

# Kinetic And Mechanism Of Uncatalyzed Oxidation Of 4-(3-Hydroxy Phenyl Amino)-4-Oxo Butanoic Acid By Alkaline Hexacyanoferrate (III)

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**Abstract:** The kinetics and mechanism of hexacyanoferrate (HCF (III)) oxidation of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid (4-Oxo acid) in aqueous alkaline medium has been studied at  $26 \pm 0.1^\circ\text{C}$ . The reaction shows first order dependence in [HCF (III)], fractional order dependence in each [4-Oxo acid] and  $[\text{OH}^-]$ . Variation of ionic strength by the addition of  $\text{KNO}_3$  has no significant effect on the rate. The stoichiometry of the reaction is found to be 1:2 and the main oxidative products are N-(4-hydroxy phenyl) formamide and malonic acid. Suitable mechanism has been proposed and the reaction constants involved in different steps of mechanism are calculated. Activation parameters with respect to slow step of the mechanism are calculated and tabulated.

**Key words:** 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid, Kinetic, Mechanism, Oxidation, Hexacyanoferrate (III).

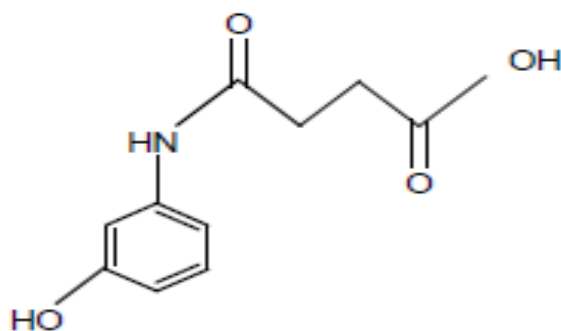
## 1. INTRODUCTION:

4-Oxo acids are interesting substrates meant for enolization. Generally, in 4-oxo acids, two carbon atoms separate the carboxyl and carbonyl groups and hence they behave both as acids and as oxo compounds without the direct influence of other group. Many of 4-oxo acids and their esters possess fungicidal, anti-inflammatory and bactericidal activities <sup>1</sup>.

4-phenyl 4-oxo acids derivatives are generally used in the therapy: particularly as Kynurenine-3-hydroxylase inhibitors, in the prevention and / or treatment of a neurodegenerative diseases like Huntington's chorea, Acquire immune deficiency syndrome (AIDS), Cerebral ischemia, Cerebral hypoxia, Parkinson's disease, Head and spinal cord injury and Amyotrophic lateral sclerosis etc., wherein the inhibition of such an enzyme is needed.

Various oxidants like Permanganate, Pyridinium fluorochromate, N-bromo succinimide, N-chloro saccharin, N-bromo saccharin, N-chloro benzamide and N-bromo acetamide have been used to oxidize 4-oxo acids<sup>2-8</sup>.

Hexacyanoferrate (III) is one of the most efficient oxidizing agent in alkaline medium. It is a complex ion capable of abstracting one electron from an electron rich site. HCF (III) has been widely used to oxidize numerous organic and inorganic compounds in basic, acidic and neutral medium<sup>9,10</sup>. HCF (III) bears redox potential of +0.36V in acidic medium and +0.45V in basic medium. In most of its oxidation, hexacyanoferrate (III) is mainly used as a hydrogen atom abstractor<sup>11</sup> and / or free radical generator<sup>12</sup>. The mechanism may be quite interesting due to the formation of different intermediates, hence this paper reports the kinetic features of the oxidation of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid by HCF (III) in alkaline medium with mechanistic aspects.



**Fig.1: Structure of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid.**

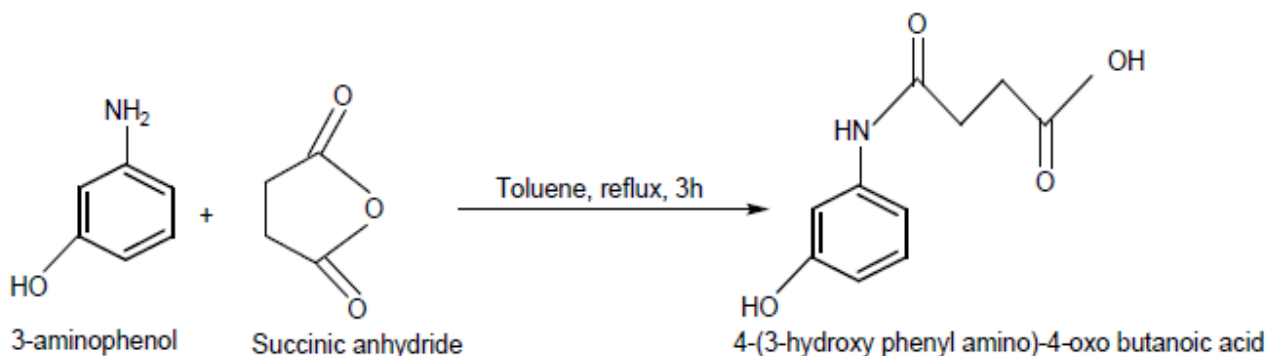
## 2. EXPERIMENTAL:

### 2.1 Materials and Reagents:

#### Preparation of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid:

4-(3-hydroxy phenyl amino)-4-oxo butanoic acid was synthesized (Succinic anhydride (0.01 M) was taken in toluene and heated to get clear solution. To this solution, 3-amino phenol in toluene (0.01 M) was added drop wise and heating was continued for 1 hr. Completion of reaction was monitored by TLC, obtained precipitate was filtered under vacuum, dried to give 4-(3-hydroxy

phenyl amino)-4-oxo butanoic acid as white solid, which was crystallized by using aqueous ethanol and its purity was checked by its melting point).



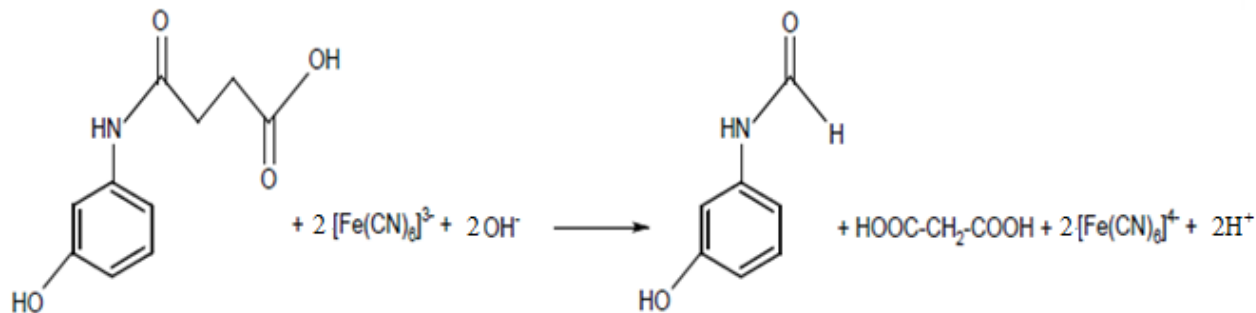
NaOH,  $\text{KNO}_3$ , Hexacyanoferrate (III) (Merck) were of analytical reagent grade and were used as received. Spectrophotometer (Systronics Double beam 2203 smart) was used for absorption studies.

## 2.2 Kinetic measurements

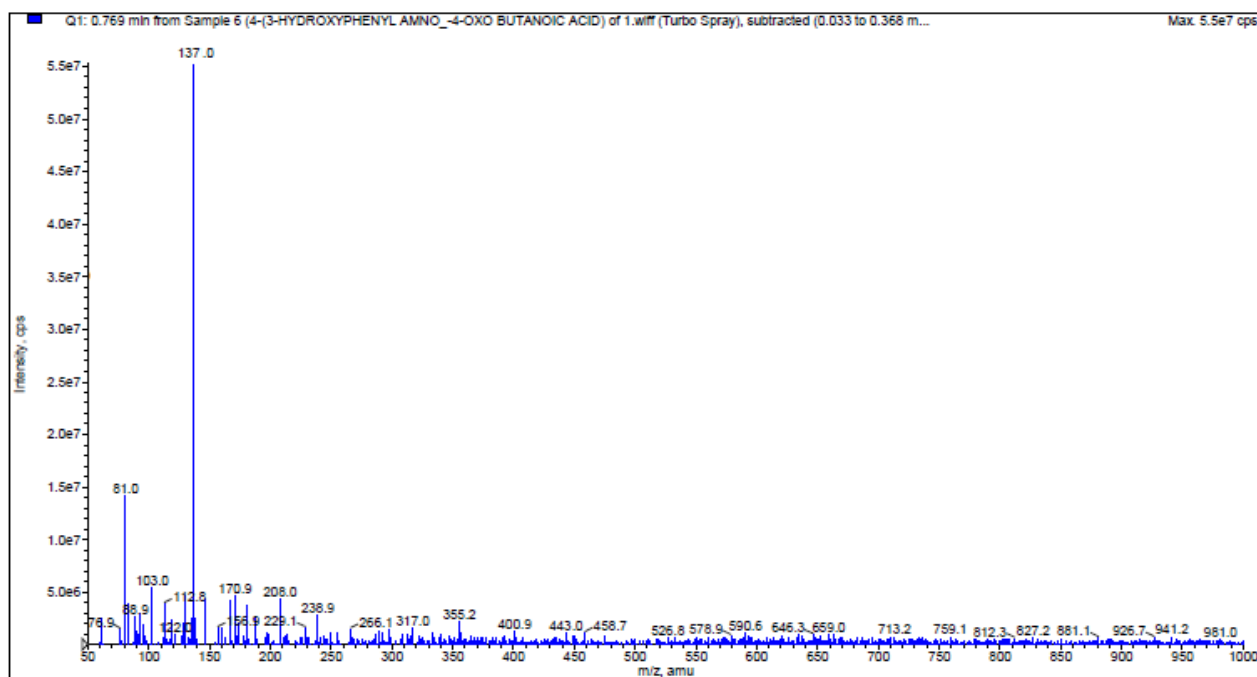
Reaction of 4-Oxo acid with HCF (III) was studied under pseudo first order condition where the [4-oxo acid] is ten times greater than [HCF (III)] at  $26 \pm 0.1^\circ\text{C}$ . The reaction was initiated by mixing HCF (III) to 4-Oxo acid containing required amount of NaOH and  $\text{KNO}_3$ . The progress of reaction was observed spectrophotometrically by measuring decrease in absorbance of HCF (III) at 420 nm wavelength. Graphs of  $\log [\text{HCF (III)}]$  versus time were plotted for pseudo first order reactions which are linear up to 80% completion of reaction and the rate constants ( $k_{\text{obs}}$ ) were calculated.

## 2.3 Stoichiometry and product analysis

Stoichiometry of the reaction was determined by equilibrating reaction mixture of various [HCF (III)] and [4-Oxo acid] at  $26^\circ\text{C}$  for 24 hrs, keeping all other reagents constant. The unreacted hexacyanoferrate was estimated spectrophotometrically at 420 nm, which reveals that one mole of 4-oxo acid requires two moles of HCF (III) for oxidation.



The oxidative products were identified as N-(4-hydroxy phenyl) formamide, which gives molecular ion peak at 137 MHz as shown in (Fig.2) and malonic acid is identified by its melting point (135°C) and with its characteristic spot test through conversion into barbituric acid<sup>13</sup>.



**Fig.2: LC-MS of product N-(4-hydroxy phenyl) formamide shows intense molecular ion peak at 137 MHz.**

### 3. REACTION ORDER:

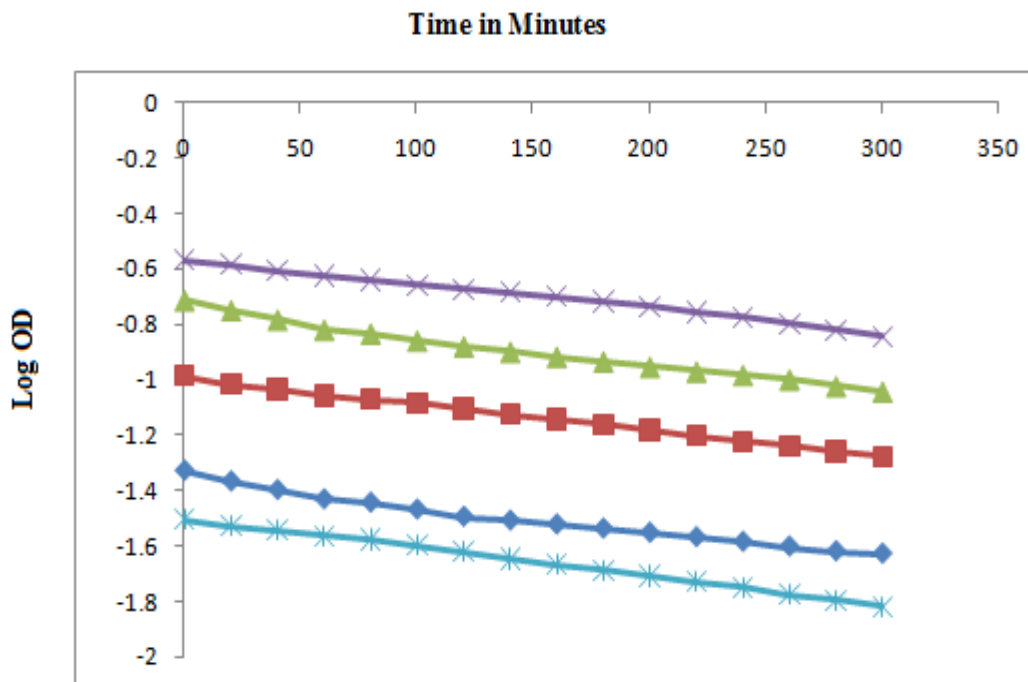
#### 3.1 HCF (III) dependence:

The concentration of HCF (III) was varied from  $0.25 \times 10^{-4}$  to  $2.25 \times 10^{-4}$  mol dm<sup>-3</sup> at fixed concentrations of 4-Oxo acid ( $1.25 \times 10^{-3}$  mol dm<sup>-3</sup>), KNO<sub>3</sub> (0.01 mol dm<sup>-3</sup>) and OH<sup>-</sup> (0.1 mol dm<sup>-3</sup>). A plot of log OD of HCF (III) versus time (sec) result in straight line, which is linear up to

80% completion of reaction as shown in Fig.3, hence the reaction is first order with respect to oxidant.

### 3.2 4-Oxo acid dependence:

The concentration of 4-Oxo acid was varied from  $0.25 \times 10^{-3}$  to  $2.25 \times 10^{-3}$  mol dm<sup>-3</sup> at fixed concentration of HCF (III) ( $1.25 \times 10^{-4}$  mol dm<sup>-3</sup>), KNO<sub>3</sub> (0.01 mol dm<sup>-3</sup>) and OH<sup>-</sup> (0.1 mol dm<sup>-3</sup>).



**Fig.3: A Plot of Log Absorbance versus Time in minutes shows first order dependence in hexacyanoferrate (III).**

A plot of log [4-oxo acid] against log k indicates the reaction to be fractional order as shown in Fig.4.

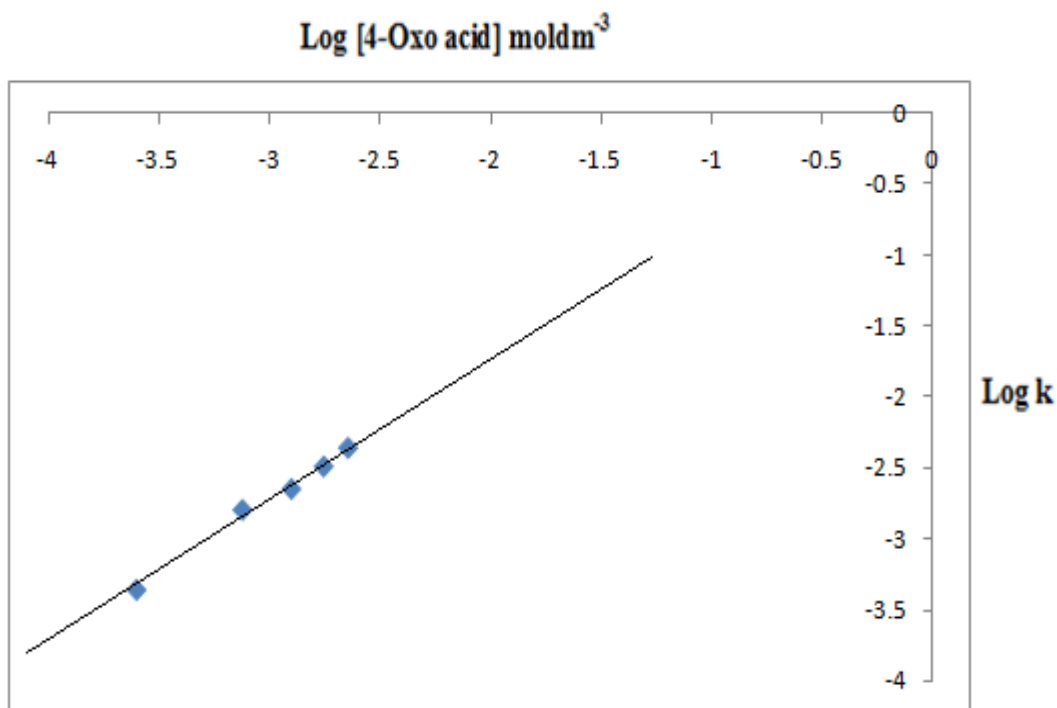
### 3.3 Hydroxyl ion dependence:

The reaction was carried out by varying the concentration of [OH<sup>-</sup>] from 0.025 to 0.3 mol dm<sup>-3</sup> at fixed concentration of HCF (III) ( $1.25 \times 10^{-4}$  mol dm<sup>-3</sup>), 4-Oxo acid ( $1.25 \times 10^{-3}$  mol dm<sup>-3</sup>), and KNO<sub>3</sub> (0.01 mol dm<sup>-3</sup>). The rate constants of the reaction were found to increase with increase in

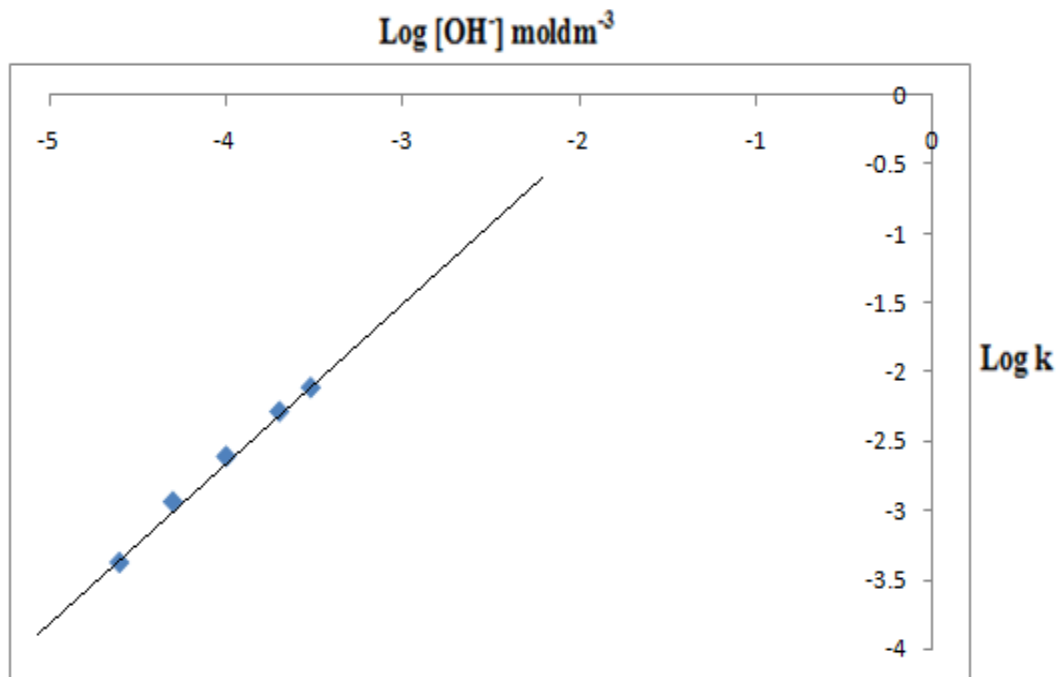
[OH<sup>-</sup>] as shown in Table 1. A plot of log k<sub>obs</sub> versus log [OH<sup>-</sup>] was linear suggesting that reaction to be fractional order as shown in Fig.5.

### 3.4 Nitrate dependence:

Ionic strength of the reaction was studied by varying concentration of KNO<sub>3</sub> from 0.0025 to 0.03 mol dm<sup>-3</sup> at fixed concentration of HCF (III) ( $1.25 \times 10^{-4}$  mol dm<sup>-3</sup>), 4-Oxo acid ( $1.25 \times 10^{-3}$  mol dm<sup>-3</sup>), and OH<sup>-</sup> (0.1 mol dm<sup>-3</sup>). From rate constant values as shown in Table 1 which clearly indicates, concentration of KNO<sub>3</sub> has no significant effect on reaction rate.



**Fig.4: A Plot of Log [4-Oxo acid] versus Log k shows fractional order dependence in 4-oxo acid.**



**Fig.5: A Plot of Log [OH<sup>-</sup>] versus Log k shows fractional order dependence in hydroxyl ion dependence.**

[HCF] X 10 <sup>-4</sup> (mol dm <sup>-3</sup> )	[4-Oxo acid] X 10 <sup>-3</sup> (mol dm <sup>-3</sup> )	[NaOH] X (mol dm <sup>-3</sup> )	[KNO <sub>3</sub> ] X 10 <sup>-2</sup> (mol dm <sup>-3</sup> )	k <sub>obs</sub> X 10 <sup>-3</sup> Experimental	k <sub>obs</sub> X 10 <sup>-3</sup> Calculated
0.25	1.25	0.1	1.0	1.826	2.734
0.75	1.25	0.1	1.0	1.927	2.734
1.25	1.25	0.1	1.0	2.055	2.734
1.75	1.25	0.1	1.0	2.085	2.734
2.25	1.25	0.1	1.0	2.139	2.734
1.25	0.25	0.1	1.0	0.438	0.555
1.25	0.75	0.1	1.0	1.604	1.665
1.25	1.25	0.1	1.0	2.255	2.734
1.25	1.75	0.1	1.0	3.257	3.885
1.25	2.25	0.1	1.0	4.398	4.995
1.25	1.25	0.025	1.0	0.418	0.693
1.25	1.25	0.05	1.0	1.155	1.387
1.25	1.25	0.1	1.0	2.452	2.734

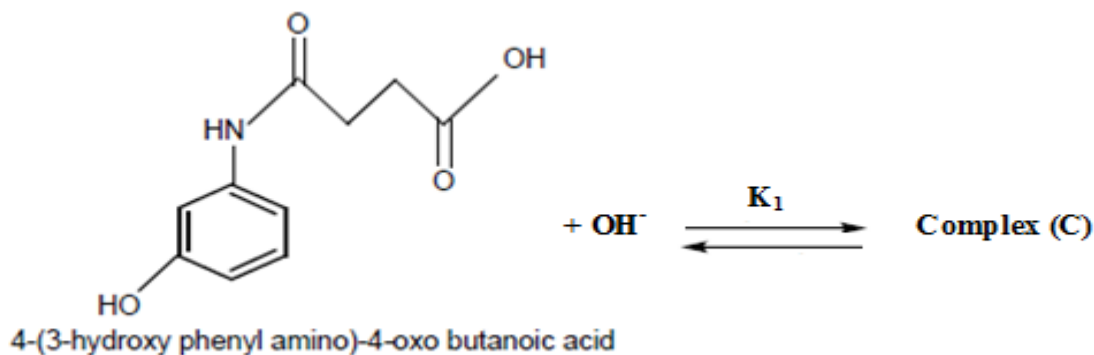
1.25	1.25	0.2	1.0	5.187	5.550
1.25	1.25	0.3	1.0	7.739	8.325
1.25	1.25	0.1	0.25	1.732	2.734
1.25	1.25	0.1	0.5	1.928	2.734
1.25	1.25	0.1	1.0	1.728	2.734
1.25	1.25	0.1	2.0	1.864	2.734
1.25	1.25	0.1	3.0	2.008	2.734

**Table 1: Effect of Variation of HCF (III), 4-Oxo acid, NaOH and KNO<sub>3</sub> Concentrations on the Reaction Rate at Temperature 26 ± 0.1°C.**

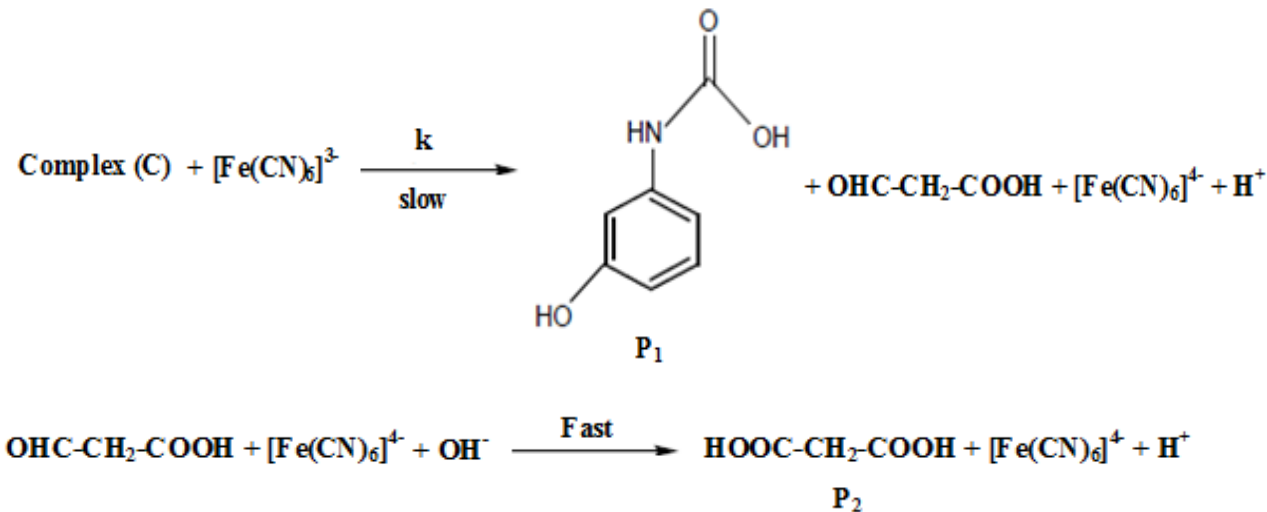
#### 4. POLYMERIZATION TEST:

Involvement of free radical during oxidation of 4-Oxo acid by HCF (III) was studied by adding acrylonitrile followed by dilution with methanol resulted in non-preceptible precipitation, which clearly indicates reaction is free from intervention of free radical.

#### SCHEME-1







Rate law can derived by considering scheme-1 as follows,

$$\text{Rate} = k [\text{Complex}] [\text{Fe}(\text{CN})_6^{3-}]$$

$$= kK_1 [4\text{-Oxo acid}]_f [\text{OH}^-]_f [\text{Fe}(\text{CN})_6^{3-}]_f \dots\dots\dots (1)$$

$$[4\text{-Oxo acid}]_T = [4\text{-Oxo acid}]_f + [\text{Complex}]_f$$

$$= [4\text{-Oxo acid}]_f + K_1 [4\text{-Oxo acid}]_f [\text{OH}^-]$$

$$= [4\text{-Oxo acid}]_f (1 + K_1 [\text{OH}^-])$$

$$[4\text{-Oxo acid}]_f = [4\text{-Oxo acid}]_T / (1 + K_1 [\text{OH}^-]) \dots\dots\dots (2)$$

$$[\text{OH}^-]_T = [\text{OH}^-]_f + [\text{Complex}]_f$$

$$= [\text{OH}^-]_f + K_1 [4\text{-Oxo acid}]_f [\text{OH}^-]_f$$

$$= [\text{OH}^-]_f (1 + K_1 [4\text{-Oxo acid}]_f)$$

$$[\text{OH}^-]_f = [\text{OH}^-]_T / (1 + K_1 [4\text{-Oxo acid}]_f) \dots\dots\dots (3)$$

Substitute Equations (2) and (3) in equation (1)

$$\text{Rate} = kK_1 [4\text{-Oxo acid}]_T [\text{OH}^-]_T [\text{Fe}(\text{CN})_6^{3-}] / (1 + K_1 [\text{OH}^-]) (1 + K_1 [4\text{-Oxo acid}])$$

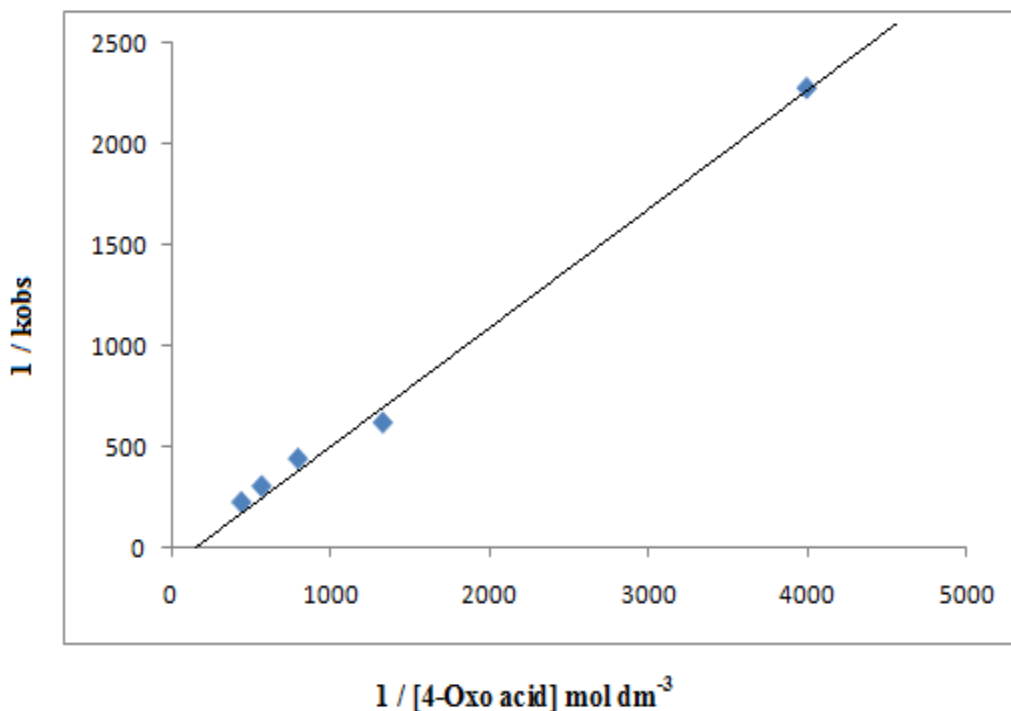
$$\text{Rate} / [\text{Fe}(\text{CN})_6^{3-}] = k_{\text{obs}} = kK_1 [4\text{-Oxo acid}]_T [\text{OH}^-]_T / 1 + K_1 [\text{OH}^-] + K_1 [4\text{-Oxo acid}] +$$

$$K_1^2 [\text{OH}^-] [4\text{-Oxo acid}]$$

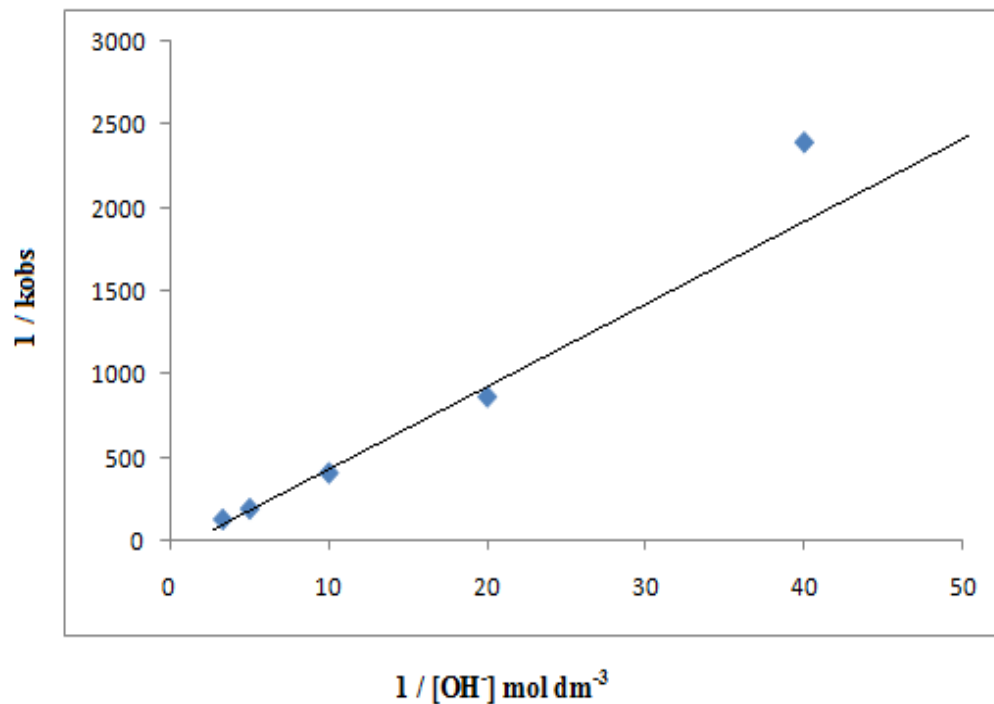
Therefore, the rate law can be derived as

$$k_{obs} = kK_1 [4\text{-Oxo acid}] [\text{OH}^-] / 1 + K_1 [\text{OH}^-] + K_1 [4\text{-Oxo acid}] \quad \dots\dots\dots (4)$$

On rearranging equation (1) and plotting graph of  $1 / k_{obs}$  versus  $1 / [4\text{-Oxo acid}]$  and  $1 / k_{obs}$  versus  $1 / [\text{OH}^-]$ ,  $k$  and  $K_1$  can be calculated.  $1 / k_{obs}$  versus  $1 / [4\text{-Oxo acid}]$  gives straight line with intercept (Fig.6) and from the intercept ‘ $k$ ’ can be calculated. The plot of  $1 / k_{obs}$  versus  $1 / [\text{OH}^-]$  also gives straight line (Fig.7) with slope equal to ‘ $K_1$ ’. The value of ‘ $k$ ’ is found to be  $150 \pm 0.5$  and ‘ $K_1$ ’ is 0.148. The results are in good agreement with calculated readings.



**Fig.6: A plot of  $1/k_{obs}$  versus  $1/[4\text{-Oxo acid}]$  for the verification of rate law.**



**Fig.7: A plot of  $1/k_{\text{obs}}$  versus  $1/[\text{OH}]$  for the verification of rate law.**

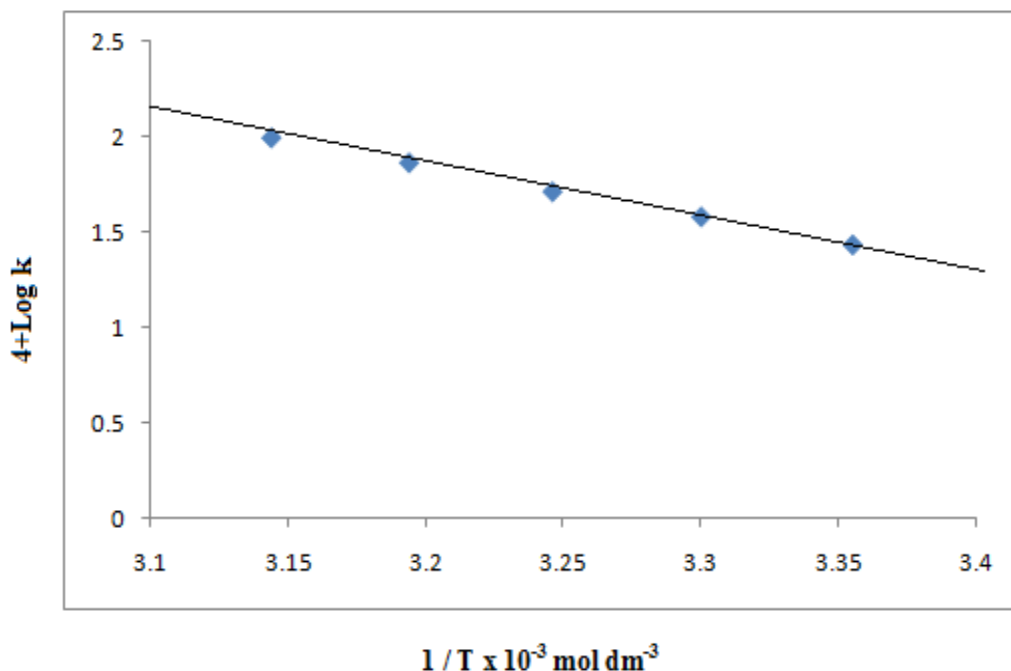
### 5. EFFECT OF TEMPERATURE:

Effect of temperature on reaction rate was measured at temperature ranging from 298K-318K maintaining fixed concentration of 4-Oxo acid ( $1.25 \times 10^{-3} \text{ mol dm}^{-3}$ ), HCF (III) ( $1.25 \times 10^{-4} \text{ mol dm}^{-3}$ ) NaOH ( $0.1 \text{ mol dm}^{-3}$ ) and  $\text{KNO}_3$  ( $0.01 \text{ mol dm}^{-3}$ ) (Fig.8). The reaction rate enhances with increase in temperature (Table 2).

Temp. (K)	$k_{\text{obs}} \times 10^{-3}$
298	2.734
303	3.826
308	5.168
313	7.322
318	9.876

**Table 2: Effect of Temperature on Rate of Oxidation of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid by alkaline hexacyanoferrate (III).**

The graph of  $\log k$  versus  $1/T$  (Arrhenius plot) gives straight line and the experimental energy of activation  $E_a$  and the frequency factor  $\log_{10}A$  were calculated from the slope and the intercept. The Eyrings parameters  $\Delta H^\ddagger$ ,  $\Delta S^\ddagger$ ,  $\Delta G^\ddagger$  were calculated and tabulated (Table 3).



**Fig.8: A graph of  $\log k$  versus  $1/T$  ( $K^{-1}$ ) (Arrhenius plot) for the calculation of activation parameters.**

Activation Parameters	Values
$E_a$ (kJ/mol)	22.86
$\Delta H^\ddagger$ (kJ/K/mol)	20.386
$\Delta S^\ddagger$ (J/K/mol)	-321.29
$\Delta G^\ddagger$ (kJ/K/mol)	116.13
$\text{Log}_{10}A$	2.2

**Table 3: Activation Parameters for Oxidation of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid by alkaline hexacyanoferrate (III).**

## 6. CONCLUSION:

Oxidation of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid by hexacyanoferrate (III) in aqueous alkaline medium is first ordered with respect to HCF (III), fractional order with respect to 4-Oxo acid and NaOH. 4-Oxo acid in alkaline medium result in formation of complex which on oxidation produces N-(4-hydroxy phenyl) formamide and an intermediate biproduct which on further oxidation result in malonic acid. Ionic strength has no significant effect on reaction rate. The mechanism of scheme-1 and rate law was verified by linear plot of  $1 / k_{obs}$  versus  $1 / [4\text{-Oxo acid}]$  and  $1 / k_{obs}$  versus  $1 / [\text{OH}^-]$ . From the slope and the intercept  $k$  and  $K_1$  were obtained. These values were further used to calculate rates for experimental conditions. Rate calculated were in good agreement with experimental results (Table 1). The reaction path way involves complex formation and free from radical mechanism. Hydroxyl ion places an important role during the formation of complex with 4-oxo acid. The observed large negative value of entropy of activation indicates the formation of complex in the reaction. The moderate values of  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$  are favorable for electron transfer reaction. The present method shows a path for the synthesis of carboxylic acid.

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