SYNTHESIS AND PHYSIOCHEMICAL ASPECTS OF 2-IMINO CHLORROSUBSTITUTED-1, 3-THIAZINES

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ABSTRACT
As a part of systematic investigation of synthesis, spectral analysis of 4-phenyl-2-hydroxy chloro substituted 2-imino-1,3-thiazines with phenyl thiourea and diphenyl thiourea from chalcone gives series, 4-(2-hydroxy-3,5-dichlorophenyl)-6-(hexyl)-2-imino phenyl-1,3-thiazines and 4-(2-hydroxy-3,5-dichlorophenyl)-6-(hexyl)-2-iminophenyl-3-phenyl-1,3-thiazines (3a-6a) from phenyl thiourea and diphenyl thiourea and the interaction of transition metal ion (cobalt II) and (copper II) have been investigated by pH metric technique at 0.1M ionic strength and at 27 ± 0.5 °C in 70% DMF-water medium.

Keywords: 1,3-Thiazines, proton-ligand and metal-ligand stability.

INTRODUCTION
Thiazine is the six member ring system which contains two heteroatoms (N & S) placed in the heterocyclic ring at 1,3 positions. Thiazines are very useful units in the field of medicinal and pharmaceutical chemistry.

In the present study, various 4-phenyl-2-substituted imino thiazines were synthesized from chalcones by using phenylthiourea and diphenylthiourea. Chalcones and their analogues having an α,β-unsaturated carbonyl system are very versatile substrates for the evolution of various reactions and physiologically active compounds. The reaction of phenyl thiourea and diphenylthiourea with brominated chalcone give 1,3 thiazines carried out in presence of ethanol as energy transfer medium in aq. NaOH.

It has been well established that the presence of 4-phenyl (2'-hydroxy-3’, 5’-dichloro) moieties shows the M-L stability with the transition metal complexes. Recent studies on complex formation have revealed that the ligand structure plays a critical role in selectivity for metal ions. 4-phenyl-2-imino chloro substituted thiazines are good complexing agents due to electron donor nitrogen. So far meagre work have been carried out on the stability constants of transition metal complexes with the above moiety.

It was, therefore, thought of interest to study the chelating complexes of 4-phenyl-2-imino chlorosubstituted thiazine under suitable conditions pH metrically.

The solutions of ligands were prepared in 70% DMF water medium. The solutions of NaOH, HNO3, cobalt nitrate and copper nitrate of (Analytical grade) were used. The metal content in its solution was estimated by standard method. The pH measurements were carried out with 335 Systronics pH meter (accuracy ± 0.1 °C. The β values (pH meter reading) in 70% DMF water mixture were converted to H+ proposed by Van Uiterts and Hass. The pH meter was calibrated by standard buffer solution (pH 4.00, 7.00, 9.00)

EXPERIMENTAL
Melting points have been determined in open capillary and are uncorrected. Purity of compound was monitored on silica gel coated TLC plate. The I.R. spectra were recorded on FTIR FTLA 2000 Spectrophotometer in KBr pelates. PMR spectra on spectrometer in CDCl3. U. V. spectra on spectrophotometer (Shimadzu U.V. 1601). The analytical data of compound were highly satisfactory. All
the chemicals used were analytical grade. Physical characterization data of all the compounds are given in Table-1.

**Experimental procedure involves the following three sets of titrations**

1. Free acid titration (HNO$_3$ x 10$^{-2}$ M), (A)
2. Free acid + ligand titration (ligand 20 x 10$^{-4}$ M), (A+L)
3. Free acid ligand + metal ion titration (4 x 10$^{-4}$ M), (A+L+M)

The titrations were carried out with standard NaOH solution (0.12 M) in presence of an inert atmosphere by bubbling a constant flow of nitrogen gas at constant temperature (27 ± 0.5 °C). The pH were recorded for each addition of 0.2 ml. Ionic strength was kept constant at 0.1 M by adding an appropriate volume of 0.1 M KNO$_3$ solution.

The following systems were studied:

1. pK values of L$_1$ and L$_2$ in 70% DMF water medium at 27°C
2. Log k values of Co(II), Cu(II), with ligands L$_1$ and L$_2$ were investigated.

Both ligands are monobasic containing only one –OH group; hence its dissociation is represented as below:

\[ HL \rightleftharpoons H^+ + L^- \]

The deviation between acid curves and acid ligand curves started at about pH 2.0; it remained constant up to pH 2.8 and it increased continuously up to pH 12. This induced the dissociation of –OH group, which is present in the ligand part of complex structure. For all system this deviation gradually increases up to pH 11.00 to 12.00, which shows dissociation of –OH group of ligands.

**Proton-ligand formation number (\(\eta_A\))**

The proton ligand formation numbers \(\eta_A\) were calculated from acid titration curves (A) and (A +L) by Irving and Rossotti’s expression$^{10}$ The pK values were estimated from formation curves (\(\eta_A\) vs. pH) by noting the pH at which \(\eta_A\) = 0.5. The accurate values of pK were determined by half-integral method, which are presented in Table-2.

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**2-Hydroxy- 3',5'-dichloro acetophenone (3a)**

2'-Hydroxy 5'-chloro acetophenone (3gm) was dissolved in acetic acid (5mL). Sodium acetate (3gm) was added to the reaction mixture and then chlorine in acetic acid reagent (40ml, 7.5 W/V) was added drop wise with stirring. The temperature of the reaction mixture was maintained below 20 °C. The mixture was allowed to stand for 30 minutes. It was then poured into water with stirring. A pale-yellow solid then obtained was filtered, dried and crystallized from ethanol.

**I.R. (KBr):**
- 3068 cm$^{-1}$ (-OH phenolic), 1652 cm$^{-1}$ (>C=O in ketone), 1304 cm$^{-1}$ (-OH bending in phenol), 737 cm$^{-1}$ (C-Cl stretching);
- **PMR:**
  - δ 2.65; (s, 3H, -CH$_3$);
  - δ 7.25 -7.63 (m, 2H, ArH);
  - δ 12.71 (s, 1H, Ar-OH);
- **U. V.:** 344 nm

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**Preparation of 2'-hydroxy-3',5'-dichloro-4-hexylchalcone (4b)**

2'-hydroxy-3',5'-dichloro acetophenone (3a), 0.1M was dissolved in ethanol (50 mL), heptanaldehyde (0.1 M) was added to the above solution and mixture was heated to boiling. Aq. sodium hydroxide solution (405, 40 ml) was added drop wise with constant stirring. The mixture was stirred mechanically at room temperature for about half an hours and kept for overnight. Then it was acidified by hydrochloric acid solution (50 %). The solid separated was filtered, acid washed with sodium bicarbonate 10% followed by water. The crude product was crystallized from ethanol acetic acid mixture (4b).

**IR (KBr):**
- 3068(-OH phenolic), 2926(aliphatic –CH stretching), 1646(>C=O stretching), 641(C-Cl stretching); **PMR:**
  - δ 2.6(s, 3H, -CH3),δ 7.4to 7.4 (m, 2H,Ar-H),δ 7.25 - 7.63 (m, 2H,Ar-H); δ 12.71 (s, 1H, Ar-OH); **U. V.:** 342 nm

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**Preparation of 4-(2'-hydroxy-3', 5'-dichlorophenyl)-6-hexyl-2-iminophenyl-1,3-thiazines (5b)**

2'-hydroxy-3',5'-dichloro-4-hexyl chalcone (4b), (0.01 M) dissolved in ethanol (25 mL), were added n-phenyl thiourea (0.01M). To this solution aq. KOH solution (0.02 M) was added (prepared from KOH in
small amount of distilled water). The reaction mixture was reflux for 2.5 hours, cooled, diluted with water and acidified with conc. HCl. The product was filtered, dried and crystallized from ethanol (5b).

**IR (KBr):** 3068 (-OH phenolic stretching); 3300 (NH stretching); 1305 (-OH bending in phenol); 1022 (C-S stretching); 736 (C-Cl stretching); **PMR:** δ 2.7 (s, 3H, -CH$_3$); δ 7 to 8 (s, -ArH); δ 6.1 (s, 1H, NH stretching); δ 12.7 (s, 1H, Ar-OH); **UV:** 294 nm

**Preparation of 4-(2'-hydroxy-3', 5'-dichlorophenyl)-6-(hexyl)-2-iminophenyl-3-phenyl-1,3-thiazines (6b)**

Synthesis of (6b) compound was in similar manner as such (5b), instead of phenylthiourea was used diphenylthiourea.

**IR (KBr):** 3067 (-OH phenolic stretching); 3206 (NH stretching); 2950 (aliphatic C-H stretching); 1304 (OH bending in phenol); 1045 (C-S stretching); 696 (C-Cl stretching);

**PMR:** δ 2.70 (s, 1H, -CH$_3$); δ 7 to 8 (s, -ArH); δ 4.7 (s, 1H, NH); δ 12.7 (s, 1H, Ar-OH); **UV:** 273 nm

From the table, it appears that dissociation of these ligands occurred at higher pH. All ligands showed their dissociation in the pH range 9-12. The pK value of L$_1$ is found to be greater (i.e., 11.7) as compared
to ligand 2. This may be due to the presence of phenyl ring group as an electron-releasing group that there is reduction in pK values.

The pK values are found decrease in the order ligand L₁ > ligand L₂.

**Metal ligand stability constant**

The deviation between (acid + ligand) and (acid + ligand + metal) curves started from pH 2.8 and increased continuously up to pH 12.0. It showed the commencement of complex formation. Intense colouration was observed which also indicated the formation of complex. The formation curves were constructed between η and pH. The metal ligand stability constants were determined by half-integral method at η = 0.5 and 1.5. The values of η are estimated by applying Irving-Rossotti expression. The maximum values of η was obtained at about of K₁ and log K₂ for complexes are calculated and presented in Table-3.

**Table-3: Determination of metal-ligand stability constants (log k) of Co (II), Cu (II) complexes with Chloro substituted -1,3 thiazines at 0.12 M ionic Strength.**

<table>
<thead>
<tr>
<th>Systems</th>
<th>Metal ligand stability constant (Log k)</th>
<th>Metal ligand stability constant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Log k₁</td>
<td>Log k₂</td>
</tr>
<tr>
<td>Co (II)L₁ complex</td>
<td>11.4</td>
<td>6.25</td>
</tr>
<tr>
<td>Cu (II)L₁ complex</td>
<td>7.99</td>
<td>5.78</td>
</tr>
<tr>
<td>Co (II)L₂ complex</td>
<td>10.1</td>
<td>4.75</td>
</tr>
<tr>
<td>Cu (II)L₂ complex</td>
<td>6.42</td>
<td>4.22</td>
</tr>
</tbody>
</table>

It was observed from Table 3 that log k₁ values are greater than log k₂ values for all metal complexes. The log k₁ and log k₂ values follow the order as Co (II), Cu (II). It could be seen (Table-3) that log k values follow increasing trend. This may be due to phenyl group as electron releasing group.

It could be seen from data in all the cases that the differences between log k₁ and log k₂ are found to be greater which shows formation of stepwise complex. The value of ratio of log k₁ / log k₂ is positive in all the cases (Table3). The implies that there is no steric hindrance to the addition of secondary ligand molecule.

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