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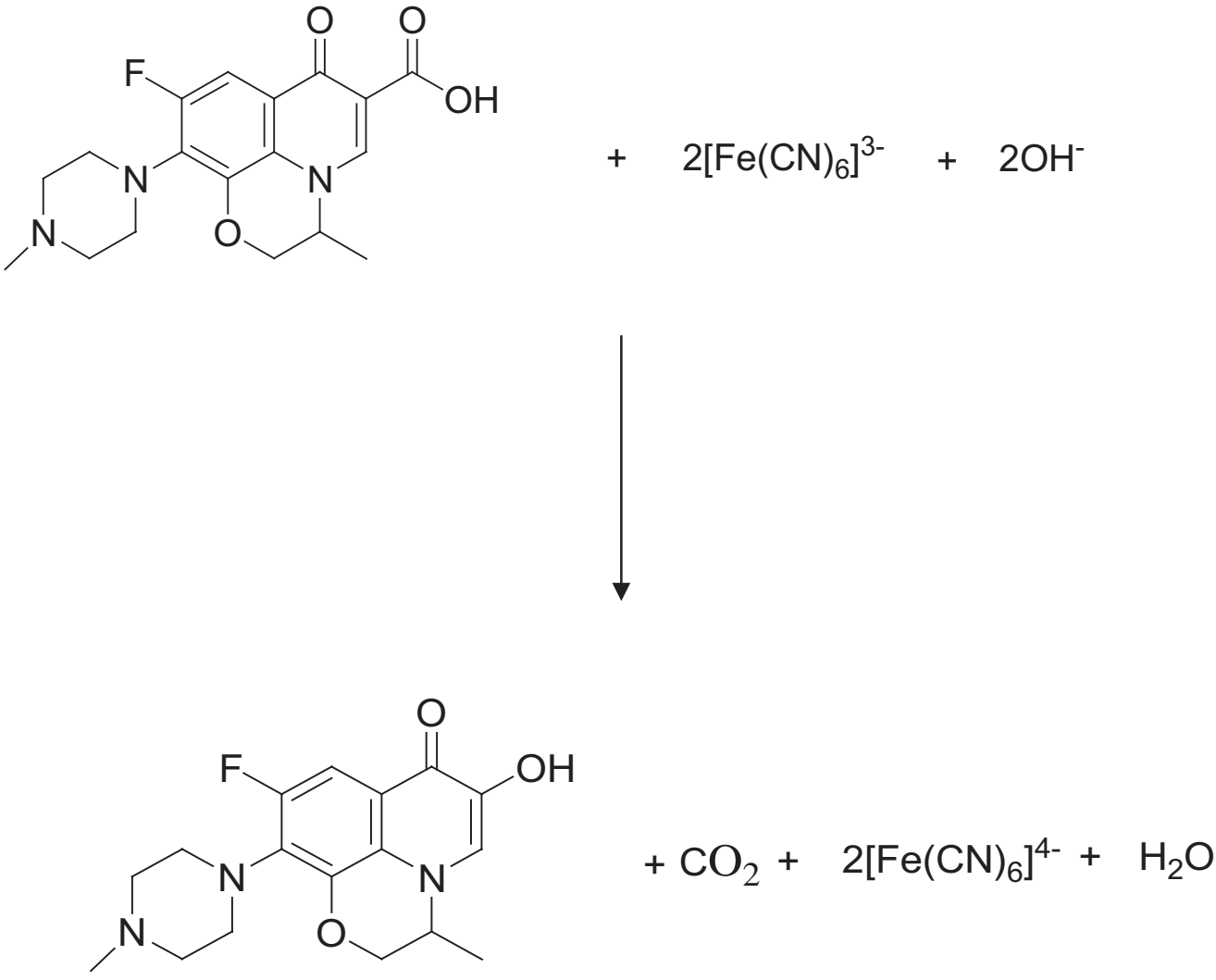

PHYSICAL CHEMISTRY | RESEARCH ARTICLE

Spectroscopic investigations of the oxidation of levofloxacin by hexacyanoferrate(III) in aqueous alkaline medium—A kinetic and mechanistic approach

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Spectroscopic investigations of the oxidation of levofloxacin by hexacyanoferrate(III) in aqueous alkaline medium—A kinetic and mechanistic approach

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Abstract: Kinetics and mechanism of oxidation of levofloxacin (LF) by hexacyanoferrate(III) in aqueous alkaline medium at constant ionic strength of 1.10 mol dm^{-3} is studied spectrophotometrically. The reaction exhibits, 2:1, $[Fe(CN)_6]^{3-}$:levofloxacin, stoichiometry. The main products identified are 9-fluoro-2,3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4]oxazino[2,3,4-ij] quinolin-7-one and $[Fe(CN)_6]^{4-}$ were isolated and identified with the help of TLC and characterized by FT-IR and GCMS. The reaction is first order in hexacyanoferrate(III) concentration but fractional order in both levofloxacin and alkali concentrations. Decrease in the dielectric constant of the medium results in a decrease in the rate of reaction. The effects of added products and ionic strength have also been investigated. A mechanism involving free radicals is proposed. In a composite equilibrium step, levofloxacin binds to hexacyanoferrate(III) to form a complex that subsequently decomposes to the products. Investigations of the reaction at different

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PUBLIC INTEREST STATEMENT

This paper demonstrate the kinetic study of oxidation of levofloxacin by hexacyanoferrate(III) in alkaline medium. In view of commercial and effective antibacterial activity and low frequency of adverse effects on oral administration of levofloxacine, such oxidation studies may throw some light on the mechanism of conversion of the compounds into biological systems. The present study deals with the title reaction in order to investigate the redox chemistry of $[Fe(CN)_6]^{3-}$ in alkaline medium and to compute the thermodynamic quantities of varies steps involved in the mechanism to those derived on the basis of kinetic and spectroscopic results.

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temperatures allowed the determination of the activation parameters with respect to the slow step of the proposed mechanism.

Subjects: Food Science & Technology; Medicine, Dentistry, Nursing & Allied Health; Physical Sciences

Keywords: kinetics; mechanism; levofloxacin; hexacyanoferrate(III)

1. Introduction

Hexacyanoferrate(III) is a transition metal complex, consisting of a central iron ion, surrounded by six negative cyanide ions, or ligands, in an octahedral arrangement. Iron is a transition metal, and transition metal complexes and ions are often coloured. The reason for colour is the loss of degeneracy of the d orbitals. It acts as oxidants in basic, acidic and neutral medium. Hexacyanoferrate(III) is also one of an oxidants and has been widely used to oxidize numerous organic and inorganic compounds in basic, acidic and neutral medium (Kelson & Phengsy, 2000; Vovk, Muraveva, Kukhar, & Baklan, 2000). The oxidation capacity completely depends on their redox potential (Day & Selbin, 1964). Hexacyanoferrate(III) is a one electron oxidant with a redox potential of couple $[Fe(CN)_6]^{3-}/Fe(CN)_6]^{4-}$ is +0.36 V in acidic medium and +0.45 V in basic medium. In most of the oxidations, hexacyanoferrate(III) is mainly used as hydrogen atom abstractor (Kelson & Phengsy, 2000; Martinez, Pitarque, & van Eldik, 1996) and/or free radical generator (Svehla, 2002). Hexacyanoferrate(III), due to its strong oxidizing properties, has been extensively employed as reagent in analytical investigation of many compounds like hydrazine hydrate, atropine sulphate and arginine (Meti, Nandibewoor, & Chimatadar, 2014; Goel & Sharma, 2012), esters (Hussaina, Agrawal, & Pakhare, 2011), etc. The oxidation of levofloxacin by different oxidants like Cr(VI), Ce(IV) and diperiodatocuprate(III) (DPC) were tried in both alkaline and acid medium, but the reaction rate was not measurable. However, the reaction is facile only when hexacyanoferrate(III) is used as an oxidant in alkaline medium.

Levofloxacin(LF), (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7Hpyrido [1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate, is one of the commonly used fluoroquinolone antimicrobials, being the active S-isomer isolated from racemic ofloxacin. Levofloxacin possesses a broad spectrum of activity against various bacteria, including Gram-positive and Gram-negative microorganisms (Croisier et al., 2004). It is also active against the causes of a typical respiratory infection such as *Chlamydia pneumoniae* and *Mycoplasma pneumonia* (Roblin & Hammerschlag, 2003). 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 (Owens & Ambrose, 2000). The antibacterial action of the quinolones is not linearly proportional to their concentration, and the optimum concentration must be maintained to prevent the surviving bacteria from regrowing (Shul'gina, Fadeeva, Bol'shakova, Levshin, & Glushkov, 1999).

The oxidation of levofloxacin was done using the oxidants such as permanganate (Aftab Aslam, Ayaz, Shaista, Ahmad, & Siddiqi, 2010) and chloroamine-T (Aftab Aslam et al., 2012). In view of the pharmaceutical importance of levofloxacin and lack of literature on the oxidation of levofloxacin by hexacyanoferrate(III) in alkaline medium, the title reaction is undertaken to understand the mechanism of the reaction and active species involved.

2. Experimental

2.1. Materials and reagents

The materials employed in the present work were of analytical reagent grade. All stock solutions were prepared in Millipore water. The stock solution of levofloxacin (Sigma-Aldrich) was prepared by dissolving a known amount of its hydrochloride salt in Millipore water. Solutions of levofloxacin were always freshly prepared before use. The stock solution of the oxidant, hexacyanoferrate(III), was prepared by dissolving $K_3Fe(CN)_6$ (SISCO CHEM) in Millipore water and the solution was standardized

iodometrically (Gregory, Jeffrey, Lauren, & Marvin, 2011). The hexacyanoferrate(II) solution was prepared by dissolving a known amount of $K_4Fe(CN)_6$ (s.d. fine-Chem) in Millipore water. In the reaction solutions, the required alkalinity and ionic strength were maintained with KOH (Fisher Scientific) and KNO_3 (Fisher Scientific), respectively. *t*-Butyl alcohol (SPECTROCHEM) was used to vary the dielectric constant of the medium.

2.2. Instruments used

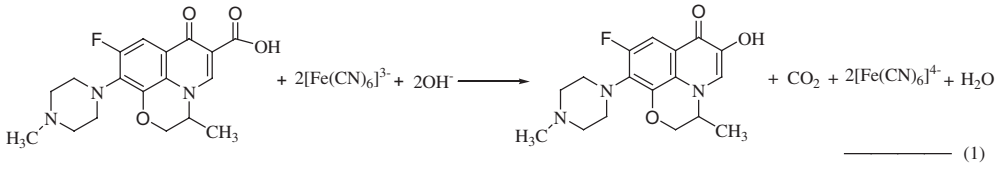
(i) For kinetic measurements, a Peltier Accessory (temperature control) attached Varian CARY 50 Bio UV–vis spectrophotometer (Varian, Victoria-3170, Australia) was used. (ii) For product analysis, a QP-2010S Shimadzu gas chromatograph mass spectrometer and Nicolet 5700-FT-IR spectrometer were used.

2.3. Kinetic measurements and procedure

The oxidation of levofloxacin (LF) by hexacyanoferrate(III) was followed under pseudo-first-order conditions where concentration of LF ≥ 10-fold in excess over concentration of hexacyanoferrate(III) at a constant ionic strength of 1.10 mol dm^{-3} in alkaline medium and at a constant temperature, 25 ± 0.1°C. The reaction was initiated by mixing thermally equilibrated solutions of hexacyanoferrate(III) and LF which also contained the required quantities of KOH and KNO_3 to maintain alkalinity and ionic strength, respectively. The reaction was monitored by decrease in absorbance of hexacyanoferrate(III) at its maximum absorption of 420 nm. It was verified that there are no interference from other reagents at this wavelength. Beer's law was verified under present experimental conditions, and ε was found to be 1,050 ± 10 dm^3 mol^{-1} cm^{-1}. The pseudo-first-order rate constants k_{obs} were evaluated from the plots of log $[Fe(CN)_6]^{3-}$ versus time. The plots in all cases were linear over 70% completion of the reaction (Figure 1). The k_{obs} values were reproducible within ± 5% and are the averages of minimum three sets of kinetic runs (Table 1).

2.4. Stoichiometry and product analysis

The reaction mixture containing excess concentration of hexacyanoferrate(III) over concentration of levofloxacin was mixed in the presence of 0.8 mol dm^{-3} KOH, adjusted to a constant ionic strength of 1.10 mol dm^{-3} and allowed to react for about 4 h at 25°C in a closed vessel under nitrogen atmosphere. The remaining hexacyanoferrate(III) was then analysed spectrophotometrically at 420 nm. The results indicated that one mole of levofloxacin requires two moles of hexacyanoferrate(III) according to Equation (1)



(1)

The remaining reaction mixture was acidified, concentrated and extracted with ether. The main reaction product, 9-fluoro-2,3- dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4] oxazino[2,3,4-ij]quinolin-7-one, was isolated and identified with the help of TLC and characterized by FT-IR and GCMS. The FT-IR spectra of LF, the (C=O) band of acid group is appears at 1,722 cm^{-1} and the carbonyl stretching of 7-oxo- group appears at 1,623 cm^{-1}. (Figure 2(A)); after oxidation, FT-IR spectra of product, 9-fluoro-2,3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4] oxazino[2,3,4-ij]quinolin-7-one, show this band at 1,623 cm^{-1}, this was carbonyl stretching of 7-oxo-group, a broad peak at 3,431 cm^{-1} is due to υ(OH) stretching and the carbonyl stretching of acid is disappear (Figure2(B)). The presence of 9-fluoro-2,3- dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4]oxazino[2,3,4-ij]quinolin-7-one was also confirmed by GC-MS analysis. The mass spectrum showed the molecular ion peak at 333 amu (Figure 3) and the melting point of product was 206°C (literature mp 207). The UV absorbance bands of PQS (Pseudomonas Quinolone Signal (2-heptyl-3-hydroxy-4-quinolone; PQS) have shown absorption band at 340 nm (Gregory et al., 2011) similarly analogue of PSQ (Pseudomonas Quinolone Signal (2-heptyl-3-hydroxy-4-quinolone; PQS),

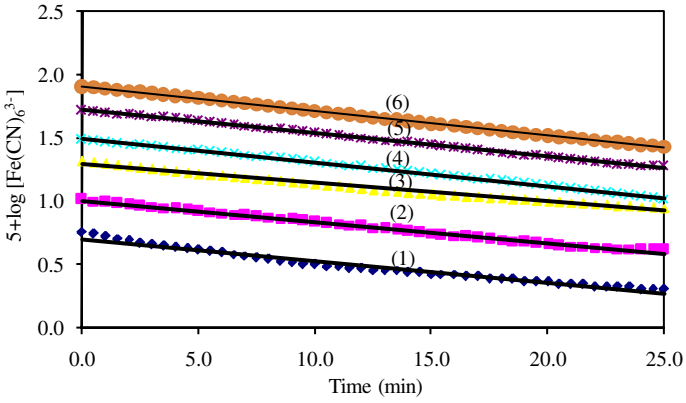


Figure 1. First-order plots of oxidation of levofloxacin by hexacyanoferrate(III) in alkaline medium at 25°C, [levofloxacin] = 4.0 × 10^{-3} mol dm^{-3}, [OH^-] = 0.8 mol dm^{-3}; *I* = 1.10 mol dm^{-3}, $[Fe(CN)_6]^{3-}$ × 10^4 mol dm^{-3} = (1) 0.50 (2) 1.0 (3) 2.0 (4) 3.0 (5) 4 and (6) 5.

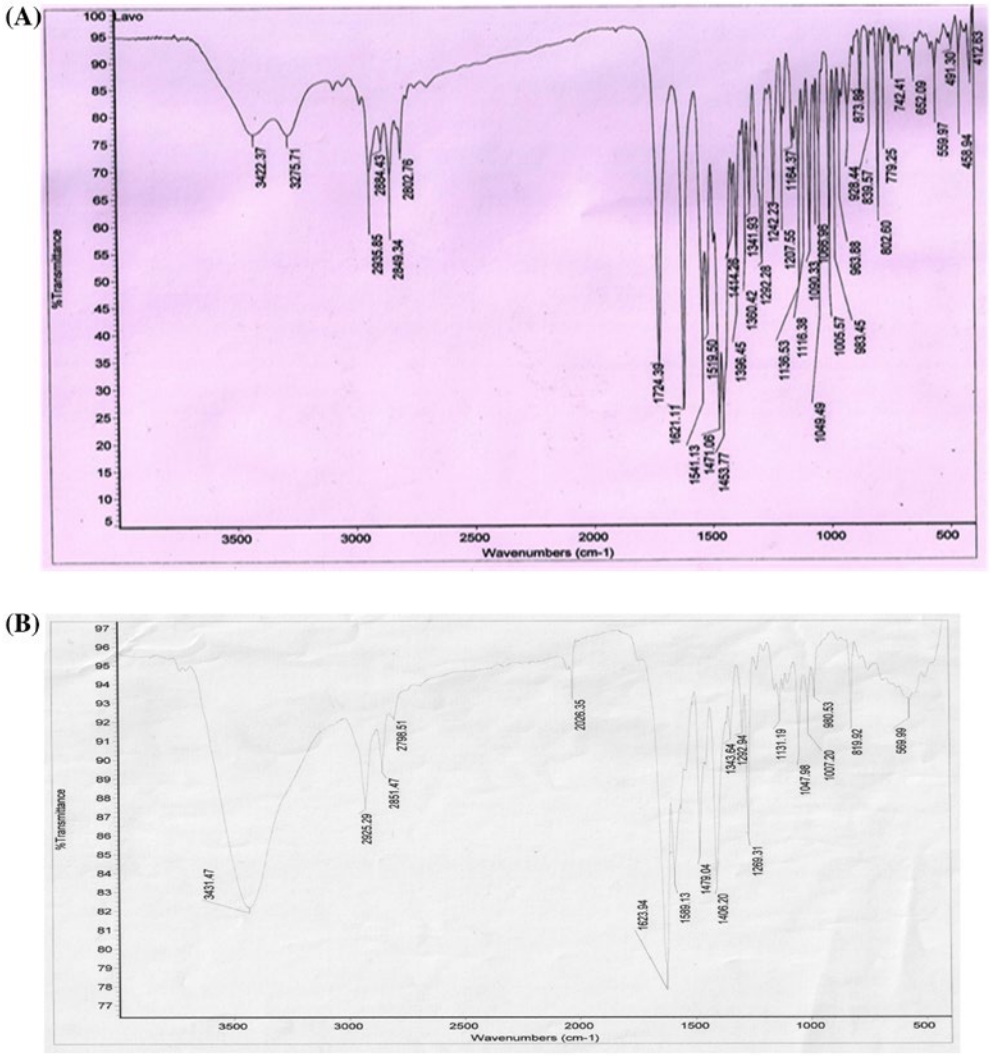


Figure 2. (A) FT-IR spectrum of levofloxacin; (B) FT-IR spectrum of product, 9-fluoro-2,3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4]oxazino[2,3,4-ij] quinolin-7-one obtained during the oxidation of levofloxacin by hexacyanoferrate(III) in alkaline medium.

9-fluoro-2,3- dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4]oxazino[2,3,4-ij]quinolin-7-one has shown UV absorption band at 341 nm (Figure 4) and substrate, levofloxacin has shown UV absorption band at 295 nm (Makarand & Bonde, 2009) (Figure 5). The other product, $[Fe(CN)_6]^{4-}$,

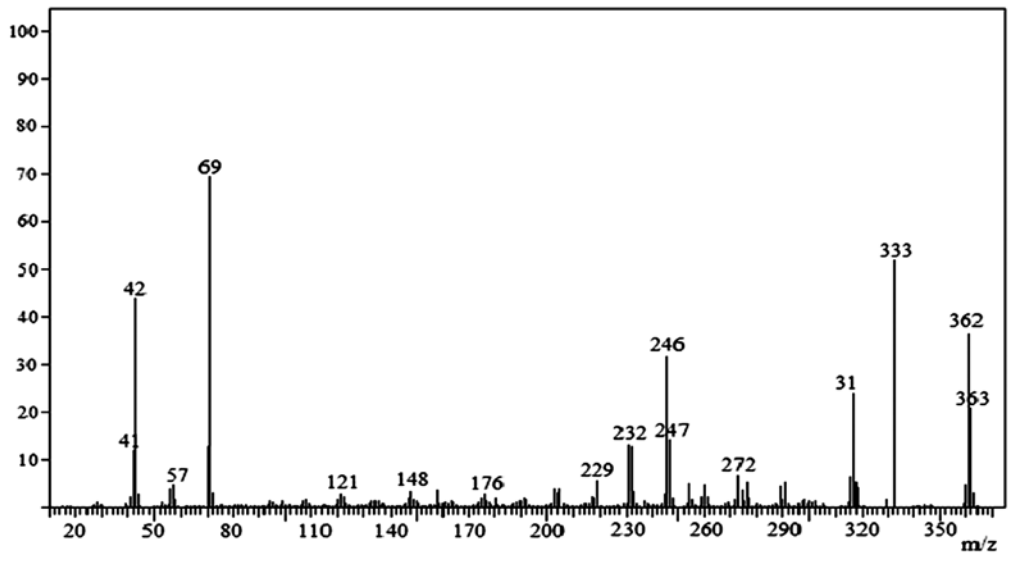


Figure 3. GC–MS spectra of the product, 9-fluoro-2,3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4] oxazino[2,3,4-ij]quinolin-7-one showing a molecular ion peak at 333 amu.

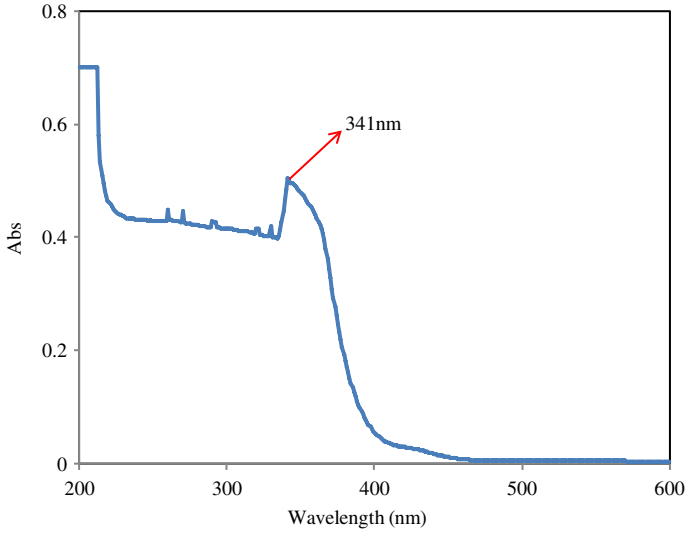


Figure 4. UV absorbance band for product, 9-fluoro-2,3-dihydro-6-hydroxy-3-methyl-10-(4-methylpiperazin-1-yl)–[1,4]oxazino[2,3,4-ij]quinolin-7-one occurs at approximately 341 nm.

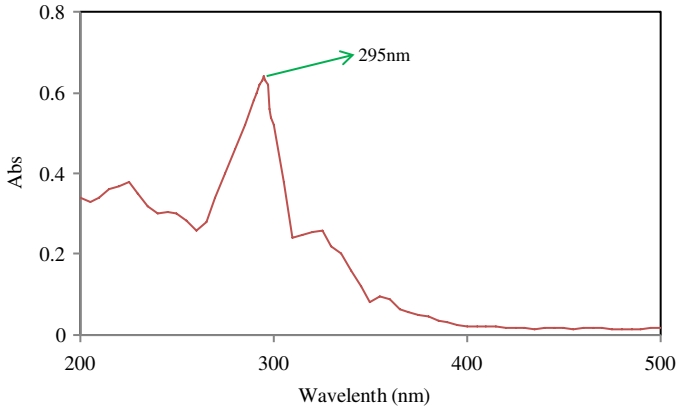


Figure 5. UV absorbance band for levofloxacin.

was determined by titrating against Ce(IV) solution (Jeffery, Bassett, Mendham, & Denny, 1996). The liberation of CO_2 was identified by lime water test.

3. Results

3.1. Reaction orders

The reaction orders were determined from the slope of log k_{obs} versus log concentration plots, by varying the concentration of the reductant, and alkali in turn while keeping the others constant.

3.2. Effect of [Hexacyanoferrate(III)]

With invariable concentration of [LF], 4.0×10^{-3} mol dm^{-3} and [OH^-], 0.80 mol dm^{-3}, at constant ionic strength, 1.10 mol dm^{-3}, the oxidant, hexacyanoferrate(III) concentration was varied in the range of 0.50×10^{-4}–5.0×10^{-4} mol dm^{-3}, the observed rate constants, k_{obs}, were almost constant (Table 1) and the linearity of the plot of log $[Fe(CN)_6]^{3-}$ versus time (Figure 1) over 70% completion of the reaction indicates the unit order with respect to hexacyanoferrate(III) concentration.

3.3. Effect of [Levofloxacin]

The substrate, levofloxacin, concentration was varied in the range of 1.0×10^{-3}–10.0×10^{-3} mol dm^{-3} at 25°C keeping all other reactant concentration and conditions constant, as the concentration of levofloxacin increases the k_{obs} also increases (Table 1). The apparent order in [LF] was found to be less than unity (0.61).

3.4. Effect of [KOH]

The concentration of OH^- was varied in the range of 0.10–1.0 mol dm^{-3} at constant $[Fe(CN)_6]^{3-}$, [levofloxacin], ionic strength and temperature. The rate of reaction increased with an increase in the [alkali] (Table 1) and the order was found to be less than unity.

Table 1. Effect of $[Fe(CN)_6]^{3-}$, [Levofloxicin], and [OH^-] on the oxidation of levofloxacin by alkaline hexacyanoferrate(III) at 25°C, I = 1.10 mol dm^{-3}

[HCF] × 10^4 (mol dm^{-3})	[LF] × 10^3 (mol dm^{-3})	[OH^-] × 10 (mol dm^{-3})	k_{obs} × 10^3 (s^{-1})	k_{cal} × 10^3 (s^{-1})
0.5	4.0	8.0	0.66	0.65
1.0	4.0	8.0	0.67	0.65
2.0	4.0	8.0	0.64	0.65
3.0	4.0	8.0	0.67	0.65
4.0	4.0	8.0	0.65	0.65
5.0	4.0	8.0	0.66	0.65
2.0	1.0	8.0	0.24	0.25
2.0	2.0	8.0	0.41	0.42
2.0	4.0	8.0	0.64	0.64
2.0	6.0	8.0	0.77	0.78
2.0	8.0	8.0	0.88	0.88
2.0	10.0	8.0	1.08	0.96
2.0	4.0	1.0	0.34	0.33
2.0	4.0	2.0	0.46	0.45
2.0	4.0	4.0	0.56	0.57
2.0	4.0	6.0	0.60	0.61
2.0	4.0	8.0	0.64	0.64
2.0	4.0	10.0	0.69	0.65

3.5. Effect of initially added reaction product

The initially added product, hexacyanoferrate(II), did not has any significant effect on the rate of reaction.

3.6. Effect of ionic strength and solvent polarity

The reaction was studied by varying the ionic strength from 1.10 mol dm^{-3} to 2.0 mol dm^{-3} by adding potassium nitrate solution at constant concentrations of hexacyanoferrate(III), levofloxacin and alkali. The values of k_{obs} were found to increase with increasing the ionic strength. The plot of log k_{obs} versus $\sqrt{I}/(\sqrt{I}+1)$ linear with positive slope (Figure 6) indicating that the reaction between two ions of similar charges.

The effect of dielectric constant was studied by varying the *t*-butyl alcohol-water (v/v) composition from 0 to 20%. It was found that as the composition of *t*-butyl alcohol increased in the reaction medium, the rate of reaction decreased and the plot of log k_{obs} versus 1/D is linear with negative slope (Figure 6).

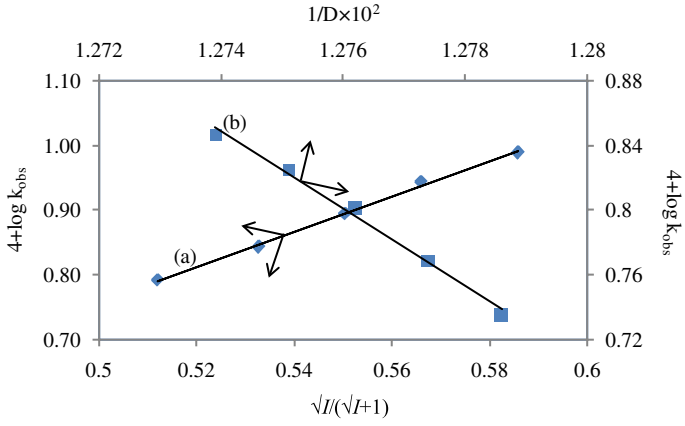


Figure 6. Effect of (a) ionic strength and (b) dielectric constant on the oxidation of LF by alkaline hexacyanoferrate(III) at 25°C.

Table 2. Activation parameters and thermodynamic quantities for the oxidation of LF by alkaline hexacynoferrate(III)

(a) Effect of temperature with respect to slow step of Scheme 1 and activation parameters

Temperature (K)	k × 10^3 (s^{-1})	Parameter	Values
288	0.78	*Ea* (kJ mol^{-1})	47 ± 3
298	1.43	$\Delta H^{\neq}$ (kJ mol^{-1})	44 ± 3
308	2.75	$\Delta S^{\neq}$ (J K^{-1} mol^{-1})	−151 ± 4
318	4.89	$G^{\neq}$ (kJ mol^{-1})	89 ± 3
		Δ log A	8 ± 0.1

(b) Equilibrium constants K_1 and K_2 at different temperatures

Temperature (K)	K_1 (dm^3 mol^{-1})	K_2 × 10^{-2} (dm^3 mol^{-1})
288	1.804	3.55
298	4.602	2.61
308	6.290	2.41
318	8.035	2.37

(c) Thermodynamic quantities with respect to K_1 and K_2

Quantities	Using K_1 values	Using K_2 values
Δ*H* (kJ mol^{-1})	21	−10
Δ*S* (J K^{-1} mol^{-1})	134	14
Δ*G* (kJ mol^{-1})	−4	−14

3.7. Test for free radicals

To test for the involvement of free radicals, acrylonitrile (Hiremath, Mulla, & Nandibewoor, 2005; Shettar & Nandibewoor, 2004) was added to the reaction mixture, which was then kept for 24 h under nitrogen atmosphere. Addition of methanol resulted in the precipitation, suggesting the involvement of free radicals in the reaction. The blank experiment did not induce polymerization under the same conditions. The added acrylonitrile decreases the rate of reaction also indicates the involvement of free radical in the reaction (Bhattacharya & Banerjee, 1996).

3.8. Effect of temperature

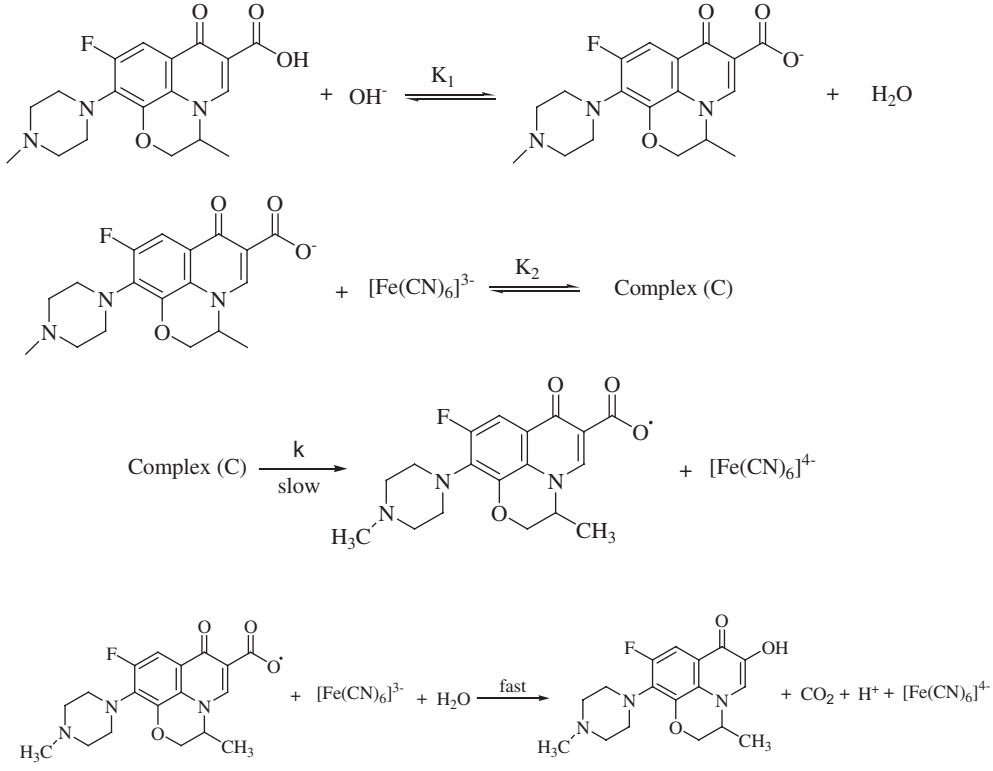
The reaction was studied at four different temperatures, 15, 25, 35 and 45°C with variation in concentration of LF and alkali, keeping other conditions constant. The rate of reaction increased with an increase in the temperature. The rate constant, k, of the slow step of the Scheme 1 was obtained from the slopes and intercepts of $1/k_{obs}$ versus 1/[LF] and $1/k_{obs}$ versus $1/[OH^-]$ plot at four different temperatures. The activation energy corresponding to these rate constants was evaluated from the Arrhenius plot of log k versus 1/T from which other activation parameters were also obtained (Table 2).

4. Discussion

The variation in the concentrations of the oxidant, substrate and alkali, while keeping the others constant, showed that the reaction is first order in oxidant and less than the unit order in substrate and alkali concentrations (Table 1). The reaction between levofloxacin and $[Fe(CN)_6]^{3-}$ has a stoichiometry of 1:2. Based on the experimental results, a mechanism can be proposed for which all the observed orders in each constituent such as [oxidant], [reductant] and $[OH^-]$ may be well accommodated. Oxidation of levofloxacin by hexacyanoferrate(III) in KOH media, the oxidant and reductant change their oxidation state by different number of units hence this oxidation is a non-complementary reaction with oxidant undergoing one equivalent change.

In the present study, alkali combines first with levofloxacin to give the anionic form of levofloxacin in a prior equilibrium step, which is also supported by the observed fractional order in $[OH^-]$ and [LF]. The hexacyanoferrate(III) species reacts with the anionic form of levofloxacin to give a complex (C),

Scheme 1. Detailed scheme for the oxidation of levofloxacin by hexacyanoferrate(III).

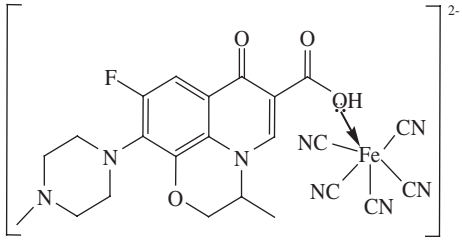


which decomposes in a slow step to form an intermediate levofloxacin free radical species. This intermediate levofloxacin free radical species further reacts with another mole of hexacyanoferrate(III) in a fast step to form final products, 9-fluoro-2,3- dihydro-3-methyl-5-hydroxy-10-(4-methyl-1-piperazinyl)- 7-oxo-7H pyrido [1,2,3-de]-1,4-benzoxazine-6 carboxylic acid and $[Fe(CN)_6]^{4-}$. All these results may be interpreted in the detailed mechanistic Scheme 1.

In most of the oxidation reactions, hexacyanoferrate(III) resembles the Cu(II) oxidation reactions (Kochi, Graybill, & Kurz, 1964; Singh & Ghosh, 1955; Wilberg & Nigh, 1965). In an alkaline medium, $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$ has the redox potential +0.45 V which is higher than the redox potential of the couple Cu(II)/Cu(I) (−0.34 V), substantiates a better possibility for the rapid oxidation of the free radical with hexacyanoferrate(III) in the alkaline medium.

Spectroscopic evidence for the complex formation between oxidant and substrate was obtained from UV-visible spectra of levofloxacin (4.0×10^{-3} mol dm^{-3}), hexacyanoferrate(III) (2.0×10^{-4} mol dm^{-3}), $[OH^-]$ = 0.80 mol dm^{-3} and mixture of both. A bathochromic shift of about 11.0 nm from 422.0 to 433.0 nm was observed (Figure 7).

The probable structure of the complex is given below:



The formation of the complex (Aftab Aslam, Ayaz, Shaista, & Siddiqi, 2011) is proven kinetically by the non-zero intercept of $1/k_{obs}$ versus 1/[LF] (Figure 8(b)).

From Scheme 1, the following rate law can be derived as follows:

$$\begin{aligned}\text{Rate} &= \frac{-d[Fe(CN)_6]^{3-}}{dt} = k[\text{Complex}] \\ &= kK_2[Fe(CN)_6]^{3-}[LF^-] \\ &= kK_1K_2[Fe(CN)_6]^{3-}_f[OH^-]_f[LF]_f\end{aligned} \tag{2}$$

But, total hexacyanoferrate(III) concentration can be written as

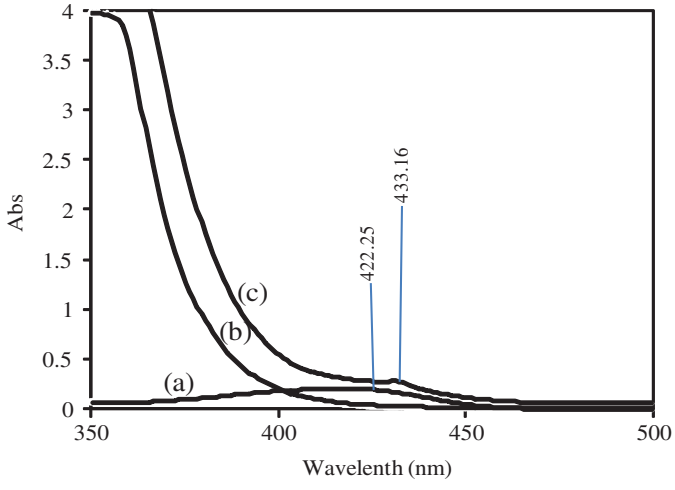


Figure 7. Spectroscopic evidence for the complex formation between levofloxacin and $[Fe(CN)_6]^{3-}$. (a) UV-vis spectra of $[Fe(CN)_6]^{3-}$ complex, (b) UV-vis spectra of levofloxacin and (c) UV-vis spectra of mixture of $[Fe(CN)_6]^{3-}$ and levofloxacin.

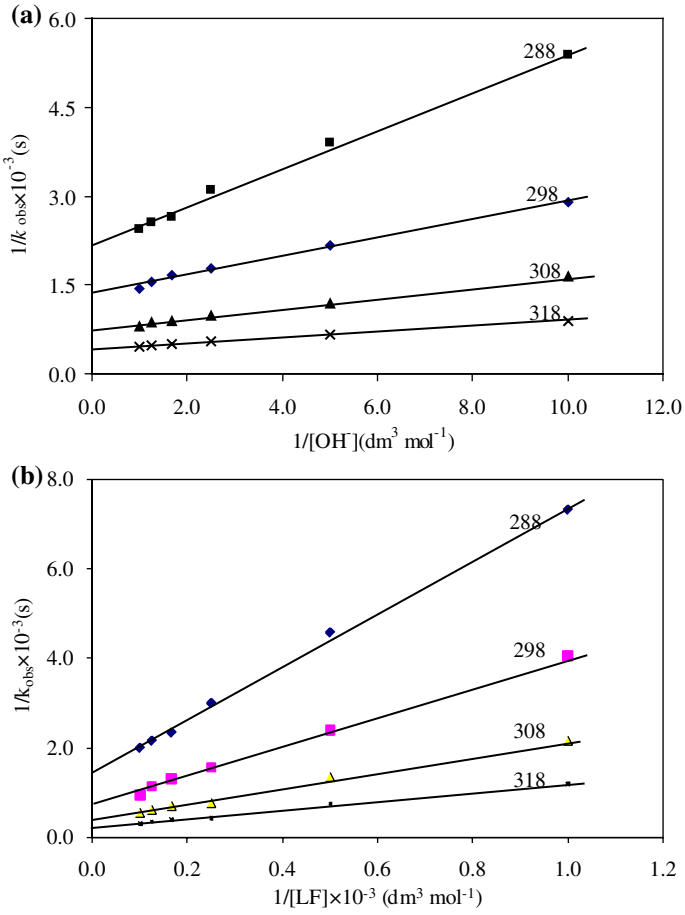


Figure 8. Verification of rate law (8) in the form of Equation (9) for the oxidation of levofloxacin by hexacyanoferrate(III) in alkaline medium. Plot of $1/k_{obs}$ versus (a) $1/[OH^-]$ and (b) 1/[LF] at different temperature (condition as in Table 1).

$$\begin{aligned}[Fe(CN)_6]_t^{3-} &= [Fe(CN)_6]_f^{3-} + [Complex] \\ &= [Fe(CN)_6]_f^{3-} + K_1K_2[Fe(CN)_6]_f^{3-}[OH^-]_f[LF]_f \\ &= [Fe(CN)_6]_f^{3-}\left\{1 + K_1K_2[OH^-]_f[LF]_f\right\}\end{aligned}$$

Therefore,

$$[Fe(CN)_6]_f^{3-} = \frac{[Fe(CN)_6]_t^{3-}}{\left\{1 + K_1K_2[OH^-]_f[LF]_f\right\}} \tag{3}$$

where subscripts "t" and "f" stands for total and free hexacyanoferrate(III) concentration, respectively.

Similarly,

$$\begin{aligned}[LF]_t &= [LF]_f + [LF^-]_f + [Complex] \\ &= [LF]_f + K_1[OH^-]_f[LF]_f + K_1K_2[Fe(CN)_6]_f^{3-}[OH^-]_f[LF]_f \\ &= [LF]_f\left\{1 + K_1[OH^-]_f + K_1K_2[OH^-]_f[Fe(CN)_6]^{3-}\right\}\end{aligned}$$

Therefore,

$$[LF]_f = \frac{[LF]_t}{\left\{1 + K_1[OH^-]_f + K_1K_2[OH^-]_f[Fe(CN)_6]^{3-}\right\}}$$

In view of low concentration of $[Fe(CN)_6]^{3-}$ used in the experiment, the term $K_1K_2[OH][Fe(CN)_6]^{3-}$ is neglected

$$[LF]_f = \frac{[LF]_t}{\{1 + K_1[OH^-]\}} \tag{4}$$

and

$$\begin{aligned}[OH^-]_t &= [OH^-]_f + [LF^-]_f + [\text{Complex}] \\ &= [OH^-]_f + K_1[OH^-]_f[LF]_f + K_1K_2[Fe(CN)_6]_f^{3-}[OH^-]_f[LF]_f \\ &= [OH^-]_f\left\{1 + K_1[LF]_f + K_1K_2[Fe(CN)_6]_f^{3-}[LF]_f\right\}\end{aligned}$$

Therefore,

$$[OH^-]_t = [OH^-]_f \tag{5}$$

Substituting Equations (3), (4) and (5) in Equation (2) and omitting the subscripts, we have

$$\text{Rate} = \frac{-d[Fe(CN)_6]^{3-}}{dt} = \frac{kK_1K_2[Fe(CN)_6]^{3-}[OH^-][LF]}{1 + K_1K_2[OH^-][LF] + K_1[OH^-] + K_1^2K_2[LF][OH^-]^2} \tag{6}$$

The denominator on right-hand side of Equation (6) should also contain a term $(1 + K_2[Fe(CN)_6]^{3-})$ which is neglected as it almost tends to unity due to low concentrations of $[Fe(CN)_6]^{3-}$ used in the present study. Equation (6) can also be written as:

$$\frac{\text{Rate}}{[Fe(CN)_6]^{3-}} = k_{obs} = \frac{kK_1K_2[OH^-][LF]}{1 + K_1K_2[OH^-][LF] + K_1[OH^-] + K_1^2K_2[LF][OH^-]^2} \tag{7}$$

The term $K_1^2K_2[LF][OH^-]^2$ in Equation (7) can be omitted due to the low concentrations of levofloxacin and OH^- used in the experiment. Thus Equation (7) becomes,

$$k_{obs} = \frac{kK_1K_2[OH^-][LF]}{(1 + K_1K_2[OH^-][LF] + K_1[OH^-])} \tag{8}$$

Equation (8) is verified in the following form

$$\frac{1}{k_{obs}} = \frac{1}{kK_1K_2[LF][OH^-]} + \frac{1}{kK_2[LF]} + \frac{1}{k} \tag{9}$$

The plots of $1/k_{obs}$ versus $1/[OH^-]$ (Figure 8(a)) and $1/k_{obs}$ versus 1/[LF] (Figure 8(b)) should be linear and were found to be so. From the intercepts and slopes, the constants k, K_1 and K_2 were calculated as: $(1.43) \times 10^{-3}$ s^{-1}, (4.602) and $(2.61) \times 10^2$ dm^3 mol^{-1}, respectively at 25°C. Using these values in Equation (8), the rate constants for various concentrations of $[Fe(CN)_6]^{3-}$, levofloxacin and OH^- were calculated and compared with experimental values. The calculated values are in good agreement with experimental values (Table 1).

The thermodynamic quantities for the different equilibrium steps in Scheme 1 can be evaluated as follows. The [LF] and $[OH^-]$ (Table 1) were varied at four different temperatures. According to Equation (9), the plots of $1/k_{obs}$ versus 1/[LF] and $1/k_{obs}$ versus $1/[OH^-]$ should be linear and are found to be so (Figure 8(a) and (b)). From the intercepts and slopes, the values of k, K_1 and K_2 were calculated at different temperatures (Table 2). A van't Hoff plot was made for the variation in K_1 and K_2 with temperature (log K_1 versus 1/T and log K_2 versus 1/T). The values of enthalpy of reaction ΔH, entropy of reaction ΔS and free energy of reaction ΔG were calculated for the first and second equilibrium steps of Scheme 1. These values are given in Table 2(c).

The effect of ionic strength on the rate of the reaction is also in the expected direction as similar charged species, $[Fe(CN)_6]^{3-}$ and the anionic form of levofloxacin is involved in the reaction. Thus, ion pairing between K^+ and $[Fe(CN)_6]^{3-}$ appears to be reduced due to the expected value of slope (2.7≈ 3 in Figure 6). Similar ion paring is also experienced for other reactions (Abu-Nawwas, Hameed, & Fayez, 2014). Similarly, decrease in the dielectric constant of the medium results in a decrease in the rate of reaction which supports the involvement of same charged species (Scheme 1). The activated complex may be more polar than the reactants, $[Fe(CN)_6]^{3-}$ and the levofloxacin anion, which also may be more solvated in water than in the low dielectric medium (Laidler, 2004) as compared to its reactants. The lower energy of activation and high free energy of activation support the formation of highly solvated transition state (activated complex). The high negative value of $\Delta S^{\neq}$ (−151 J K^{-1} mol^{-1}) also supports the proposed mechanism and indicates the formation of a transition state fairly rapidly with a lower degree of freedom (Khan, Mohd, & Bano, 2011). The activated complex could be more ordered than the reactants. The small value of k also indicates the formation of activated complex.

4. Conclusion

The oxidation of levofloxacin by hexacyanoferrate(III) in aqueous alkaline media was investigated. The observed stoichiometry indicates that, the oxidation of one mole of levofloxacin requires two moles of hexacyanoferrate(III). Based on the experimental observations, a mechanism was proposed via the formation of an intermediate complex between levofloxacin and hexacyanoferrate(III). The rate constant of the slow step and other equilibrium constants involved in the mechanism were evaluated and activation parameters with respect to the slowest step of the reaction were computed. The overall sequence described here is consistent with all experimental findings, including the product, mechanistic and kinetic studies.

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