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CATALYTIC OXIDATION OF LEVOFLOXACIN BY HEXACYANOFERRATE (III) IN AQUEOUS ALKALINE MEDIUM: A KINETIC STUDY

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ABSTRACT

The Cu(II) catalyzed oxidation of levofloxacin by hexacyanoferrate(III) has been investigated spectrophotometrically in an aqueous alkaline medium at 25˚C. The stoichiometry for the reaction indicates that, the oxidation of one mole of levofloxacin requires two moles of hexacyanoferrate(III). The reaction exhibited first order kinetics with respect to [hexacyanoferrate(III)] and less than unit order with respect to [levofloxacin] and [OH¯]. The products were also identified on the bases of stoichiometric results and confirm by the characterization results of LC-MS analysis. All the possible reactive species of the reactants have been discussed and a most probable kinetic model has been envisaged. The activation parameters with respect to the slow step of the mechanism were computed and thermodynamic quantities were also determined.

Keywords: Cu(II) catalysis, Hexacyanoferrate(III), Kinetics, Mechanism, Oxidation.

I. INTRODUCTION

In the past few decades, there has been great concern on pharmaceuticals waste which is a key source of impurities in the aquatic ecosystem, ground water and soil, and which leads to the bacterial resistance against antibiotics even at their low concentrations [1]. Fluoroquinolones are anthropogenic contaminants which are comprehensively used as pharmaceuticals for both human and veterinary purposes [2]. Due to their extensive usage, fluoroquinolones may enter in the environment via waste water effluent and bio solids from sewage treatment plants. The presence of pharmaceuticals including in the surface water is an emerging environmental issue and provides a new challenge to engineers and scientists dealing with drinking water, waste water and water reuse systems [3]. There are studies on the modified pharmacological and toxicological properties of these drugs in the form of metallic complexes [4-6].

Levofloxacin (LF), (-)-(S)-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 hemihydrates "Fig. 1", is one of the commonly used third-generation fluoroquinolone antimicrobials, being the active S-isomer isolated from racemic ofloxacin and is twice as active as the parent drug.

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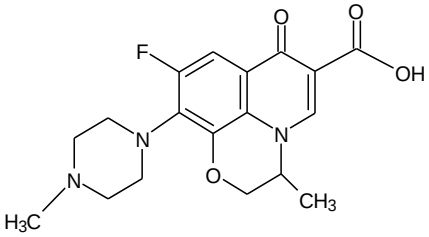

Fig.1 Structure of levofloxacin (LF).

Levofloxacin is a broad spectrum drug of activity against various bacteria, including gram-positive and gram-negative microorganisms [7, 8]. Because of its effective antibacterial activity and low frequency of adverse effects on oral administration, levofloxacin has been widely used for the treatment of infectious diseases, such as community-acquired pneumonia and acute exacerbation of chronic bronchitis [9].The interaction of fluoroquinolone with metal ions is of interest not only for the development of analytical techniques but also to afford information about the mechanism of action of the pharmaceutical preparation [10]. The increase of fluoroquinolone in aquatic environments, even in low concentration, may cause intimidation to the ecosystem and human health by including the multiplication of drug resistance bacteria owing to long term exposure [11].

In recent years the use of transition metal ion such as ruthenium, osmium, palladium, manganese, chromium, iridium and copper as catalyst in various redox processes has attracted considerable interest [12-14]. Copper (II) is act as a catalyst has been reported in the oxidation of omeprazole by hexacyanoferrate(III) [15]. It has been shown [16] 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. The mechanism of the catalysis depends on the nature of substrate, oxidant and experimental conditions.

Hexacyanoferrate (III) (HCF) [17], a one electron oxidant with a redox potential of +0.45V for the $[Fe(CN)_6]^{-3}$/ $[Fe(CN)_6]^{-4}$ couple in alkaline medium leading to its reduction to hexacyanoferrate(II) [18,19].In most of the oxidations, HCF is mainly used as hydrogen atom abstractor [20, 21] and free radical generator [22]. HCF is a transition metal complex, consisting of a central iron ion, surrounded by six negative cyanide ions, or ligands, in an octahedral arrangement. A literature survey revealed that the kinetics and mechanism of oxidation of some drugs by HCF in alkaline media have been studied [14, 23-25]. The oxidative study of Levofloxacin has been effectuated by various oxidants in aqueous acidic/alkaline media [25, 26] but the lack of literature on the catalytic oxidation of LF by HCF in alkaline medium so the title reaction is undertaken to understand the mechanism of the reaction and active species involved in Cu(II) catalyzed reaction.

II. MATERIALS AND METHODS

2.1 Chemicals

All chemicals used in this investigation were of analytical grade. Reaction solutions were prepared using double distilled water. Solution of levofloxacin (KORES India Limited) was always freshly prepared before experiment. A stock solution of oxidant, hexacyanoferrate(III) was prepared by dissolving $K_3[Fe(CN)_6]$ (BDH) in double distilled water and standardizing the solution iodometrically [27]. Copper sulphate was also prepared

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in double distilled water and standardized by standard method. Corning glassware was employed both for storing the solutions and the kinetics of the reaction unless specified otherwise.

2.2 Instrumentation

For kinetic measurements, a Peltier accessory (temperature-Controlled) attached to a U.V.3000$^+$ UV-Visible spectrophotometer (LABINDIA) was used. For product analysis, LC-ESI-MS, (Q-TOF Micromass, WATERS Company, UK), Alpha-T FTIR spectrophotometer (BRUKER, Germany), were used.

2.3 Kinetic measurements

All kinetic measurements were conducted under pseudo first order conditions, where [LF] was always in excess over [HCF], at a constant ionic strength in alkaline medium at temperature of 25±1ºC. The reaction was initiated by mixing the thermostatted solutions of HCF and LF which also contained the required concentration of Cu(II), NaOH and $NaNO_3$. The progress of the reaction was followed by observing the absorbance of $[Fe(CN)_6]^{3-}$ in the reaction mixture at 420 nm in a placed in the cell compartment of an UV-Visible spectrophotometer. Pseudo-first-order rate constant (k_c) was calculated from the plot of the logarithm of absorbance versus time. The pseudo first order plot was linear up to 80% completion of the reaction and k_{obs} value was reproducible within ±6%.

2.4 Stoichiometry and product analysis

The stoichiometry of the reaction was determined with various ratio of reactants in the presence of Cu(II) as catalyst and constant concentration of NaOH and $NaNO_3$ were kept for 24 hours at 25ºC in a closed vessel. The results indicated that one mole of LF reacts with two mole of HCF as given in the following “equation 1”

(1)

The products were extracted from the reaction mixture with ether. The main product (-)-(S)-9-fluoro-6-hydroxy-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7H-pyrido [1,2,3-de]-1,4-benzoxazin-7-one hemihydrates, was identified with the help of TLC and characterized by LC-MS analysis. LC-MS analysis of LF oxidation reaction indicates the formation of product with molecular ion of m/z 333 amu “Fig.2”. The m/z 333 amu corresponds to decarboxylation of quinolones ring and yield (-)-(S)-9-fluoro-6-hydroxy-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7H-pyrido[1,2,3-de]-1,4-benzoxazin-7-one hemihydrates as oxidation product.

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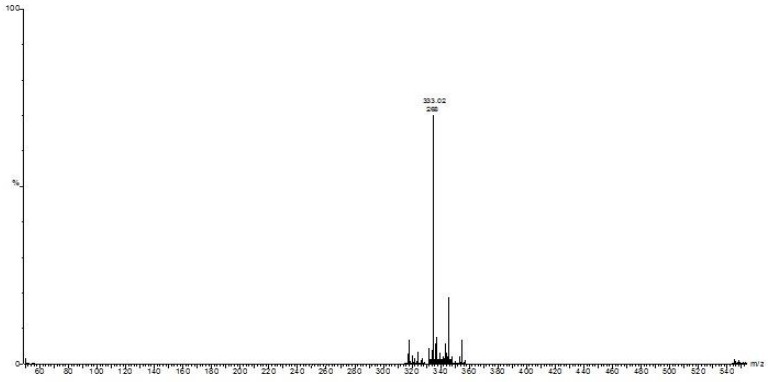

Fig.2 LC-ESI-MS spectra of oxidation product of levofloxacin.

III. RESULTS

3.1 Hexacya no ferrate (III) dependence

The oxidant hexacyanoferrate(III) [HCF] concentration in Cu(II) catalyzed reaction was varied from1.0×10^{-4} to 1.0×10^{-3} moldm^{-3}, and all other reactant concentrations and conditions were constant. The plot of log absorbance versus time was linear indicating that the reaction is first order with respect to [HCF]. The observed pseudo first order rate constant (k_{obs}) was independent of the concentration of HCF.

3.2 Levofloxacin Dependence

The effect of different concentration variation of LF in Cu(II) catalyzed reaction on the rate of reaction was studied in the range 0.5×10^{-2} to 5×10^{-2} mol dm^{-3} at constant concentration of HCF, Cu(II), alkali and ionic strength at 20˚, 25˚, 30˚C respectively. The rate of reaction increases with increasing concentration of LF "TABLE 1". A plot of log k_{obs} versus log [LF] was linear with a slope of 0.73, thus indicating a fractional-order dependence on LF concentration.

3.3 Hydroxyl ion dependence

The effect of concentration variation of sodium hydroxide in Cu(II) catalyzed reaction on the rate of reaction was studied in the concentration range 0.2 to 1.4 mol dm^{-3} at fixed concentration of HCF, LF, Cu(II) and ionic strength at three temperatures viz. 20˚, 25˚, 30˚C respectively. Pseudo first-order rate constant (k_{obs}) was found to be increased with increase in [OH^-] "TABLE 1". A plot of log k_{obs} versus log [OH^-] was linear with a fractional slope of 0.64.

3.4 [Cu (II)] ion dependence

The concentration of Cu(II) catalyst was varied from 0.25×10^{-3} to 2.0×10^{-3} mol dm^{-3} at three different concentration of LF viz. 0.5×10^{-2}, 1×10^{-2}, 2×10^{-2} mol dm^{-3} respectively at constant [HCF], [OH^-], ionic strength and temperature. The rate constant (k_{obs}) increases with increasing [Cu(II)] "TABLE 1".

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3.5 Effect of ionic strength and dielectric constant

At constant concentration of reactants, the ionic strength was varied by varying concentration of sodium nitrate 1.0 to 2.0 mol dm^{-3} at 25˚C. Ionic strength had negligible effect on the rate of reaction. At constant acidity and other constant conditions, as the t-butyl alcohol content increase from 0 to 50% (v/v) in the reaction, change in dielectric constant had negligible effect on the rate of reaction.

3.6 Effect of added product

The initial added products, 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.

3.7 Test for Free Radical

The formation of free radical was confirmed by the addition of acrylonitrile in the reaction mixture. After 5 hours then diluted with methanol, white precipitate was formed, indicating the presence of free radical during the progress of reaction.

TABLE 1: Effect of variation of [HCF], [LF], [NaOH] and [Cu(II)] on the oxidation of levofloxacin by alkaline hexacyanoferrate(III) at 25°c and I=2.0 mol dm^{-3}

10^4 [HCF] (mol dm^{-3})	10^2 [LF] (mol dm^{-3})	[NaOH] (mol dm^{-3})	10^3 [Cu(II)] (mol dm^{-3})	$10^4 k_{obs}$ (sec^{-1})
1.0	1.0	1.0	1.0	20.50
2.5	1.0	1.0	1.0	20.00
5.0	1.0	1.0	1.0	20.00
7.5	1.0	1.0	1.0	20.00
10	1.0	1.0	1.0	20.00
10	0.5	1.0	1.0	09.50
10	0.75	1.0	1.0	14.08
10	1.0	1.0	1.0	22.00
10	2.0	1.0	1.0	32.10
10	3.0	1.0	1.0	46.70
10	4.0	1.0	1.0	55.22
10	5.0	1.0	1.0	54.78
10	1.0	0.2	1.0	05.80
10	1.0	0.4	1.0	10.80
10	1.0	0.6	1.0	14.60
10	1.0	0.8	1.0	18.05
10	1.0	1.0	1.0	21.00
10	1.0	1.2	1.0	22.12
10	1.0	1.4	1.0	23.25

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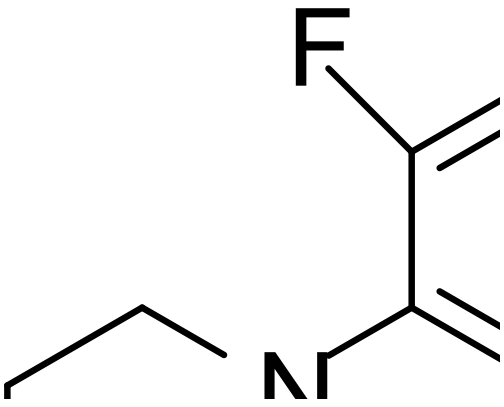
10	1.0	1.0	0.25	03.05
10	1.0	1.0	0.5	06.50
10	1.0	1.0	0.75	12.50
10	1.0	1.0	1.0	18.60
10	1.0	1.0	1.25	24.50
10	1.0	1.0	1.5	31.50
10	1.0	1.0	1.75	35.60
10	1.0	1.0	2.0	42.02

IV. DISCUSSION

Cu(II) is known to be a catalyst in many redox reactions, particularly in alkaline medium [15] and catalysis has usually been explained by assuming the intermediate complex formed by an interaction of anionic form of LF and Cu(II). This intermediate complex reacts with the oxidant in rate determining step, since order with respect to HCF and Cu(II) is one each and less than unit order with respect to[LF]. Furthermore, rate also increases with increasing of hydroxyl ion with fractional first order dependence. Thus a mechanism consisting of scheme and also accounting for all experimental observations can be proposed as follows:



Scheme 1: Proposed mechanism for the Cu(II) catalyzed oxidation of LF by HCF(III) in alkaline medium.

Following rate law can be derived from the above "scheme1":

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$$Rate = \frac{-d[HCF]}{dt} = k[C][HCF]$$

(2)

$$K_1 = \frac{[LF^-]}{[LF]_F[OH^-]_F}$$

(3)

$$[LF^-] = K_1[LF]_F[OH^-]_F$$

$$K_2 = \frac{[C]}{[LF^-][Cu(II)]_F}$$

$$[C] = K_2[LF^-][Cu(II)]_F$$

$$[C] = K_1K_2[LF]_F[OH^-]_F[Cu(II)]_F$$

(4)

Substituting “equation 4” into “equation 2” leads to,

$$Rate = kK_1K_2[LF]_F[OH^-]_F[Cu(II)]_F[HCF]$$

(5)

The total concentration of LF is given by,

$$[LF]_T = [LF]_F + [LF^-] + [C]$$

(6)

where ‘T’ and ‘F’ stand for total and free concentrations.

Substituting “equations 3 and 4” into “equation 6” and rearrangement gives,

$$[LF]_T = [LF]_F + K_1[LF]_F[OH^-]_F + K_1K_2[LF]_F[OH^-]_F[Cu(II)]_F$$

(7)

$$[LF]_T = [LF]_F\{1 + K_1[OH^-]_F + K_1K_2[OH^-]_F[Cu(II)]_F\}$$

(8)

Therefore,

$$[LF]_F = \frac{[LF]_T}{1 + K_1[OH^-]_F + K_1K_2[OH^-]_F[Cu(II)]_F}$$

(9)

In view of low $[Cu(II)]_F$, the third denominator term $K_1 K_2[OH^-] [Cu(II)]$ in the above equation can be neglected. Therefore, “equation 9” can be simplified to the following,

$$[LF]_F = \frac{[LF]_T}{1 + K_1[OH^-]_F}$$

(10)

The concentration of Cu(II) can be calculated as,

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$$[Cu(II)]_T = [Cu(II)]_F + [C]$$

(11)

$$[Cu(II)]_T = [Cu(II)]_F \{1 + K_1 K_2 [LF]_F [OH^-]_F\}$$

(12)

$$[Cu(II)]_F = \frac{[Cu(II)]_T}{1 + K_1 K_2 [LF]_F [OH^-]_F}$$

(13)

Regarding to the concentration of OH^-,

$$[OH^-]_F = [OH^-]_T$$

(14)

Substituting "equations 10, 13 and 14" into "equation 15" (and omitting 'T' and 'F' subscripts) leads to,

$$Rate = \frac{kK_1 K_2 [LF][OH^-][Cu(II)][HCF]}{\{1 + K_1 [OH^-]\}\{1 + K_1 K_2 [LF][OH^-]\}}$$

(15)

$$Rate = \frac{kK_1 K_2 [LF][OH^-][Cu(II)][HCF]}{1 + K_1 [OH^-] + K_1 K_2 [LF][OH^-] + K_1^2 K_2 [LF][OH^-]^2}$$

(16)

The term $K_1^2 K_2 [LF][OH^-]^2$ in the denominator of "equation 16" is negligibly small compared to unity in view of the low concentration of LF used.

Therefore "equation 16" can be written as,

$$Rate = \frac{kK_1 K_2 [LF][OH^-][Cu(II)][HCF]}{1 + K_1 [OH^-] + K_1 K_2 [LF][OH^-]}$$

(17)

Under Pseudo-first order condition, the rate-law can be expressed by "equation 18",

$$Rate = \frac{-d[HCF]}{dt} = k_{obs}[HCF]$$

(18)

Therefore, comparing "equation 17 and 18", the following relationship is obtained,

$$k_{obs} = \frac{Rate}{[HCF]} = \frac{kK_1 K_2 [LF][OH^-][Cu(II)]}{1 + K_1 [OH^-] + K_1 K_2 [LF][OH^-]}$$

(19)

"Equation 17" can be rearranged to the following forms, which is suitable for verification,

$$\frac{[Cu(II)]}{k_{obs}} = \left[\frac{1}{kK_1 K_2 [OH^-]} + \frac{1}{kK_1}\right]\frac{1}{[LF]} + \frac{1}{k}$$

(20)

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$$\frac{[Cu(II)]}{k_{obs}} = \left[\frac{1}{kK_1K_2[LF]}\right]\frac{1}{[OH^-]} + \frac{1}{kK_2[LF]} + \frac{1}{k}$$

(21)

According to "equation 20" the plot of $[Cu(II)]/k_{obs}$ versus 1/ [LF] "Fig.3" is linear with positive intercept and slope at three different temperatures. The rate constant k, of the slow step, "scheme 1" was obtained from the intercept of the plots $[Cu(II)]/k_{obs}$ versus 1/ [LF]). The energy of activation was determined by the plot of log k versus 1/T from which activation parameters were calculated. Also, the values of the equilibrium constants associated with the mechanistic "scheme 1" ($K_1$and K_2) are evaluated from the intercept and slope of the plots of $[Cu(II)]/k_{obs}$ versus 1/ [LF] and $[Cu(II)]/k_{obs}$ versus 1/ $[OH^-]$ "Fig.4 ". The value of equilibrium constant K_1 is in good agreement with earlier work [14] at 25˚C. Thermodynamic quantities were calculated from the Van't Hoff plot.

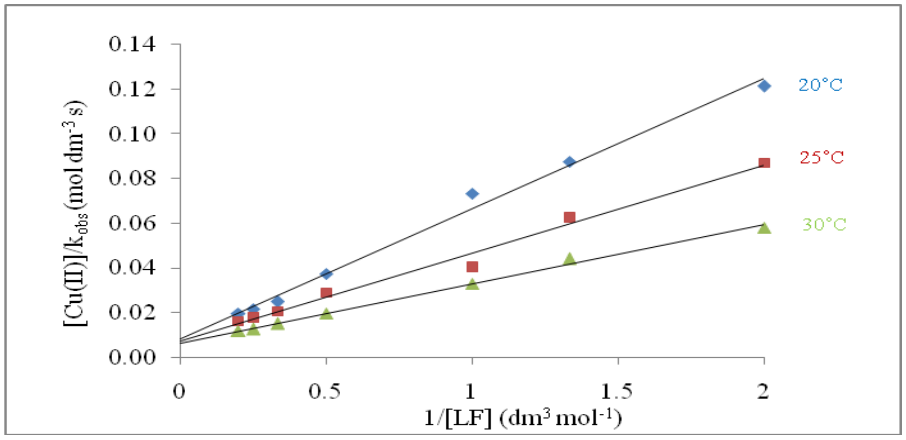

Fig.3 Plots of [Cu (II)]/k_{obs} versus 1/ [LF] at three different temperatures.

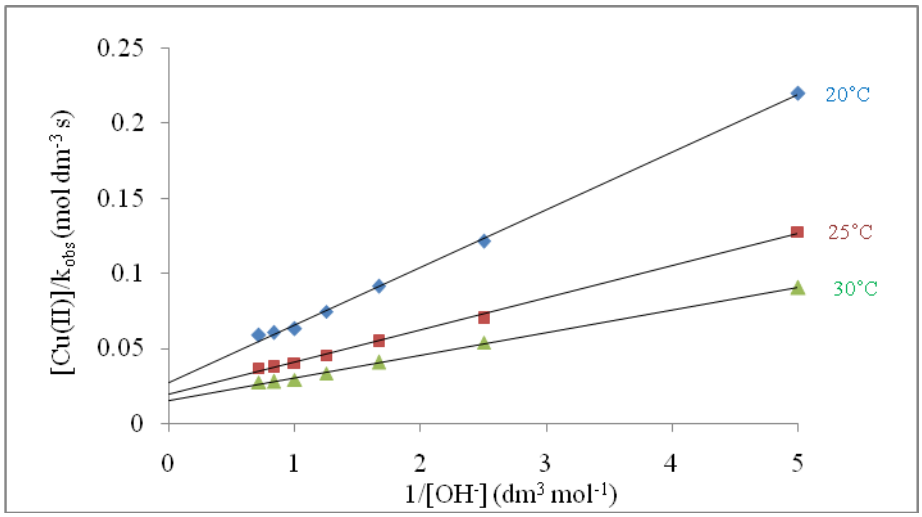

Fig.4 Plots of [Cu(II)]/k_{obs} versus 1/ [OH^-] at three different temperatures.

The entropy of activation ($\Delta S^{\neq}$) tends to be more negative for reaction of an inner-sphere nature, where as the reactions of positive $\Delta S^{\neq}$ values proceed via an outer-sphere mechanism [28]. The obtained large negative

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values of $\Delta S^{\neq}$ (-195 JK^{-1} mol^{-1}) express that the mechanism is one-electron transfer of inner-sphere nature which indicate that there is a decrease in the randomness during the reaction process. This leads to the formation of intermediate complex andsuch activated complex is more ordered than the reactants due to loss of degree of freedom. Whether, the positive value of $\Delta H^{\neq}$ (18.05 kJ mol^{-1}) indicates that the complex formation is endothermic and the value of $\Delta G^{\neq}$ (80.50 kJ mol^{-1}) suggests enhanced formation of the intermediate with raising temperature as well as to the non-spontaneity of the complex formation.

V. CONCLUSION

Cu(II) catalyzed oxidation of levofloxacin by hexcyanoferrate(III) in aqueous alkaline medium was found to be first order with respect to oxidant and fractional order with respect to substrate and alkali. The reaction pathway involves complex formation and free radical mechanism. The observed stoichiometry indicates that, the oxidation of one mole of levofloxacin requires two moles of hexacyanoferrate(III). The major product of reaction obtained by the decarboxylation of quinolones moiety and hence, it may retain the antibacterial activity. Thus the degradation of fluoroquinolones plays an important role in the field of waste water treatment. The overall sequence described here is consistent with all experimental findings, including the product, mechanistic and kinetic studies.

VI. ACKNOWLEDGMENT

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