

Stability Constant Determination of Substituted Thiopyrimidine Glucosides with Ni(II), Cu(II) and Zn(II)

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Abstract Substituted thiopyrimidine glucosides are of great biological importance, but their metal-binding properties with biologically-relevant metal ions are not well investigated. Stability constants of the substituted thiopyrimidine glucosides with Ni(II), Cu(II) and Zn(II) metal were determined by pH-metric titration. Substituted Thiopyrimidine Glucosides drugs are synthesized 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. This study is useful to understand type of complex formation between transition metal ion and thiopyrimine glucosides 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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1. Introduction

In medicinal chemistry thiopyrimidine derivative are very well known for their therapeutic applications. Many thiopyrimidine derivatives have been developed as chemotherapeutic agents are widely used. A survey of literature has shown that compounds have antiviral, antibacterial [1], antimalarial [2], antihypertensive [3] and anti-inflammatory activities [4]. Glucosides are the water soluble and widely distributed in plants and animals. The important role of glucoside is to increase the water solubility of organic compounds and decrease toxicity of aglycone moieties. They have been increasing antitumor and metabolic activities. Glucosylation reaction is the key reaction for the synthesis of many carbohydrate based biomolecules, oligosaccharides, complex carbohydrate conjugates and many complex glucosides. They serve as a handle of pharmacophoric group for recognition of the structure by target cells and acts as a main carrier of the aglycone moiety.

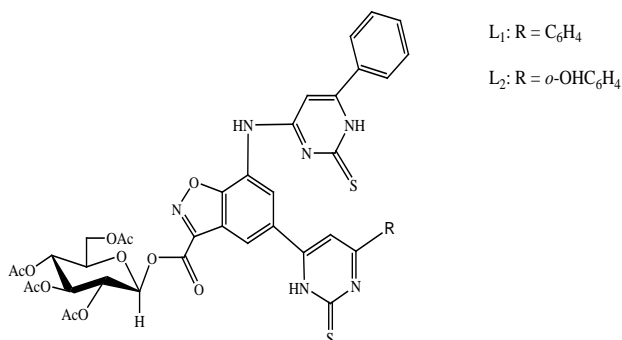
In glucosides, the noncarbohydrate moiety attached to the sugar molecule is the aglycone, hence glycosides composed of a sugar residue attached to aglycone moiety [5,6]. Many glycosides are used as sweeteners, food additives, non-ionic surfactants, antibiotics in pharmaceutical preparations, artificial primers for glyco-gen biosynthesis

and cosmetics [7,8,9]. Aglycone moieties attached to glucose shows profound effects such as anticancer, cytotoxicity, antitumor, anti-inflammatory, antioxidant, antiviral, antifungal, antimicrobial, molluscicidal, anti-hypercholesteremic and as a plant growth stimulant activities have been reported for steroidal glycosides. The sulphur analogues of alcohols are thiols which bears the –SH group and important functional groups which have been studied for two main reasons those of biological interest. Firstly it is very reactive towards free radicals and dominant role in biological processes and secondly, it gave considerable protection against the harmful effects of ionizing radiation and immense importance in drug metabolism. Thiopyrimidines glucosides of higher molecular weight are often trace constituents of natural flavours, the lower molecular weight have violently disagreeable odour and widely used abroad for the treatment of the emergency of thyroid storm. Mixed metal complexes play vital role in various biological systems [10] and in different fields of chemistry [11]. Hence, the stability and reactivity of these complexes have been an active field of research [12]. 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 glucosides drugs are taken in present study. The significance of these thiopyrimidine glucosides enhanced by the fact that it

displays independent therapeutic activity. 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 [13]. 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.

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



L1: 7-(2,3,4,6-tetra-O-acetyl-3-acetyl-β-D-glucopyranosyl)-1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-ylamino-5-(2,3-dihydro-6-phenyl-2-thioxopyrimidin-4-yl) benzoisoxazole-3-carboxylates

L2: 7-(2,3,4,6-tetra-O-acetyl-3-acetyl-β-D-glucopyranosyl)-1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-ylamino-5-(2,3-dihydro-6-orthophenyl-2-thioxopyrimidin-4-yl) benzoisoxazole-3-carboxylates

2. Materials and Method

All chemicals of AR grade are used. The ligands (L₁) & (L₂) were synthesized in the laboratory by reported protocol. The stock solutions of the ligand were prepared by dissolving required amount of ligand in 70% (DMF+water) mixture.

Metal ions used (divalent metal ion in nitrates forms)

Ni(II), Cu(II) and Zn(II).

Stock solution

1M KNO₃ solution, 0.1M HNO₃ solution, 0.1M NaOH and 0.01M Transition metal ions solution are prepared in

double distilled water . 0.01 M ligand (L₁ and L₂) solution in 70% (DMF –water) mixture.

• Calvin –Bjerrum titration methods

All pH-metric titrations and pH-measurements were carried out with EQUIP-TRONIC DIGITAL pH meter model EQ-610 (accuracy ±0.05 units) with a glass and calomel electrodes assembly, at (36±0.1)⁰c in 70% (DMF-water) mixture and at an inert atmosphere by bubbling nitrogen gas.

General procedure:

Types of Titrations

- i) Free acid HNO₃(0.01 M)
- ii) Free acid HNO₃(0.01 M) and ligand (20 x 10⁻⁴M)
- iii) Free acid HNO₃ (0.01 M) and ligand (20 x 10⁻⁴) and metal ion (4 x 10⁻⁴M) against standard 0.1N NaOH solution.

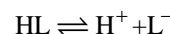
The ionic strength of all the solutions was maintained constant 1M by adding appropriate amount of KNO₃ solution. All the titrations were carried out in 70% (DMF-water) mixture and the reading were recorded for each 0.2 ml addition. The graph of volume of alkali added (NaOH) against pH were plotted.

3. Calculation

Titration curves are used to estimate the values of $\overline{n_A}$ (proton -ligand formation number) which are presented in Table 1 to Table 2. Formation curve are constructed between $\overline{n_A}$ and pH. The pH values at 0.5 $\overline{n_A}$ 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.

4. Result 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 can be shown as.



By the law of mass action, we have,

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

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

Calculation of Proton-Ligand Stability Constant

($\overline{n_A}$) 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 (V₂-V₁) 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 [15,16]

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

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 Table 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

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

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

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.

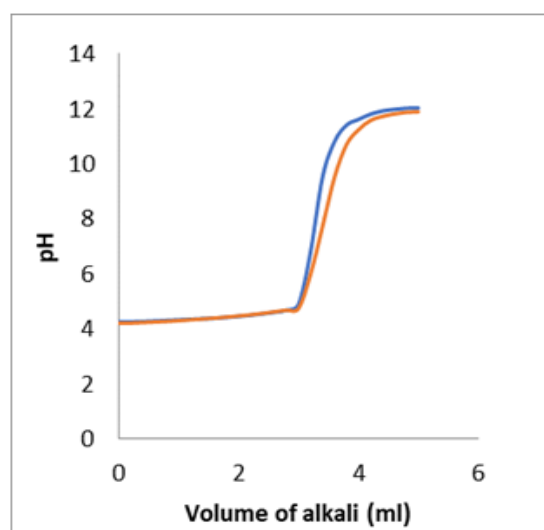


Figure 1. pH metric titration Free acid + Ligand L_1

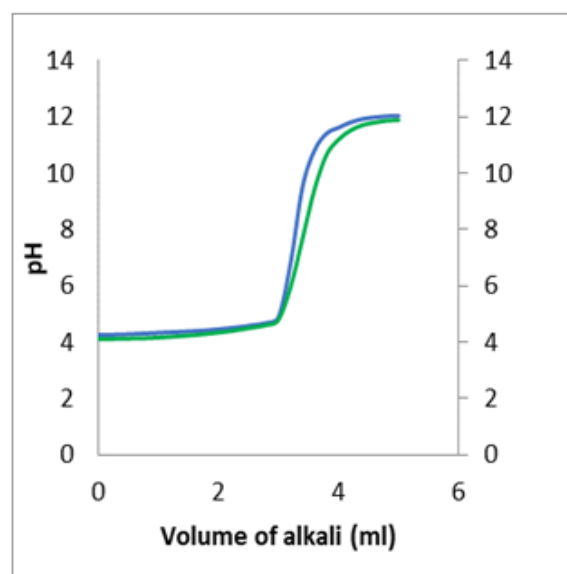


Figure 2. pH metric titration Free acid + Ligand L_2

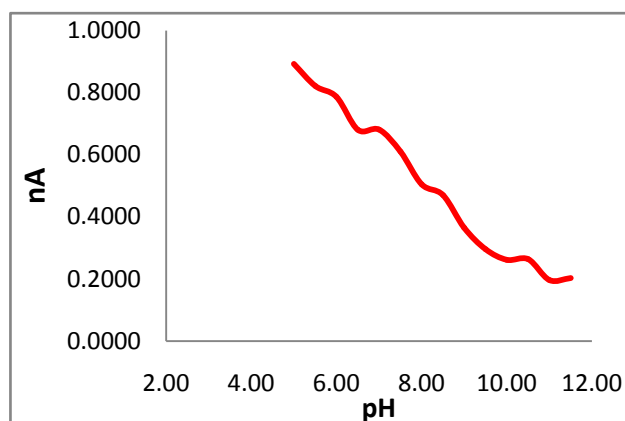


Figure 3. Formation of nA Vs pH Ligand- L_3

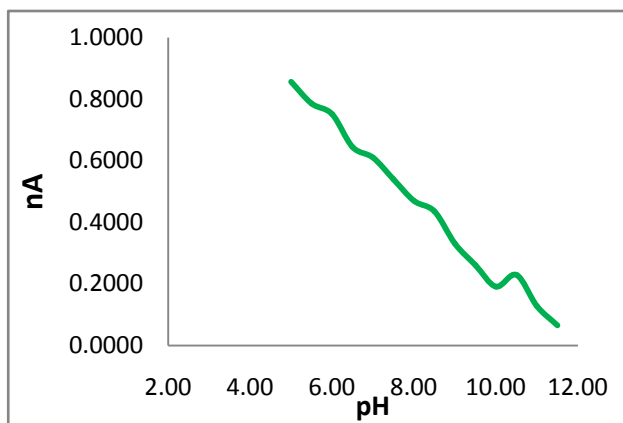


Figure 4. Formation of nA Vs pH Ligand-L4

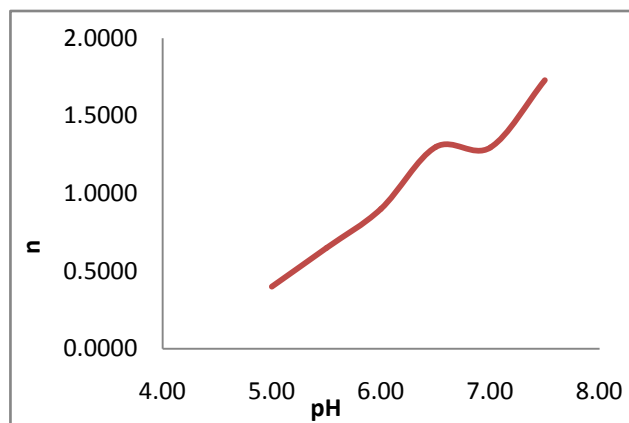


Figure 7. plot of n Vs pH of System L1-Zn(II)

Table 3. Proton-Ligand stability Constants (pk)

Ligand	pK (Half Integral Method)	pK (Pointwise Method)
L1: 7-(2,3,4,6-tetra- <i>O</i> -acetyl-3-acetyl- β -D-glucopyranosyl)-1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-ylamino-5-(2,3-dihydro-6- <i>phenyl</i> -2-thioxopyrimidin-4-yl) benzoisoxazole-3-carboxylates	8.10	8.07
L2: 7-(2,3,4,6-tetra- <i>O</i> -acetyl-3-acetyl- β -D-glucopyranosyl)-1,2-dihydro-6-phenyl-2-thioxopyrimidin-4-ylamino-5-(2,3-dihydro-6- <i>orthophenyl</i> -2-thioxopyrimidin-4-yl) benzoisoxazole-3-carboxylates	7.60	7.69

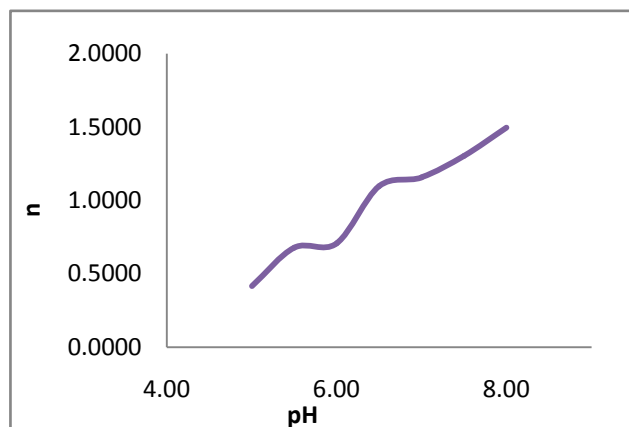


Figure 8. plot of n Vs pH of System L2-Ni(II)

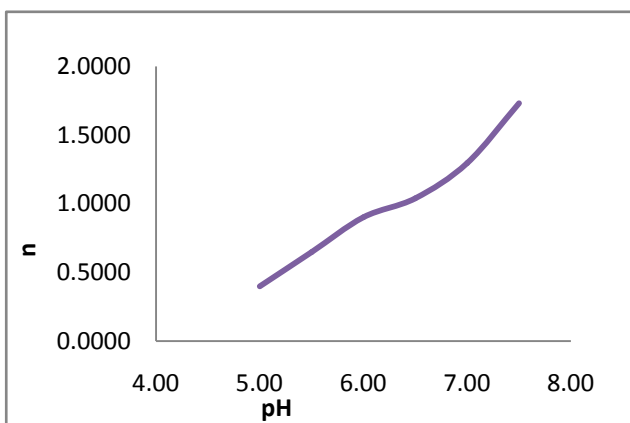


Figure 5. plot of n Vs pH of System L1-Ni(II)

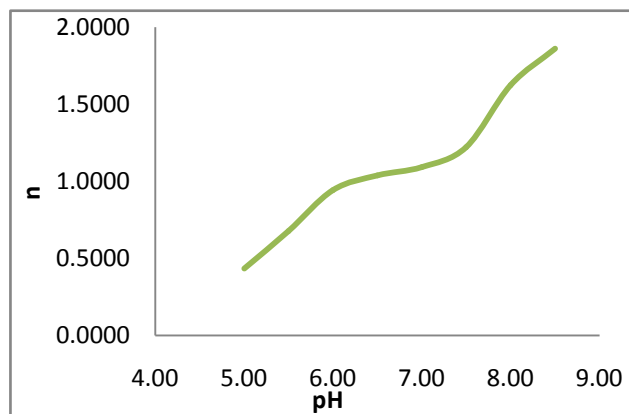


Figure 9. plot of n Vs pH of System L2-Cu(II)

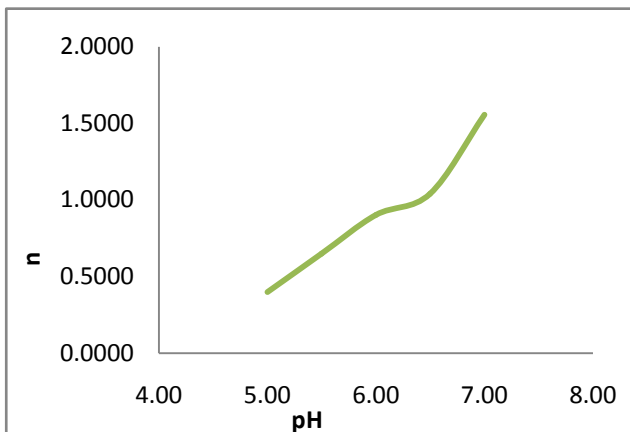


Figure 6. plot of n Vs pH of System L1-Cu(II)

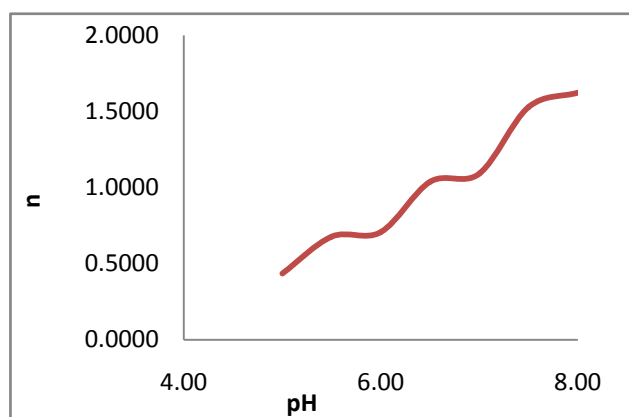


Figure 10. plot of n Vs pH of System L2-Zn(II)

Table 4. Metal–Ligand stability Constants (LogK values)

System: Ligand + Metal		logK ₁	logK ₂	logK ₁ /logK ₂	logk ₁ -logk 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

5. Conclusion

From graph 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 (L₁) is higher than ligand (L₂). From table-4 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 is greater than 1.5 then there is a stepwise formation of metal ligand complex. From the table-4 it is observed that, ratio of stability constant of ligand L₁ and L₂ is more than or close to 1.5 for all metal ion, indicate stepwise complex formation.

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Conflicts of Interest

Author has declared that no conflict interests exist.

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