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Kinetic and mechanistic study of ciprofloxacin in aqueous alkaline medium

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Abstract

The existence of fluoroquinolone drugs in environment, may harmful to the human health. Hence the present study aimed to oxidative degradation of antibacterial drug ciprofloxacin by hexacyanoferrate(III) (HCF) in aqueous alkali medium at 40˚C temperature. The stoichiometry for the reaction indicates that the oxidation of a mole of ciprofloxacin requires twice moles of HCF. The reaction exhibited first order kinetics with respect to [HCF] and [ciprofloxacin] and less than unit order with respect to [OH¯]. The products were also distinguished on the basis of stoichiometric results and confirm by the characterization results of LC-MS and FT-IR analysis. The major product of the reaction obtained by the decarboxylation of the quinolones moiety and hence it may retain the antibacterial activity. From the experimental results the rate law is derived. The activation results with respect to the slowest step of the proposed mechanism were evaluated and thermodynamic parameters are calculated.

Keywords: Poultry dust, allergy, occupational asthma, working practices, health surveillance.

Introduction

Ciprofloxacin (CIP) {1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazine-1-yl)-quinolone-3-carboxylic acid} is a second generation fluoroquinolone antibacterial agent[1].The fluoroquinolones are most popular class of antibiotics for different uses so they are excessively used in the world. Most of them are partially metabolized and excreted by humans and animals and spilled into water. The existence and collection of fluoroquinolone antibiotics in ecosystem, requires progression of the different oxidation methods for the conversion of fluoroquinolones in environment. CIP possess two concerning ionisable functional groups: a basic piperazinyl group and a carboxylic group which relevant to antimicrobial activity.

These antibiotics react with various antibacterial agents and natural supplements. Such reactions increase the problem of anticoagulation and the preparation of non-absorbable complexes, as well as increasing the possibility of toxicity.

The great attention is being paidtooxidizing agents in attacking particular groups in simple and large molecules. Among these a potassium hexacyanoferrate(III) {HCF(III)}[2], a single electron oxidant with + 0.45V redox potential for the HCF(III)/ HCF(II) couple in alkali medium preeminent to its degradation to hexacyanoferrate (II)[3,4]. HCF(III) has widely being used as oxidizing agent for various chemicals in alkaline media. The earlier studies[5,6] reveals that alkali HCF(III) ion act as one electron intellectual testing agent for redox processes. On the other hand Speakman and Wats[7]recommendedvarious path of aldehydes, ketone and nitroparaffins oxidation reactions by HCF(III). Singh et al[8] reported about the formation of free radical intermediate the oxidation of formaldehyde, acetone and ethyl methyl ketone by HCF(III) access through an electrone transfer process. Although, HCF(III) has some assistance that becomes proper oxidizing agent for various organic substrate[9]. In accurate, its stability over the entire pH scale and being a moderate oxidant, its reactions with some nitrogen containing compounds are not facile and requires the catalyst[10]. Although the oxidative study of CIP by different oxidants has been finalized[11-14], no study have existence about the oxidation of this drug by HCF(III). Such studies have importance in considering the properties of CIP in redox processes and furnish an observation for the reaction of such ion with the substrate to determine the active forms of HCF(III), a description of this work becomes beneficial. Consequently, this work designed to originate the reactivity of CIP towards HCF(III) in the reaction and attempt to explore the mechanism on the basis of kinetic parameters. Furthermore, the oxidation products of the CIP are previously reported and the distribution of products appears to depend upon the nature and potentiality of the oxidants. This was the additional interest of undertaking the title study.

Materials and methods

Chemicals: The solution of CIP (KORES India Limited) was formed by accurate amount of the samples and cleanness of this solution was analyzed by their melting point (205ºC). A stock solution of oxidant, HCF (III) was prepared by dissolving $K_3[Fe(CN)_6]$ (BDH) and standardizing the solution iodometrically[15]. Other chemicals were either Analar or guaranteed reagent grade and used as received.

Twice distilled water, second distillation being from alkaline permanganate solution in an all glass still, was used in all preparations and kinetic studies.

Instrumentation: A Peltier accessory (temperature-Controlled) attached to a U.V.3000$^+$ UV-Visible spectrophotometer (LAB INDIA) was used for kinetic measurements. For product analysis, LC-ESI-MS, (Q-TOF Micro mass, WATERS Company, UK) and Alpha-T FTIR spectrophotometer (BRUKER, Germany), were used.

Kinetic determinations: Kinetic measurements were conducted in glass Stoppard flasks immersed in a thermo stated water bath at 40±1ºC. Reaction mixture were prepared by mixing the desired concentration of various reaction components, Fe(III) was the last to be added. Through the calibration of $[Fe(CN)_6]^{3-}$ absorbance in the reaction solution for the progress of the reaction at 420 nm with the help of U.V.3000$^+$ UV-Visible spectrophotometer (Figure-1). The relevance of Beer's law of HCF(III) at 420 nm had been verified giving ε =1050 dm^3/mol/cm[16]. The pseudo first order plots in whole reactions were linear up to 80% fulfillment of the process and values of constants were reproducible within ±6%.

Results and discussion

Stoichiometry and Product Separation: The reaction mixture containing excess of HCF (III) over CIP were allowed for 12 h to react at 40^{o}C. The excess of hexacyanoferrate(III) concentration determined with calibrating the absorption at 420 nm. The stoichiometry of the reaction indicates (Equation-1) that a mole of CIP reacts with twice mole of HCF(III).

The product was separated out with ether after the completion of the kinetic experiments. The main product {1-cyclopropyl-3-hydroxy-6-fluoro-1,4-dihydro-7-(piperazine-1-yl)-quinolin-4-one}, was identified with the help of TLC and characterized by FT-IR and LC-MS analysis. FT-IR spectra of product show carbonyl stretching of 7-oxo group at 1640.35 Cm^{-1} and a broad peak at 3472.09 Cm^{-1} is due to OH-stretching and the carbonyl stretching of acid is disappear (Figure-2). An LC-MS spectrum of CIP oxidation process indicates the formation of product with molecular ion of m/z 304 amu (Figure-3).

The molecular ion of CIP is m/z 332, the m/z 304 corresponds to decarboxylation of quinolones ring and yield {1-cyclopropyl-3-hydroxy-6-fluoro-1,4-dihydro-7-(piperazine-1-yl)-quinolin-4-one}as oxidation product and the melting point of product was 205ºC[17]. The product was also short written as (m-28), describe the degradation in net mass of end product from the parent CIP. The liberated CO_2 was identified by the lime water test.

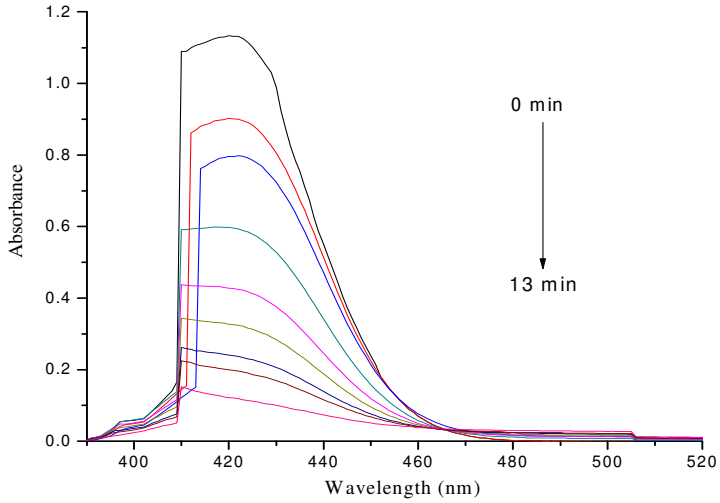
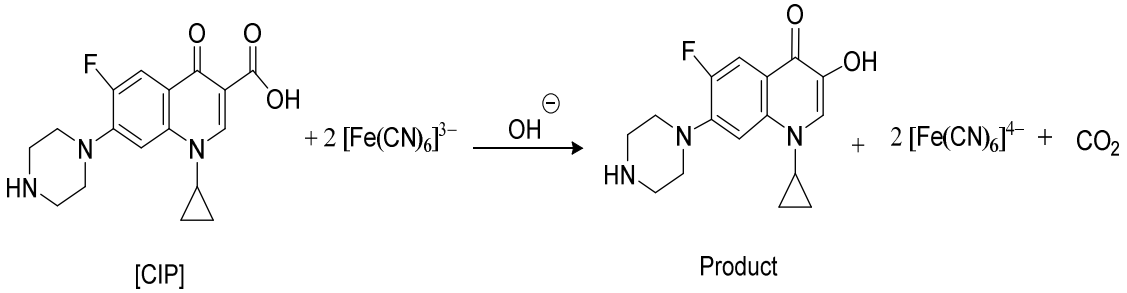


Figure-1: Spectra of the oxidation of CIP by HCF(III) in alkaline medium at 40^{o}C. [HCF(III)] = 1.0 × 10^{-3} mol/dm^3, [CIP] = 1.0 × 10^{-2} mol/dm^3, [OH$^-$] = 1.0 mol/dm^3 and [$NaNO_3$] = 1.0 mol/dm^3.



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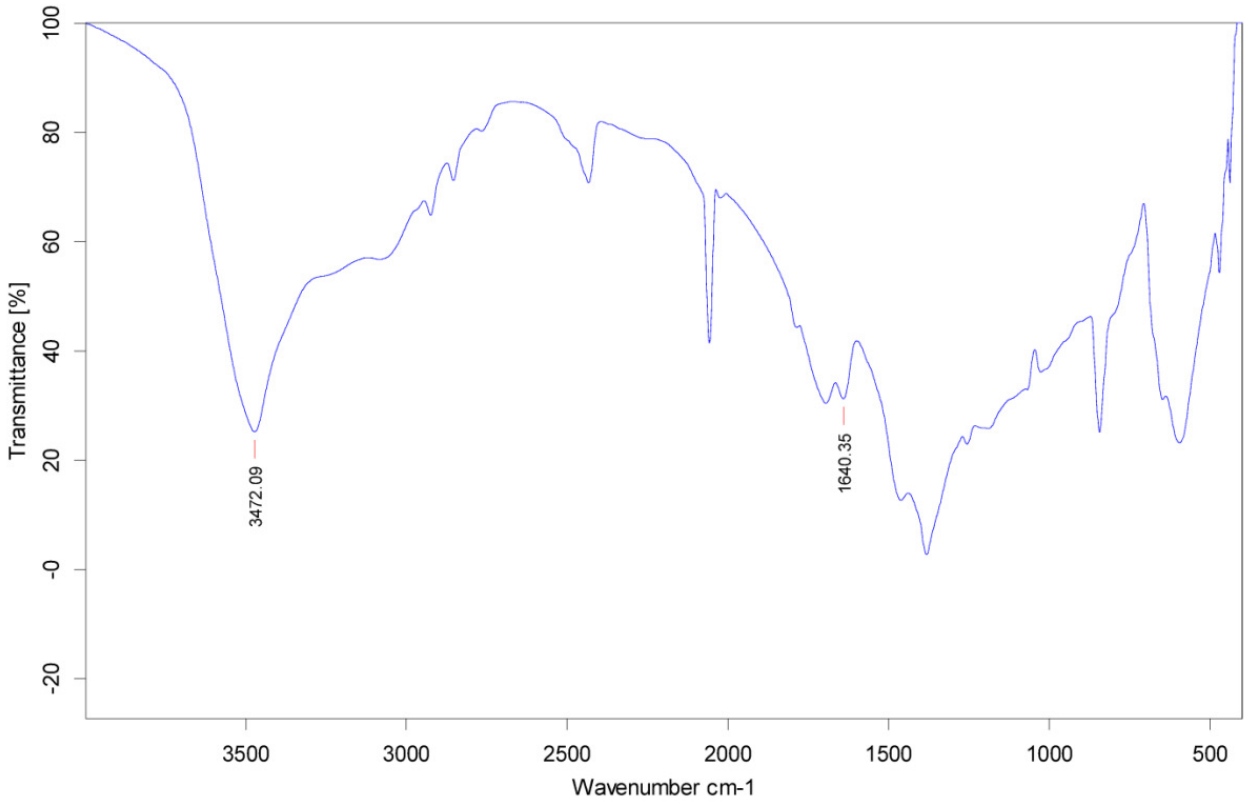


Figure 2 Fourier Transform Infrared spectra of oxidative product of CIP.

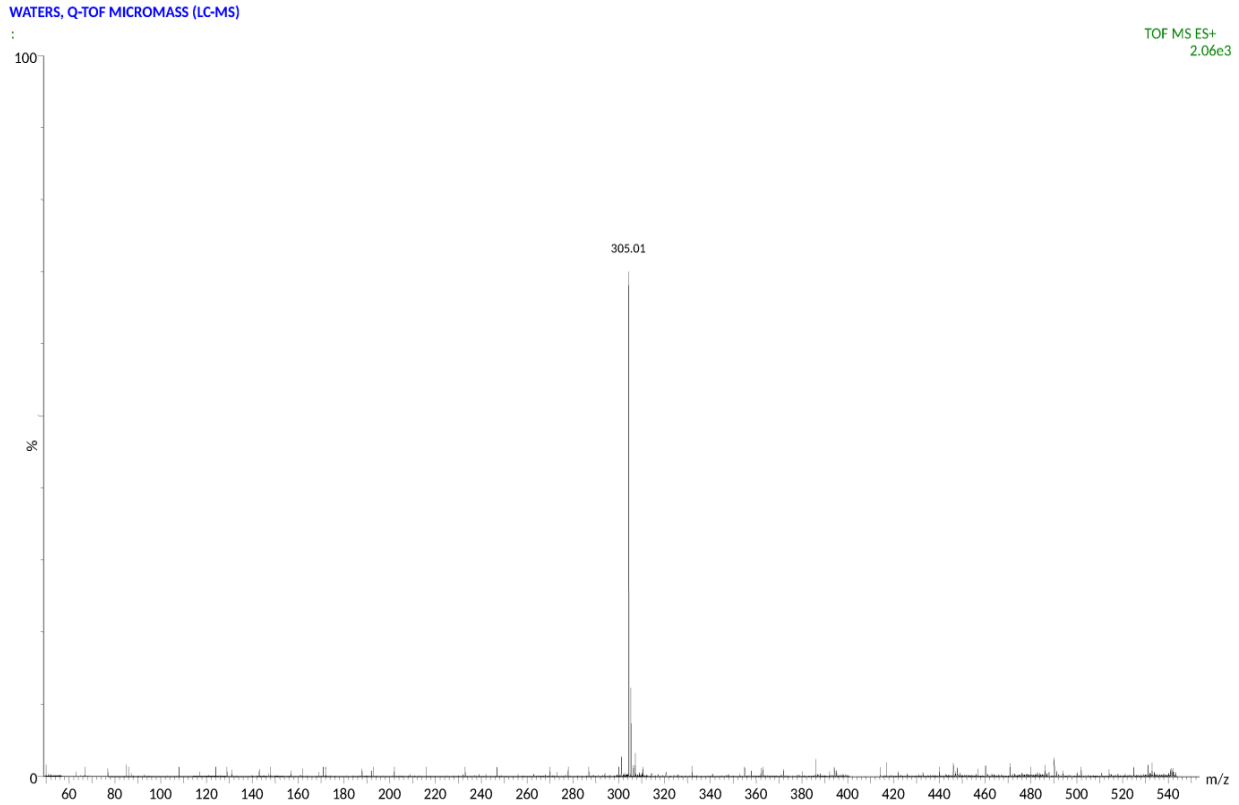


Figure 3 Liquid Chromatography-Mass Spectroscopy spectra of oxidative product of CIP.

Hexacyanoferrate (III) dependence: The concentration of HCF(III) was varied in the range (1×10^{-4} to 1×10^{-3} mol/dm^3) at fixed concentration of CIP, alkali and ionic strength at 40ºC. Pseudo first order plots were made and the pseudo first order rate constants were found to be independent of the initial concentration of HCF(III) in the reaction (Figure-4). Results are collected in (Table-1).

Table-1: Dependence of [HCF(III)], [CIP], [NaOH], [$NaNO_3$] variation for the oxidative study of CIP by HCF(III) in alkali medium at 40^{o}C.

10^4 [HCF(III)] (mol/dm^3)	10^2 [CIP] (mol/dm^3)	[NaOH] (mol/dm^3)	[$NaNO_3$] (mol/dm^3)	10^4k_{obs} (Sec^{-1})
1.0	1.0	1.0	1.0	11.13
2.5	1.0	1.0	1.0	11.13
5.0	1.0	1.0	1.0	11.32
7.5	1.0	1.0	1.0	11.32
10	1.0	1.0	1.0	11.51
10	0.5	1.0	1.0	6.35
10	0.75	1.0	1.0	8.54
10	1.0	1.0	1.0	11.51
10	2.0	1.0	1.0	21.35
10	3.0	1.0	1.0	30.85
10	4.0	1.0	1.0	40.73
10	5.0	1.0	1.0	52.00
10	1.0	0.25	1.0	4.00
10	1.0	0.5	1.0	6.58
10	1.0	0.75	1.0	9.24
10	1.0	1.0	1.0	11.51
10	1.0	1.25	1.0	14.05
10	1.0	1.5	1.0	16.11
10	1.0	1.75	1.0	17.68
10	1.0	2.0	1.0	19.00
10	1.0	1.0	1.0	11.51
10	1.0	1.0	1.25	11.60
10	1.0	1.0	1.5	11.71
10	1.0	1.0	1.75	11.89
10	1.0	1.0	2.0	11.99

Ciprofloxacin dependence: The concentration of CIP was varied from 0.5×10^{-2} to 5×10^{-2} mol/dm^3 at fixed concentration of HCF, alkali and ionic strength at 40ºC. The plot of pseudo first order rate constant (k_{obs}) verses [CIP] yielded a straight line passing through the origin determining first order dependence with respect to CIP (Table-1).

Hydroxyl ion dependence: Hydroxyl ion concentration was varied employing NaOH from 0.25 to 2.0mol/dm^3 at fixed concentration of other reactants and three temperatures viz 35, 40, 45ºC respectively. The rate initially increases and tends towards a limiting value with increasing concentration of hydroxide ion concentration in reaction (Table-1).

Ionic Strength dependence: Ionic strength in the reaction was varied employing sodium nitrite from 1.0 to 2.0mol/dm^3 at fixed concentration of HCF, CIP, alkali at 40ºC for reaction. For reaction increase in ionic strength increases the rate of reaction indicating the reaction between two ions of similar charges.

Initially added product dependence: At the beginning, addition of hexacyanoferrate(II) was studied in the range of 1×10^{-4} to 10×10^{-4} mol/dm^3 while other reactants concentration and conditions constant, the rate of reaction was unaffected in the reaction.

Test of free radical (Polymerisation test): To test the intervention of free radicals, a known quantity of acrylonitrile had been added initially in the reaction mixture, was stored for two hours under nitrogen atmosphere.

On dilution with methanol, white precipitate of polymer was formed, indicating the presence of intervention of free radicals in the reaction. The same experiment was repeated in the absence of CIP under similar conditions, the test was negative. This confirms that the reaction was routed through free radical pathway[18].

Discussion and Mechanism: Variation of concentration of each of the oxidant HCF(III), substrate CIP, base and ionic strength, although mainly the other concentration constant shows that the reaction is unity for oxidant, substrate and with respect to alkali in fractional order.

Through the stoichiometric and experiential outcomes, a reaction scheme can be prepared in this mechanism all the evaluated order in every fraction i.e. [Oxidant], [substrate], [alkali] and ionic strength may be proper estimated for.

In recent investigation, alkali conjoins initially with CIP to describe negative species of CIP, in a pre-equilibrium step. The anionic form of CIP interact with the HCF(III) species and give a free radical in a slow step. Then free radical react with another molecule of HCF(III) to give final products, as given in Scheme-1.

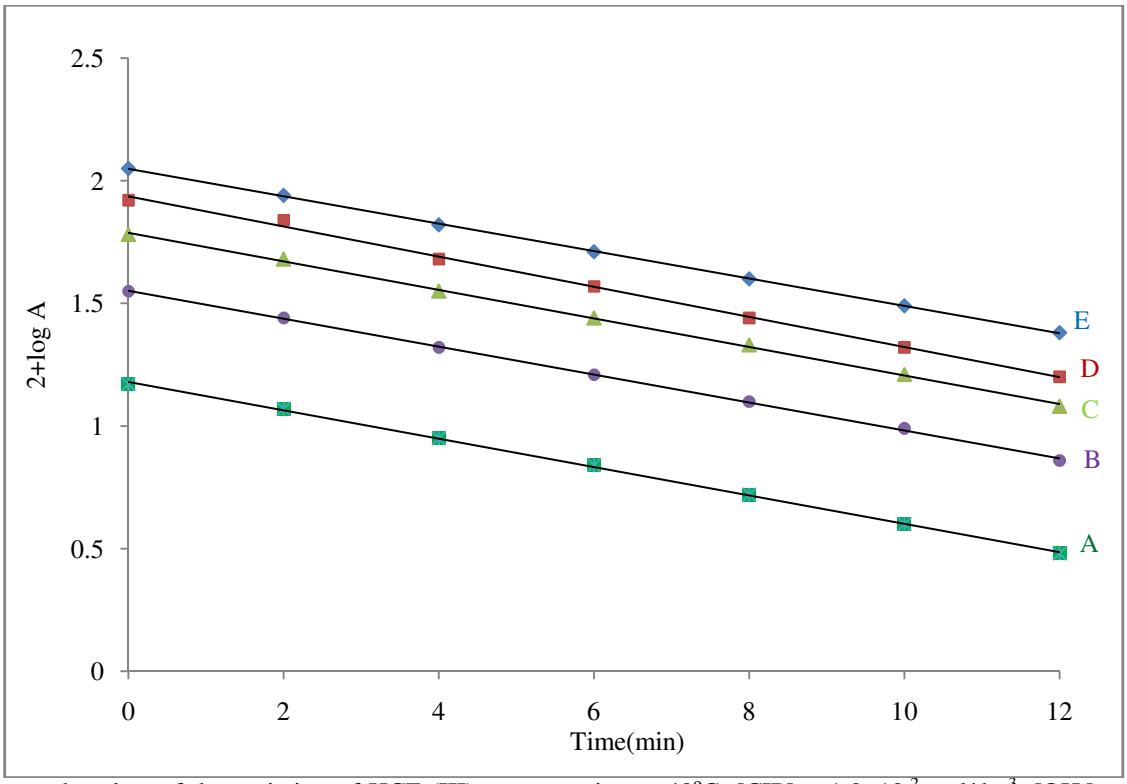
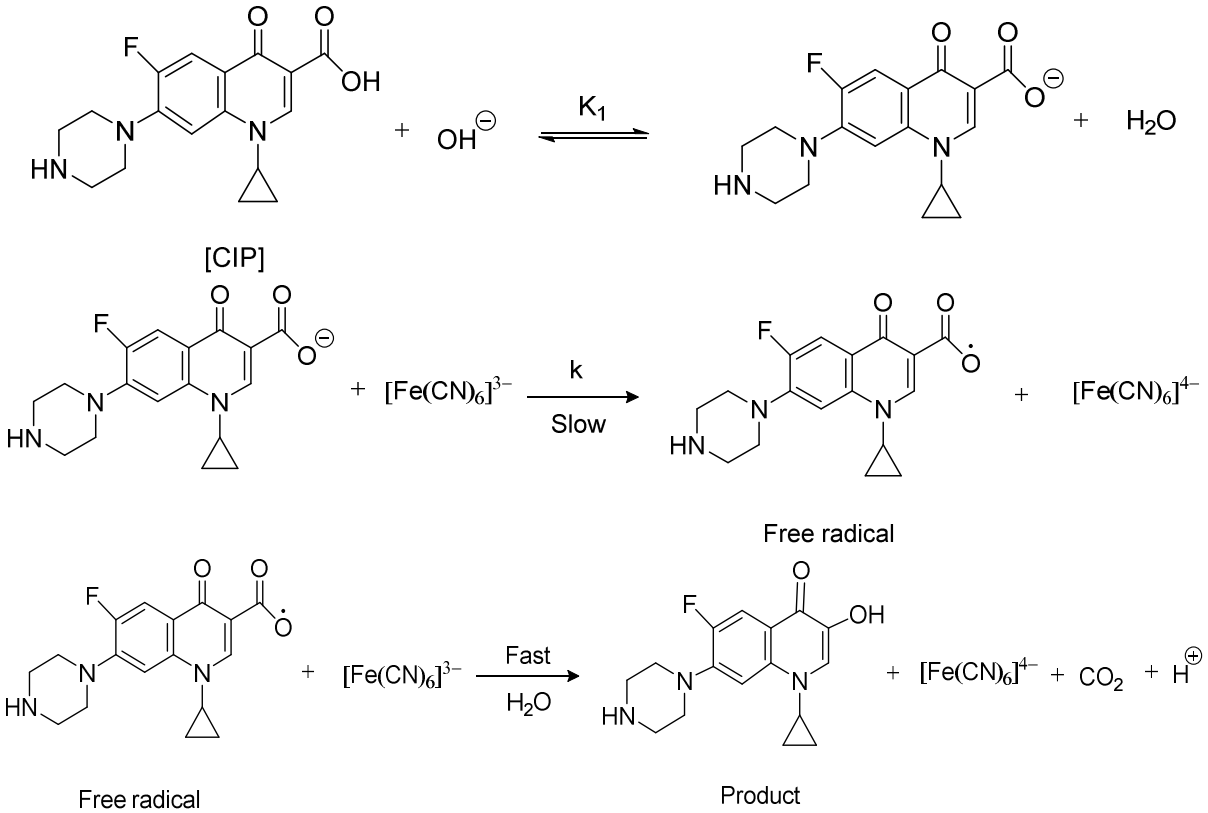


Figure-4: First order plots of the variation of HCF (III) concentration at 40°C. [CIP] = 1.0×10^{-2} mol/dm^3, [OH^-] = 1.0 mol/dm^3, [$NaNO_3$] = 1.0 mol/dm^3 and [HCF] mol/dm^3 = (A) 1×10^{-4} , (B) 2.5×10^{-4}, (C) 5×10^{-4}, (D) 7.5×10^{-4}, (E) 10×10^{-4}.



Scheme-1: Mechanism for the oxidative study of CIP by HCF(III).

The proposed mechanism induce the rate law (2) accounting for an experimental observations.

$$\frac{-d\left[Fe(III)\right]}{dt} = \frac{K_1 k\left[Fe(III)\right]\left[OH^-\right][CIP]}{1+K_1\left[OH^-\right]} \quad (2)$$

$$k_{obs} = \frac{Rate}{\left[Fe(III)\right]} = \frac{K_1 k\left[OH^-\right][CIP]}{1+K_1\left[OH^-\right]} \quad (3)$$

$$\frac{k_{obs}}{[CIP]} = k' = \frac{K_1 k\left[OH^-\right]}{1+K_1\left[OH^-\right]} \quad (4)$$

Rearrange the Equation (4)

$$\frac{1}{k'} = \frac{1}{K_1 k\left[OH^-\right]} + \frac{1}{k} \quad (5)$$

Where: k´ is observed second order rate constant.

A plot of 1/k´ verses 1/[OH^-] was made from the equation (5) at three different temperatures, that yielded at straight line with non zero intercept (Figure-5). The intercept gives the value of slow step (k) 27.77×10^{-2}, 37.03×10^{-2}, 47.61×10^{-2} dm^3/mol/sec at 35°, 40°, 45ºC respectively and the ratio of intercept and gradient gives the value of K_1 to be 39.13×10^{-2}, 47.36×10^{-2}, 63.63×10^{-2} dm^3/mol at 35°, 40°, 45 ºC respectively**.**

The activation energy of the reaction was estimated by plotting a graph between log k verses 1/T to be 44.03 K J/mol and the entropy of the reaction is evaluated by plotting a graph between log K_1 verses 1/T to be -121.39 J /K/mol. However energy of activation is closer to the value normally found in bimolecular reaction and entropy of activation indicates a more organized transition state.

Conclusion

The oxidative study of CIP by HCF(III) in aqueous alkali media was evaluated. The inspected stoichiometry determines that, the oxidation of a mole of CIP requires twice moles of HCF(III). The observed major product obtained by the decarboxylation of quinolone moiety and hence, it may retain the antibacterial activity. The kinetic study indicates that in the reaction the outer sphere formation of $[Fe(CN)_6]^{4-}$ and free radical in slow step which is followed by the rapid reaction of free radical by $[Fe(CN)_6]^{3-}$ to give product.

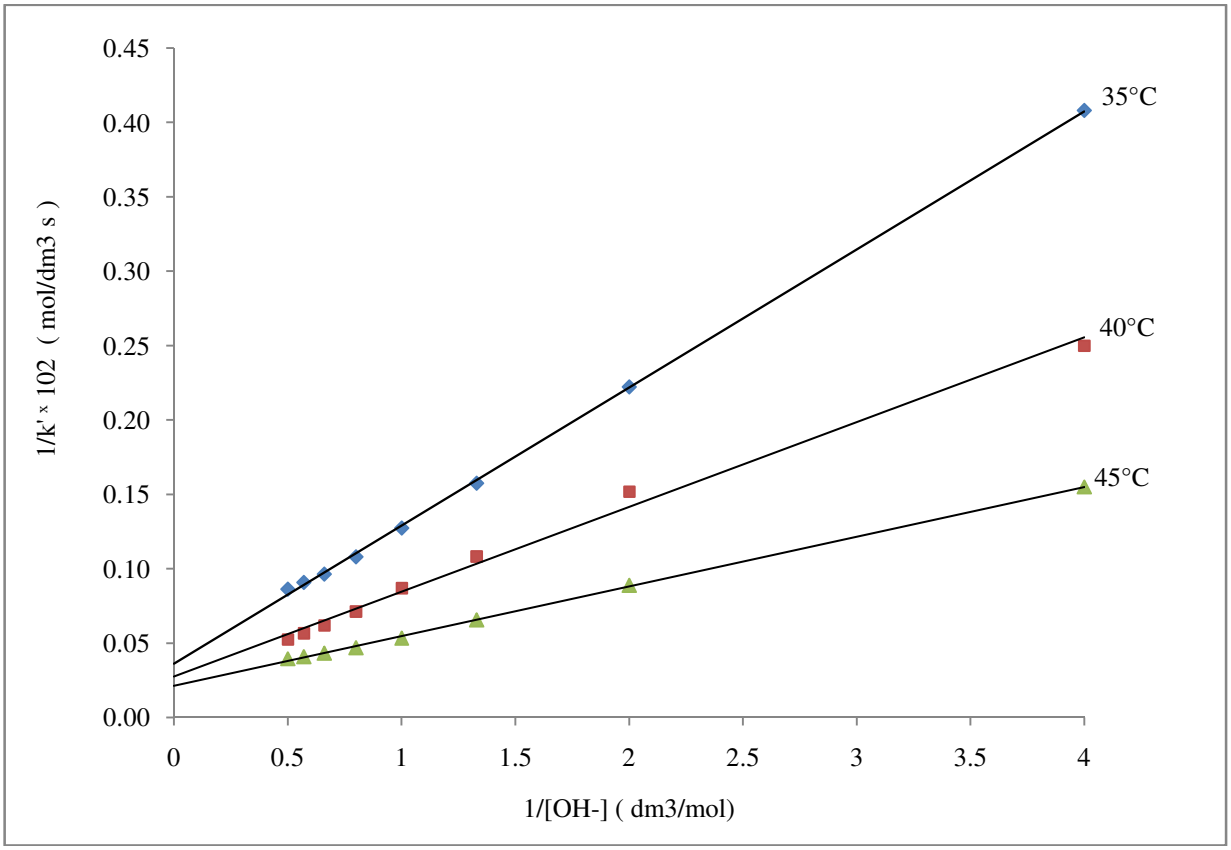


Figure-5: Plot of 1/k´verses 1/[OH^-] at three various temperatures.

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