



Stability Constant Determination of Substituted Imidazolinone Drugs pH-Metrically

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Abstract

In the present work, effect of metal ion Fe(III) on the properties of complexes of substituted imidazolinone in 70% (DMF+water) mixture at 298K had studied. The interaction have been studied at 0.1M ionic strength by Bjerrum method as adopted by Calvin and Wilson. It is observed that Fe(III) metal ion form 1:1 complex with ligands (L1& L2). 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 effect of substituents were studied. Ligand used for present work were (L₁) 1-[2-hydroxy-5-(3 Chloro phenyl azo) benzylidene amino]-2-phenyl-4-benzylidene-5-oxoimidazoline (L₂)1-[2-hydroxy-5-(4-bromo phenyl azo) benzylidene amino]-2-phenyl-4-benzylidene-5-oxoimidazoline.

Keywords: substituted imidazolinone, proton-ligand stability Constant (pk), metalligand stability constant(logk).

Introduction

Substituted imidazolinone exhibit promising biological and pharmacological activity. Interest in the chemistry of imidazoline continuesly increases because of their usefulness as antibacterial¹ and antiinflammatory² agents. Some of them may be useful in the polymer chemistry. Moreover imidazoline and imidazolinone have great therapeutic importance such as anticonvulsant, potent CNS depressant, sedative and hypnotics, hypotensive and potent antiparkinsonian activity³ promoted by these observations. Imidazolinone ring system is of biological and chemical interest since long. The imidazolinones⁴ are associated with therapeutic activities such as MAO inhibitory, antihelmintical and herbicidal activities. Some workers have recognized imidazolone as having anticancer activity. The therapeutic importance of the compounds inspired us to study physicochemical properties of substituted imidazolinone.

The complexes have been extensively studied in solution as well as in solid state by many workers⁵⁻⁸, due to it's remarkable properties and high stability. With the help of various Experimental techniques, the



extensive work in coordination complexes has been made possible and has lead in a number of empirical conclusions which have been detailed by Martell⁶. The strength of binding of ligand to the central metal ion is depending on structure of ligand molecule or ions⁹⁻¹⁰. 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. The stability order of metal complexes of transition metal ion was found by Irving and Williams¹¹ as $Mn^{2+} < Fe^{2+} < Ni^{2+} < Cu^{2+} >Zn^{2+}$ and concluded Fe³⁺ has ability to form more sTable complexes because it has more nuclear charge, small size and high value of ionization potential.

In the present work, effect of metal ions such as Fe(III) on the properties of complexes of substituted imidazolinone in 70% DMF+water mixture at 298K had studied.

Materials And Method

a. Ligands (Substituted imidazolinone drugs)

 $(L_1) 1-[2-hydroxy-5-(3-chloro phenyl azo) benzylidene amino]-2-phenyl-4-benzylidene-5-oxoimidazoline \\ (L_2)1-[2-hydroxy-5-(4-bromo phenyl azo) benzylidene amino]-2-phenyl-4-benzylidene- 5-oxoimidazoline \\$

The ligands (L_1) & (L_2) were synthesized in the laboratory by known literature method⁵. The purity of these compounds exceeds 99.5% and structures were confirmed by NMR, IR and melting points. The stock solutions of the ligand was prepared by dissolving required amount of ligand in a minimum volume of 70% (DMF+water) mixture subsequently diluted to final volume.

b. Metal ions (divalent metal ion in nitrates forms)

Fe(III) In FeCl₃ form.

c. 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 . 0.01M ligand (L1 and L2) solution in 70% DMF –water mixture. All the chemical used in Experimental work are of AR grade.

d. 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 $(25\pm0.1)^{0}$ c in 70% DMF-water mixture and at an inert atmosphere by bubbling nitrogen gas.

General procedure :

Types of Titrations

i) Free acid HNO₃(0.01M)

ii) Free acid HNO₃(0.01M) and ligand (20×10^{-4} M)





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

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

e. Detection Method :

Titration curves are used to estimate the values of $\overline{n_A}$ (proton -ligand formation numbers) which are presented in Table 1 to 2. Formation curve are constructed between $\overline{n_A}$ values and p^H . The p^H values at 0.5 $\overline{n_A}$ corresponds the pK values (proton-ligand dissociation constants) of respective ligand. Proton ligand dissociation constants (pK values) are evaluated and presented in Table (3), which are calculated by Half Integral method and verified by Pointwise calculations method.

Result and Discussion

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

HL == H⁺ + L[·]

By the law of mass action, we have,

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

Calculation of Proton-Ligand Stability Constant $(\overline{n_A})$

The plot between volume of NaOH and p^{H} 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 p^{H} 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 n_{A} at various pH values and fixed ionic strength $\mu = 0.1M$ using Irving and Rossotti's equation^{12,13}

$$\overline{n_{A}} = \gamma - \frac{(V_{2} - V_{i})(N + E^{\circ})}{(V^{\circ} + V_{i})T_{L}^{\circ}} \qquad (2)$$

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 $\overline{n_A}$ 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 (n) is estimated by Irving-Rossotti's equation.

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 n using Irving Rossotti's equation.



Table –1				Table – 2					
De	Determination of $\overline{n_A}$ Values of L_1				Determination of $\overline{n_A}$ Values of L ₂				
p ^H	V_1	V_2	$V_2 - V_1$	n _A	p^{H}	V_1	V_2	$V_2 - V_1$	n _A
4.50	3.00	3.06	0.06	0.7857	4.50	3.00	3.05	0.05	0.8214
5.00	3.15	3.22	0.07	0.7513	5.00	3.15	3.21	0.06	0.7869
5.50	3.21	3.30	0.09	0.6810	5.50	3.21	3.29	0.08	0.7164
6.00	3.25	3.35	0.10	0.6460	6.00	3.25	3.34	0.09	0.6814
6.50	3.28	3.39	0.11	0.6110	6.50	3.28	3.38	0.10	0.6464
7.00	3.33	3.46	0.13	0.5411	7.00	3.33	3.44	0.11	0.6117
7.50	3.36	3.51	0.15	0.4711	7.50	3.36	3.49	0.13	0.5416
8.00	3.40	3.56	0.16	0.4366	8.00	3.40	3.55	0.15	0.4718
8.50	3.43	3.61	0.18	0.3669	8.50	3.43	3.59	0.16	0.4372
9.00	3.46	3.65	0.19	0.3324	9.00	3.46	3.65	0.19	0.3324
9.50	3.49	3.70	0.21	0.2629	9.50	3.49	3.69	0.20	0.2980
10.00	3.53	3.75	0.22	0.2289	10.00	3.53	3.75	0.22	0.2289

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International Journal of Chemical and Physical Sciences, ISSN:2319-6602 IJCPS Vol. 4 Special Issue – NCSC Jan-2015 www.ijcps.org



10.50	3.56	3.80	0.24	0.1597	10.50	3.56	3.80	0.24	0.1597
11.00	3.59	3.85	0.26	0.06	11.00	3.59	3.85	0.26	0.06
11.50	3.65	3.93	0.28	0.0227	11.50	3.65	3.93	0.28	0.0227



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

Ligand	pK (Half Integral Method)	pK (Pointwise Method)	
(L ₁) 1-[2-hydroxy-5-(3-chlorophenyl azo) benzylidene amino]-2-phenyl-4-benzylidene-5-oxoimidazoline	7.20	7.27	
(L ₂) 1-[2-hydroxy-5-(4-bromo phenyl azo) benzylidene amino]-2-phenyl-4-benzylidene- 5-oxoimidazoline	7.50	7.54	

Table – 4						Table – 5				
Determination of \overline{n} system L ₁ + Fe(III)						Determination of \overline{n} system L ₂ + Fe(III)				
pН	V ₂	V ₃	V ₃ -V ₂	n		pН	V ₂	V ₃	V ₃ -V ₂	n
4.50	3.06	3.08	0.02	0.4535		4.50	3.05	3.06	0.01	0.2170
5.00	3.22	3.24	0.02	0.4716		5.00	3.21	3.23	0.02	0.4504
5.50	3.30	3.33	0.03	0.7783		5.50	3.29	3.32	0.03	0.7401
6.00	3.35	3.39	0.04	1.2000		6.00	3.34	3.38	0.04	1.0356
6.50	3.39	3.44	0.05	1.4412		6.50	3.38	3.43	0.05	1.3627
7.00	3.46	3.51	0.05	1.6234		7.00	3.44	3.50	0.06	1.7244
7.50	3.51	3.57	0.06	2.2336		7.50	3.49	3.56	0.07	2.2682

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Table 6 :	Metal -	Ligand	stability	Constants	(LogK	values)
		0	2		$\sim $	

System	$log K_1$	$logK_2$	$logK_1/logK_2$	$logk_1$ - $logk_2$
$L_1 + Fe(III)$	5.14	3.65	1.40	1.49
$L_2 + Fe(III)$	5.19	3.65	1.42	1.54

Conclusion

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 = 3.40 this indicated the commencement of complex formation. Also change in colour from yellow to brown in the pH range from 3.40 to 11.50 during titration showed the complex formation between metal and ligand. The order of pK values of ligands is found to be as (Table-3)

pK ligand (L₂). > pK ligand (L₁).

pK value for both the ligand is small because substituent group present on a structure of ligand both are ring deactivating or electron withdrawing. but ligand L_2 has comparatively greater value than ligand L_1 . Substituent at ligand L_1 is -3-Chroro and at ligand L_2 is -4-bromo, and it is known that chloro group is more deactivating than Bromo group. Hence increment in pK value of ligand (L_2) is attributed to presence of less electron withdrawing group which decrease the activity of ligand L_2 in less amount than L_1 to form more sTable complex.



From the Table-6 it is observed that, there is a small difference between $logK_1$ and $logK_2$ values not more than 2.5 indicates the simultaneous formation of complex between metal ion Fe(III) and ligand. Greater pK value of Ligand L₂ show it form more sTable complex with Fe(III) than ligand L₁.

If the ratio between metal- ligand stability $constant(logK_1/LogK_2)$ is greater than 1.5 then in such case there is a stepwise formation of metal ligand complex. From the Table-6 it is observed that, both ligand have ratio near to 1.5 indicate there is stepwise and simultaneous complex formation at a time.

Acknowledgement

The author is very thankful to the Head, Department of chemistry, Govt. Vidarbha Institute of Science and Humanities, Amravati, Maharashtra for kindly cooperation during research work.

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