



Original Article

Copper Catalyzed Oxidation of Rabeprazole by Hexacyanoferrate in Alkaline Medium: A Kinetic and Mechanistic Study

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Rabeprazole is oxidized by hexacyanoferrate(III) and the kinetics of oxidation has been studied spectrophotometrically. The reaction exhibits 1:1 stoichiometry. The reaction rate shows first-order with respect to [HCF], [Cu] and fractional order with respect to [RAB]. Temperature effect on reaction rate was studied. Different activation parameters E_a (kJ/mol⁻¹), ΔH^\ddagger (kJmol⁻¹), ΔS^\ddagger (JK⁻¹mol⁻¹) and ΔG^\ddagger (kJmol⁻¹) with respect to the slow step of the mechanism are computed and tabulated. Effect of ionic strength and dielectric constant of medium has been studied. Rate constant for rate determining step was calculated and a suitable mechanism has been proposed. Hydrated Cu-HCF complex reacts with rabeprazole sodium which forms an intermediate complex which dissociates to form products rabeprazole sulphone. The rate law was derived as $\text{Rate} = kK_2[\text{RAB-Na}][\text{Cu-HCF}]/K_1 + K_2[\text{RAB-Na}]$.

Keywords- Kinetics and mechanism, Oxidation, Rabeprazole, Hexacyanoferrate, Cu(II) catalysis.

1. INTRODUCTION

Rabeprazole, chemical structure is presented in Fig:(I), chemically it is(±)-sodium2-[[4-(3-methoxypropoxy)-3-methylpyridine-2-yl]methylsulfinyl]-1*H*-benzimidazole is an anti ulcer drug in the class of proton pump inhibitor that covalently binds and inactivates the gastric parietal cell proton pump (H⁺/K⁺ ATPase).¹

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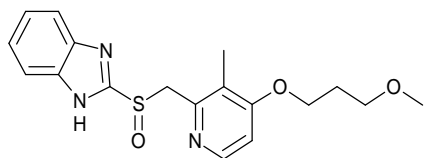


Fig 1: Chemical Structure of Rabeprazole

It was developed by Eisai Co. and marketed by Janssen-Cilag as Rabeprazole sodium under the brand names Aciphex and Periet. Rabeprazole sodium is delayed – release tablets with empirical formula of $C_{18}H_{21}N_3O_3S$ and a molecular mass of 359.44. Rabeprazole is a white to slightly yellowish –solid, easily soluble in water, has proven efficacy in healing, symptom relief, and prevention of relapse of gastric ulcer, duodenal ulcer, and gastroesophageal reflux disease.²

Another great activity rabeprazole has, is against Helicobacter pylori, an organism strongly associated with peptic ulcer disease.³ It is used to treat gastroesophageal reflux disease (GERD), a condition in which backward flow of acid from the stomach causes heartburn and possible injury of the esophagus (the tube that connects the throat and the stomach). It is a proton pump inhibitor that decreases the amount of acid produced in the stomach thus relieves symptoms such as heart burn, difficulty swallowing and persistent cough. Since it is an acid labile drug, it is commercialize as enteric coated tablet⁴. The literature survey reveals a crescent number of publications related to rabeprazole sodium determination in biological fluids⁵⁻¹⁰ and pharmaceutical formulation¹¹⁻¹⁴ by several methods, this drug is not studied for its kinetics behaviour in the presence of HCF. The objective of the present work is to develop and validate the derivative spectrophotometric method for determination of the proton pump inhibitor rabeprazole sodium in pharmaceutical formulations.

Present study was undertaken to investigate kinetics and mechanism of copper catalyzed oxidation of RAB by hexacyanoferrate in alkaline medium. A variety of organic¹⁵⁻¹⁹ and inorganic²⁰⁻²² substances are oxidized by the strong oxidizing agent hexacyanoferrate in alkaline medium.

Many transition and non-transition metal ions in their complex form acts as better oxidants in basic, acidic and neutral medium The oxidation capacity completely depends on their redox potential²³. Hexacyanoferrate (III) is an one electron oxidant with a redox potential of +0.36V in acidic medium and +0.45V in basic medium. In most of the oxidations, HCF is mainly used as hydrogen atom abstractor^{24, 25} and/or free radical generator²⁶. Uncatalyzed reaction of RAB against hexacyanoferrate is slow (rate) and it has been catalyzed by Cu(II) which results in formation of Rabeprazole sulphone[LC-MS Fig:(II)].

Hexacyanoferrate, due to its strong oxidizing properties, has been extensively employed as reagent in analytical

investigation of many compounds like hydrazine hydrate, L-Proline and arginine, Esters etc.

No literature has been reported on the oxidation of RAB in alkaline medium by inorganic oxidizing agents. Hence the present study deals with the oxidation of RAB with alkaline HCF. Uncatalyzed reaction of RAB against hexacyanoferrate is slow (rate) and it has been catalyzed by small amount of Cu (II) , which results in formation of Rabeprazole sulphone. The product Rabeprazole sulphone was identified by by LC-MS. Fig(II).

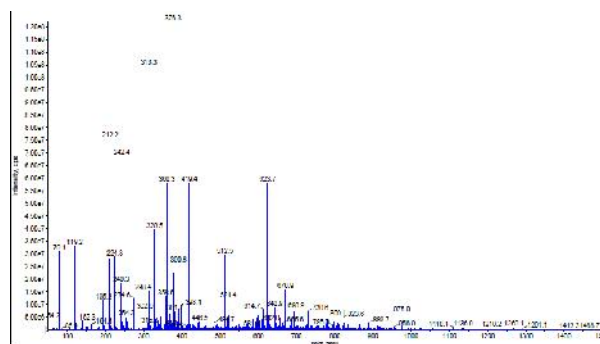


Fig 2: LC-MS spectra for rabeprazole spectra

2. EXPERIMENTAL

2.1. Materials and reagents used

All Chemicals used, Rabeprazole, hexacyanoferrate, NaOH, KNO_3 and Copper sulphate, were of analytical grade obtained from Merck. Solutions were prepared using double distilled water. Hexacyanoferrate (III) was prepared by dissolving the requisite amount of salt in doubly distilled water. The solution was standardized by iodometric method²⁷. Rabeprazole was collected from Thorab pharma and research laboratory, Pondicherry. Solution was prepared by dissolving requisite amount of sample in NaOH and diluted using distilled water. NaOH, KNO_3 and Copper sulphate were also prepared in doubly distilled water and standardized by standard methods. Absorbance was recorded on Systronic UV-Vis Spectrophotometer at wave length 420nm.

2.2 Kinetic studies

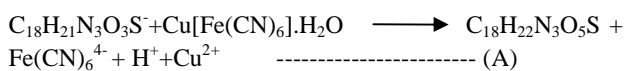
Pseudo first order conditions were maintained for the study of reaction between RAB with HCF, where concentration of RAB is 10 times greater than concentration of HCF at $25^\circ C \pm 0.1$. The reaction was initiated by mixing the thermostat ted solutions of $K_3[Fe(CN)_6]$ with gentle stirring to rabeprazole containing required amount of Cu(II), NaOH and KNO_3 . Progress in the reaction was observed spectrophotometrically by measuring decrease in absorbance of HCF at wave length 420nm vs time using a systronic UV/VIS spectrophotometer with 1.0cm cell. The isolation method was used in this study where the concentration of the substance to be monitored is changed with the others kept constant. Aqueous solutions were prepared by making a constant total volume for all runs. A graph of $\log[HCF]$ versus time were plotted for pseudo first order reaction linear upto 60% completion and rate constants(k_{obs}) were

calculated and reproducible rate constants within $\pm 4\%$ were found.

3. RESULTS

3.1. Stoichiometry and product analysis

For the determination of stoichiometry, various sets of reaction mixtures containing various ratios of reductant to oxidant in the presence of constant amount of NaOH, Cu(II), and KNO₃ was kept for 24 hours in closed beakers at room temperature and after the completion of reaction, excess of hexacyanoferrate was measured spectrophotometrically at 420 nm. The results indicate a 1:1 stoichiometry as given in the equation (A). Oxidative product was found to be Rabeprazole sulphone formed by reacting 1 mol of RAB with 1 mol hexacyanoferrate. The reaction can be represented as follows. The product Rabeprazole sulphone was identified by LC-MS spectra which give M⁺H⁺ peak at 376 mHz. ²⁸ Fig:(II).



3.2. Reaction orders

3.2.1 Rate dependence on [hexacyanoferrate]

At fixed [RAB], [Cu(II)], [NaOH] and [KNO₃], the rate constants of the reaction were measured by varying concentration of hexacyanoferrate from 0.5×10^{-4} to 4.0×10^{-4} moldm⁻³. The values of k_{obs} for reaction in the presence of varying [HCF] are shown in Table:1. By plotting graph of initial rates (k_{obs}) against concentration of HCF, straight line is obtained passing through origin, hence the reaction is first order with respect to oxidant. Discrepancy from first order might be seen because of impedance of one of the product K₄[Fe(CN)₆].

3.2.2 Rate dependence on [Rabeprazole]

Under fixed [HCF], [Cu(II)], [NaOH] and [KNO₃], reaction rate was studied by varying its concentration from 0.5×10^{-3} to 4.0×10^{-3} moldm⁻³. The values of k_{obs} for rabeprazole oxidation reactions in the presence of varying [RAB] are shown in Table:1. The plot of initial rates (k_{obs}) versus concentration of RAB was found to be fractional order.

3.2.3 Rate dependence on [Cu]

Copper sulphate, the catalyst preferred in the reaction, effect on reaction rate was studied by varying its concentration from 0.5×10^{-5} to 6.0×10^{-5} moldm⁻³ and keeping concentration of RAB, HCF, NaOH and KNO₃ as constants. The values of k_{obs} for rabeprazole oxidation reactions in the presence of varying concentration of Cu are shown in Table:1. With increase in concentration of catalyst prominent increase in reaction rate can be observed, reaction order with respect to catalyst was found to be unity.

3.2.4 Effect of Dielectric constant and Ionic Strength

Dielectric constant of medium was contemplated by differing rate of ethyl liquor and water like 1:2, 2:2, 3:2 and 4:2 in medium keeping every other condition consistent. Concentration of KNO₃ was varied from 0.025×10^{-2} to 0.3×10^{-2} moldm⁻³ keeping [RAB], [HCF], [Cu(II)] and [NaOH] as constants to study ionic strength. It was observed that dielectric constant of medium and ionic strength has no noteworthy impact on reaction rate.

Table 1: Effect of [RAB],[HCF],[NaOH],[Cu] and [KNO₃] on reaction rate at T = 25 ± 0.1°C, μ = 0.1 mol dm⁻³.

[HCF]x10 ⁴ mol dm ⁻³ .	[RAB]x10 ⁻³ mol dm ⁻³ .	[Cu]x10 ⁻⁵ mol dm ⁻³ .	[OH]	[NO ₃]	kobs x10 ⁻²	kcal x10 ⁻²
0.5	2.0	2.0	0.1	0.1	1.17	1.1
1.0	2.0	2.0	0.1	0.1	1.15	1.15
2.0	2.0	2.0	0.1	0.1	1.16	1.5
3.0	2.0	2.0	0.1	0.1	1.23	1.14
4.0	2.0	2.0	0.1	0.1	1.25	1.51
2.0	0.5	2.0	0.1	0.1	0.57	0.5
2.0	1.0	2.0	0.1	0.1	0.80	0.83
2.0	2.0	2.0	0.1	0.1	1.16	1.5
2.0	3.0	2.0	0.1	0.1	1.9	1.9
2.0	4.0	2.0	0.1	0.1	2.3	2.4
2.0	2.0	0.5	0.1	0.1	0.54	0.5
2.0	2.0	1.0	0.1	0.1	0.79	0.8
2.0	2.0	2.0	0.1	0.1	1.16	1.5
2.0	2.0	4.0	0.1	0.1	2.15	3.0
2.0	2.0	6.0	0.1	0.1	2.9	4.12
2.0	2.0	2.0	0.025	0.1	1.16	1.1
2.0	2.0	2.0	0.05	0.1	1.16	1.1
2.0	2.0	2.0	0.1	0.1	1.16	1.5
2.0	2.0	2.0	0.2	0.1	1.17	1.5
2.0	2.0	2.0	0.3	0.1	1.13	1.5
2.0	2.0	2.0	0.1	0.025	1.15	1.5
2.0	2.0	2.0	0.1	0.05	1.12	1.5
2.0	2.0	2.0	0.1	0.1	1.16	1.5
2.0	2.0	2.0	0.1	0.2	1.14	1.5
2.0	2.0	2.0	0.1	0.3	1.14	1.5

3.2.5 Rate dependence on [NaOH]

Sodium hydroxide concentration was varied from 0.5×10^{-2} moldm⁻³ to 4.0×10^{-2} moldm⁻³ by keeping all other conditions constant to study the effect of alkali medium on the oxidation reaction of rabeprazole by HCF. The values of k_{obs} for rabeprazole oxidation reactions in the presence of varying concentration of NaOH are shown in Table:1. No significant influence was noted on the rate of reaction.

3.2.6 Product effect

Reaction was started by adding HCF to rabeprazole containing required concentration of Cu(II), NaOH and KNO₃. As the response engenders there is a development of K₄[Fe(CN)₆] and with noteworthy increment in [Fe(CN)₆]⁴⁻ rate of reaction is marginally diminishes which demonstrates

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 the harmony condition amongst $K_3[Fe(CN)_6]$ and $K_4[Fe(CN)_6]$.

3.2.8 Test for free radicals (Polymerization study)

Free radical intervention in oxidation of rabeprazole by HCF was examined as follows. Acrylonitrile monomer was added to the reaction mixture[29], $[OH^-] = 0.1\text{mol/dm}^3$, $I = 0.1\text{mol/dm}^3$, followed by methyl alcohol dilution which doesn't involves precipitate formation indicating that reaction path is free from radical mechanism.

3.2.9 Effect of Temperature

The study of temperature effect on rate of oxidation of rabeprazole by HCF has been subjected to different temperature, 298K, 308K, 313K and 318K by keeping concentration of RAB and other conditions constant. With increase in temperature rate of reaction increases, rate constants at different temperature K_{obs} were calculated Table II. A graph of $\log K_{obs}$ versus $1/T$ was plotted (Arrhenius plot Fig:(III) and from the slope activation energy as calculated. Different activation parameters E_a (kJ/mol), H^\ddagger (kJmol⁻¹), S^\ddagger (J K⁻¹mol⁻¹) and G^\ddagger (kJmol⁻¹) were calculated and tabulated Table III.

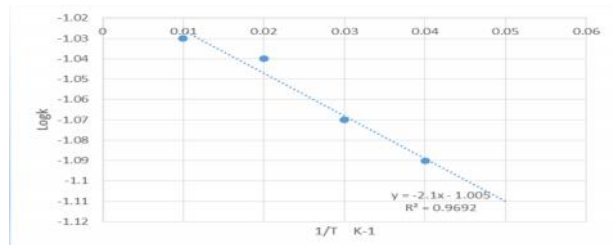


Fig 3: A plot of $\log k$ against $1/T$ (K⁻¹) for the oxidation reaction between rabeprazole and alkaline hexacyanoferrate, used to calculate activation parameters.

Table 2: Effect of variation of temperatures on reaction rate $[RAB] = 2 \times 10^{-4} \text{mol/dm}^3$, $[HCF] = 2 \times 10^{-3} \text{mol/dm}^3$, $[Cu] = 2 \times 10^{-5} \text{mol/dm}^3$, $[OH^-] = 0.1 \text{mol/dm}^3$, $[NO_3^-] = 0.1 \text{mol/dm}^3$

Temperature in (K)	298	308	313	318
$k \times 10^{-2} (S^{-1})$	1.16	2.19	4.4	8.93

Table 3: The activation parameters calculated for oxidation of rabeprazole with hexacyanoferrate in alkaline medium

Parameters	E_a (kJ/mol)	H^\ddagger (kJmol ⁻¹)	S^\ddagger (J K ⁻¹ mol ⁻¹)	G^\ddagger (kJmol ⁻¹)
Values	1.95	-2.8	-250.68	74.11

4. DISCUSSION

Cu(II) catalyst oxidation of rabeprazole is found to be first order with respect to oxidant and catalyst and fractional order with respect to rabeprazole. One of the product of reaction is $Fe(CN)_6^{4-}$ which seems to be in equilibrium with $Fe(CN)_6^{3-}$. Hence deviation from first order of $Fe(CN)_6^{3-}$ appears after completion of 80% of reaction. Effect of dielectric constant of medium and ionic strength was nil on reaction rate.

Rabeprazole gets dissolved in sodium hydroxide to form sodium salt of rabeprazole [30]. Cu(II) reacts with hexacyanoferrate the oxidant to form hydrated Cu-HCF

complex[31]. The reaction occurs between hydrated Cu-HCF complex and rabeprazole sodium which forms an intermediate complex-C which dissociates to form products rabeprazole sulphone (LC-MS Fig:(II) and $K_4[Fe(CN)_6]$ [32]. Based on these observation rate law can be understood in terms of Scheme I. The mechanism (scheme(I) & rate law (4) was verified by linear plot of $1/k_{obs}$ vs $1/Cu(II)$ & $1/k_{obs}$ vs $1/RAB$. [Fig:(IV) and Fig:(V)]. From the slope & intercept k , K_1 & K_2 were measured. k , K_1 and K_2 were substituted in the rate equation to determine the rate calculated. It was in good agreement with experimental results (Table no.1). The oxidation of the titled reaction occurs from the catalysed complex formed. From scheme-1, the mechanism of the reaction is derived.

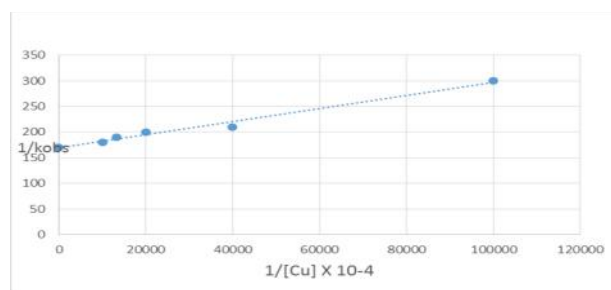


Fig 4: Plot of $1/k_{obs}$ against $1/[Cu(II)]$ at $[K_3Fe(CN)_6] = 2.0 \times 10^{-4} \text{mol/dm}^3$, $[RAB] = 2.0 \times 10^{-3} \text{mol/dm}^3$, $[CuSO_4] = 2.0 \times 10^{-5} \text{mol/dm}^3$, $[KNO_3] = 0.1 \text{mol/dm}^3$ and $[NaOH] = 0.1 \text{mol/dm}^3$

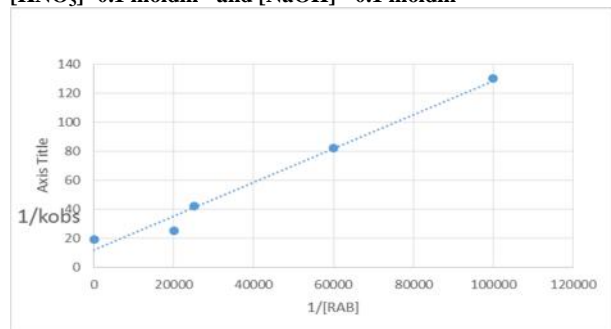
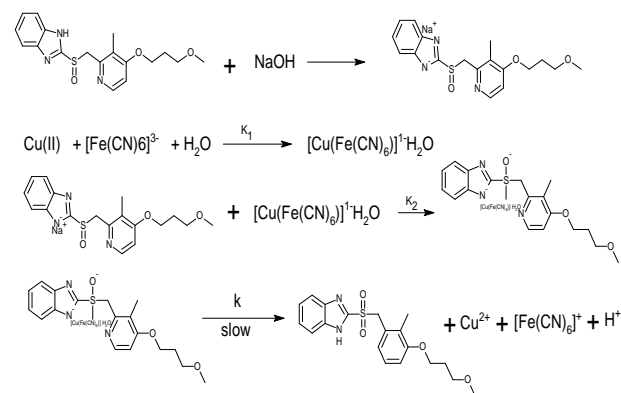


Fig 5: Plot of $1/k_{obs}$ and $1/[RAB]$ at $[K_3Fe(CN)_6] = 2.0 \times 10^{-4} \text{mol/dm}^3$, $[RAB] = 2.0 \times 10^{-3} \text{mol/dm}^3$, $[CuSO_4] = 2.0 \times 10^{-5} \text{mol/dm}^3$, $[KNO_3] = 0.1 \text{mol/dm}^3$ and $[NaOH] = 0.1 \text{mol/dm}^3$

Scheme I



5. REACTION MECHANISM

The catalyst complex formation is followed by oxidation in succeeding steps. From scheme I the mechanism of the reaction can be given as follows.

$$\text{Rate} = -d[\text{HCF}]/dt = k [\text{complex-C}]$$

$$\text{Rate} = kK_2 [\text{RAB-Na}]_f [\text{Cu-HCF}]_f \dots \dots \dots (1)$$

$$[\text{RAB-Na}]_T = [\text{RAB-Na}]_f \dots \dots \dots (2)$$

$$[\text{Cu-HCF}]_T = K_1 [\text{Cu-HCF}]_f + K_2 [\text{Cu-HCF}]_f [\text{RAB-Na}]$$

$$[\text{Cu-HCF}]_T = [\text{Cu-HCF}]_f (K_1 + K_2 [\text{RAB-Na}])$$

$$[\text{Cu-HCF}]_f = [\text{Cu-HCF}]_T / K_1 + K_2 [\text{RAB-Na}] \dots \dots \dots (3)$$

$$\text{Rate} = kK_2 [\text{RAB-Na}] [\text{Cu-HCF}]_T / K_1 + K_2 [\text{RAB-Na}] \dots (4)$$

$$K_{\text{obs}} = kK_2 [\text{RAB-Na}] [\text{Cu}] / K_1 + K_2 [\text{RAB-Na}] \dots \dots (5)$$

On re-arranging equation (5), we will get

$$1/K_{\text{obs}} = K_1 + K_2 [\text{RAB-Na}] / k K_2 [\text{RAB-Na}] [\text{Cu}]$$

$$1/K_{\text{obs}} = K_1 / k K_2 [\text{RAB-Na}] [\text{Cu}] + 1 / k [\text{Cu}]$$

By plotting graph of $1/k_{\text{obs}}$ versus $1/[\text{RAB}]$ and $1/k_{\text{obs}}$ versus $1/[\text{Cu(II)}]$, k , K_1 and K_2 are calculated and found to be 3115, 170.0 and 0.30 respectively. And are found to be in good agreement with rate law equation.

6. CONCLUSION

In the research work, based on results and discussion, Cu(II) catalysed oxidation of Rabeprazole by hexacyanoferrate in aqueous alkaline medium was found to be first order with respect to oxidant, catalyst and fractional order with respect to reductant. The reaction path way involves complex formation and no involvement of radical mechanism. The valculated large negative value of entropy of activation is indicative of the complex formation of activated complex in the reaction. LC-MS spectra helps to identify the product as rabeprazole sulphone and $K_4[\text{Fe}(\text{CN})_6]$.

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