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Mechanistic investigations of uncatalysed and ruthenium (III) catalysed oxidation of amoxicillin an antibiotic drug by hexacyanoferrate (III) in aqueous alkaline medium: A comparative kinetic approach

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ABSTRACT

The oxidation of amoxicillin (AMX) an antibiotic drug by hexacyanoferrate (III) (HCF) has been investigated spectrophotometrically both in absence and presence of ruthenium (III) catalyst in alkaline medium at a constant ionic strength 0.01 moldm^{-3}. Stoichiometry of the reaction remains same in both the cases i.e. [AMX] : [HCF] = 1 : 2. In both catalyzed and uncatalyzed reactions, the order with respect to Amoxicillin and HCF concentrations remains unity. The order with respect to catalyst i.e. ruthenium (III) was found to be unity. As the concentration of catalyst increases, the reaction rate also increased. The rate increased with increase in hydroxyl ion concentration. Effect of temperature on the reaction rate was studied and activation parameters with respect to slow step of reaction were evaluated. A suitable mechanism has been proposed and derived rate laws are consistent with observed experimental kinetics.

Keywords: Amoxicillin, Hexacyanoferrate (III), Oxidation, Mechanism, Kinetics, Ruthenium (III) catalysis.

1. INTRODUCTION

Amoxicillin is (2S,5R,6R)-6-{[(2R)-2-amino-2-(4-hydroxy phenyl}-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylic acid used to treat pneumonia, gonorrhea, ear infections, bladder infections, *E.coli* or salmonella infections. Amoxicillin, D-α-amino-p-hydroxybenzyl pencillin as shown in figure 1 is the most frequently used antibiotic possess a β-lactum ring responsible for the antibacterial activity and variable side chains that account for the major difference in their chemical and pharmacological properties. It is a synthetic antibiotic derived from ampicillin, which has fast absorption in the intestinal tract and good resistance to acidity, facilitating its oral administration [1]. AMX possess antimicrobial activity against microorganisms such as proteus mirabilis, E.coli, haemophilus influenzae and due to this activity is used as active principle in several pharmaceutical formulations used in the treatment of bacterial infections in human and domestic animals [2,3]. Amoxicillin degraded in presence of penicillin acylase to form D-4-hydroxyphenyl glycine and 6-amino penicillin acid [4]. It is used along with clarithromycin to treat stomach ulcer caused by helicobacter pylori infection [5]. Photo degradation of amoxicillin catalyzed by Fe^{3+}/H_2O_2 has been studied by Xiaoming li etal [6] and spectrophotometric determination of amoxicillin based on its oxidative condensation with 4-amino antipyrine was studied by Mouayed Q, Al-abachi and Hadi etal [7]. Amoxicillin undergo oxidation by Ce (IV) and Fe (III) [8].

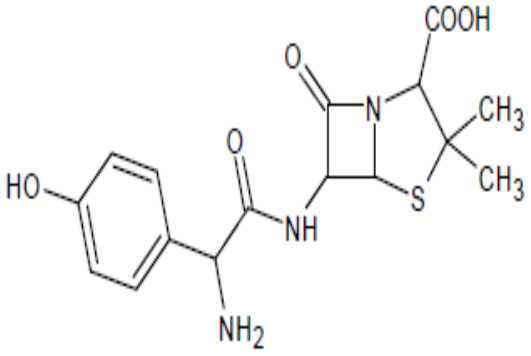


Figure - 1: Structure of amoxicillin.

2. EXPERIMENTAL

2.1. Chemicals used

All chemicals used viz. Fe(III), KCl, NaOH, Ru(III), CH_3OH and acrylonitrile were of analytical grade. Reaction solutions were prepared using double distilled water free from dissolved oxygen and carbon dioxide.

Ruthenium(III) solution was prepared by dissolving known mass of $RuCl_3$ (S.d fine) in 0.2 moldm^{-3} HCl. Mercury was added to ruthenium (III) solution to reduce any ruthenium(IV) formed during the preparation of ruthenium (III) stock solution and kept for about 24 hours. Its concentration of ascertained by EDTA titration [9].

KCl, NaOH, HCF(III) (Merck) were of analytical reagent grade and were used without further purification. Systronics double beam 2203 smart spectrophotometer was used for absorption studies. Product identification was done using LC-MS shown in figure 2

2.2. Kinetic measurements

The oxidation of amoxicillin by hexacyanoferrate (III) was followed under pseudo first order condition where [Amox] was exess over [HCF(III)]. The reaction was initiated by mixing HCF (III) to amoxicillin containing required amount of Ru(III), KCl, and NaOH. The progress of reaction was followed spectrophotometrically at 420 nm by monitoring decrease in absorbance due to HCF (III). The reaction is followed to more than 80% completion and the plots of log absorbance versus time result in first order rate constant 'k'. The plots were linear up to 80% completion of reaction and the rate constants were reproducible within ± 4%.

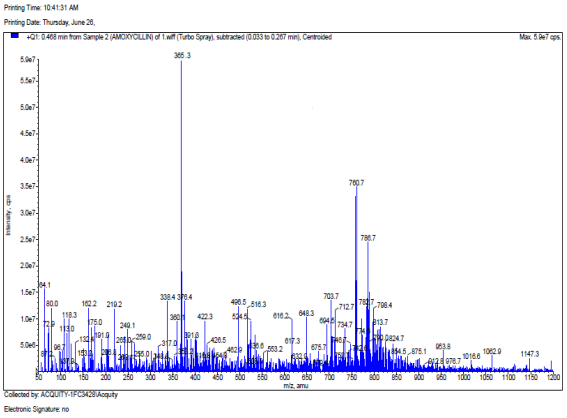


Figure - 2: LC-MS of the 6-{[amino(4-oxocyclohexa-2,5-dien-1-ylidene)acetyl]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-caboxylic acid.

The obedience of HCF (III) under the condition (as in the reaction) to Beer's law has been verified in the concentration range 0.5×10^{-4} to 4.5×10^{-4} mol dm^{-3} at constant concentration of 0.1 mol dm^{-3} of NaOH as shown in Fig.3. The orders for various species were determined from the slopes of logk versus respective concentration of species.

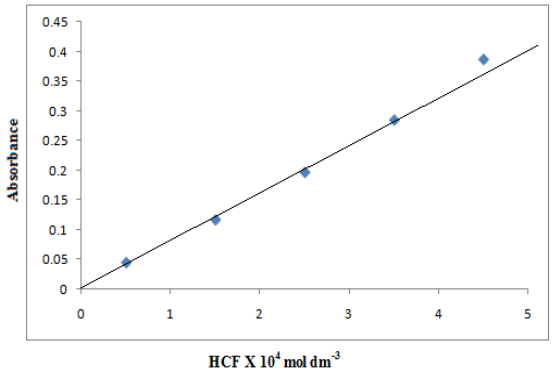
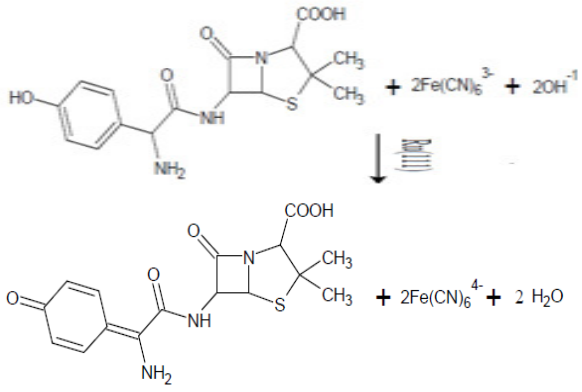


Figure - 3: Verification of Beer's law for HCF(III) at 420 nm in 0.1 mol dm^{-3} NaOH.

2.3 Stoichiometry and product analysis

Stoichiometry of the reaction was determined by equilibrating the reaction mixture containing excess of HCF(III) over amoxicillin containing required quantities of ruthenium(III), KCl, NaOH for 24 hours at room temperature.

The unreacted HCF(III) was determined by spectrophotometrically and the estimated amount of HCF(III) showed that one mole of amoxicillin consumes two moles of HCF(III). Product of the reaction was identified as 6-{[amino(4-oxocyclohexa-2,5-dien-1-ylidene)acetyl]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-caboxylic acid [10] gives molecular ion peak at 365 MHz and which is confirmed by LC-MS shown in figure 2.



3. RESULTS

3.1. HCF (III) dependence

For uncatalyzed reaction, the concentration of HCF (III) was varied from 0.5 X 10^{-4} moldm^{-3} to 4.5 X 10^{-4} moldm^{-3} at fixed concentrations of Amoxicillin (2.5 X 10^{-3} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}) and KCl (1.0 X 10^{-2}

moldm^{-3}) for uncatalysed reaction. Pseudo first order plots were made as shown in figure 4 and pseudo first order rate constants (k) were found to be independent of concentration of HCF (III).

For catalyzed reaction, the concentration of HCF (III) was varied from 0.5 X 10^{-4} moldm^{-3} to 4.5 X 10^{-4} moldm^{-3} at fixed concentrations of Amox (2.5 x 10^{-3} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}), Ru(III) (1.0 X 10^{-5} moldm^{-3}) and KCl (1.0 X 10^{-2} moldm^{-3}), pseudo first order plots of log[HCF(III)] versus time shown in figure 5 were made and the values of pseudo first order rate constants (k) were calculated. The first order rate constants in Ru(III) catalyzed were also independent of initial concentration of HCF (III).

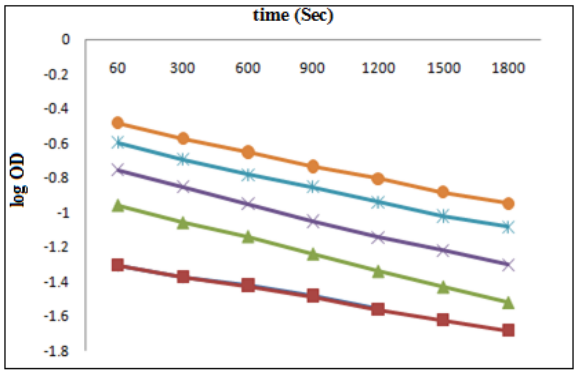


Figure - 4: A graph of Log OD versus time (Sec) shows first order with respect to Hexacyanoferrate (III) for uncatalyzed reaction.

3.2 Amoxicillin dependence

The concentration of Amoxicillin was varied from 0.5 X 10^{-3} moldm^{-3} to 4.5 X 10^{-3} moldm^{-3} at fixed concentrations of HCF(III) (2.5 X 10^{-4} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}) and KCl (1.0 x 10^{-2} moldm^{-3}) for uncatalysed reaction, the plot of logk versus logc of amoxicillin indicates first order dependence with respect to amoxicillin.

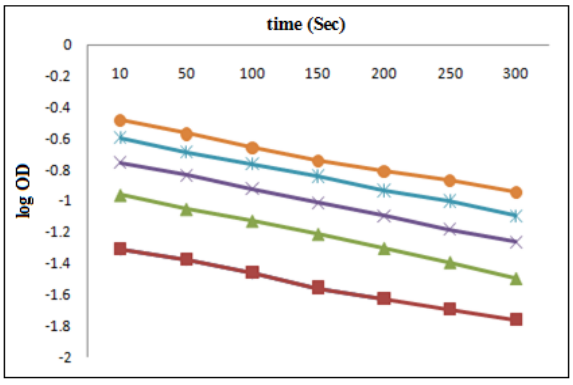


Figure - 5: A graph of Log OD versus time (Sec) shows first order with respect to Hexacyanoferrate (III) for Ru (III) catalyzed reaction.

The concentration of Amoxicillin in Ru(III) catalyzed reaction was varied from 0.5 X 10^{-3} moldm^{-3} to 4.5 X 10^{-3} moldm^{-3} at fixed concentrations of HCF(III) (2.5 X 10^{-4} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}), Ru(III) (1.0 X 10^{-5} moldm^{-3}) and KCl (1.0 X 10^{-2} moldm^{-3}). The pseudo first order rate constants (k) calculated in this reaction exhibits proportionate increase with increasing amoxicillin concentration, further confirming first order dependence with respect to amoxicillin shown in table 1.

3.3. Ruthenium (III) dependence

The concentration of Ru(III) was varied from 0.25 X 10^{-5} moldm^{-3} to 3.0 X 10^{-5} moldm^{-3} at fixed concentrations of Amoxicillin (2.5 X 10^{-3} moldm^{-3}), HCF(III) (2.5 X 10^{-4} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}) and KCl (1.0 X 10^{-2} moldm^{-3}). Pseudo first order rate constants (k) on plotting against the concentration of Ru(III) yielded straight line with non-zero intercept. This behavior confirms first order dependence with respect to Ruthenium (III) as given in table 1.

3.4. Hydroxyl ion Dependence:

Hydroxyl ion concentration was varied by employing NaOH from 0.25 X10^{-2}moldm^{-3} to 3.0 X 10^{-2} moldm^{-3} at fixed concentrations of Amoxicillin (2.5 X 10^{-3} moldm^{-3}), HCF (III) (2.5 X 10^{-4} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}) and KCl (1.0 X 10^{-2} moldm^{-3}). The rate increases with increase in hydroxyl ion concentration and the plot of logk versus logc indicates fractional order dependence.

For catalyzed reaction, the concentration of NaOH varied from 0.25 X 10^{-2}moldm^{-3} to 3.0 X 10^{-2} moldm^{-3} at fixed concentrations of Amoxicillin (2.5 X 10^{-3} moldm^{-3}), HCF(III) (2.5 X 10^{-4} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}), Ru(III) (1.0 X 10^{-5} moldm^{-3}) and KCl (1.0 X 10^{-2} moldm^{-3}). The increase in rate with increase in hydroxyl ion shows first order kinetics at lower concentration.

3.5. KCl Dependence

The effect of ionic strength on the reaction rate was studied by varying concentration of KCl from 0.25 X 10^{-2}moldm^{-3} to 3.0 X 10^{-2} moldm^{-3} at fixed concentrations of Amoxicillin (2.5 X10^{-3} moldm^{-3}), HCF(III) (2.5 X 10^{-4} moldm^{-3}), NaOH (1.0 X 10^{-2} moldm^{-3}) and Ru(III) (1.0X 10^{-5} moldm^{-3}) in both catalyzed and uncatalyzed reactions. The pseudo first order rate constants (k) shows no significant effect on reaction rate. Therefore the rate was independent of ionic strength in this reaction.

Table 1. Effect of Variation of [Fe (III)], [Amox], [NaOH], KCl and [Ru (III)] on Oxidation of Amoxicillin by Hexacyanoferrate (III) in alkaline medium at 25^{0}C and I = 0.01 mol dm^{-3}.

Fe(III)X10^4 (mol dm^{-3})	[Amox]X10^3 (mol dm^{-3})	[NaOH] X10^{-2} (mol dm^{-3})	[Ru(III) X 10^{-5} (mol dm^{-3})	KCl X10^{-2} (mol dm^{-3})	kobs x 10^{-3} Experi-mental	kobs x10^{-3} Calcu-lated	kobs x10^{-4} Experi-mental	kobs x10^{-4} Calcu-lated
					For catalyzed		For Uncatalyzed	
0.5	2.5	1.0	1.0	1.0	1.698	1.747	3.211	3.368
1.5	2.5	1.0	1.0	1.0	1.688	1.747	3.267	3.368
2.5	2.5	1.0	1.0	1.0	1.742	1.747	3.287	3.368
3.5	2.5	1.0	1.0	1.0	1.713	1.747	3.263	3.368
4.5	2.5	1.0	1.0	1.0	1.727	1.747	3.285	3.368
2.5	0.5	1.0	1.0	1.0	0.398	0.406	0.721	0.673
2.5	1.5	1.0	1.0	1.0	1.123	1.127	1.919	2.021
2.5	2.5	1.0	1.0	1.0	1.742	1.747	3.287	3.368
2.5	3.5	1.0	1.0	1.0	2.280	2.286	4.637	4.716
2.5	4.5	1.0	1.0	1.0	2.752	2.756	5.921	6.064
2.5	2.5	0.25	1.0	1.0	0.847	0.853	0.879	0.887
2.5	2.5	0.5	1.0	1.0	1.297	1.295	1.744	1.743
2.5	2.5	1.0	1.0	1.0	1.742	1.747	3.287	3.368
2.5	2.5	2.0	1.0	1.0	2.108	2.116	6.880	6.312
2.5	2.5	3.0	1.0	1.0	2.274	2.277	9.494	8.906
2.5	2.5	1.0	0.25	1.0	1.703	1.747	-	-
2.5	2.5	1.0	0.5	1.0	1.693	1.747	-	-
2.5	2.5	1.0	1.0	1.0	1.742	1.747	-	-
2.5	2.5	1.0	2.0	1.0	1.697	1.747	-	-
2.5	2.5	1.0	3.0	1.0	1.734	1.747	-	-
2.5	2.5	1.0	1.0	0.25	1.718	1.747	3.271	3.368
2.5	2.5	1.0	1.0	0.5	1.737	1.747	3.297	3.368
2.5	2.5	1.0	1.0	1.0	1.742	1.747	3.287	3.368
2.5	2.5	1.0	1.0	2.0	1.740	1.747	3.301	3.368
2.5	2.5	1.0	1.0	3.0	1.738	1.747	3.294	3.368

3.5 POLYMERIZATION STUDY:

Intervention of free radical during oxidation of amoxicillin by HCF (III) was studied by adding acrylonitrile (free radical scavenger) followed by dilution with methanol result in precipitation, which clearly indicates free radical involvement in reaction path.

The reaction rate can be written for catalyzed reaction as,

$$\text{Rate} = -d[Fe(CN)_6]^{3-} / dt = k\,[Amox]\,[OH^-]\,[Ru(III)] \quad \ldots (1)$$

Scheme - 1

$$[Ru(H_2O)_6]^{3+} + OH^- \underset{}{\overset{K1}{\rightleftharpoons}} [Ru(H_2O)_5OH]^{2+} + H_2O \quad \ldots (2)$$

$$[Ru(H_2O)_5OH]^{2+} + \text{Amoxicillin} \overset{K2}{\rightleftharpoons} \text{Intermediate Complex} \quad \ldots (3)$$

$$\text{Intermediate Complex} \xrightarrow{k,\ slow} \text{Product} + [Ru(H_2O)_5H]^{2+} \quad \ldots (4)$$

$$[Ru(H_2O)_5H]^{2+} + 2OH^- + 2[Fe(CN)_6]^{3-} \xrightarrow{fast} [Ru(H_2O)_5OH]^{2+} + 2[Fe(CN)_6]^{4-} + H2O \quad \ldots (5)$$

The reactive aqua complex of ruthenium $[Ru(H_2O)_5OH]^{2+}$ is formed in first step which in turn reacts with amoxicillin to give an intermediate complex. The intermediate complex slowly disproportionate to give a final product and the hydride species of ruthenium (III). In last step, the ruthenium (III) hydride species re-oxidized to its original reactive species $[Ru(H_2O)_5OH]^{2+}$.

Equation (4) is rate determining step which can be given by,

$-d[Fe(CN)_6]^{3-}/dt = k\,[\text{Intermediate complex}]$.. (6)

Substituting equation (2) and (3), equation (6) becomes

$-d[Fe(CN)_6]^{3-}/dt = kK_1K_2[Amox][OH^-][Ru(III)]$.. (7)

By considering equation (2) and (3), $[Ru(III)]_T$ can be written as

$[Ru(III)]_T = [Ru(III)]_e + [Ru(H_2O)_5OH]^{2+} + [\text{Intermediate complex}]$

The rate law reduces to

$-d[Fe(CN)_6]^{3-}/dt = kK_1K_2\,[Amox]\,[OH^-]\,[Ru(III)]_T / 1+ K_1[OH^-] + K_1K_2\,[Amox]\,[OH^-]$

$-d[Fe(CN)_6]^{3-}/dt = kK_1K_2\,[Amox]\,[OH^-]\,[Ru(III)]_T / 1+ K_1[OH^-]\,(1+ K_2\,[Amox])$ ..... (8)

At lower concentration of amoxicillin, the inequality $1 >> K_2[Amox]$, Equation (8) becomes

$-d[Fe(CN)_6]^{3-}/dt = kK_1K_2\,[Amox]\,[OH^-]\,[Ru(III)]_T / 1+ K_1[OH^-]$ ..... (9)

Equation (8) shows first order kinetics at lower concentration of amoxicillin. Further at lower concentration of alkali, $1 >> K_1[OH^-]$, equation (9) becomes

$-d[Fe(CN)_6]^{3-}/dt = kK_1K_2[Amox][OH^-][Ru(III)]_T$ ....(10)

Equation (10) holds good first order kinetic with hydroxyl ion at lower concentration and at higher concentration $K_1[OH^-] >> 1$, equation (10) becomes

$-d[Fe(CN)_6]^{3-}/dt = kK_1K_2\,[Amox]\,[Ru(III)]_T$ ..(11)

Equation (11) holds good zero order kinetics with respect to $[OH^-]$ at higher concentration, equation (8) at constant $[Ru(III)]_T$ becomes,

$-d[Fe(CN)_6]^{3-}/dt = kK_1K_2\,[Amox]\,[OH^-] / 1+ K_1[OH^-]+ K_1K_2\,[Amox]\,[OH^-]$ ..... (12)

Equation (12) in reciprocal form can be written as,

$1/Rate = 1 / [Amox]\,(1 / kK1K2\,[OH^-] + 1 / kK2) + 1/k$ ..... (13)

The plot of 1/ kobs versus 1 / [Amox] and 1/ kobs versus 1 / $[OH^-]$ were found to be linear and from the slope and intercepts k, K_1, K_2 were calculated and values are found to be 0.01, 136.11 and 146.93 respectively as shown in figure 6 and figure 7.

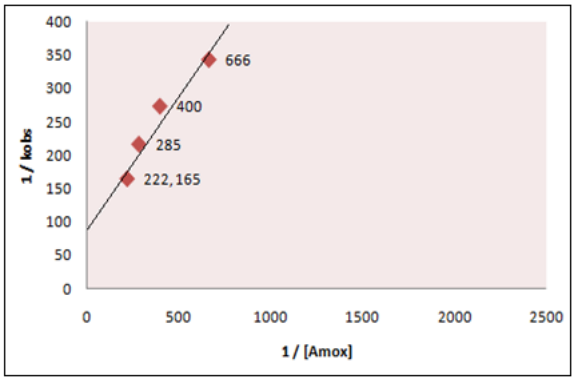


Figure - 6: Plot of 1 / kobs versus 1 / [Amox] for catalyzed reaction supporting the verification of rate law.

For uncatalyzed reaction, the reaction scheme can be written as follows,

Scheme-2

$Amox + OH^- \underset{}{\overset{K1}{\rightleftharpoons}} Amox^- + H_2$ ..... (14)

$Amox^- + HCF \overset{K2}{\rightleftharpoons} Amox\cdot + Fe(II)$..... (15)

$Amox\cdot + HCF + OH^- \xrightarrow{k,\ slow} Product + Fe(II)$. (16)

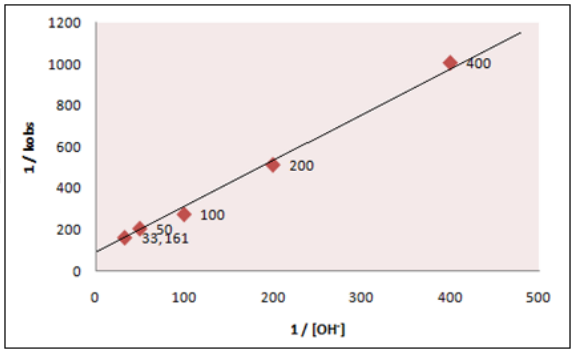


Figure - 7: Plot of 1 / kobs versus 1 / $[OH^-]$ for catalyzed reaction supporting the verification of rate law.

$Rate = -d[Fe(CN)_6]^{3-}/dt = k\,[Amox\cdot]\,[OH^-]\,[HCF]$

$= k\,K_1\,K_2\,[Amox]\,[HCF]\,[OH^-]$ ..... (17)

$[Amox]_T = [Amox]_f + K_1[Amox][OH^-] + K_2[Amox][HCF]$

$[Amox]_f = [Amox]_T / 1+ K_1\,[OH^-]\,K_2\,[HCF]$ ... (18)

$[HCF]_f = [HCF]_T / 1+ K_2\,[Amox]$ ..... (19)

$[OH^-]_f = [OH^-]_T / 1+ K_1\,[Amox]$ ..... (20)

Substitute equations 18, 19 and 20 in equation 17 gives

-

$$d[Fe(CN)_6]^{3-}/dt = k K_1 K_2 [Amox] [HCF] [OH^-] / (1+ K_1 [OH^-]+ K_2 [HCF]) (1+ K_2[Amox]) (1+ K_1 [Amox])$$

On seeing the [HCF] and [Amox] can be neglected

$$Rate = k K_1 K_2 [Amox] [HCF] [OH^-] / 1+ K_1 [OH^-]$$

$$Rate / [HCF] = kobs = k K_1 K_2 [Amox] [OH^-] / 1+ K_1 [OH^-] \quad \ldots\ldots\ldots (21)$$

On rearranging the above equation,

$$1/kobs = 1/ k K_1 K_2 [Amox] [OH^-] + 1/ k K_2 [OH^-]$$

By plotting a graph of 1 / kobs v/s 1 / [Amox], Slope and intercept gives the values of $1/ k K_1 K_2 [OH^-]$ and $1 / k K_2$ [Amox] as shown in Fig.8 and values are found to be $k K_1 K_2 = 14.45$ and $K_1 = 7.225$ respectively.

3.6. Effect of temperature

The rate of reaction for both catalyzed and uncatalyzed reactions were measured at different temperatures and at constant concentrations of reactants with other conditions being constant. The rate of reaction increased with increase in temperature. The Arrhenius plot shown in Fig.9 of logk versus 1/T gives straight line and from the slope and intercept, the experimental energy of activation Ea was calculated. The Eyring's parameters $\Delta H^{\#}$, $\Delta S^{\#}$, and $\Delta G^{\#}$ were calculated for both catalysed and uncatalyzed reactions and tabulated in table 3.

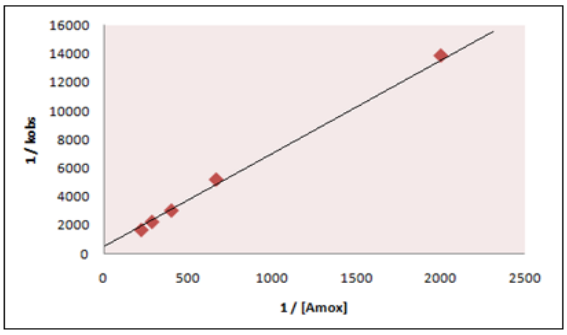


Figure - 8: Plot of 1 / kobs versus 1 / [Amox] for uncatalyzed reaction supporting the verification of rate law.

Table - 2: Effect of temperature on the Rate of oxidation of Amoxicillin by hexacyanoferrate (III) in aqueous alkaline medium at concentration of Amoxicillin (2.5 X 10^{-3} $moldm^{-3}$), HCF (III) (2.5 X 10^{-4} $moldm^{-3}$), NaOH (1.0 X 10^{-2} $moldm^{-3}$), Ru (III) (1.010^{-5} $moldm^{-3}$) and KCl (1.0 X 10^{-2} $moldm^{-3}$)

Temp. (K)	kobs x 10^{-4} sec^{-1} (For uncatalyzed)	kobs x $10^{-3}$$sec^{-1}$ For catalyzed)
298	3.612	1.747
303	5.406	2.482
308	7.084	3.468
313	10.347	4.162
318	13.492	5.912

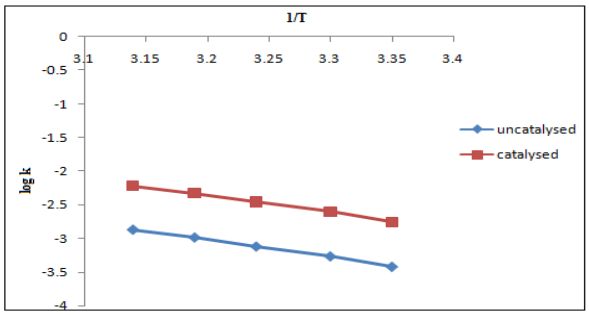


Figure - 9: Arrhenius plot for variation of temperature for Ru (III) catalyzed and uncatalyzed reaction.

Table - 3: Activation Parameters for Oxidation of Amoxicillin by Hexacyanoferrate (III) in aqueous alkaline medium

Activation Parameters	Values (For uncatalyzed)	Values (For catalyzed)
Ea (kJ/mol)	58.02	32.82
$\Delta H^{\#}$ (kJ/K/mol)	55.54	30.34
$\Delta S^{\#}$ (J/K/mol)	-125.20	-195.87
$\Delta G^{\#}$ (kJ/K/mol)	92.85	88.74

4. CONCLUSION

The kinetics of oxidation of Amoxicillin with HCF has been carried out in the absence and presence of Ru (III) catalyst in alkaline medium. The rate of reaction increases with increase in hydroxyl ion concentration in presence of ruthenium hence it involves the formation of aqua complex of $[Ru(H_2O)_5OH]^{2+}$ which reacts to form an intermediate complex which slowly decomposes to form final product. It was observed that transition metal complexes are good abstracting agents for hydride ions and similar studies have revealed that hydride ion transfer may takes place from carbon atom of substrate to metal atom [11,12]. This provides sufficient evidence that hydride ion transfer will takes place during oxidation by HCF. In the last step ruthenium hydride species was reoxidised to reactive species $[Ru(H_2O)_5H]^{2+}$. Product of the reaction was identified as 6-{[amino(4-oxocyclohexa-2,5-dien-1-ylidene)acetyl]-3,3-dimethyl-7- oxo-4-thia-1-

azabicyclo [3.2.0] heptane-2-caboxylic acid gives molecular ion peak at 365 MHz and which is confirmed by LC-MS. The rate constant in the present study is much higher than the Ru(III) catalyzed oxidation of amines by HCF [11]. The activation parameters give additional support to the given mechanism. The observed k values are in good agreement with experimental values.

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