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Determination of stability constant of substituted thiopyrimidine drugs

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ABSTRACT

Substituted thiopyrimidine drugs are synthesize in laboratory by reported method. The physic-chemical study of substituted thiopyrimidine carried out by pH-metric method by considering their interaction with Ni(II), Cu(II) and Zn(II) metal ions at 0.1 M ionic strength in 70 % DMF-water mixture by Bjerrum method as adopted by Calvin and Wilson. These study useful to understand type of complex formation between transition metal ion and thiopyrimine drugs(L_1 *and* L_2*). Present work deals with determination and comparison of stability constant.*

Keywords: substituted thiopyrimidines, stability constants (pK), pH-metry

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INTRODUCTION

In medicinal chemistry pyrimidine derivative are very well known for their therapeutic applications. Many pyrimidine derivative have been developed as chemotherapeutic agents and are widely used. A survey of literature has shown that compounds having a Antiviral [1], antibacterial[2], antimalarial[3], antihypertensive[4] and anti-inflammmatory activities[5,6]. So physico-chemical study of substituted thiopyrimidine has an importance.

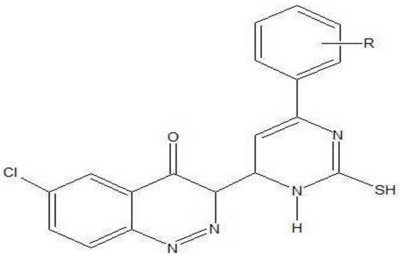
Mixed metal complexes play vital role in various biological systems[7] and in different fields of chemistry[8,9]. Hence, the stability and reactivity of these complexes have been an active field of research[10]. Due to growing interest in the use of sulphur containing compounds in analytical as well as structural studies of metal complexes, sulphur containing substituted thiopyrimidine drugs are taken in present study. The significance of these thiopyrimidine enhanced by the fact that it displays independent therapeutic activity[11].

Coordination compounds also played a very important role in biological activities for removal of undesirable and harmful metals from living organisms. The application of coordination chemistry is varied in the field of biology, 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 to help for determination the properties of metal-ligand reactions in water and biological system[12]. In the study of coordination compound in solution, first and foremost requirement is the knowledge of stability constant of complex. For correct interpretation of complex, the knowledge of stability constant is essential. 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.

Many workers study the effect of transition metal on a stability of complex by pH metrically[13,14,15,16]. The most important characteristics of the central atom which influence the stability of complex compounds are the degree of oxidation, the radius and electronic structure. The strength of binding of ligand to the central metal ion is depending on structure of ligand molecule or ions[17,18,19]. The stability of complexes is dependent upon the size and number of chelating rings also. The structure of chelating agent determines the size of the chelating rings and the number of rings formed on chelation. It has concluded that five and six member rings of amino acid chelates are the most stable and it is observed that, in general the five member ring is more stable when the ring is entirely saturated[20,21].

In the present work, effect of metal ions such as Ni(II), Cu(II) and Zn(II) on the properties of substituted thiopyrimidine complexes in 70% DMF+water mixture at 309K had studied. Ligands used (Substituted thiopyrimidine drugs)



L_3: R = -3-Chloro

L_4: R = -3-Bromo

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

MATERIALS AND METHODS

All chemicals of AR grade are used. 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 (20×10^{-4}M)
iii)Free acid HNO_3 (0.01 M) and ligand (20×10^{-4}) and metal ion (4×10^{-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,

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

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[22,23]

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

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.

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

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.

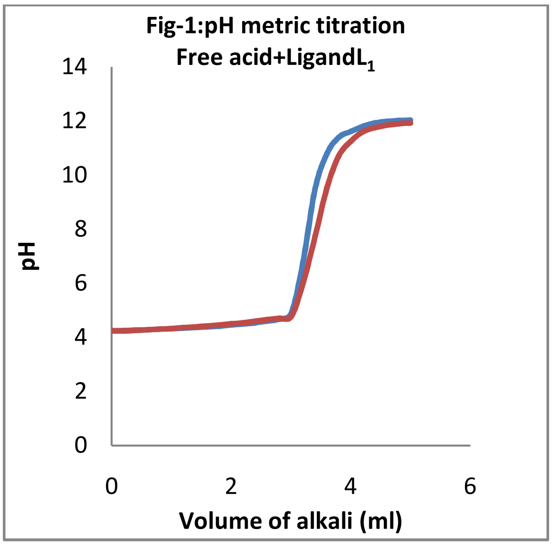


Fig-1:pH metric titration Free acid+LigandL_1

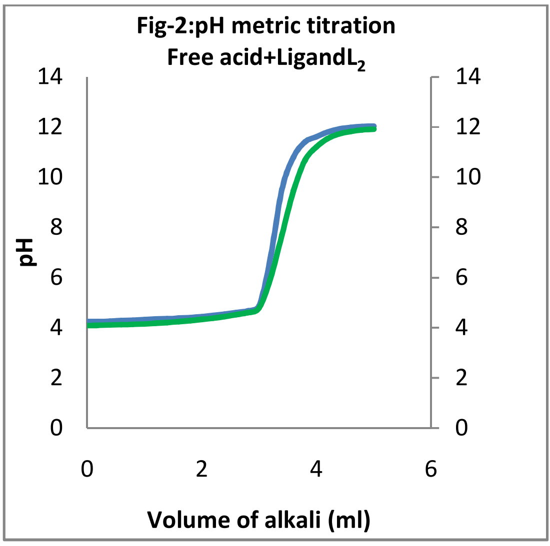


Fig-2:pH metric titration Free acid+LigandL_2

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

pH	V_1	V_2	V_2-V_1	$\bar{n}_A$
4.50	3.00	3.08	0.08	0.7143
5.00	3.15	3.24	0.09	0.6803
5.50	3.21	3.32	0.11	0.6101
6.00	3.25	3.37	0.12	0.5752
6.50	3.28	3.41	0.13	0.5403
7.00	3.33	3.47	0.14	0.5058
7.50	3.36	3.52	0.16	0.4358
8.00	3.40	3.57	0.17	0.4014
8.50	3.43	3.61	0.18	0.3669
9.00	3.46	3.65	0.19	0.3324
9.50	3.49	3.69	0.20	0.2980
10.00	3.53	3.75	0.22	0.2289
10.50	3.56	3.80	0.24	0.1597
11.00	3.59	3.84	0.25	0.1256
11.50	3.65	3.92	0.27	0.0576

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

pH	V_1	V_2	V_2-V_1	$\bar{n}_A$
4.50	3.00	3.05	0.05	0.8214
5.00	3.15	3.21	0.06	0.7869
5.50	3.21	3.28	0.07	0.7519
6.00	3.25	3.34	0.	0.6814
6.50	3.28	3.38	0.10	0.6464
7.00	3.33	3.45	0.12	0.5764
7.50	3.36	3.49	0.13	0.5416
8.00	3.40	3.55	0.15	0.4718
8.50	3.43	3.59	0.16	0.4372
9.00	3.46	3.64	0.18	0.3675
9.50	3.49	3.68	0.19	0.3331
10.00	3.53	3.74	0.21	0.2639
10.50	3.56	3.78	0.22	0.2297
11.00	3.59	3.83	0.24	0.1605
11.50	3.65	3.90	0.25	0.1274

Table 3 : Proton –Ligand stability Constants (pk)

Ligand	pK (Half Integral Method)	pK (Pointwise Method)
(L_1): 6-chloro-3-(6-(3-chlorophenyl)-2-mercapto-3,4-dihydropyrimidin-4-yl) chlorocinnolin-4(3H) one	8.30	8.27
(L_2): 3-(6-(3-bromophenyl)-2-mercapto-3,4-dihydropyrimidin-4-yl)-6-chlorocinnolin-4(3H)one	7.80	7.89

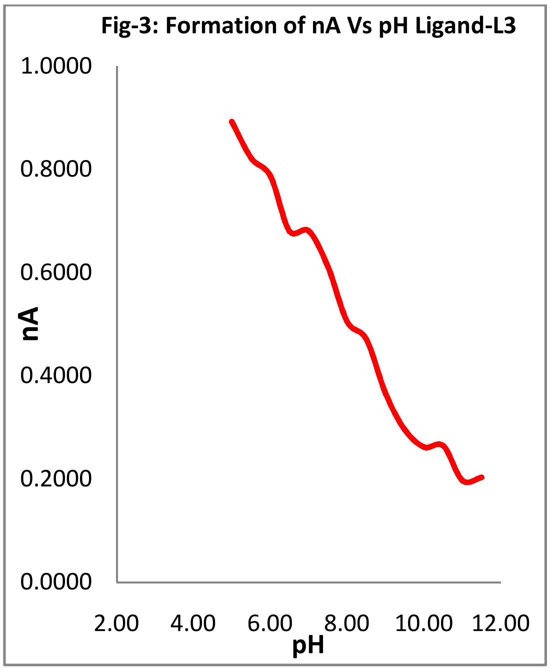


Fig-3: Formation of nA Vs pH Ligand-L3

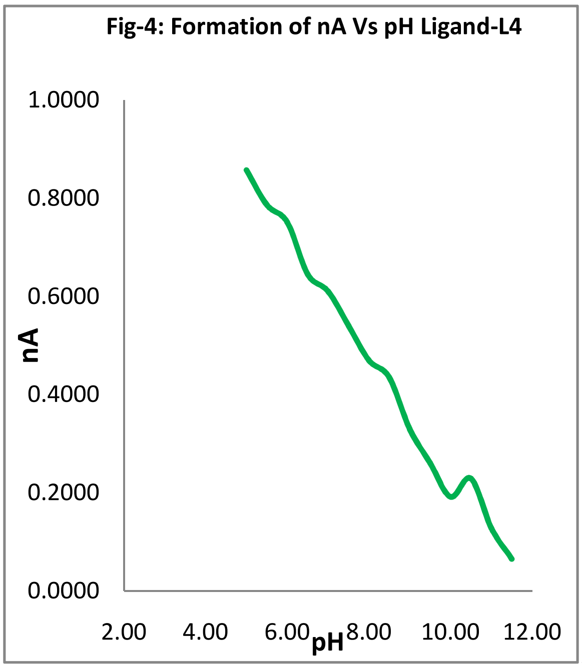


Fig-4: Formation of nA Vs pH Ligand-L4

Table – 4:

Determination of $\bar{n}$

System L_1 + Ni(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.05	3.07	0.02	0.3993
5.50	3.13	3.16	0.03	0.6488
6.00	3.20	3.24	0.04	0.9014
6.50	3.26	3.30	0.04	1.0400
7.00	3.31	3.36	0.05	1.2966
7.50	3.37	3.43	0.06	1.7314
8.00	3.43	3.49	0.06	2.0890
8.50	3.48	3.55	0.07	2.6118

Table – 5:

Determination of $\bar{n}$

System L_1 + Cu(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.05	3.07	0.02	0.3993
5.50	3.13	3.16	0.03	0.6488
6.00	3.20	3.24	0.04	0.9014
6.50	3.26	3.30	0.04	1.0400
7.00	3.31	3.37	0.06	1.5559
7.50	3.37	3.44	0.07	2.0199
8.00	3.43	3.50	0.07	2.4372
8.50	3.48	3.55	0.07	2.6118

Table – 6:

Determination of $\bar{n}$

System L_1 + Zn(II)

pH	V_2	V_3	V_3-V_2	$\bar{n}$
5.00	3.05	3.07	0.02	0.3993
5.50	3.13	3.16	0.03	0.6488
6.00	3.20	3.24	0.04	0.9014
6.50	3.26	3.31	0.05	1.3000
7.00	3.31	3.36	0.05	1.2966
7.50	3.37	3.43	0.06	1.7314
8.00	3.43	3.50	0.07	2.4372
8.50	3.48	3.56	0.08	2.9849

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	3.21	3.24	0.03	0.7078
6.50	3.27	3.31	0.04	1.0968
7.00	3.33	3.37	0.04	1.1569
7.50	3.39	3.43	0.04	1.3046
8.00	3.44	3.48	0.04	1.4970
8.50	3.49	3.54	0.05	2.0162

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	0.4339
5.50	3.14	3.17	0.03	0.6774
6.00	3.21	3.25	0.04	0.9429
6.50	3.27	3.31	0.04	1.0383
7.00	3.33	3.37	0.04	1.0921
7.50	3.39	3.43	0.04	1.2222
8.00	3.44	3.49	0.05	1.6230
8.50	3.49	3.54	0.05	1.8599

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	0.4339
5.50	3.14	3.17	0.03	0.6774
6.00	3.21	3.24	0.03	0.7072
6.50	3.27	3.31	0.04	1.0383
7.00	3.33	3.37	0.04	1.0921
7.50	3.39	3.44	0.05	1.5277
8.00	3.44	3.49	0.05	1.6230
8.50	3.49	3.55	0.06	2.2319

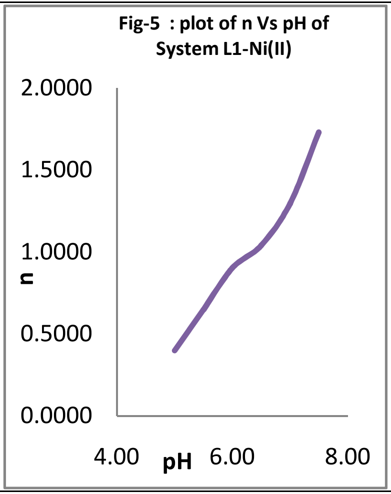


Fig-5 : plot of n Vs pH of System L1-Ni(II)

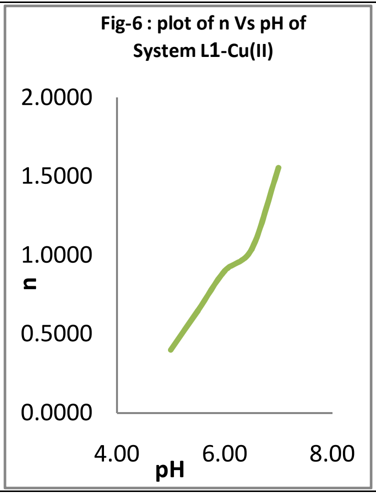


Fig-6 : plot of n Vs pH of System L1-Cu(II)

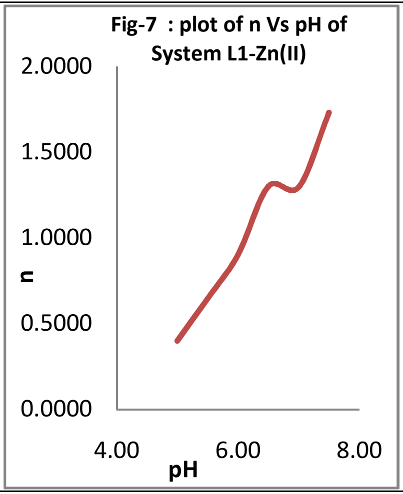


Fig-7 : plot of n Vs pH of System L1-Zn(II)

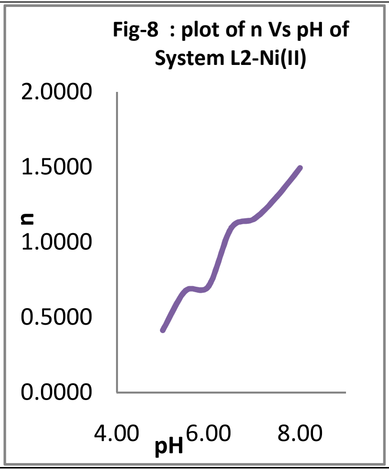


Fig-8 : plot of n Vs pH of System L2-Ni(II)

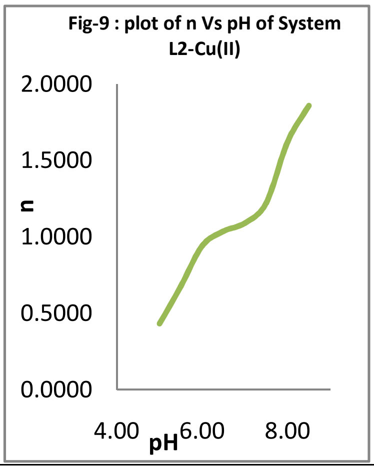


Fig-9 : plot of n Vs pH of System L2-Cu(II)

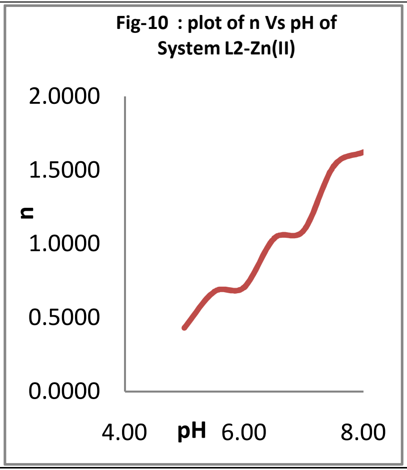


Fig-10 : plot of n Vs pH of System L2-Zn(II)

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	Zn(II)	5.8447	4.0038	1.459788	1.8409
	Cu(II)	5.7947	4.0538	1.429449	1.7409
	Ni(II)	5.7947	3.9038	1.484374	1.8909
L_2	Zn(II)	5.2947	2.9538	1.792505	2.3409
	Cu(II)	5.4447	2.8538	1.907877	2.5909
	Ni(II)	5.3947	2.6538	2.032821	2.7409

CONCLUSION

From figure 1 and 2, it is observed that the deviation of (acid + ligand) curve and (acid +ligand + metal) curve for all systems started from pH = 4.40 this indicated the commencement of complex formation. Colour change from yellow to brown in the pH range from 4.40 to 11.50 during titration support the complex formation between metal and ligand. Table 3 show proton-ligand stability constant of ligand (L_1) is higher than ligand (L_2). Due to greater +R effect of bromo than chloro substituent, ligand (L_1) from more stable metal complex than ligand (L_2). From table-10 it is observed that difference of stability constant in all system is more than 2.5 indicate there is a simultaneous complex formation. If the ratio between metal- ligand stability constant($\log k_1/\log k_2$) is greater than 1.5 then there is a stepwise formation of metal ligand complex. From the table-10 it is observed that, ratio of stability constant of ligand L_1 and L_2 is more than or close to 1.5 for all metal ion, indicate stepwise complex formation.

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