
7.50	3.26	3.37	0.11	0.6108
8.00	3.29	3.42	0.13	0.5405
8.50	3.33	3.48	0.15	0.4705
9.00	3.36	3.54	0.18	0.3653
9.50	3.40	3.60	0.20	0.2958
10.00	3.45	3.66	0.21	0.2619
10.50	3.54	3.76	0.22	0.2292
11.00	3.65	3.90	0.25	0.1274
11.50	3.88	4.15	0.27	0.0651

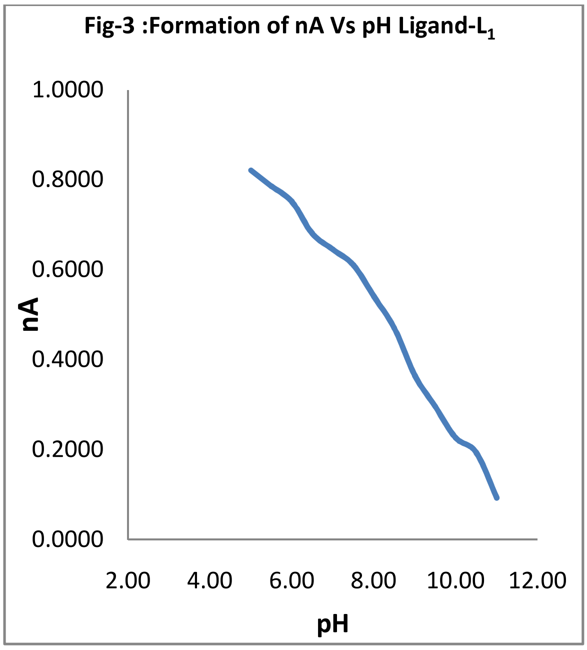


Fig-3 :Formation of nA Vs pH Ligand-L_1

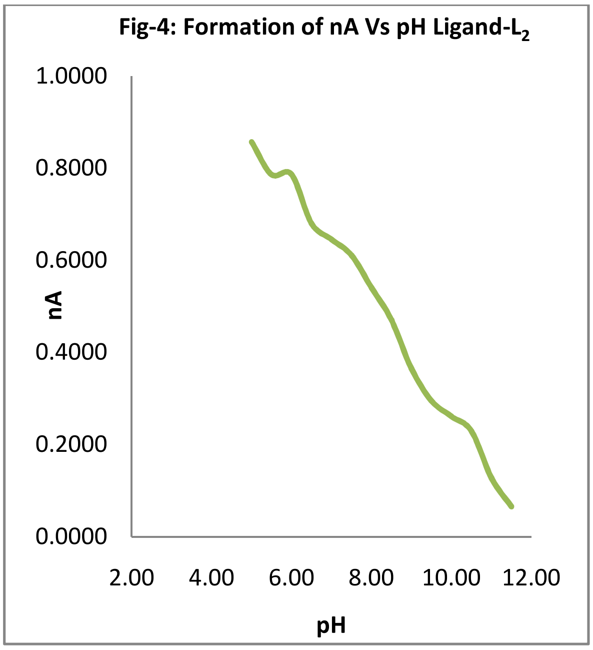


Fig-4: Formation of nA Vs pH Ligand-L_2

Table 3 : Proton –Ligand stability Constants (pk values)

Ligands	pK (Half Integral Method)	pK (Pointwise Method)
L_1: 6-chloro-3-(2-mercapto-6-phenyl-3,4-dihydropyrimidin-4-yl)cinnolin-4(3H)one	8.30	8.20
L_2: 6-chloro-3-(6-(2-chlorophenyl)-2-mercapto-3,4-dihydropyrimidi -4-yl) cinnolin-4(3H) one	8.10	8.00

Table – 4:
Determination of $\bar{n}$ System
L_1 + Ni(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.07	3.09	0.02	0.4336
5.50	3.14	3.17	0.03	0.6778
6.00	3.21	3.24	0.03	0.7077
6.50	3.26	3.30	0.04	1.0399
7.00	3.32	3.36	0.04	1.0938
7.50	3.37	3.42	0.05	1.4428

Table – 5:
Determination of $\bar{n}$ System
L_1 + Cu(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.07	3.09	0.02	0.4336
5.50	3.14	3.17	0.03	0.6778
6.00	3.21	3.24	0.03	0.7077
6.50	3.26	3.30	0.04	1.0399
7.00	3.32	3.36	0.04	1.0938
7.50	3.37	3.43	0.06	1.7313

Table – 6:
Determination of $\bar{n}$ System
L_1 + Zn(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.07	3.09	0.02	0.4336
5.50	3.14	3.16	0.02	0.4533
6.00	3.21	3.24	0.03	0.7077
6.50	3.26	3.29	0.03	0.7799
7.00	3.32	3.36	0.04	1.0938
7.50	3.37	3.42	0.05	1.4428

Table – 7:
Determination of $\bar{n}$ System
L_2 + Ni(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.06	3.08	0.02	0.4157
5.50	3.14	3.17	0.03	0.6779
6.00	3.20	3.23	0.03	0.6761
6.50	3.26	3.29	0.03	0.7800
7.00	3.32	3.36	0.04	1.0938
7.50	3.37	3.42	0.05	1.4428

Table – 8:
Determination of $\bar{n}$ System
L_2 + Cu(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.06	3.08	0.02	0.4157
5.50	3.14	3.17	0.03	0.6779
6.00	3.20	3.23	0.03	0.6761
6.50	3.26	3.29	0.03	0.7800
7.00	3.32	3.36	0.04	1.0938
7.50	3.37	3.41	0.04	1.1543

Table – 9:
Determination of $\bar{n}$ System
L_2 + Zn(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.06	3.08	0.02	0.4157
5.50	3.14	3.17	0.03	0.6779
6.00	3.20	3.24	0.04	0.9014
6.50	3.26	3.30	0.04	1.0400
7.00	3.32	3.37	0.05	1.3673
7.50	3.37	3.43	0.06	1.7314

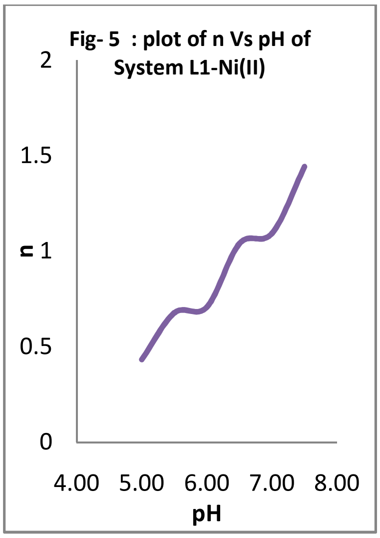


Fig- 5 : plot of n Vs pH of System L1-Ni(II)

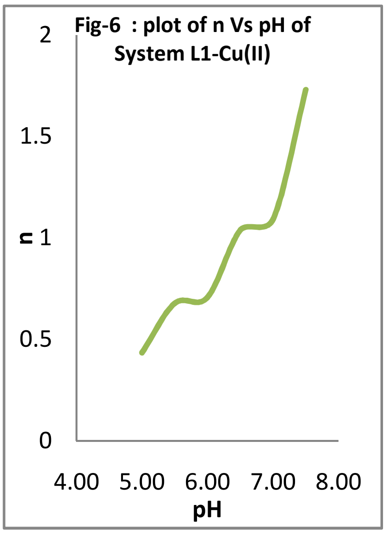


Fig-6 : plot of n Vs pH of System L1-Cu(II)

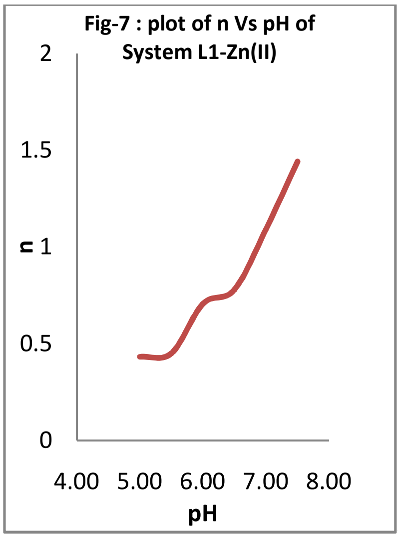


Fig-7 : plot of n Vs pH of System L1-Zn(II)

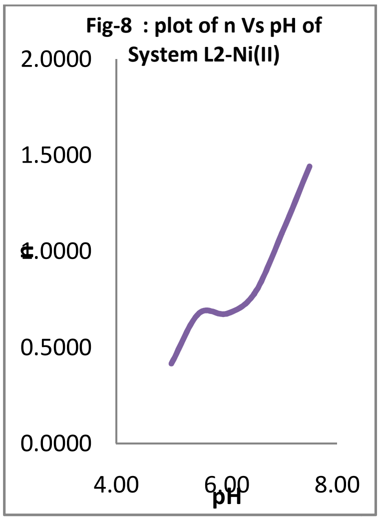


Fig-8 : plot of n Vs pH of System L2-Ni(II)

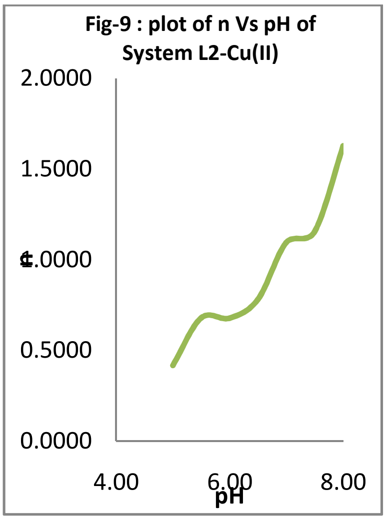


Fig-9 : plot of n Vs pH of System L2-Cu(II)

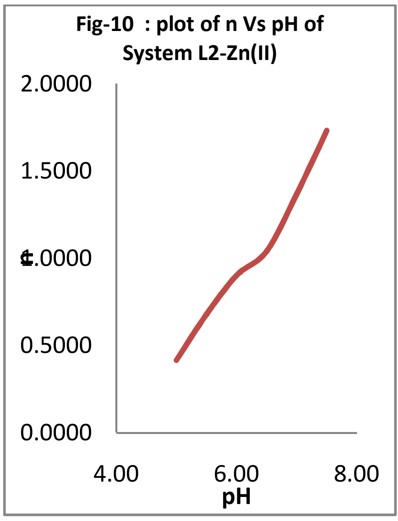


Fig-10 : plot of n Vs pH of System L2-Zn(II)

Table 10 : Metal –Ligand stability Constants (LogK values)

System : Ligand	+ Metal	$\log k_1$	$\log k_2$	$\log k_1/\log k_2$	$\log k_1-\log k_2$
L_1	Ni(II)	4.49	2.95	1.52	1.54
	Cu(II)	4.44	2.20	2.01	2.24
	Zn(II)	4.94	3.75	1.31	1.19
L_2	Ni(II)	5.84	4.45	1.31	1.39
	Cu(II)	5.34	3.15	1.69	2.19
	Zn(II)	5.49	4.00	1.37	1.49

CONCLUSSION

From the titration curves, it is observed that the deviation between (acid + ligand) curve and (acid +ligand + metal) curve for all systems started from pH = 4.10 this indicated the commencement of complex formation. Also change in colour from yellow to brown in the pH range from 4.10 to 11.50 during titration showed the complex formation between metal and ligand. The order of pK values of ligands are found to be pK ligand (L_2). < pK ligand (L_1). The more pK value of ligand (L_1) is attributed because (L_2) has electron withdrawing -Cl group which decrease the activity of ligand to form more stable complex.

From the table 10 it is observed that small difference between log K_1 and logK_2 values not more than 2.5 indicates the simultaneous formation of complex between metal ion and ligand. But in case of Cu(II) difference of stability constant is nearly 2.5 indicated than there is a stepwise formation of complex.

From the table-10 it is observed that, in case of Cu(II) ion there is a simultaneous formation of complex for both ligand L_1 and L_2 and in case of Zn(II) ion there is a stepwise formation of complex with both the ligand. But in case of Ni(II) ion, it shows simultaneous complex formation with Ligand L_1 and Stepwise complex formation with ligand L_2.

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