Kinetic study of uncatalyzed and Cu(II) catalyzed oxidation of ofloxacin in aqueous alkaline medium and their mechanistic aspects

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Abstract

The presence and accumulation of antibacterial drugs in environment, may pose threats to the ecosystem and human health. Hence, oxidation process is of significant to minimize possibility of health risk. The present study aimed to uncatalyzed and Cu(II) catalyzed oxidative degradation of antibacterial drug ofloxacin by hexacyanoferrate(III) in aqueous alkaline medium at 40 °C temperature. The stoichiometry of the reaction indicates that the oxidation of 1 mol of ofloxacin requires 2 mol of hexacyanoferrate(III). The uncatalyzed reaction exhibited first order kinetics with respect to [hexacyanoferrate(III)] and [ofloxacin] and less than unit order with respect to [OH⁻]. The catalyzed reaction gives first order kinetics with respect to [hexacyanoferrate(III)] and [OH⁻] and less than unit order with respect to [ofloxacin]. The products were also identified on the basis of stoichiometric results and confirm by the characterization results of liquid chromatography mass spectroscopy and Fourier transform infrared analysis. The major product of the reaction obtained by the decarboxylation of the quinolones moiety and hence it may retain the antibacterial activity. Uncatalyzed reaction simultaneously occurs with the Cu(II) catalyzed reaction and the following rate law confirms to all experimental data observed in the reaction: $k'' = k_{un} + \frac{K_1 K_3 k [Cu(II)] [OH^-] [OFL]}{K_2 + K_3 [OFL]}$, where $k'' = (k_{un} + k_c)$ is the total observed first order rate constant, k_{un} = Pseudo first order rate constant for uncatalyzed reaction, K_c = Pseudo first order rate constant for catalyzed reaction. A reaction mechanism accounting for all these experimental results has been suggested.

Keywords Cu(II) catalysis · Hexacyanoferrate(III) · Kinetics · Mechanism · Ofloxacin

1 Introduction

Ofloxacin (OFL) [9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid] belongs to the fluoroquinolone class of antibiotics [1]. The fluoroquinolones have become a more famous class of antibiotics for use in a variety of infections so they are excessively used in the world. Most of them are partially metabolized and excreted by humans, animals and spilled into water. The presence and accumulation of fluoroquinolone antibiotics in aquatic environments, requires development of the various oxidation processes for the transformation of fluoroquinolones in water. OFL have a basic piperazinyl group and a carboxylic group

asionisable functional groups. The carboxylic group and the carbonyl groups are responsible for antimicrobial activity. These antibiotics connect with a number of other drugs, as well as many herbal and natural supplements. These interactions increase the anticoagulation, non-absorbable complexes formation and the possibility of toxicity.

The huge attention is being paid to various oxidizing agents in attacking distinct groups in simple and large molecules. Among these a potassium hexacyanoferrate(III) {HCF(III)} [2], a one electron oxidant with a redox potential of +0.45 V for the $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$ couple in alkaline medium leading to its reduction to hexacyanoferrate(II) [3, 4]. It has widely used as oxidizing agent for degradation of various organic and inorganic compounds in alkaline media.

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Literature survey [5, 6] informed that alkaline HCF(III) ion act as an electron abstracting reagent in redox reactions. However Speakman and Wats [7] proposed various path of oxidation of aldehydes, ketone and nitroparaffins by HCF(III). Singh et al. [8] suggested the oxidation of formaldehyde, acetone & ethyl methyl ketone by HCF(III) takes place via an electron transfer mechanism resulting in the free radical intermediate formation. Although, HCF(III) has a few advantage that become useful oxidizing agent for many organic substrate [9]. Especially, its stability over the full pH scale and being a balanced oxidant, its reactions with some nitrogen containing compounds are not facile and requires the presence of catalyst [10]. Transition metals have multiple oxidation states, so they are use as catalyst in many oxidation–reduction reactions. In recent years the transition metal ion such as ruthenium, osmium, palladium, manganese, chromium, iridium and copper has attracted considerable interest as catalyst in various redox processes [11–14]. The mechanism of the catalysis depends on the nature of substrate, oxidant and experimental conditions. It has been observed [15] that metal ion act as catalyst by one of several different paths, such as formation of complexes with reactants or oxidation of the substrate itself or through the formation of free radicals. Although the oxidation of OFL by various oxidants has been carried out [16, 17], there is a lack of literature on the oxidation of this drug by HCF(III) in the absence and presence of catalyst Cu(II). Such studies have importance in understanding the mechanistic profile of OFL in redox reactions and provide an insight into the interaction of metal ion with the substrate and to determine the active species of HCF(III) and Cu(II) catalyst, a detailed study of the reaction becomes important. Hence, the present study aimed to establish the reactivity of OFL towards HCF(III) in both uncatalyzed and Cu(II) catalysed reaction and attempt to explore the mechanism on the basis of kinetic parameters. Furthermore, the oxidation products of the OFL 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.

2 Materials and methods

2.1 Chemicals

The solution of OFL (KORES India Limited) was prepared by dissolving known amount of the samples in double distilled water. The purity of the sample was checked by their melting point (205 °C). Solutions of OFL were always freshly prepared before experiment. A stock solution of oxidant, HCF(III) was prepared by dissolving $K_3[Fe(CN)_6]$ (BDH) in double distilled water and standardizing the solution iodometrically [18]. 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.

2.2 Instrumentation

A Peltier accessory (temperature-Controlled) attached to a U.V.3000⁺ UV–visible spectrophotometer (LABINDIA) 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.

2.3 Kinetic measurements

Kinetic runs for the reaction mixtures were conducted following the procedure reported in previous studies [19]. Kinetic measurements were conducted under pseudo-first-order conditions of higher concentrations of OFL maintained over that of HCF(III). For each kinetic run, reaction mixture were prepared by mixing the desired concentration of OFL, NaOH (to maintain a constant basicity), and $NaNO_3$ (to maintain a constant ionic strength), in a glass stoppard flasks. Sufficient water was added to maintain a constant total volume. The solution was thermostated in a water bath set at a given temperature 40 ± 1 °C. The reaction was initiated by adding a measured volume of ferricyanide solution, which was also thermally equilibrated. Each aliquot of the reaction mixture was transferred into a quartz cuvette of 0.01 m path length and placed in the temperature controlling unit of the spectrophotometer. The progress of the reaction was followed by measuring absorbance of $[Fe(CN)_6]^{3-}$ in the reaction mixture at 420 nm in a placed in the cell compartment of an U.V.3000⁺ UV–visible spectrophotometer (Fig. 1). The application of Beer's law of HCF(III) at 420 nm had been verified giving $\epsilon = 1050 \text{ dm}^3/\text{mol/}$

Fig. 1 Spectral changes during the Cu(II) catalyzed oxidation of OFL by HCF(III) in alkaline medium at 40 °C. $[HCF(III)] = 1.0 \times 10^{-3} \text{ mol/dm}^3$, $[OFL] = 1.0 \times 10^{-2} \text{ mol/dm}^3$, $[Cu(II)] = 1.0 \times 10^{-3} \text{ mol/dm}^3$, $[OH^-] = 1.0 \text{ mol/dm}^3$ and $[NaNO_3] = 1.0 \text{ mol/dm}^3$

cm [20]. The pseudo first order plots in almost all the cases were linear up to 80% completion of the reaction and values of constants were reproducible within $\pm 6\%$.

3 Results

3.1 Stoichiometry and product analysis

The reaction mixture containing excess of HCF(III) over OFL were allowed for 12 h to react at 40 °C. The excess of HCF(III) concentration determined by measuring the absorbance at 420 nm. The stoichiometry of the reaction indicates Eq. 1 that 1 mol of OFL reacts with 2 mol of HCF(III) [21]. Results are obtained in the Table 1.

Table 1 Stoichiometry of Hexacyanoferrate(III) and ofloxacin in aqueous alkaline medium

[HCF(III)] (mol dm ⁻³)	[OFL] (mol dm ⁻³)	$\frac{\Delta[\text{OFL}]}{\Delta[\text{HCF(III)}]}$
0.001	0.0002	1:2
0.001	0.0003	1:2
0.001	0.0004	1:1.98
0.0012	0.0004	1:1.98

The remaining reaction mixture was extracted with ether. The main product, 9-fluoro-2, 3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazine-1-yl)-[1,4]oxazinoquinolon-7-one, was isolated, identified with the help of Thin Layer Chromatography (TLC) and characterized by FT-IR and LC-MS analysis. The FT-IR spectra of pure OFL, the (C=O) band of acid group is appears at 1718 cm⁻¹ and the carbonyl stretching of 7-oxo group appears at 1621 cm⁻¹. After oxidation, FT-IR spectra of product 9-fluoro-2,3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazine-1-yl)-[1,4]oxazinoquinolon-7-one, show this band at 1619 cm⁻¹, this was carbonyl stretching of 7-oxo group, a broad peak at 3457 cm⁻¹ is due to OH stretching and the carbonyl stretching of acid is disappear (Fig. 2). LC-MS analysis of

OFL oxidation product indicates the molecular ion of *m/z* 333 amu (Fig. 3). The *m/z* 333 corresponds to decarboxylation of quinolone ring and yield 9-fluoro-2, 3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazine-1-yl)-[1,4]oxazinoquinolon-7-one as oxidation product and the melting point of product was 205 °C [21]. Fe(II) another product was confirmed by the spectral change during the oxidation reaction at 510 nm (Fig. 1).

Fig. 2 Comparative FT-IR spectra of **a** pure ofloxacin, **b** oxidation product of ofloxacin by hexacyanoferrate(III) in aqueous alkaline medium

Fig. 3 LC-MS spectra of oxidation product of ofloxacin

3.2 Hexacyanoferrate (III) dependence

The concentration of HCF(III) was varied in the range (1×10^{-4} – 1×10^{-3} mol/dm³) at fixed concentration of OFL, alkali and ionic strength at 40 °C for uncatalyzed reaction. The variation of HCF(III) in presence of Cu(II) as catalyst were performed in same concentration of other reactants and conditions. 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 both uncatalyzed (k_{un}) and catalyzed reaction (k_c) (Fig. 4). Results are collected in Table 2.

3.3 Ofloxacin dependence

The concentration of OFL was varied from 0.5×10^{-2} to 5×10^{-2} mol/dm³ at fixed concentration of HCF, alkali and ionic strength at 40 °C for uncatalyzed reaction. The plot of pseudo first order rate constant (k_{un}) [OFL] yielded a straight line passing through the origin indicating first order dependence with respect to OFL (Table 2). The concentration of OFL in Cu(II) catalyzed reaction was varied from 0.5×10^{-2} to 5×10^{-2} mol/dm³ at three concentration of [OH[−]] viz. 0.5, 1.0, 1.5 mol/dm³ respectively and fixed concentration of other reactants and constant conditions. The value of pseudo first order rate constant (k_c) increases

Fig. 4 First order plots of the variation of HCF (III) concentration at 40 °C for Cu(II) catalyzed reaction. [OFL] = 1.0×10^{-2} mol/dm³, [OH[−]] = 1.0 mol/dm³, [Cu(II)] = 1.0×10^{-3} mol/dm³, [NaNO₃] = 1.0 mol/dm³ and [HCF] mol/dm³ = (A) 1×10^{-4} , (B) 2.5×10^{-4} , (C) 5×10^{-4} , (D) 7.5×10^{-4} , (E) 10×10^{-4}

at lower concentration of OFL then tends towards a limiting value at higher concentration of OFL (Table 2). The plot of $\log k_c$ versus $\log$ [OFL] shows the order with respect to the OFL was less than unity (0.663).

Table 2 Effect of variation of [HCF(III)], [OFL], [NaOH], [NaNO₃] and [Cu(II)] on the oxidation of OFL by HCF(III) in alkaline medium at 40 °C

10^4 [HCF(III)] (mol/dm ³)	10^2 [OFL] (mol/dm ³)	[NaOH] 10^3 (mol/dm ³)	10^3 [Cu (II)] (mol/dm ³)	[NaNO ₃] (mol/dm ³)	10^4 k_u (s ⁻¹) For uncatalyzed	10^4 k_c (s ⁻¹) For catalyzed
1.0	1.0	1.0	1.0	1.0	11.13	22.07
2.5	1.0	1.0	1.0	1.0	11.13	22.07
5.0	1.0	1.0	1.0	1.0	11.32	22.07
7.5	1.0	1.0	1.0	1.0	11.32	22.07
10	1.0	1.0	1.0	1.0	11.51	22.07
10	0.5	1.0	1.0	1.0	6.35	13.40
10	0.75	1.0	1.0	1.0	8.54	18.20
10	1.0	1.0	1.0	1.0	11.51	22.07
10	2.0	1.0	1.0	1.0	21.35	37.80
10	3.0	1.0	1.0	1.0	30.85	49.70
10	4.0	1.0	1.0	1.0	40.73	56.30
10	5.0	1.0	1.0	1.0	52.00	57.20
10	1.0	0.25	1.0	1.0	4.00	11.82
10	1.0	0.5	1.0	1.0	6.58	15.40
10	1.0	0.75	1.0	1.0	9.24	18.50
10	1.0	1.0	1.0	1.0	11.51	22.07
10	1.0	1.25	1.0	1.0	14.05	25.10
10	1.0	1.5	1.0	1.0	16.11	27.40
10	1.0	1.75	1.0	1.0	17.68	30.80
10	1.0	2.0	1.0	1.0	19.00	34.70
10	1.0	1.0	0.25	1.0	–	15.00
10	1.0	1.0	0.5	1.0	–	17.20
10	1.0	1.0	0.75	1.0	–	19.80
10	1.0	1.0	1.0	1.0	–	22.07
10	1.0	1.0	1.25	1.0	–	24.20
10	1.0	1.0	1.5	1.0	–	25.80
10	1.0	1.0	1.75	1.0	–	27.60
10	1.0	1.0	2.0	1.0	–	29.50
10	1.0	1.0	1.0	1.0	11.51	22.07
10	1.0	1.0	1.0	1.25	11.60	22.07
10	1.0	1.0	1.0	1.5	11.71	22.07
10	1.0	1.0	1.0	1.75	11.89	22.07
10	1.0	1.0	1.0	2.0	11.99	22.07

3.4 Hydroxyl ion dependence

Hydroxyl ion concentration was varied employing NaOH from 0.25 to 2.0 mol/dm³ at fixed concentration of other reactants and three temperatures viz 35, 40, 45 °C respectively. The rate initially increases and tends towards a limiting value with increasing concentration of hydroxide ion concentration in uncatalyzed reaction (Table 2). Similarly in case of Cu(II) catalyzed reaction the hydroxyl ion concentration was varied from 0.25 to 2.0 mol/dm³ employing sodium hydroxide at three different concentration of OFL viz 1×10^{-2} , 2×10^{-2} , 3×10^{-2} mol/dm³ respectively and fixed concentration of other reactants. First order rate constants (k_c) increases with increasing concentration of hydroxyl ion (Table 2).

3.5 [Cu(II)] ion dependence

Copper(II) ion concentration was varied from 0.25×10^{-3} to 2.0×10^{-3} mol/dm³ at three different concentration of OFL viz. 1×10^{-2} , 2×10^{-2} , 3×10^{-2} mol/dm³ respectively and fixed concentration of other reactants. The reaction rate increases with increasing concentration of Cu(II) ion (Table 2). A plot of rate constant (k_c) against [Cu(II)] yields a straight line with non-zero intercept that confirms to a simultaneous uncatalyzed reaction (Fig. 5).

3.6 Effect of ionic strength

Ionic strength in the reaction was varied employing sodium nitrite from 1.0 to 2.0 mol/dm³ at fixed

Fig. 5 Variation of copper ion at different ofloxacin concentration (A) 1.0×10^{-2} , (B) 2.0×10^{-2} , (C) 3.0×10^{-2} mol/dm³, [HCF] = 1.0×10^{-3} mol/dm³, $I = 2.0$ mol/dm³, $[\text{OH}^-] = 1.0$ mol/dm³, temp. = 40 °C

concentration of HCF, OFL, alkali at 40 °C for uncatalyzed reaction and at 1.0×10^{-3} mol/dm³ concentration of Cu(II) for catalyzed reaction. For uncatalyzed reaction increase in ionic strength increases the rate of reaction indicating the reaction between two ions of similar charges. However the effect of ionic strength did not exhibit in catalyzed reaction.

3.7 Effect of initially added product

The initially added products hexacyanoferrate(II) was studied in the range of 1×10^{-4} to 10×10^{-4} mol/dm³ while other reactants concentration and conditions constant, the rate of reaction was unaffected in uncatalyzed as well as catalyzed reaction.

3.8 Test of free radical (polymerisation test)

The possible intervention of free radicals during the oxidation reactions was examined by a polymerization test. A known quantity of acrylonitrile had been added in the reaction mixture. After 2 h diluting the reaction mixture with methanol, a white precipitate was formed, indicating the intervention of free radicals in the reaction. The same experiment was repeated in the absence of OFL under similar conditions, the test was negative. This confirms that the reaction was routed through free radical pathway [22].

4 Discussions

4.1 Mechanism for uncatalyzed reaction

Variation of concentration of each of the oxidant HCF(III), substrate OFL, base and ionic strength, while mainly the other concentration constant shows that the reaction is first order in oxidant, substrate and with respect to alkali in fractional order. The fractional order for $[\text{OH}^-]$ suggests deprotonation of ofloxacin by the alkali in a pre-equilibrium step to form a more reactive species of the reductant [23]. On the basis of stoichiometric and experimental results, a reaction mechanism can be prepared for which all the observed order in each constituent i.e. [Oxidant], [substrate] and $[\text{OH}^-]$ and ionic strength may be well accounted for.

In the present investigation, alkali combines first with OFL to give anionic form of OFL, in a pre-equilibrium step. The anionic form of OFL reacts 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.

The proposed mechanism leads to the rate law (5) accounting for an experimental observations.

$$\frac{-d[\text{Fe(III)}]}{dt} = \frac{K_1 k [\text{Fe(III)}][\text{OH}^-][\text{OFL}]}{1 + K_1 [\text{OH}^-]} \quad (5)$$

$$k_{un} = \frac{\text{Rate}}{[\text{Fe(III)}]} = \frac{K_1 k [\text{OH}^-][\text{OFL}]}{1 + K_1 [\text{OH}^-]} \quad (6)$$

$$\frac{k_{un}}{[\text{OFL}]} = k' = \frac{K_1 k [\text{OH}^-]}{1 + K_1 [\text{OH}^-]} \quad (7)$$

Rearrange the Eq. 7

$$\frac{1}{k'} = \frac{1}{K_1 k [\text{OH}^-]} + \frac{1}{k} \quad (8)$$

where k' is observed second order rate constant.

A plot of $1/k'$ versus $1/[\text{OH}^-]$ was made from the Eq. 8 at three different temperatures, that yielded at straight line with non-zero intercept (Fig. 6). The intercept gives the value of slow step (k) 27.86×10^{-2} , 36.50×10^{-2} , 47.17×10^{-2} dm³/mol/s at 35 °C, 40 °C, 45 °C respectively and the ratio of intercept and gradient gives the value of K_1 to be 38.64×10^{-2} , 48.07×10^{-2} , 63.28×10^{-2} dm³/mol at 35 °C, 40 °C, 45 °C respectively.

The activation energy of the reaction was calculated by plotting a graph between $\log k$ versus $1/T$ to be 42.12 KJ/mol [21] and the entropy of the reaction is determined by plotting a graph between $\log K_1$ versus $1/T$ to be

Scheme 1 Proposed mechanism for the uncatalyzed oxidation of OFL by HCF(III)

Fig. 6 Plot of $1/k'$ versus $1/[\text{OH}^-]$ at three different temperatures

– 126.95 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 [24].

4.2 Mechanism for Cu(II) catalyzed reaction

Copper (II) is known to be a catalyst in many redox reactions, particularly in alkaline medium [14] and catalysis has usually been explained by assuming the intermediate complex formed [25, 26] by an interaction of anionic form of OFL and Cu(II). This intermediate complex reacts with the oxidant in rate determining step, since order with respect to HCF(III) and Cu(II) is one each, the order with respect to OFL is fractional. Furthermore, rate also increases with increasing concentration of hydroxyl ion [27].

The reaction proceed more rapidly with the presence of copper(II) ion as a catalyst. These catalyzed reactions follow complex kinetics. Although catalysis by transition metal ions depends on the nature of the substrate, oxidant, and experimental conditions, that metal ions act as catalysts by one of several different paths, such as the formation of complexes with reactants, oxidation of the substrate itself or through the formation of free radicals. The present study deals with the title reaction in order to determine the selectivity of ofloxacin toward hexacyanoferrate(III) in an alkaline medium, to examine the catalytic activity of the copper(II)

catalyst, to understand the kinetically active species of the reactants, to identify the reaction products [28]. Thus a mechanism consisting of Scheme 2 and also accounting for experimental observations can be proposed.

Following rate law can be derived from Scheme 2

$$\text{Rate} = \frac{-d[\text{Fe(III)}]}{dt} = \frac{K_1 K_3 k [\text{Fe(III)}][\text{Cu(II)}][\text{OH}^-][\text{OFL}]}{K_2 + K_3 [\text{OFL}]} \quad (13)$$

$$k_c = \frac{K_1 K_3 k [\text{Cu(II)}][\text{OH}^-][\text{OFL}]}{K_2 + K_3 [\text{OFL}]} \quad (14)$$

where k_c is observed first order rate constant for catalyzed reaction. Since effect of Cu(II) ion on the rate also indicates

uncatalyzed path, the rate law (14) accounting for this path can be written as Eq. 7.

$$k'' = k_{un} + \frac{K_1 K_3 k [\text{Cu(II)}][\text{OH}^-][\text{OFL}]}{K_2 + K_3 [\text{OFL}]} \quad (15)$$

where $k'' = k_{un} + k_c$ is the total observed first order rate constant.

A plot of $(k'' - k_{un})$ versus $[\text{Cu(II)}]$ made from Eq. 15 at three different concentrations of yields straight line passing through the origin (Fig. 7). The gradient (G) of the line from Eq. 15 at constant hydroxyl ion concentration can be represented by Eq. 16

$$\text{Gradient (G)} = \frac{K_1 K_3 k [\text{OH}^-][\text{OFL}]}{K_2 + K_3 [\text{OFL}]} \quad (16)$$

Scheme 2 Proposed mechanism for the Cu(II) catalyzed oxidation of OFL by HCF(III)

Fig. 7 A plot of $(k'' - k_{un})$ versus $[Cu(II)]$ at different OFL concentrations at 40 °C. $[HCF(III)] = 1.0 \times 10^{-3}$ mol/dm³, $[OH^-] = 1.0$ mol/dm³, $[NaNO_3] = 1.0$ mol/dm³ and $[OFL]$ mol/dm³ = (A) 1×10^{-2} , (B) 2×10^{-2} , (C) 3×10^{-2}

Fig. 9 A plot of $(k'' - k_{un})$ versus $[OH^-]$ at different OFL concentrations at 40 °C. $[HCF(III)] = 1.0 \times 10^{-3}$ mol/dm³, $[Cu(II)] = 1.0 \times 10^{-3}$ mol/dm³, $[NaNO_3] = 1.0$ mol/dm³ and $[OFL]$ mol/dm³ = (A) 1×10^{-2} , (B) 2×10^{-2} , (C) 3×10^{-2}

which on further rearrangement yields Eq. 17

$$\frac{G}{[OH^-]} = \frac{K_1 K_3 k [OFL]}{K_2 + K_3 [OFL]} \quad (17)$$

Taking reciprocal of both the sides of Eqs. 17 and 18 is obtained

$$\frac{[OH^-]}{G} = \frac{K_2}{K_1 K_3 k [OFL]} + \frac{1}{K_1 k} \quad (18)$$

A plot of $[OH^-]/G$ versus $[OFL]^{-1}$ made from Eq. 18 also yielded a straight line with non-zero intercept (Fig. 8). The ratio of slope and intercept from Fig. 8 gives the value of K_2/K_3 to be 1.18×10^{-2} mol/dm³ at 2.0 mol/dm³ ionic

Fig. 8 A plot of $[OH^-]/G$ versus $1/[OFL]$ from variation of $[Cu(II)]$ at different OFL concentrations (reference Fig. 7)

strength at 40 °C. Similar plot of $(k'' - k_{un})$ versus $[OH^-]$ made from Eq. 15 at constant concentration of copper ion also yields a straight line passing through the origin (Fig. 9) with the gradient of the line as represented by Eq. 19.

$$G' = \frac{K_1 K_3 k [Cu(II)] [OFL]}{K_2 + K_3 [OFL]} \quad (19)$$

That on rearrangement further gives Eq. 20

$$\frac{[Cu(II)]}{G'} = \frac{K_2}{K_1 K_3 k [OFL]} + \frac{1}{K_1 k} \quad (20)$$

A plot of $[Cu(II)]/G$ versus $[OFL]^{-1}$ was also made from Eq. 20 also yielded a straight line with non-zero intercept (Fig. 10). The ratio of slope and intercept (K_2/K_3) from

Fig. 10 A plot of $[Cu(II)]/G$ versus $1/[OFL]$ from variation of $[OH^-]$ at different OFL concentrations (reference Fig. 9)

Table 3 Experimental and calculated ($k''-k_{un}$) in the $[OH^-]$ variation at different OFL concentration. $[HCF(III)] = 1.0 \times 10^{-3}$ mol/dm³, $[Cu(II)] = 1.0 \times 10^{-3}$ mol/dm³, $[NaNO_3] = 1.0$ mol/dm³, temperature = 40 °C

$10^2 [OFL]$ (mol/dm ³)	1.0×10^{-2}		2.0×10^{-2}		3.0×10^{-2}	
$[OH^-]$ (mol/dm ³)	$(k''-k_{un})_{exp} \pm SD$	$(k''-k_{un})_{cal}$	$(k''-k_{un})_{exp} \pm SD$	$(k''-k_{un})_{cal}$	$(k''-k_{un})_{exp} \pm SD$	$(k''-k_{un})_{cal}$
0.5	5.97 ± 0.17	6.22	6.99 ± 0.46	7.56	9.37 ± 0.04	9.43
0.75	9.07 ± 0.18	9.33	11.09 ± 0.17	11.34	15.37 ± 0.86	14.15
1.0	12.64 ± 0.13	12.45	14.89 ± 0.16	15.13	19.57 ± 0.49	18.87
1.25	15.67 ± 0.07	15.56	19.19 ± 0.19	18.91	22.67 ± 0.64	23.58
1.5	17.97 ± 0.49	18.67	22.69 ± 0.00	22.69	28.57 ± 0.19	28.30
1.75	21.37 ± 0.28	21.78	26.47 ± 0.00	26.47	33.47 ± 0.31	33.02
2.0	25.27 ± 0.26	24.90	30.26 ± 0.00	30.26	37.97 ± 0.16	37.74

Fig. 10 was calculated to be 1.01×10^{-2} mol/dm³. Thus the value of K_2/K_3 obtained from hydroxyl and copper ions variations are in good agreement.

These values of K_2/K_3 were further substituted in Eq. 15 and $(k''-k_{un})$ were calculated. The agreement between $(k''-k_{un})_{cal.}$ and $(k''-k_{un})_{exp.}$ as collected in Table 3 is an addition support to the mechanism and negation of (OFL^-) as the reactive species of OFL.

5 Conclusion

The uncatalyzed and Cu(II) catalyzed oxidation of OFL by HCF(III) in aqueous alkaline media was investigated. The observed stoichiometry indicates that, the oxidation of 1 mol of OFL requires 2 mol of HCF(III). The observed major product obtained by the decarboxylation of quinolone moiety and hence, it may retain the antibacterial activity. The product of the oxidation is antibacterial and the benefit of this study is that the degradation product has lower toxicity than pure ofloxacin. This study reduced potential side effects and increased antibacterial efficiency in the environment. The kinetic study indicates that in uncatalyzed 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 where as in catalyzed reaction, a mechanism was proposed via the formation of an intermediate complex between OFL and HCF(III) in presence of Cu(II) as catalyst. The Schemes 1 and 2 are consistent with all experimental findings, including the product and kinetic studies.

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Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

Appendix: Derivation of rate law for uncatalyzed reaction

According to the proposed mechanistic Scheme 1,

$$Rate = \frac{-d[Fe(III)]}{dt} = k[Freeradical] \quad (21)$$

$$K_1 = \frac{[OFL^-]}{[OFL][OH^-]}, [OFL^-] = K_1[OFL][OH^-] \quad (22)$$

and

$$k = \frac{[Freeradical]}{[OFL^-][Fe(III)]}, [Freeradical] = k[OFL^-][Fe(III)] \quad (23)$$

$$= K_1 k [OFL^-][Fe(III)][OH^-]$$

Substituting Eq. 23 into Eq. 21 leads to,

$$Rate = K_1 k [OFL^-][Fe(III)][OH^-] \quad (24)$$

The total concentration of OFL is given by,

$$[OFL]_T = [OFL] + [OFL^-] + [Freeradical] \quad (25)$$

where 'T' stands for total concentration.

Substituting Eqs. 22 and 3 into Eq. 25 and rearrangement gives,

$$[OFL]_T = [OFL] + K_1[OFL][OH^-] + K_1 k [OFL^-][Fe(III)][OH^-] \quad (26)$$

$$[OFL]_T = [OFL](1 + K_1[OH^-] + K_1 k [Fe(III)][OH^-]) \quad (27)$$

Therefore,

$$[OFL] = \frac{[OFL]_T}{1 + K_1[OH^-] + K_1 k [Fe(III)][OH^-]} \quad (28)$$

In view of the low [HCF], the third denominator term, $kK_1[\text{Fe(III)}][\text{OH}^-]$, in the above equation can be neglected.

Therefore,

$$[\text{OFL}] = \frac{[\text{OFL}]_T}{1 + K_1[\text{OH}^-]} \quad (29)$$

Also

$$[\text{HCF}]_T = [\text{HCF}] + [\text{Freeradical}] \quad (30)$$

Substituting Eq. 23 into Eq. 30 gives,

$$[\text{HCF}]_T = [\text{HCF}](1 + K_1k[\text{OFL}][\text{OH}^-]) \quad (31)$$

$$[\text{HCF}] = \frac{[\text{HCF}]_T}{1 + K_1k[\text{OFL}][\text{OH}^-]} \quad (32)$$

In view of the concentration of $[\text{OH}^-]$

$$[\text{OH}^-] = [\text{OH}^-]_T \quad (33)$$

Substituting Eqs. 29, 32 and 13 into Eq. 24 and omitting 'T' subscript gives,

$$\text{Rate} = \frac{K_1k[\text{OFL}][\text{Fe(III)}][\text{OH}^-]}{(1 + K_1[\text{OH}^-])(1 + K_1k[\text{OFL}][\text{OH}^-])} \quad (34)$$

In view of the low concentration of OFL used, the term $(1 + K_1k[\text{OFL}][\text{OH}^-])$ in the denominator of Eq. 34 is negligible. Therefore, Eq. 34 can be written as,

$$k_{un} = \frac{\text{Rate}}{[\text{Fe(III)}]} = \frac{K_1k[\text{OFL}][\text{OH}^-]}{1 + K_1[\text{OH}^-]} \quad (35)$$

The rate law for the copper(II) catalyzed reaction was also derived similarly.

References

- Kaur K, Kumar A, Malik AK, Singh B et al (2008) Spectrophotometric methods for the determination of fluoroquinolone: a review. *Crit Rev Anal Chem* 38:2–18
- Dasgupta G, Mahanti K (1986) Kinetics of oxidation of anilines by alkaline hexacyanoferrate (III). Oxidation of N-alkyl side chains. *Fr Bull Soc Chim* 4:492–496
- Farokhi SA, Nandibewoor ST (2003) Kinetic, mechanistic and spectral studies for the oxidation of sulfanilic acid by alkaline hexacyanoferrate(III). *Tetrahedron* 59:7595–7602
- Nowdari A, Adari KK, Gollapalli NR et al (2009) Kinetics and mechanism of oxidation of L-cystine by hexacyanoferrate(III) in alkaline medium. *Eur J Chem* 6:93–98
- Kelson EP, Phengsy PP (2000) Kinetic study of 2-propanol and benzyl alcohol oxidation by alkaline hexacyanoferrate (III) catalysed by a terpyridyl ruthenium complex. *Int J Chem Kinet* 32:760–770
- Vovk AI, Muraveval V, Kukhar VP et al (2000) Kinetics of oxidation of vitamin b_1 and its O-acyl analogs with ferricyanide—a mechanistic model of thiamine-binding protein. *Russ J Gen Chem* 70:1108–1112
- Speakman PT, Waters WA (1955) Kinetic features of the oxidation of aldehydes, ketones, and nitroparaffins with alkaline ferricyanide. *J Chem Soc.* <https://doi.org/10.1039/JR9550000040>
- Singh VN, Gangwar MC, Saxena BBL et al (1969) Kinetics and mechanism of the oxidation of formaldehyde by hexacyanoferrate(III) ion. *Can J Chem* 47:1051–1056
- Al-Subu MM (1992) Kinetics and mechanism of oxidation of diallylamine by alkaline hexacyanoferrate (III). *An-Najah J Res* 7:37–44
- Nath N, Singh LP (1985) Kinetics and mechanism of ruthenium(III)-catalyzed oxidation of benzylamine by hexacyanoferrate (III) in alkaline medium. *J Indian Chem Soc* 62:108–111
- Das AK (2001) Kinetic and mechanistic aspects of metal ion catalysis in cerium(IV) oxidation. *Coord Chem Rev* 213:307
- DiabN Abu-Shquair I, Al-Subei M et al (2013) Kinetics of oxidation of some fluoroquinolone by hexacyanoferrate(III) in aqueous alkaline medium. *Int J Chem* 4:1388–1394
- Meti MD, Bayadgi KS, Nandibewoor ST et al (2014) Mechanistic studies of uncatalyzed and ruthenium(III)-catalyzed oxidation of the antibiotic drug chloramphenicol by hexacyanoferrate(III) in aqueous alkaline medium: a comparative kinetic study. *Montash Chem* 145:1561–1573
- Sateesh BC, Shastri V, Shashidhar S et al (2013) Copper catalyzed oxidation of omeprazole by hexacyanoferrate in alkaline medium: a kinetic and mechanistic study. *Int J Res Phys Chem* 3:18–23
- Singh AK, Srivastava S, Srivastava J et al (2007) Kinetics and mechanism of oxidation of D-glucose and D-fructose by alkaline solution of potassium oxide in the presence of Ru(III) as homogeneous catalyst. *J Mol Catal A Chem* 278:72–81
- Devra V, Jain A, Jain S (2014) Kinetic analysis of oxidation of ofloxacin by permanganate in sulphuric acid medium: a mechanistic approach. *World J Pharm Res* 4:963–977
- Hubicka U, Zmudzki P, Witek BZ et al (2013) Separation and characterization of ciprofloxacin, difloxacin, lomefloxacin, norfloxacin, and ofloxacin oxidation products under potassium permanganate treatment in acidic medium by UPLC-MS/MS. *Talanta* 109:91
- Jeffery GH, Bassett J, Mendham J et al (1996) Vogel's text book of quantitative chemical analysis, 5th edn. ELBS, Longman, Essex, p 339
- Yerneni KK, Cholkar K, Guin M et al (2015) Oxidation of glycylglycine by ferricyanide in acid medium: kinetics and mechanism. *Cogent Chem* 1:1087296
- Nowduri A, Duggada AB, Kurimella VR (2014) Kinetics and mechanism of oxidation of labetalol by hexacyanoferrate(III) in alkaline medium. *Int J Sci Res* 3:131–133
- Patgar MB, Nandibewoor ST, Chimatadar SA (2015) Spectroscopic investigation of the oxidation of levofloxacin by hexacyanoferrate (III) in aqueous alkaline medium—a kinetic and mechanistic approach. *Cogent Chem* 1:1–14. <https://doi.org/10.1080/23312009.2015.1088778>
- Jagdeesh RV, Puttuswamy (2008) Ru(III), Os(VIII), Pd(II) and Pt(IV) catalyzed oxidation of glycylglycine by sodium-N-chloro-p-toluenesulfonamide: comparative mechanistic aspects and kinetic modelling. *J Phys Org Chem* 21:844–858
- Fawzy A, Zaafarany I, Yarkandi N et al (2016) Science kinetic and mechanism of oxidation of methylaminopyrazole formamidine by alkaline hexacyanoferrate(III) and the effect of divalent transition metal ions. *J Chem* 4:1–8
- Khan AAP, Mohd A, Bano S (2011) Kinetics and mechanism of deamination and decarboxylation of 2-aminopentanedioic acid by quinolinium dichromate (QDC) in aqueous perchloric acid medium. *Ind Eng Chem Res* 50:9883–9889

25. Wilberg KB, Nigh WG (1965) The kinetics of the cupric ion oxidation of α -hydroxyacetophenone. *J Am Chem Soc* 87:3849–3855
26. Kochi JK, Graybill BM, Kurz M (1964) Reactions of peroxides with halide salts. Electrophilic and hemolytic halogenations. *J Am Chem Soc* 86:5257–5264
27. Tazwar G, Jain A, Mittal N, Devra V (2017) Oxidation of ciprofloxacin by hexacyanoferrate (III) in the presence of Cu(II) as a catalyst: a kinetic study. *Int J Chem Kinet* 49:534–542
28. Basim H, Asghar Hatem M, Altass Ahmed Fawzy (2017) Copper(II) catalysis for oxidation of L-tryptophan by hexacyanoferrate(III) in alkaline medium: a kinetic and mechanistic approach. *J Saudi Chem Soc* 21:887–898

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