

International Journal of Scientific Research in Science and Technology

Available online at : www.ijsrst.com

Print ISSN: 2395-6011 | Online ISSN: 2395-602X



doi : https://doi.org/10.32628/IJSRST

Protonation Dynamics and Metal-Ligand Stability of Beta-Ketone Ligands: Insights from pKa, nA, and LogK Constants

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ABSTRACT				
This work investigated the interactions of Cu(II) and Zn(II) with the				
tautomeric equilibrium of the β -diketo moiety. Two alternative ligands, 1-				
(2-hydroxyphenyl-5-bromo)-3-(2,4-dichloro)propane-1,3-dione and 1-(2-				
hydroxyphenyl-5-bromo)-3-(4-fluoro)propane-1,3-dione, were produced				
and assessed. Utilizing Irving and Rossotti's modified Bjerrum technique.				
At a constant temperature of 32°C and an ionic strength of 0.1 M (NaOH)				
in a 70% DMF-water medium, the stability constants for the 1:1 and 1:2				
complexes with Cu(II) and Zn(II) were calculated. The simultaneous				
occurrence of 1:1 and 1:2 complicated structures was noted.				
Keywords: propane-1,3-dione, keto–enol equilibrium, β-diketo				
ligandsCu(II) and Zn(II), pH meter, stability constant				

I. INTRODUCTION

The research of metal complexes in solutions has advanced significantly over the last four decades (1). The field's foundation was established by Bjerrum's groundbreaking dissertation (2). Low dissociation constants, distinct redox potentials, particular electron distributions, and enhanced solubilitiesas a result of metal complex formation are some of the essential properties of these complexes that boost their biological activities. These characteristics affect how well medications dissolve in lipids and pass through cell membranes (3). Additionally, the creation of metal complexes promotes bond formation, bond breakage, and group transfer events. It polarizes electrons from the ligands toward the metal in addition to aiding in the formation of an activated complex by bringing reactive molecules together (4) (5). The values for the stability constant and free energy change indicate the stability and basicity of ligands (6). Bulkier groups tend to make ligands more basic and stable. These complexes' stability is dictated by the ligands and the core metal atom. Electronic structure, radius,

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and degree of oxidation are important variables. The type of atoms that are directly connected to the core atom or ion determines the binding strength of polytomic ions and ligand molecules, which is influenced by these properties (7) (8).

According to Irving and Williams' study, metal complexes containing transition metal ions can be examined for stability order by looking at their ionic radii and second ionization potentials (9). This is especially true for ligands that have donors of oxygen and nitrogen. The size and quantity of chelating rings that develop have a major impact on the stability of these complexes. These characteristics are determined by the structure of chelating agents; according to Daniele Sanna research on peptide chelates, rings with five or six members are the most stable (10). Numerous researchers have made significant contributions to the subject of metal-ligand chemistry over the years (11) (12) (13) (14).

Existing synthetic substituted diketones(15)were used in this investigation due of their possible biological and analytical uses. These substances, both diketones, have antihelminthic and fungicidal qualities. Because of their varied biological actions, several substituted diketones have been reported to exhibit antibacterial, anti-inflammatory, insecticidal, bactericidal, pharmacological, and fungicidal properties.

II. EXPERIMENTAL SECTION

Materials and Instruments

All of the reagents and solvents used were purchased from commercial sources and did not undergo additional purification. Analytical thin-layer chromatography (TLC) was performed on 60 F254 silica gel plates. The Baker-Venkataraman rearrangement in a pyridine medium was described by Rajendra M. Pathade and Pravin S. Bodkhe (15). At a controlled temperature of 32°C, pH was measured using a pH-meter.

Synthesis of 5-Bromo-2-hydroxyacetophenone

2-hydroxyacetophenone (5.0 g, 36.3 mmol) and acetic acid (40 mL) were mixed in a round-bottom flask fitted with a reflux condenser. After stirring, the mixture was cooled to 0°C. Then, dropwisefor 15 minutes, a bromine solution (5.0 mL, 99.9%, 98.0 mmol) in acetic acid (10 mL) was added. For four hours, the reaction mixture was agitated at room temperature. After the reaction was finished, as determined by TLC, the mixture was placed over crushed ice and agitated for an extra sixty minutes. After filtering, washing with water, and recrystallizing the resulting yellow solid from ethanol, 5-bromo-2-hydroxyacetophenonewas obtained as yellow crystals with an 85% yield.

Preparation of 1-(5-bromo-2-hydroxyphenyl)-2/4--halo-1,3-dione(IV)(16)

Already prepared 2-acetyl-4-bromophenol (I) 1-(5-bromo-2-hydroxyphenyl)ethanone-bromophenyl 2 and 4-halogen (II). The 1-(5-bromo-2-hydroxyphenyl)ethanone-bromophenyl 2 and 4-halogen (II) and 2/ 4-halobenzoic acid were dissolved in pyridine (40 ml). Then KOH solution was added to the warmed compound (III) solution with constant stirring. After that, the resultant solution was acidified by chilled (1:1) dilHCl. The obtained solid organic molecule was washed with NaHCO₃ (10%) and washed with distilled water. It was then recrystallized by using ethanol to obtain 1-(5-bromo-2- hydroxyphenyl)- 2 and 4-halogen-1,3-dione (IV). The resultant product was characterized by melting point determination, spectroscopic analysis, and elemental analysis to confirm its purity and identity. The typical yield for this synthesis ranged from 58% to 62%. All reactions were conducted under appropriate laboratory conditions with necessary safety precautions.The synthesis of 2 and 4 - Substituted Halogen Propane-1,3-Diones (β -Diketones) is shown below in Figure-1.



Ligand (L₂): 1-(5-bromo-2-hydroxyphenyl)-3-(4-fluorophenyl)propane-1,3-dione

pH-Metric Measurements

For accurate measurements, a Systronics microprocessor-based device with a glass electrode and a saturated calomel electrode was utilized. The device was accurate to 0.01 units. Before the titrations, the instrument was calibrated using buffer solutions with pH values of 4.00, 7.00, and 9.20 at 32°C. The titration process involved three stages: first, titrating a free acid solution (0.01 M); second, titrating a mixture of free acid (0.01 M) and ligand (20×10^{-4} M); and third, titrating a combination of free acid (0.01 M), ligand (20×10^{-4} M), and metal ion (4×10^{-4} M) against a standard NaOH solution. Throughout the experiments, the ionic strength of all solutions was maintained at a constant 0.1 M by adding an appropriate amount of 1 M KNO₃ solution. The titrations were conducted in a 101 mL Pyrex glass beaker placed in an ice-cold water bath, which was maintained at a constant temperature of $32 \pm 0.1^{\circ}$ C. To produce a chemically inert atmosphere, nitrogen gas was purged. Measurements were made only after the gas bubbling stopped, and pH values were noted for every 0.5 mL addition of NaOH. The volume of alkali added was then displayed against the pH values in graph form.

III.RESULTS AND DISCUSSION

Determination of Proton-Ligand Stability Constants

At an ionic strength of 0.1 M, the pH-metric dissociation constants of the substituted diketones (1, 2) were measured. The ligands or reagents employed in this study are monobasic acids, which are denoted by the symbol HL since they each have a single dissociable proton from the hydroxyl group: HL \rightleftharpoons H⁺ +L⁻

The titration curves of the acid and the ligand diverge at approximately pH 1.5 and continue to rise to pH 7.5. The deviations observed between the acid and ligand curves indicate the dissociation of H⁺ ions from the

hydroxyl groups of the ligands. Proton-ligand formation numbers (\bar{n}_A) were calculated using the Irving and Rossotti method.

 $\bar{n}_{A} = {}^{v} - \frac{(V_{2} - V_{1})(N + E^{o})}{(V_{o} + V_{1})T_{L}}$

The values of n_A are calculated using the parameters mentioned, where:

(V₀) is the initial volume of the solution.

(T_L) is the initial concentration of the ligand.

(V1) is the volume of alkali required during the acid titration at a given pH.

(V2) is the volume of alkali required during the ligand titration at a given pH.

 $({}^{\mathrm{Y}})$ is the number of replaceable protons from the ligand.

(E⁰) is the initial concentration of the mineral acid.

N: It is the normality of the alkali solution used in the titration.

1) Methods for Calculation of Proton-Ligand Stability Constant

a) Half Integral Method

The proton-ligand stability constants are found using the formation curves. The pH values at which the pK value for a system with a single dissociable group is equal to $n_A = 0.5$. The point at which half of the available dissociable groups have been ionized is indicated by this pK value.

b) Pointwise Calculations Method

The precise determination of pKa values is achieved through pointwise calculations. For values of $n_{A} < 1.0$ the formation function of a 1:1 complex can be expressed using the following equation:

$$\log\left(\frac{\bar{n}_A}{1-\bar{n}A}\right) = pK - pH$$

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

The Irving-Rossotti expression is used to calculate the metal ligand formation number.

$$\overline{\mathbf{n}} = \frac{(\mathbf{V}_3 - \mathbf{V}_2)(\mathbf{N} + \mathbf{E}^{\mathrm{o}})}{(\mathbf{V}_0 + \mathbf{V}_2)\overline{\mathbf{n}_A}T_M}$$
(2)

Using the Irving-Rossotti expression, n is computed as the horizontal difference (V3-V2) that appears between the ligand curve (A+L) and the metal curve (A+L+M). Additionally, at a specific pH, the onset of turbidity during (A+L+M) titration indicates the creation of metal hydroxide.

Using Irving-Rossotti's expression, the metal-ligand stability constants (log K = pL) were determined as follows:

$$pL = pK + log(\frac{T_L^0 - (nT_M^0)}{nT_M^0})$$

pL: Negative logarithm of the free ligand concentration

b) Pointwise Calculations Method

For value of $\overline{n} < 1.0$, metal ligand stability constants for 1:1 complex formations are calculated by using.

$$\log\left(\frac{\overline{n}}{1-\overline{n}}\right) = \log K_1 - pL$$

For value in the region 1< ⁿ <2, metal-ligand stability constants for the 1:2 complex are calculated by using an equation.

$$\log \frac{(\overline{n}-1)}{(2-\overline{n})} = \log K_2 - pL$$

The values of logK1 and logK2are shown in Tables 2 and 3

Table 1 displays the results of the half-integral and Pointwise Calculation methods used to determine the pKa values for both systems. The dissociation constants can be precisely determined using this method, which reflects the ligands' protonation states at different pH values.

Ligands	pK (Pointwise Calculation Method)	pK (Half Integral Method)
L1	7.02	7.84
L2	7.06	8.25

Table-1. Proton-Ligand Stability Constants

Table-2. Metal-ligand stability constants by Pointwise calculation.

Ligand	Metal	Log K1	Log K ₂
т.	Zn(II)	8.27	7.45
11	Cu(II)	8.14	7.01
Та	Zn(II)	8.17	7.29
12	Cu(II)	8.13	7.31

Table-3. Metal-ligand stability constants by Half integral method.

Ligand	Metal	Log K1	logK2
T.	Zn(II)	7.98	7.39
	Cu(II)	7.99	7.39
T.	Zn(II)	8.02	7.42
	Cu(II)	8.03	7.45

IV.CONCLUSION

The titration curves for (acid + ligand), (acid + ligand + Cu(II)), and (acid + ligand + Zn(II)) vary across all systems, indicating that the complex formation begins at approximately pH 1.5. During the titration procedure, the color of the solution changes from light blue to dark blue for acid + ligand + Cu(II), and there is no change in color for acid + ligand + Zn(II). Table 1 shows the ligands' pKa values in the following order: pK_a (ligand 1)> pK_a (ligand 2). The reason for this discrepancy is that ligand 1 contains chloro (-Cl) electron-withdrawing groups, which lower its pK_a values.

The sequential complex formation between the ligands and the metal ions, Cu(II) and Zn(II), is indicated by the very large difference between the log K_1 and log K_2 values, as seen in Tables 2 and 3. When it comes to 1:1 complexes, Zn(II) typically forms more stable complexes with both ligands (L_1 and L_2) than Cu(II). In Ligand 2 (L_2), the 1:2 complexes with Cu(II) are somewhat more stable than those with Zn(II).

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