Oxidation of N-acetyl glutamic acid by hexacyanoferrate (III) in aqueous alkaline medium: A kinetic and mechanistic study

Ravindra Shimpi[a], Rajesh Fadat[a], BhagwansingDobhal[a], D M Janrao[b], SiddharthJanrao[d]

[a]*Department of Chemistry, Badrinarayan Barwale Mahavidyalaya, Jalna-431203 (MH) India.*
[b]*Department of Chemistry, JES college, Jalna-431203 (MH) India.*
[c]*Dr. Rafiq Zakaria College for Women Aurangabad [Post graduate and Research Centre, Maulana Azad College, Aurangabad(MH) India]*
[d]*Dr. Vedprakash Patil Pharmacy College, Aurangabad*

ABSTRACT:

The kinetics of oxidation of N-acetyl glutamic acid (NAGA) by hexacyanoferrate (abbreviated as HCF) (III) in aqueous alkaline medium at constant ionic strength $0.0225 mol/dm^3$ and temperature 298K has been studied spectrophotometrically. The reaction exhibit 1:2 stoichiometry of substrate to oxidant and follows fractional order kinetics in [HCF (III)] and first order in [alkali]. The dependence of the rate on substrate concentration has been found to be of fractional order type. The ionic strength of the reaction mixture shows positive salt effect on the reaction rate. To calculate thermodynamic parameters the reaction has been studied at six different temperatures from 283K to 333K. Mechanism involving formation of complex between HCF and NAGA has been proposed. 2-keto pentanedioic acid and acetamidehas been identified chromatographically and spectroscopically as the final product of oxidation of NAGA. Based on the kinetic data and product analysis a reaction mechanism is proposed.

Keywords- Oxidation, Mechanism, Hexacyanoferrate (III), N-acetyl glutamic acid

INTRODUCTION

Iron (III) complexes as oxidant has acknowledged great interest due to cost-effective availability, less difficulty involved in the estimation and its capability to act in both acidic and alkaline medium. Also one of the form of Iron (VI) is an environment friendly oxidant and used as coagulant for water and waste water treatment[1,2]. It is possible to use HCF (III) as a moderate oxidant because the oxidation potential of the couple $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$ (0.36V).

N-Acetylglutamic acid is biosynthesized from glutamic acid and acetyl-CoA by the enzyme N-acetylglutamate synthase. Arginine is the activator for this reaction. The reverse reaction hydrolysis of the acetyl group is catalyzed by a specific hydrolase. NAGA activates carbamoyl phosphate synthetase in the urea cycle. A substance apparently identical with *N*-acetyl-l-glutamic acid was isolated from an aqueous extract from human brain[3] by a combination of paper and ion exchange chromatography. The isolated substance does not react with ninhydrin reagent but yields glutamic acid upon acid hydrolysis. Acetyl hydrazide was identified by paper chromatography of hydrazinolysates of the isolated substance and *N*-acetyl-l-glutamic acid.*N*-acetylaspartylglutamate (NAAG) are highly concentrated acetylated compounds found predominantly in the nervous system of vertebrates and invertebrates.[4-6] NAAG and *N*-acetylaspartate (NAA) are found primarily in neurons[7-14] although much lower levels may be present in some glialcells[15,16] and in somatic tissues.[5] Because of their predominant neuronal localization, and the fact that the two molecules provide strong acetate signals have been used as a noninvasive diagnostic marker for neuronal loss or dysfunction.[17-20] The N-terminal acetyl groups of NAAG and NAA make their localization by immunohistochemistry problematic because both molecules lack an amine group and thus lack a reactive group that would permit standard fixation coupling with glutaraldehyde. Due to some synthetic utility ferricyanide oxidation has become known as Decker oxidation[21]

A survey on earlier literature indicates that no attention was paid to the oxidation of NAGA by this oxidant. The present work has been undertaken with a view to shed some light on the influence of the nature of both the oxidant and the media on the kinetics and mechanistic of the redox reactions as well as on the nature of oxidation products. Moreover, the results obtained may give some information on the chemistry of NAGA in aqueous solutions.HCF (III) has been widely used to oxidise numerous organic and inorganic compounds in alkaline media. Researchers[22] have suggested that alkaline HCF (III) ion simply acts as an electron abstracting reagent in redox reactions. Though, Speakman and Waters[23] have recommended different paths of oxidation of aldehydes, ketones and nitroparaffins. While, Singh and co-workers[24,25] during discussion of the oxidations of formaldehyde, acetone and ethyl methyl ketone have suggested that the oxidation takes place through an electron transfer process resulting in the formation of a

free radical intermediate. In view of the lack of literature on the oxidation of NAGA by HCF (III) and in order to explore the mechanistic aspects of HCF (III) oxidation in alkaline medium, we have chosen NAGA as a substrate. In continuation of our earlier work[26,27] the present study deals with the title reaction to investigate the redox chemistry of HCF (III) in such media and to reach a suitable mechanism for the oxidation of NAGA by alkaline HCF (III) on the basis of kinetic results.

EXPERIMENTAL

Materials and methods

Reagent grade chemicals and doubly distilled water were used throughout. A solution of $Fe(CN)_6^{3-}$ was prepared by dissolving $K_3Fe(CN)_6$ (SD fine chem.) in H_2O and was standardized iodometrically. NAGA is soluble in aqueous bases. The solution of NAGA (Himedia) was prepared by dissolving appropriate amount of sample in very dilute alkaline solution. Sodium hydroxide (Merck) and sodium nitrate (SD fine chem.) were used to provide the required alkalinity and to maintain the ionic strength, respectively.

Instruments

A double beam bio-spectrophotometer BL-198 Elico was used for scanning. Thermostat used was of 'Toshniwal' Instrument. The constancy of the temperature maintained was to an accuracy of ±0.5 ºC

Kinetic Procedure:

Stoichiometry and Product Analysis:

Reaction mixture containing various ratios of HCF (III) to PYD in presence of 10×10^{-2} mol dm^{-3} NaOH at 298K, under the condition [NAGA]>>[HCF], were equilibrated for 24h. Determination of unreacted HCF showed 1:2 stoichiometry of substrate to oxidant. Oxidation product 2-keto pentanedioic acid and acetamidewas detected by thin layer chromatography. Further it was confirmed by its MP, IR and NMR spectra. Strong peak for

$-\overset{\overset{\text{O}}{\|}}{\text{c}}-$ group was observed at1685 cm^{-1}

Results and Discussion:

λ_{max} for potassium hexacyanoferrate $(1x10^{-4}M)$ determined spectrophotometrically using bio-spectrophotometer BL-198 Elico and found to be 420nm.(Figure.1)

1. Reaction orders

The reaction orders were determined from the slope of log k_{obs} versus log concentration plots, by varying the concentration of each substrate, oxidant and alkali while keeping others constant.

2. Effect of Reactants on the Reaction Rate

With substrate in excess, at constant [HCF], [OH$^-$] [NaNO$_3$] and temperature, plots of log [HCF] Vs time were linear indicating fractional order dependence of rate on [HCF]. Plot of log[HCF] Vs logk_{obs} was found to be linear (Table.1) with slope 0.329 confirming fractional order dependence on [HCF]. At constant [HCF], [NaOH], [NaNO$_3$] and temperature (Table.1) Plot of log[NAGA] Vs logk_{obs} (Figure.2) was linear with a slope of 0.50 indicating fractional order dependence on [NAGA]. The rate increases with increase in [NaOH] (Table.1) and plot of log[NaOH] Vs logk_{obs} (Figure 3) was linear with slope of 0.995, showing first order dependence on [OH$^-$]

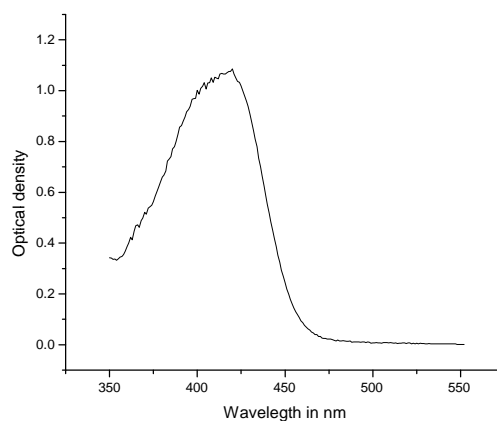Figure.1. Spectral scan of potassium hexacyanoferrate (III) $1x10^{-4}M$ in alkaline medium at [OH$^-$] $= 10x10^{-2}$ M and 298K

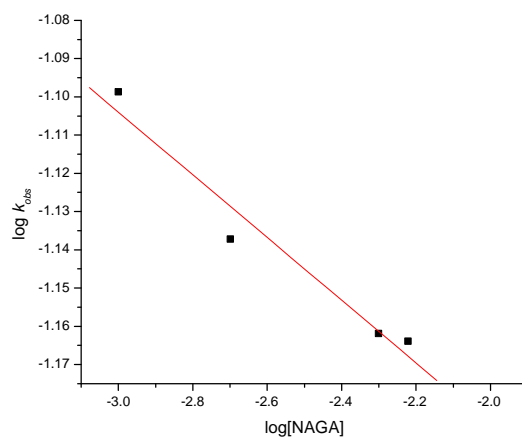Figure.2. Plot of log[NAGA] Vs log k_{obs}
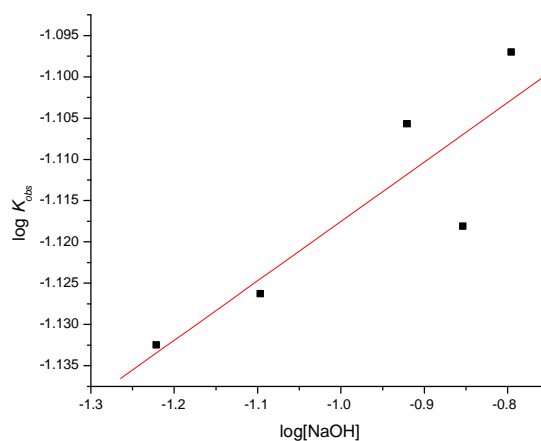

Figure.3. Plot of log[NaOH] Vs logk_{obs}

3. Effect of salts on the rate constant of the reaction

To study the effect of variation of salts, the concentration of salts were varied from 1×10^{-2} to 9×10^{-2} M, keeping constant concentration of other reaction ingredients such as

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[HCF]$=7\times10^{-4}$ M,[NAGA]$=5\times10^{-3}$M, [NaOH] $=10\times10^{-2}$M and [NaNO$_3$] $=18\times10^{-2}$M. These results are given in the table.6. From the obtained results, it is clear that pseudo observed first order rate constant k_{obs} increased with increase in concentration for KCl, KBr, KI, KNO$_3$ and NH$_4$Br. A plot of log k_{obs} vs √μ according to extended Bronsted-Debye-Huckel equation was found to be linear with positive slopes indicating positive salt effect. On the other hand pseudo first order rate constant decreased with increase in concentration for NaHCO$_3$, NH$_4$Cl, NaCl, K$_2$SO$_4$ and Na$_2$CO$_3$. A plot of log k_{obs} vs √μ was found to be linear with negative slopes indicating negative salt effect (Table.6).

4. Effect of Ionic Strength and Dielectric Constant on the rate constant of the reaction

Variation in ionic strength using NaNO$_3$ solution (2×10^{-2} moldm^{-3} to 18×10^{-2} mol dm^{-3}) affect (Table.2)the rate of the reaction indicating that species are involved in the rate limiting step.Dielectric constant (D) of the medium was varied by adding methanol, ethanol, acetonitrile, DMSO and 1,4-dioxane (Table.3). It was found that rate constant increased on decreasing the dielectric constant of DMSO, 1,4-dioxane and ethanol, while rate constant decreased on decreasing the dielectric constant of acetonitrile and methanol. The relative permittivity (*D*) effect was studied by varying solvent-water content in the reaction mixture with all other conditions being constant. Attempts to measure the relative permittivity were not successful. However, they were computed from the values of pure liquids[28]Plot of (1/D) Vs log$k_{obs}$was found to be linear.

5. Effect of Temperature on the Reaction Rate

Reaction was studied over a range of temperature 283K to 333K by varying the concentration of NAGAkeeping other experimental conditions constant. It was found that the rate increased with increase in temperature (Table.5)

From the Arrhenius plot, activation parameters like energy of activation (Ea), enthalpy of activation ($\Delta H^{\#}$), entropy of activation ($\Delta S^{\#}$), energy of activation ($\Delta G^{\#}$) and logA were computed (Table.5).

6. Test of Free Radicals

Addition of aqueous acrylonitrile solution to reaction mixture did not initiate polymerization showing absence of free radical species.

Table.1-Effect of Reactant Concentrations on the rate constant of the reaction at 298K

10^4[HCF]	10^3[NAGA]	10^2[NaOH]	10^2[NaNO$_3$]	10^4 k_{obs}
Mol dm^{-3}	Mol dm^{-3}	Mol dm^{-3}	Mol dm^{-3}	s^{-1}
1.0	10	20	20	8.200
3.0	10	20	20	7.840
5.0	10	20	20	7.390
8.0	10	20	20	6.940
7.0	1.0	20	20	7.970
7.0	2.0	20	20	7.290
7.0	5.0	20	20	6.890
7.0	6.0	20	20	6.860
7.0	5.0	6	20	7.370
7.0	5.0	8	20	7.480
7.0	5.0	14	20	7.620
7.0	5.0	16	20	8.000

Table.2-Effect of Ionic strength on the Reaction Rate at 298K

10^4[HCF]	10^3[NAGA]	10^2 [NaOH]	10^2 [NaNO$_3$]	10^4 k_{obs}
Mol dm^{-3}	Mol dm^{-3}	Mol dm^{-3}	Mol dm^{-}$_3$	s^{-1}

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7.0	5.0	10.0	2	6.580
7.0	5.0	10.0	4	7.440
7.0	5.0	10.0	6	7.550
7.0	5.0	10.0	10	8.020

Table.3. Effect of Variation of Solvents on oxidation of PYD in basic media.

$K_3[Fe(CN)_6]=7x10^{-4}$ M   [NAGA]= $5x10^{-3}$ M [NaOH]=$10x10^{-2}$M [NaNO$_3$]=$18x10^{-2}$M

Variation of solvents (k_{obs}), s^{-1}									
Conc. %	Methanol	Conc. %	Ethanol	Conc. %	Acetonitrile	Conc. %	DMSO	Conc. %	1,4-dioxane
10	0.0713	30	0.0799	10	0.0754	20	0.0780	10	0.0836
20	0.0750	20	0.0785	20	0.0756	40	0.0761	30	0.0777
50	0.0791	30	0.0712	30	0.0807	50	0.07.37	40	0.0744
				40	0.0816			50	0.0734
								60	0.0711

Table.4-Effect of Temperature on Oxidation of NAGA in basic media.

$K_3[Fe(CN)_6]=7x10^{-4}$ M   [NAGA]= $5x10^{-3}$ M [NaOH]=$10x10^{-2}$M [NaNO$_3$]=$18x10^{-2}$M

Activation Energy = -2.5848 KJ/mole

temp °K	$\Delta H^{\#}$ (KJ/mole)	$\Delta S^{\#}$ (KJ/mole)	$\Delta G^{\#}$ (KJ/mole)
283	-4.9377	-0.1235	30.0356
293	-5.0208	-0.1236	31.1996
303	-5.1040	-0.1231	32.2040
313	-5.1871	-0.1232	33.3998
323	-5.2702	-0.1234	34.6138
333	-5.3534	-0.1230	35.6140
Avg.	-5.1455	-0.1233	32.8445

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Table.5- Effect of Temperature on the observed first order rate constant & Activation parameters

Temperature (K)	$10^4 k_2$ (s^{-1})	Activation parameters	
		Parameter	Value
283	6.570	Ea(J mol^{-1})	2584.8
293	6.690	$\Delta H^{\#}$(J mol^{-1})	-5145.5
303	7.420	$\Delta G^{\#}$(J mol^{-1})	32844.5
313	7.510	$\Delta S^{\#}$ (J K^{-1}mol^{-1})	-123.3
323	7.580		
333	7.650	logA	-135.0

Table.6 Effect of added Salt on observed first order rate constant

K$_3$[Fe(CN)$_6$]=7x10^{-4} M [PYD]= 7x10^{-3} M [NaOH]=8x10^{-2}M [NaNO$_3$]=8x10^{-2}M

Observed first order rate constant (k_{obs}), s^{-1}																			
Conc. of salts (M)	KCl	Conc. of Salt (M)	KBr	Conc. of Salt (M)	KI	Conc. of Salt (M)	KNO$_3$	Conc. of Salt (M)	K$_2$SO$_4$	Conc. of salts (M)	NaCl	Conc. of salts (M)	NaHCO$_3$	Conc. of Salt (M)	Na$_2$CO$_3$	Conc. of Salt (M)	NH$_4$Cl	Conc. of Salt (M)	NH$_4$Br
0.01	0.0770	0.01	0.0774	0.02	0.0773	0.01	0.0783	0.01	0.0614	0.02	0.0686	0.03	0.0704	0.01	0.0726	0.03	0.0686	0.01	0.0769
0.05	0.0766	0.02	0.0753	0.03	0.0758	0.02	0.0746	0.03	0.0741	0.05	0.0739	0.04	0.0739	0.02	0.0800	0.04	0.0719	0.03	0.0756
0.06	0.0767	0.03	0.0730	0.04	0.0746	0.03	0.0734	0.04	0.0736	0.06	0.0777	0.05	0.0753	0.03	0.0804	0.05	0.0729	0.06	0.0751
0.08	0.0741	0.05	0.0710	0.06	0.0729	0.06	0.0723	0.05	0.0771	0.07	0.0779	0.06	0.0755	0.04	0.0851	0.06	0.0764	0.08	0.0729
0.09	0.0733			0.09	0.0729	0.08	0.0717	0.06	0.0838	0.08	0.0892	0.07	0.0769			0.07	0.0820	0.09	0.0721
								0.07	0.0836										

DISCUSSION

Variation of the concentration of each of the oxidant HCF (III), substrate (PYD) base and ionic strength, while maintaining the others concentration constant showed that the reaction is fractional order in oxidant and substrate while first order in base (OH$^-$) and with respect to NO$_3^-$ ion. The stoichiometry of the reaction between NAGA and HCF (III) is 1:2. Due to higher oxidation potential of $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$ (0.36V)in alkaline medium suggests better possibility of rapid oxidation of the free radical might completely mask the polymerization. The kinetic aspects and the mechanism proposed are similar to those of oxidation of glycine, arginine and lysine, valine and glycol does not occur via free radicals, but to a certain extent through an intermediate complex between the oxidant and the anionic substrate.

During the basic oxidation l-histidine, phenyl alanine, leucine, glycine and valine [29-31] the keto acid species and NH$_3$ were the final products. The reactions are first order in substrate, oxidant and base concentrations; even though addition of Fe(CN)$_6^{4-}$ proposes a slow one electron reversible step, complexes like substrate-Fe(II) and substrate- Fe(CN)$_6^{4-}$ in basic condition was also identified [32]. Oxidation of tyrosine in basic medium proceeds via α-imino acid while oxidation of glutamic acid and aspartic acid to respective α-ketoacids and Fe(CN)$_6^{4-}$ proceeds via the imino acid through radical intermediate[33]. The kinetics of Os(VIII) catalysed oxidation are more complex[34-38]. Addition of Fe(CN)$_6^{4-}$ accelerates the reaction due to formation of reactive amino-Fe(CN)$_6^{4-}$ complex as with lysine. The reaction involves an intermediate complex between catalyst and anionic form of substrate which produces the products. D-proline and L-methionine[36] involves the oxidation of substrate-catalyst complex species in rate determining step

The reaction was also studied in presence of added acrylonitrile to understand the involvement of free radicals. There was no effect of added acrylonitrile on the reaction and also no precipitate due to the absence of polymerization of the added acrylonitrile was observed thus verifying the absence of any free radical formation in the reaction. The reaction was carried out under pseudo-first-order conditions and the plots of log [oxidant] against time were found to be linear and the fractional order (0.330) in [oxidant]. The pseudo-first-order rate constants were

found to increase as [NAGA] increases from 1.0×10^{-3} to 9.0×10^{-3} mol dm^{-3} at a constant [oxidant] of 7×10^{-4} mol dm^{-3}. The order in [NAGA] was found to be 0.500 as determined from the log k_{obs} against log [NAGA]. Since, the order in [NAGA] was fractional which indicates the formation of a complex therefore, the kinetic data were used to obtain plot of $1/k_{obs}$ against $1/$[NAGA]. Such a plot was found to be linear with an intercept supporting the formation of a complex between the reactants. In order to evaluate thermodynamic parameters the effect of [NAGA] was studied at six different temperatures. The effect of [OH$^-$] on the reaction was studied by varying the sodium hydroxide concentration between 0.02 and 0.18 mol dm^{-3} at a constant ionic strength of 0.2 mol dm^{-3}. The rate of reaction is accelerated by increase in [OH$^-$] and the order in [OH$^-$] was found to be 0.995. The effects of ionic strength and solvent polarity were studied keeping concentration of [HCF], [NAGA] and sodium hydroxide constant at 7×10^{-4} mol dm^{-3}, 5×10^{-3} moldm^{-3} and 10×10^{-2} mol dm^{-3} respectively at 25 °C. Sodium nitrate was used to vary the ionic strength. The rate of the reaction increases with varying ionic strength and the rate of reaction decreases as percentage of acetonitrile and methanol increases from 0 to 60% v/v. The plot of log k_{obs} vs $(1/D)$ is linear with a negative slope. The rate of reaction increases as percentage of DMSO, 1,4-dioxane and ethanol increases from 0 to 60% v/v. The plot of log k_{obs} vs $(1/D)$ is linear with a positive slope.

The mechanism of the reaction based on the kinetic results and spectrophotometric examination of the reactants and the reaction mixture can be represented as in Scheme 1. According to Scheme 1 the reaction proceeds with the formation of a complex Y between oxidant and anion of N-acetyl glutamic in a prior equilibrium with a constant k_2. The complex so formed will decompose in a slow second step with rate constant k_3 to form 2-keto pentanedioic acid and acetamide. The rate law explains that the rate is fractional orders with respect to the [NAGA] and the plots of $1/k_{obs}$ against $1/$[NAGA] were found to be linear (Figure.4). The rate law also explains the rate is first order with respect to the [NaOH] and the plots of $1/k_{obs}$ against [OH$^-$] were found to be linear (Figure.5).
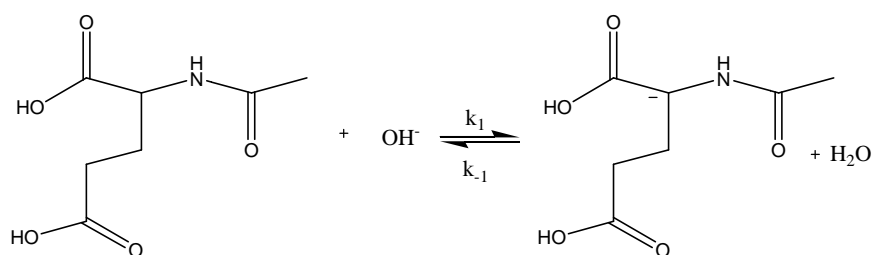
N-acetyl glutamic acid
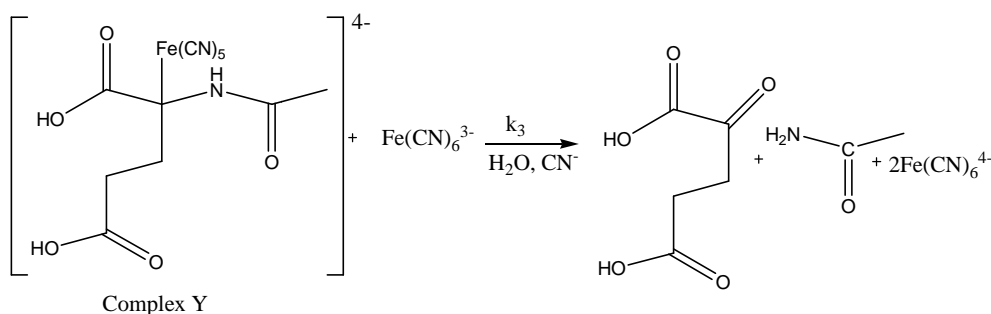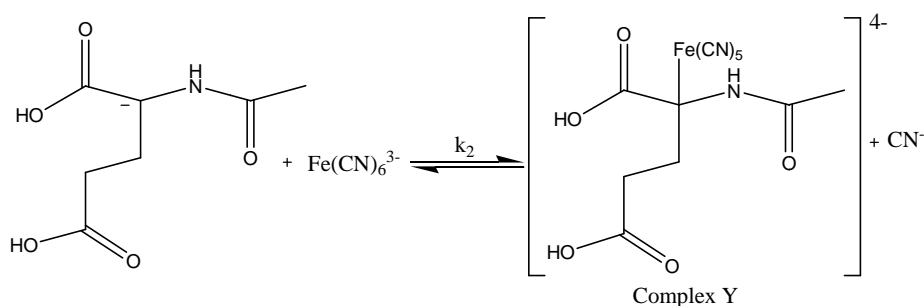
Complex Y

Complex Y

Scheme.1

From the slope and intercept ofFigure.4 the values of rate constant for the slow step, k_3 and formation constant of complex, k_2, were calculatedalong with the activation parameters. The moderate values of $\Delta H^{\#}$ and $\Delta G^{\#}$ of -5.1455 and 32.8445 kJ mol^{-1} respectively were favorable for electron transfer processes. The negative value of $\Delta S^{\#}$ can be attributed to the nature of electron pairing and unpairing processes and to the loss of degrees of freedom formerly available to the reactants upon the formation of transition state. The effect of ionic strength indicates that

reactant is ionic in natureand decrease in the rate with decrease in the dielectric constant is in conformity with ion–dipole interactions.

$$Rate = \frac{-d[\text{HCF}]}{dt} = k_3[\text{Y}]$$

$$[\text{X}] = \frac{k_1 k_2 [HCF][\text{NAGA}]}{[OH^-] + k_1(1 + k_2[\text{NAGA}])}$$

$$Rate = \frac{-d[HCF]}{dt} = \frac{k_1 k_2 k_3 [HCF][\text{NAGA}]}{[OH^-] + k_1(1 + k_2[\text{NAGA}]}$$

$$k' = \frac{k_1 k_2 k_3 [\text{NAGA}]}{[OH^-] + k_1 + k_1 k_2[\text{NAGA}]}$$

$$\frac{1}{k'} = \frac{[OH^-]}{k_1 k_2 k_3 [\text{NAGA}]} + \frac{1}{k_2 k_3 [\text{NAGA}]} + \frac{1}{k_3}$$

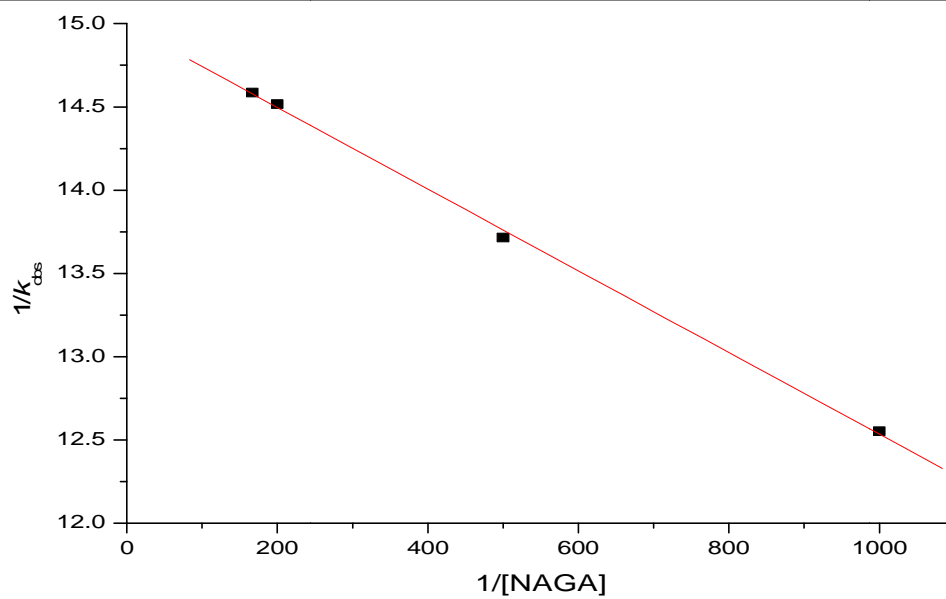Figure.4. Plot of 1/[NAGA] vs $1/k_{obs}$

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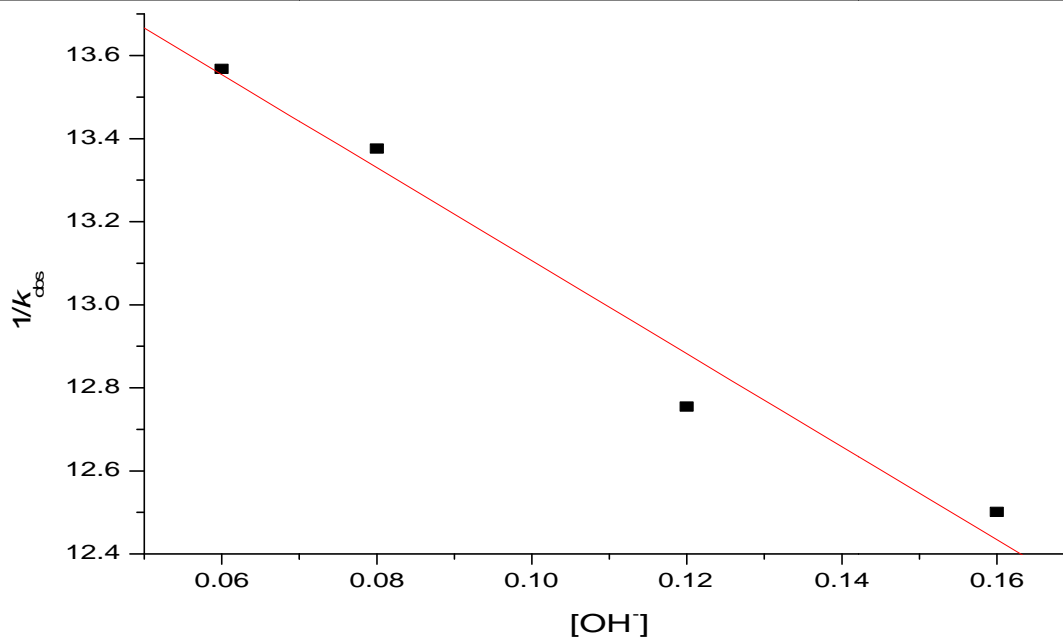**National Convention/Seminar**
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Figure.5. Plot of[base] vs $1/k_{obs}$

CONCLUSION

The oxidation of NAGA with HCF (III) in alkaline medium involves an outer-sphere mechanism and oxidations taking place in sequences of one electron steps. The overall mechanistic sequence described here is consistent with product, mechanistic and kinetic studies.

ACKNOWLEDGEMENT

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