

A Kinetic Investigation of Oxidation of Risperidone using Hexacyanoferrate(III) as Oxidant in Basic Media by Spectrophotometric Method

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Abstract: The spectrophotometric kinetic studies of oxidation reaction of Risperidone (RSP) was carried out by using Hexacyanoferrate(III) (HCF) as an oxidant in base media. Under pseudo first order condition with the concentration of RSP in excess over the HCF, kinetic experiments were carried out. It was found that the reaction is of first order with respect to HCF, fractional order with respect to RSP & OH⁻. The effect of ionic strength & dielectric constant can be determined. The stoichiometry of the reaction was calculated & identified the product by analytical techniques after isolation. On the basis of the experimental results, a suitable mechanism has been proposed. The rate constants of the rate-determining step together with the activation parameters were evaluated and also thermodynamic quantities were determined.

Keywords: Risperidone, Potassium hexacyanoferrate(III), kinetics, oxidation, & spectrophotometry

1. Introduction

Risperidone (Fig 1) belongs to the class of benzisoxazole derivative is an antipsychotic medication. It is mainly used to treat schizophrenia, bipolar disorder¹. Risperidone may also help in the treatment of the negative symptoms such as social withdrawal, apathy, lack of motivation and inability to experience pleasure². Risperidone is approved for the treatment of irritability in children & adolescents with autism³.

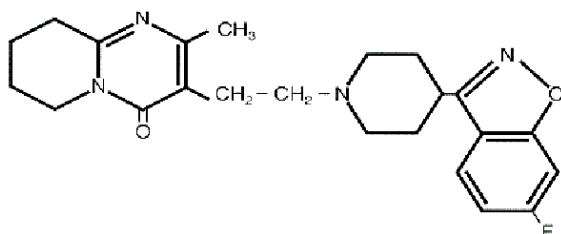


Figure 1.8: Structure of Risperidone

Literature survey reveals that few authors have studied about the oxidation of Risperidone by using oxidant. B. Narayana et al.⁴ studied a sensitive method for the spectrophotometric determination of Risperidone based on oxidation of the drug using chloramine-T & the excess oxidant is determined by malachite green which are measured at 619nm for Ris-MG dye. A. Kachukwu I et al.⁵ determined Risperidone by using Spectrophotometric method based on the charge-transfer complex reaction of risperidone with chloranilic acid to form a violet-coloured complex which absorbs at 500nm. B.K. Jayanna⁶ used spectrophotometric method to determine Risperidone based on oxidation of drug using alkaline KMnO₄ & excess of KMnO₄ Oxidises 1, 10-phenanthroline Fe (II) which is measured at 415nm.

Potassium hexacyanoferrate (III), K₃[Fe(CN)₆], is a substitution-inert transition metal complex. Oxidations by hexacyanoferrate(III) ion take place by way of a non-bonded

electron transfer or outer sphere process, in which an electron is transferred from substrate to the metal ion through the cyano ligand. It has been widely used as oxidising agent in oxidation of numerous organic & inorganic compounds. It acts as an electron abstracting reagent in redox reactions^{7,8}.

The determination & kinetics of oxidation of various organic compound by hexacyanoferrate(III) in basic media has been studied. Kamala Sharma et al.⁹ studied the kinetics of Os(VIII) catalysed oxidation of hypophosphite ion by alkaline hexacyanoferrate(III) ion. The method is based on measuring the disappearance of [Fe(CN)₆]³⁻ at 420nm after oxidation using colorimeter. R.M.Hassan et al.¹⁰ reported the kinetics of oxidation of methyl cellulose polysaccharide by alkaline hexacyanoferrate(III) ion spectrophotometrically. Praveen K. Tandon et al.¹¹ reported the kinetics of reaction between cyclopentanone & cyclohexanone with hexacyanoferrate(III) ion catalysed by rhodium(III) chloride in alkaline medium by titrimetric method at different temperatures. Amar K Durgannavar et al.¹² reported the kinetics & mechanism of oxidation of amoxicillin by hexacyanoferrate(III) in alkaline medium by spectrophotometric method. Timy P et al.¹³ studied spectrophotometric kinetics of oxidation of gabapentin by hexacyanoferrate(III) in aqueous alkaline medium. As no one used the spectrophotometric method to determine the rate laws for oxidation of RSP, our aim is to present the kinetic work at room temperature by spectrophotometric method using UV-Visible light. Hence, the present work is to report the UV-visible spectrophotometrically monitored kinetics of oxidation of RSP by HCF in alkaline medium at 298K in order to find out the rate law and to elucidate the reaction mechanism.

2. Experimental

Apparatus: All the spectrophotometric measurements were performed using an Ocean optics Model UV-visible digital Spectrophotometer provided with 1-cm matched quartz cells.

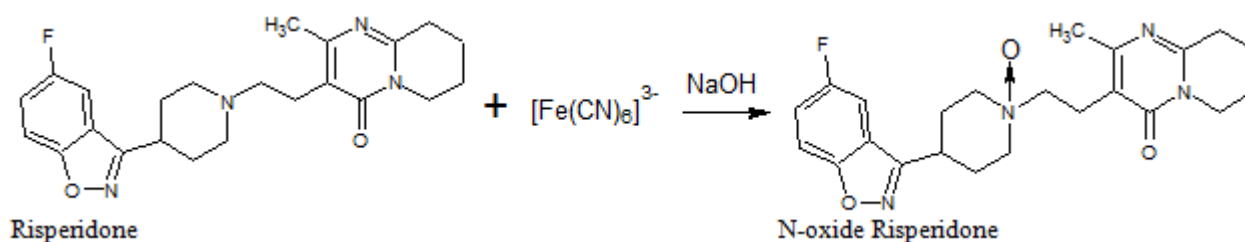
Reagents and Materials: All chemicals used were of analytical grade. Hexacyanoferrate (III) complex (Hi media) soluble in water prepared the stock solution of 2×10^{-5} mol dm⁻³. Risperidone (Hi-media) was prepared by dissolving in 10% methanol & diluted with double distilled water of 1×10^{-4} mol dm⁻³. An aqueous solution 2×10^{-2} M NaOH (E-Merck) was prepared by double distilled water. To maintain ionic strength in oxidation reactions of Risperidone, stock solution of 1.5M sodium perchlorate (NaClO₄) prepared in water. Double distilled water was used for preparing aqueous solutions.

Kinetic measurement: Kinetic runs were followed under pseudo-first order conditions with the RSP concentration in excess over HCF. Solutions containing appropriate amounts of HCF, NaOH, NaClO₄ and water (to keep the total volume constant for all the runs) were taken in a conical flask and

kept on water bath at 298K. A measured amount of RSP solution was taken in another conical flask and kept on the same water bath. After few minutes the RSP solution rapidly added to the reaction mixture and shaken well for uniform concentration. The progress of reaction was followed spectrophotometrically by monitoring the changes in absorbance. It was verified that there is a negligible interference from other species present in the reaction mixture at this wavelength. The reaction was followed to more than 80% completion of the reaction. Plot of log (absorbance) versus time leads to first order rate constant (k).

Stoichiometry & product analysis

The stoichiometry of the reaction was identified by applying mole ratio method where the concentration of oxidant was varied, keeping all other reactant concentration constant. The reaction mixtures were equilibrated at 298K till the completion of reaction & the unreacted oxidant identified by change in the absorbance. Plotting a graph of absorbance verses [HCF]/[RSP], stoichiometric ratio found to be 1:1.



The product was isolated several times by using ethyl acetate as solvent in a separating funnel, the organic layer was washed with both acid-base & finally it was treated with sodium sulphate. On drying the organic layer crude product was obtained which then purified, recrystallised & identified by TLC method. The nature of oxidised risperidone was identified by various analytical techniques such as CV, IR, LCMS & NMR.

Voltammetric method was used for determination of oxidation of RSP at carbon paste electrode (CPE). Cyclic voltammogram obtained for electrochemical oxidation of 0.5

mM RSP in phosphate buffer (pH 7) on CPE are shown in Fig 2. The oxidation peak shows at 0.95 V with respect to the RSP. Further confirmed by IR spectral analysis (Fig 3) which shows a strong peak at 1532 & 1350 cm⁻¹ for -N-O symmetric & asymmetric stretch, medium peak at 1653 cm⁻¹ for -C=O group which is conjugated with two aromatic rings, strong peak at 2753 cm⁻¹ for -C-H stretching indicates the presence of alkyl group. A broad peaks at 2944 & 3069 cm⁻¹ for aromatic -C-H stretching. The LC-MS spectra showed a molecular ion peaks at 427.3 amu (Fig 4) confirming the above product.

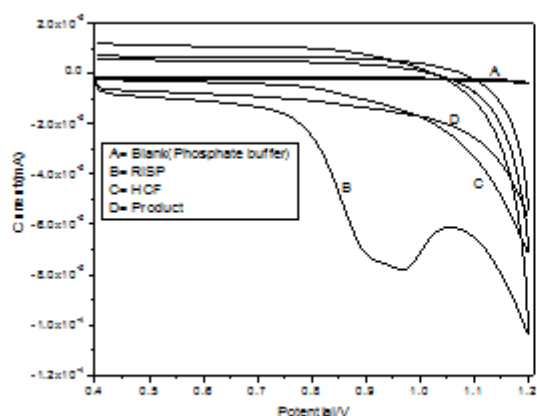


Figure 2: Voltammogram of the drug

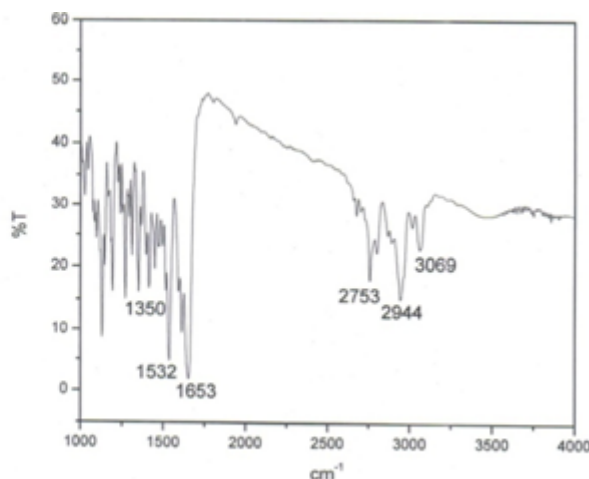


Figure 3: IR spectra of Product

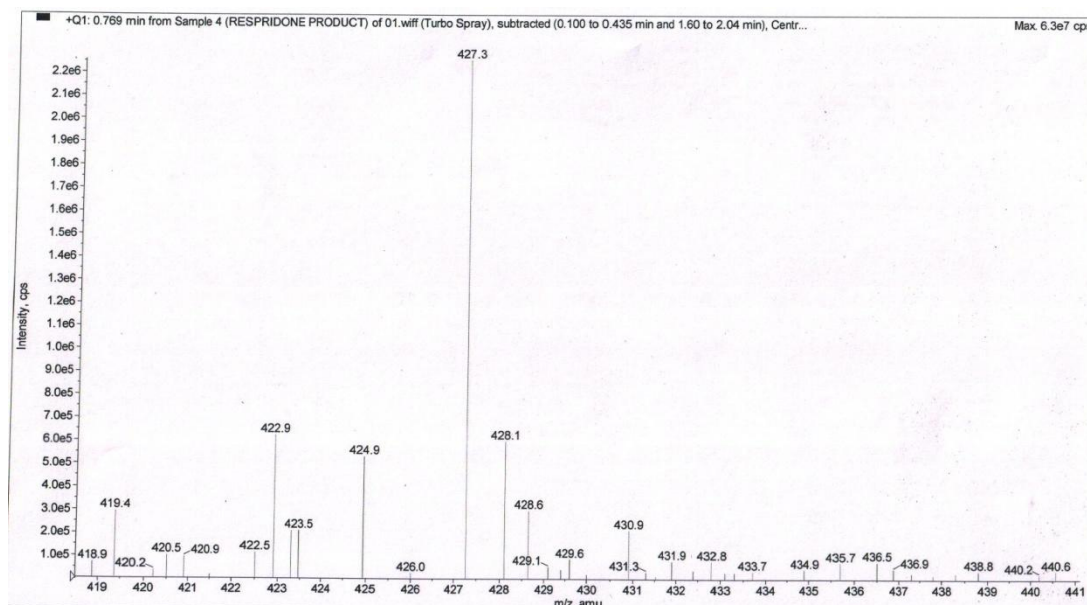


Figure 4: LCMS Spectrum of the Product shows Mol. Ion peak at 427.3 amu

3. Results

Effect of varying reactant concentrations on the reaction rate

The oxidation of Risperidone(RSP) by Hexacyanoferrate(III) (HCF) was kinetically investigated by spectrophotometric method with respect to the absorbance of drug, at different initial concentrations of reactants in NaOH medium at 298K. Under pseudo-first order conditions with the Substrate in excess (4×10^{-4} to 12×10^{-4}) at constant [HCF], [NaOH] and [NaClO₄], the rate constant *k* can be determined by a plot of absorbance verses time. The order of reaction with respect to substrate determined by plot of log [RSP] versus log *k* with a slope of 0.58 (Fig 5), indicating a fractional order. Under the same experimental conditions, an increase in [HCF] (4×10^{-5} to 12×10^{-5}) leads to an increase in the *k* values (Table 1). A plot of log [HCF] versus log *k* was linear with a slope of 0.91(Fig 6) showing a first order dependence on [HCF].

Table 1: Effect of varying concentrations of the reactants

$10^5[\text{RSP}]$ (mol dm ⁻³)	$10^6[\text{HCF}]$ (mol dm ⁻³)	$10^3[\text{OH}^-]$ (mol dm ⁻³)	$[\text{ClO}_4^-]$ (mol dm ⁻³)	10^3k (s ⁻¹)
0.4	1.0	2.0	0.1	1.12
0.6	1.0	2.0	0.1	1.19
0.8	1.0	2.0	0.1	1.28
1.0	1.0	2.0	0.1	1.31
1.2	1.0	2.0	0.1	1.34
1.0	0.4	2.0	0.1	1.11
1.0	0.6	2.0	0.1	1.34
1.0	0.8	2.0	0.1	1.74
1.0	1.0	2.0	0.1	2.18
1.0	1.2	2.0	0.1	3.03
1.0	1.0	0.5	0.1	1.31
1.0	1.0	1.0	0.1	1.50
1.0	1.0	1.5	0.1	1.65
1.0	1.0	2.0	0.1	1.74
1.0	1.0	2.5	0.1	1.85
1.0	1.0	2.0	0.04	1.55
1.0	1.0	2.0	0.06	1.45
1.0	1.0	2.0	0.08	1.36
1.0	1.0	2.0	0.10	1.29
1.0	1.0	2.0	0.12	1.15

$I = 0.098 \text{ mol dm}^{-3}$; $T = 298\text{K}$

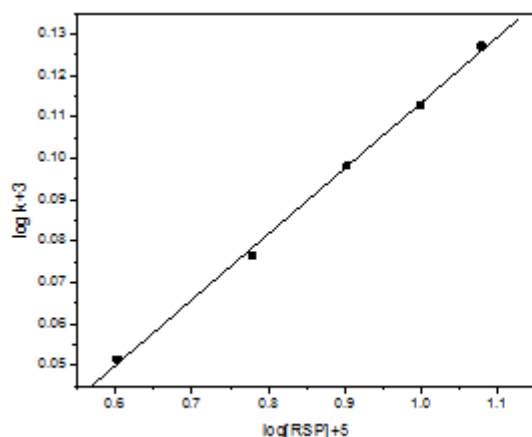


Figure 5: Effect of variation in [RSP]

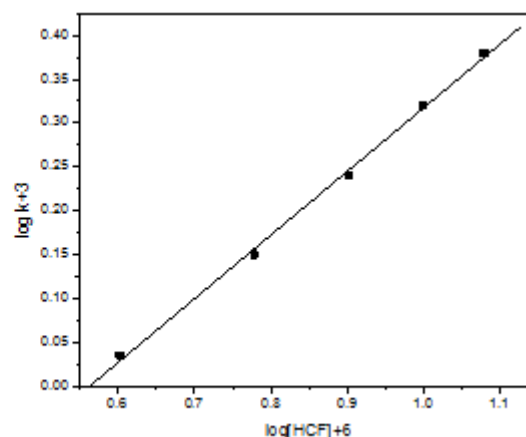


Figure 6: Effect of variation in [HCF]

Effect of varying $[\text{OH}^-]$ ion the reaction rate

The reaction rates were measured by varying the concentration of NaOH with all other reaction conditions kept constant. The rate of the reaction increases with increase in $[\text{OH}^-]$. A plot of $\log k$ versus $[\text{OH}^-]$ was linear with a slope of 0.21 (Table 1, Fig. 7) indicating fractional order dependence on $[\text{OH}^-]$.

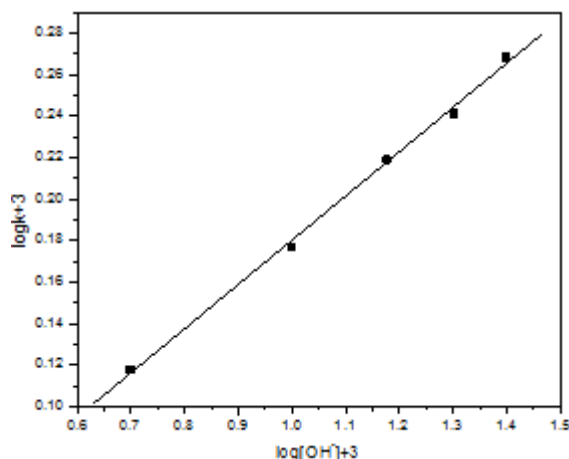


Figure 7: Effect of variation in $[\text{NaOH}]$

Effect of Ionic strength on the reaction rate

Effect of ionic strength was studied by varying the concentration of NaClO_4 at constant concentration of RSP, HCF & NaOH. It was found that increase in concentration of NaClO_4 doesn't affect much on reaction rate (Table 1). A plot of $\log k$ versus $\log [\text{NaClO}_4]$ was linear with a negative slope of 0.02 (Fig 8) indicates the non-ionic species involved in the rate determining step.

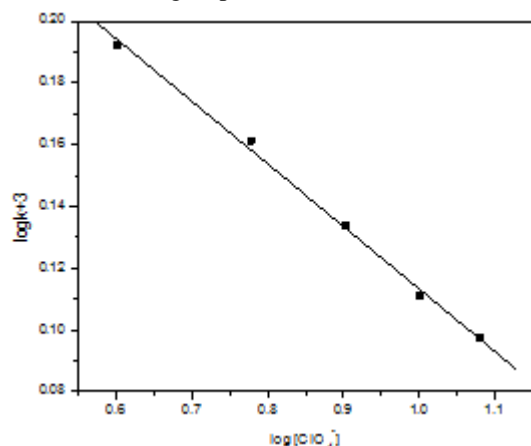


Figure 8: Effect of variation in $[\text{NaClO}_4]$

Effect of Dielectric constant of Medium

The effect of dielectric constant was studied by varying Ethanol-Water concentration (v/v) in reaction mixture with all other concentrations being maintained constant. Decreasing the dielectric constant of the medium had less effect on rate of reaction (Table 2). A Plot of $\log k$ vs. $[1/D]$ shown in Fig 9 have negative slope of 0.24.

Table 2: Effect of dielectric constant of the medium

$[\text{EtOH}]$ % v/v	D	$10^2/D$	$10^3 k (\text{s}^{-1})$
0	80.1	1.24	1.89
0.5	74.54	1.34	1.79
1.0	68.98	1.44	1.70
1.5	63.42	1.57	1.58
2.0	57.86	1.72	1.45

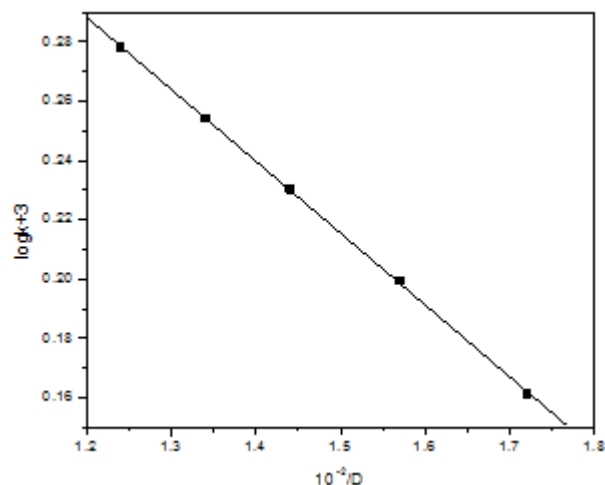


Figure 9: Effect of Dielectric constant on the oxidation of RSP by HCF in base media at 298 K
 $[\text{RSP}] = 1.0 \times 10^{-5} \text{ mol dm}^{-3}$; $[\text{HCF}] = 1.0 \times 10^{-6} \text{ mol dm}^{-3}$; $[\text{OH}^-] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$; $[\text{NaClO}_4] = 0.1 \text{ mol dm}^{-3}$

Effect of temperature

The rate constants for the oxidation of RSP with HCF at different temperature ranges from 295 K to 313 K was measured by keeping the other experimental conditions constant. The rate constant of the reaction increases with increase in temperature (Table 3). The energy of activation corresponding to these constants were evaluated from the Arrhenius plot of $\log k$ versus $1/T$ (Fig 10) & other activation parameters were also obtained as reported in Table 4.

Table 3: Effect of varying temperature

Temperature(K)	$10^3 k (\text{s}^{-1})$
295	0.99
300	1.08
305	1.10
309	1.33
313	1.91

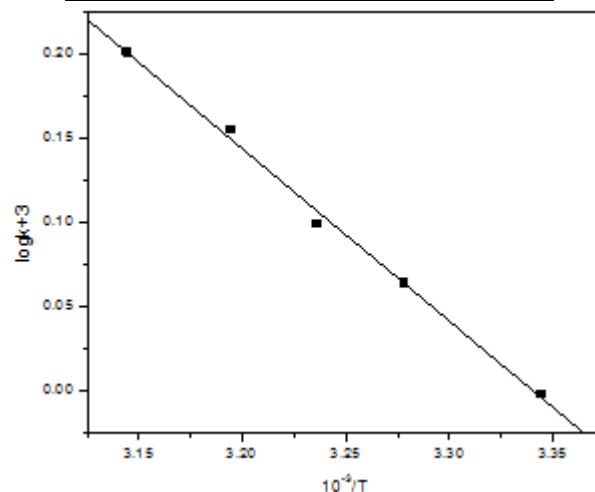


Figure 10: Arrhenius plot of $\log k$ versus $10^3/T$

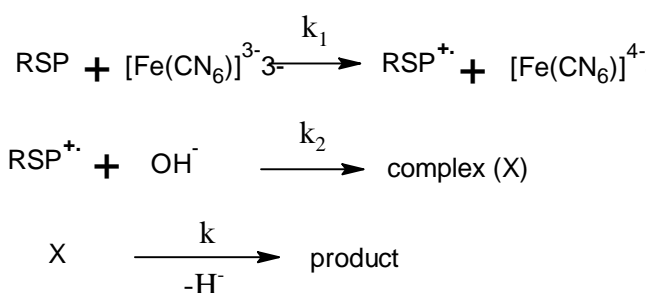
Table 4: Values of activation parameters

Parameter	Value
$E_a(\text{kJmol}^{-1})$	44.838
$\Delta H^\ddagger(\text{kJmol}^{-1})$	42.261
$\Delta G^\ddagger(\text{kJmol}^{-1})$	93.241
$\Delta S(\text{JK}^{-1}\text{mol}^{-1})$	-165.05
Log A	14.50

$[\text{RSP}] = 1.0 \times 10^{-5} \text{ mol dm}^{-3}$; $[\text{HCF}] = 1.0 \times 10^{-6} \text{ mol dm}^{-3}$; $[\text{OH}^-] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$; $[\text{NaClO}_4] = 0.1 \text{ mol dm}^{-3}$

4. Discussion

Hexacyanoferrate(III) involves in free radical formation & rapidly oxidises the organic compounds in basic medium¹⁴. The role of HCF(III) as an oxidant is already discussed in Introduction chapter. In view of the preceding discussion and experimental facts, **Scheme I & II** is proposed to explain the reaction mechanism for oxidation of RSP by HCF in basic medium.



Scheme I

From **scheme I** the rate law can be derived as follows,

$$\text{Rate} = -\frac{d[\text{HCF(III)}]}{dt} = k[\text{X}] \quad \text{..... 1}$$

Total concentration of HCF(III) can be written as,

$$[\text{HCF(III)}]_t = [\text{HCF(III)}]_f + [\text{X}] \quad \text{..... 2}$$

Where the subscripts t & f are the total & free HCF(III) concentrations respectively,

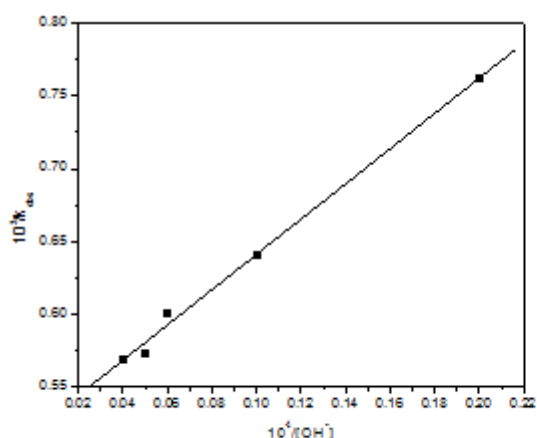


Figure 11: Reciprocal plot of $1/k_{\text{obs}}$ vs $1/[\text{OH}^-]$

$$\text{From scheme I, } k_1 = \frac{[\text{RSP}^+]}{[\text{RSP}][\text{HCF}]} \quad \text{..... 3}$$

$$[\text{RSP}^+] = k_1[\text{HCF}]_f[\text{RSP}]_f \quad \text{..... 3}$$

$$k_2 = \frac{[\text{X}]}{[\text{RSP}^+][\text{OH}^-]} \quad \text{..... 4}$$

Substituting equation 3 in 4 we get,

$$\text{X} = k_1 k_2 [\text{HCF}]_f [\text{RSP}]_f [\text{OH}^-] \quad \text{..... 5}$$

Substitute eqn. 5 in 2

$$\begin{aligned} \text{HCF(III)}_t &= [\text{HCF(III)}]_f + k_1 k_2 [\text{HCF}]_f [\text{RSP}]_f [\text{OH}^-] \\ &= [\text{HCF(III)}]_f [1 + k_1 k_2 [\text{RSP}]_f [\text{OH}^-]] \\ [\text{HCF(III)}]_f &= \frac{[\text{HCF(III)}]_t}{1 + k_1 k_2 [\text{RSP}]_f [\text{OH}^-]} \quad \text{..... 6} \end{aligned}$$

Similarly, $[\text{RSP}]_t = [\text{RSP}]_f + [\text{RSP}^+]_f + [\text{X}]$

$$[\text{RSP}]_f = \frac{[\text{RSP}]_t}{1 + k_1 [\text{HCF}]_f + k_1 k_2 [\text{HCF}]_f [\text{OH}^-]}$$

In view of low concentration of $[\text{HCF}]$ & $k_1 k_2 [\text{HCF}][\text{OH}^-]$ is neglected

$$[\text{RSP}]_f = \frac{[\text{RSP}]_t}{1 + k_1 [\text{HCF}]} \quad \text{..... 7}$$

Substituting all the equations 5, 6 & 7 in eqn 1

$$\begin{aligned} \text{Rate} &= \frac{k k_1 k_2 [\text{HCF}] [\text{RSP}] [\text{OH}^-]}{1 + k_1 k_2 [\text{RSP}] [\text{OH}^-] + k_1 [\text{HCF}] + k_1 k_2 [\text{HCF}] [\text{OH}^-]} \\ \frac{\text{Rate}}{[\text{HCF}]} = k_{\text{obs}} &= \frac{k k_1 k_2 [\text{RSP}] [\text{OH}^-]}{1 + k_1 k_2 [\text{RSP}] [\text{OH}^-] + k_2 [\text{OH}^-]} \quad \text{..... 8} \end{aligned}$$

Equation 8.8 is verified in the following eqn as,

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k k_1 k_2 [\text{RSP}] [\text{OH}^-]} + \frac{1}{k k_1 [\text{RSP}]} + \frac{1}{k} \quad \text{..... 9}$$

A plot of $1/k_{\text{obs}}$ versus $1/[\text{OH}^-]$ & $1/k_{\text{obs}}$ versus $1/[\text{RSP}]$ (Fig 11 & 12) should be linear & proved it. The complex which is formed between substrate & HCF is kinetically proved by non-zero intercept of $1/k_{\text{obs}}$ versus $1/[\text{RSP}]$. The values of k , k_1 & k_2 can be calculated from the slopes & intercepts of the above plots. The value of k is 1.464 sec^{-1} , k_1 is $6.134 \text{ dm}^3 \text{ mol}^{-1}$ & k_2 is $1.923 \text{ dm}^3 \text{ mol}^{-1}$.

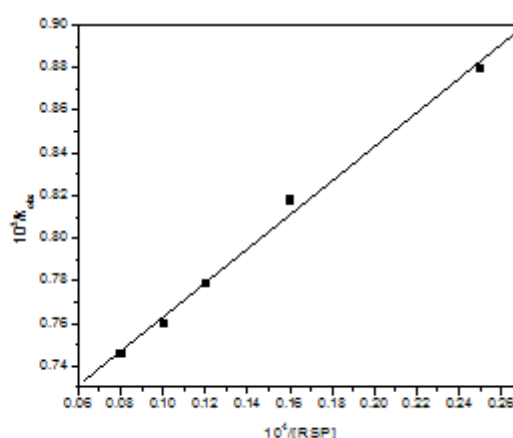


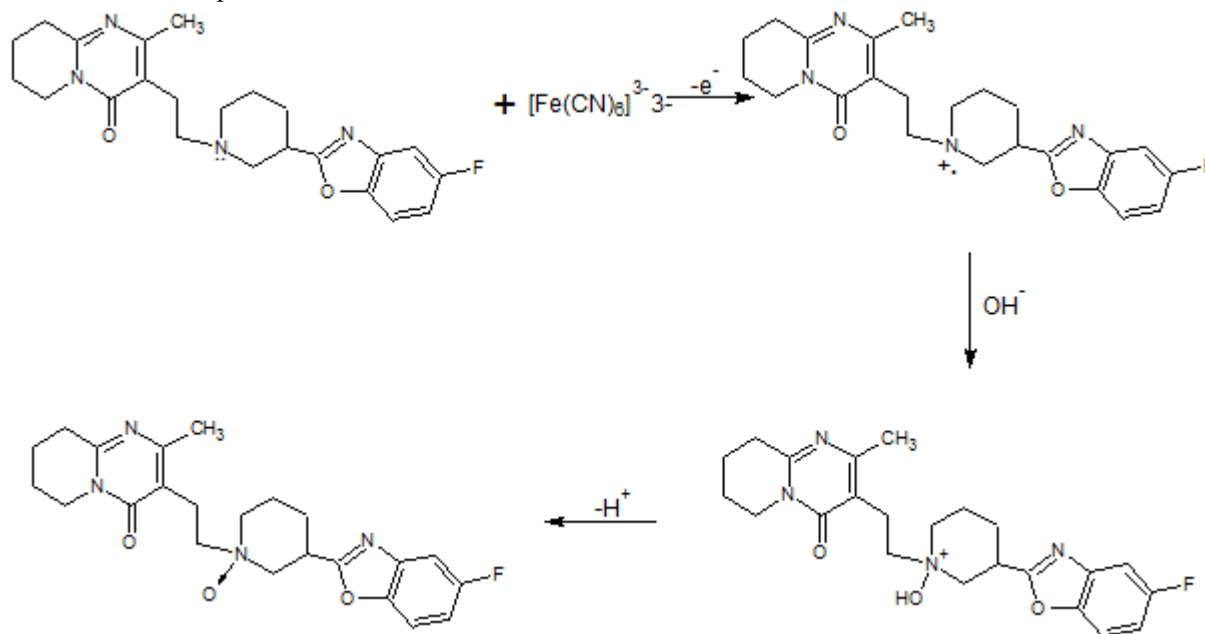
Figure 12: Reciprocal plot of $1/k_{\text{obs}}$ vs $1/[\text{RSP}]$

The decrease in dielectric constant of the medium, rate of reaction also decreases which supports the involvement of the charged species as shown in **scheme I**. The probable mechanism in **scheme II** is given below where the drug oxidised by the HCF to form a cation species which is

supported by the observed fractional order with respect to $[\text{RSP}]$. This cation form of RSP reacts with base resulting in formation of complex(X) which further decomposes in a slow step to form a major product, N-oxide risperidone¹⁵.

The negative value of ΔS^\ddagger indicates that the complex is more

ordered than the reactants. The positive value of both ΔH^\ddagger and ΔG^\ddagger confirms the endothermic formation of intermediate complexes and their non-spontaneities.



Scheme II

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