LIST OF PAPERS PUBLISHED: 12


ANNEXURE – II

Papers Presented In International and National Conferences/Seminars


6. Ankita Jain, Vijay Devra. Paper Presentation in National Seminar and Science Exhibition on “Innovations in Science and Technology for Inclusive Development” organised by Dr. B. Lal Institute of
Biotechnology and Indian Science Congress Association, Jaipur, held on 16th and 17th January, 2014.


Kinetics and mechanism of permanganate oxidation of nalidixic acid in aqueous alkaline medium

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INTRODUCTION

Potassium permanganate widely used as oxidizing agent play vital role in the kinetics of number of organic and biological active compounds (Fatiadi, 1987; Ladbury and Cullis, 1958; William, 1958; Banerji, 1988; Baljeet and Kothari, 1997). Oxidation reactions by Potassium permanganate are of considerable academic and technological importance because of variable oxidation states. Permanganate is one such powerful multi-electron oxidant which can exist in various oxidation states, among which +7 is its highest oxidation state, which occurs in the Oxo compounds like MnO₄⁻, MnO₂⁻, MnO₂F⁻. Out of which MnO₄⁻ is the most commonly used well known oxidant species to carry out kinetic studies in acidic, neutral and alkaline media. Oxidation by permanganate ion find extensive applications in organic syntheses (Fatiadi, 1987; Stewart and Wiberg, 1965; Freeman, 1976; Lee, 1980; Lee and Tranhanovsky, 1982; Simandi et al., 1983; Lee et al., 1987) especially since the introduction of phase transfer catalysis (Lee, 1980; Lee and Tranhanovsky, 1982; Lee et al., 1987) which permits the use of solvents like methylene chloride and benzene. Kinetic studies are vital sources of mechanistic information on these reactions, as validated by result stating to unsaturated acids in both aqueous (Fatiadi, 1987; Stewart and Wiberg, 1965; Freeman, 1976; Lee, 1980; Lee and Tranhanovsky, 1982; Simandi et al., 1983; Lee et al., 1987) and non-aqueous media (Wiberg et al., 1973). As is known, in aqueous alkaline medium the permanganate ion oxidizes a number of organic compounds, which are not, or only very slowly, attacked in acidic or neutral medium (Ladbury and Cullis, 1958; William, 1958), (Drummond and Waters, 1935). The mechanism of oxidation depends on the nature of the substrate and pH of the reaction mixture (Stewart et al. 1997). In strongly alkaline medium, the stable reduction product (Simandi et al., 1985; Timmanagoudar et al., 1997; Nadimpalli et al., 1993) of permanganate is manganate ion, MnO₄²⁻. MnO₂ appears only after long time, i.e., after the complete consumption of MnO₄⁻.
No mechanistic information is available to discriminate between a direct one-electron reduction to Mn(VI) and a mechanism in which a hypomanganate ion formed in a two-electron reduction followed by its rapid re-oxidation (Panari et al., 1998; Bohn et al., 1992).

The manganese chemistry involved in these multistep redox reactions is a significant source of information as the manganese intermediates are relatively easy to identify when they have sufficiently long life time and oxidation states of the intermediates permit useful deductions as to the possible reaction mechanisms including the nature of intermediates.

Fluoroquinolones are broad-spectrum antibacterial agents used to treat the bacterial infections in human beings. Pharmaceuticals, of which antibacterial groups are important, have been identified as evolving environmental contaminants (Johnson et al., 2003). A major fraction of fluoroquinolones pass into the water and domestic sewage due to partial metabolism in the human body. This represents the main route for entry of such pharmaceutical compounds into natural aquatic environment. In this perception, transformations of fluoroquinolone antibacterial agents in suitable water treatment process definitely play a major role (Halling-Sorensen et al., 1998). Nalidixic acid (NA) with molecular formula C13H12N2O3 (1-ethylm-3, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid) (Figure 1) is the first synthesized antimicrobial quinoline. NA is an ionizable, non-photosensitive molecule (Mascolo et al., 2010; Ge et al., 2010) with a carboxylic acid function having a pKa of 5.95 (Ross and Riley, 1990).

![Fig. 1: Structure of Nalidixic acid.](image)

NA is an antibacterial drug still widely used for urinary tract infections (Barlow, 1963). Its two major metabolites are 7-hydroxynalidixic acid (HNA), which exhibits antibacterial properties equal to NA (Mcchesney et al., 1964; Moore et al., 1965; Portmann et al., 1966) and 7-carboxynalidixic acid (CNA), which is inactive. Permanganate has been widely used for the water and wastewater treatment from last five decades (Hicks, 1976). The oxidation of nalidixic acid by permanganate was studied to investigate the kinetics and mechanism.

**MATERIALS AND METHODS**

**Chemicals**

All chemicals used were of analytical grade and doubly distilled water was used throughout this study. Standard solution of nalidixic acid (KORES India Limited) was prepared by dissolving calculated quantity of pure drug in double distilled water. Permanganate solution was obtained by dissolving potassium permanganate (BDH Analar) in water and standardized by titrating against oxalic acid (Vogel, 1967). Freshly prepared & standardized permanganate solutions were always used in kinetics experiments. The Mn(II) solution was made by dissolving manganese sulphate (BDH) in water. NaOH (BDH) and NaNO3 (MERCK) were used to provide required alkalinity and ionic strength respectively.

**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), and for pH measurements MSW-552 pH meter were used.

**Kinetic Measurements**

All kinetic measurements were conducted under pseudo-first-order conditions, where the concentration of nalidixic acid was much greater than permanganate ion concentration at constant temperature 40 ± 0.1°C unless otherwise stated. The reaction was initiated by mixing thermostated solution of permanganate and nalidixic acid; in addition to that required quantities of NaOH and NaNO3 are added to provide required alkalinity and ionic strength of reaction. The progress of the reaction was followed spectrophotometrically at 525nm. The application of Beer’s law to permanganate at 525nm had been verified. The molar absorptivity index of permanganate was found to be ε = 2260 ±50 dm3 mol−1 cm−1 as a function of time (compared to the literature, ε = 2200, Simandi et al., 1985). The kinetics reactions were followed more than 85 % completion of the reaction. The pseudo-first-order rate constants kobs were calculated from the plots of the logarithm of absorbance versus time, which were linear. The values of kobs were reproducible within ± 5%.

**Stoichiometry and Product Analysis**

Different sets of concentration of reactants in 0.5 mol dm−3 of OH− ion and at constant ionic strength, 0.5mol dm−3, were kept over 24 hours at 40°C in a closed container. When [permanganate] > [nalidixic acid], the remaining permanganate concentration was assayed by measuring the absorbance at 525 nm. Estimation of unreacted [MnO4−] indicates that 1 mole of nalidixic acid consumed 2 moles of Permanganate; the Stoichiometry of the reaction is given in Scheme 1. The main reaction products were identified as manganese (VI) and 1-ethyl-2-hydroxy-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid.

LC/MS analysis of the reaction indicated the presence of a product with molecular ion of m/z 248 corresponds to 1-ethyl-2-hydroxy-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid (Figure 2). The molecular ion of nalidixic acid is m/z 232.2. The IR spectroscopy shows a broad peak at 3382.39 cm−1 which is due to -OH stretching (Figure 3) and the remaining peaks are of the parent compound.
RESULTS

The reaction orders were determined from the slopes of log $k_{obs}$ versus log [concentration] plots by different concentration of nalidixic acid, permanganate and alkali in turn, keeping all other concentration and conditions constant.

Effect of Concentration of Manganese(VII)

The oxidant permanganate [MnO$_4^-$] concentration varied from $1 \times 10^{-4}$ to $7 \times 10^{-4}$ mol dm$^{-3}$, and all other concentrations and conditions were constant. The plot of log absorbance versus time was linear (Figure 4) indicating that the reaction is first order with respect to [KMnO$_4$]. The observed pseudo first order rate constant ($k_{obs}$) were independent of the concentration of KMnO$_4$.

Effect of Concentration of Nalidixic acid

The effect of concentration variation of nalidixic acid on the rate of reaction was studied in the range $2 \times 10^{-3}$ to $10 \times 10^{-3}$ mol dm$^{-3}$ at constant concentration of permanganate, alkali and ionic strength at $35^\circ$, $40^\circ$, $45^\circ$C respectively. The rate of reaction increases with increasing concentration of nalidixic acid (Table 1). A plot of log $k_{obs}$ versus log [NA] was linear with a slope of 0.52, thus indicating a fractional-order dependence on nalidixic acid concentration. This was confirmed by the plot of $1/k_{obs}$ versus $1/ [NA]$ (Figure 5) which was also linear with a positive intercept.

Effect of Concentration of Alkali

The effect of concentration variation of alkali on the rate of reaction was studied in the concentration range $2.0 \times 10^{-1}$ to $10 \times 10^{-1}$ mol dm$^{-3}$ at fixed concentration of permanganate, nalidixic acid and ionic strength at three temperatures viz. $35^\circ$, $40^\circ$, $45^\circ$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 0.56. This was confirmed by the plot of $1/k_{obs}$ versus $1/ [OH^-]$ (Figure 6) which was also linear with a positive intercept.
Table 1: Effects of variation of [MnO₄⁻], [NA] and [OH⁻] on the oxidation of nalidixic acid by alkaline permanganate at 40°C and I = 0.5 mol dm⁻³.

<table>
<thead>
<tr>
<th>10⁻⁴[MnO₄⁻] (mol dm⁻³)</th>
<th>10⁻⁴[NA] (mol dm⁻³)</th>
<th>10⁻¹[OH⁻] (mol dm⁻³)</th>
<th>10⁻⁸kobs (s⁻¹)</th>
</tr>
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<td>2.0</td>
<td>10.0</td>
<td>8.92</td>
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Fig. 3: FT-IR spectra of the product of oxidation of Nalidixic acid by permanganate.

Fig. 4: First order plots of the variation of permanganate concentration at 40°C. [NA]=5.0×10⁻³, [OH⁻] = 0.5 and I = 0.5/ mol dm⁻³, [MnO₄⁻]×10⁻⁴ mol dm⁻³ = (A) 1.0, (B) 2.0, (C) 3.0, (D) 4.0, (E) 5.0, (F) 6.0, (G) 7.0.
Effect of Ionic Strength and Dielectric Constant

At constant concentration of reactants and other conditions constant, the ionic strength was varied by varying concentration of sodium nitrate from 0.75 - 1.75 mol dm$^{-3}$. Ionic strength had negligible effect on the rate of reaction. The effect of the dielectric constant (D) was studied by varying the t-butanol–water content (v/v) in the reaction mixture with all other conditions being maintained constant. The rate of reaction increases with increasing t-butanol volume. The plot of log $k_{obs}$ versus 1/D was linear with positive slope (Figure 7).

Effect of Added Products

The manganate ion concentration was varied from $4.0 \times 10^{-5}$ to $4.0 \times 10^{-4}$ mol dm$^{-3}$ at constant concentrations of permanganate, nalidixic acid, alkali, and ionic strength. It was found that initially added manganate ion had no effect on the rate of reaction.

Tests for Free Radical

The reaction mixture (10ml) in which known quantity (2ml) of acrylonitrile has been added and kept in an inert atmosphere for 5 hours then diluted with methanol, white precipitate was formed, indicating the intervention of free radicals in the reaction.

The blank experiment of reacting either KMnO$_4$ or nalidixic acid alone with acrylonitrile did not induce polymerisation under the same conditions.
Fig. 7: Effect of dielectric constant on the oxidation of nalidixic acid by alkaline permanganate at 40°C.

Fig. 8: Spectral changes during the oxidation of nalidixic acid (NA) by permanganate in alkaline medium at 40°C: [MnO₄⁻] = 5.0 × 10⁻⁴, [NA] = 5.0 × 10⁻³, [OH⁻] = 5.0 × 10⁻¹ and I = 0.5 mol dm⁻³.

Table 2: Activation and thermodynamic quantities for the oxidation of nalidixic acid by alkaline permanganate.

<table>
<thead>
<tr>
<th>Temperature (Kelvin)</th>
<th>10⁻¹ k (s⁻¹)</th>
<th>Effect of temperature with respect to the slow step of figure 10.</th>
</tr>
</thead>
<tbody>
<tr>
<td>308</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>313</td>
<td>1.29</td>
<td></td>
</tr>
<tr>
<td>318</td>
<td>1.40</td>
<td></td>
</tr>
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</table>

Activation parameters

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<tr>
<th>Eₐ (kJ mol⁻¹)</th>
<th>Value</th>
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<tbody>
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<td>11.48</td>
<td></td>
</tr>
</tbody>
</table>

ΔH (kJ mol⁻¹) = 11.48

ΔS ± (J K⁻¹ mol⁻¹) = -289.27

ΔG ± (kJ mol⁻¹) = 88.13

Equilibrium constants at different temperatures

<table>
<thead>
<tr>
<th>Temperature (Kelvin)</th>
<th>10⁻⁻²K₁ (dm³ mol⁻¹)</th>
<th>10⁻⁻¹K₂ (dm³ mol⁻¹)</th>
</tr>
</thead>
<tbody>
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<td>308</td>
<td>12.09</td>
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<tr>
<td>313</td>
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<td>2.81</td>
</tr>
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<td>318</td>
<td>29.76</td>
<td>1.69</td>
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</tbody>
</table>

Thermodynamic quantities

<table>
<thead>
<tr>
<th>ΔH (kJ mol⁻¹)</th>
<th>ΔS ± (J K⁻¹ mol⁻¹)</th>
<th>ΔG ± (kJ mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>76.58</td>
<td>256.04</td>
<td>-3.64</td>
</tr>
<tr>
<td>-55.52</td>
<td>-168.03</td>
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</table>
DISCUSSION

Permanganate ion is a strong oxidant in an aqueous alkaline media. Since it shows various oxidation states, the stoichiometric results and the pH of reaction medium play a significant role. Under the present experimental conditions at pH > 12, the reduction product of Mn(VII) is stable and further reduction of Mn(VI) might be stopped (Simandi et al., 1985; Timmanagoudar et al., 1987). However, prolong standing, green Mn(VI) is reduced to Mn(IV) under experimental conditions. The permanganate shows various oxidation states, such as Mn(VII), Mn(V), and Mn(VI) in the alkaline medium. The colour of the reaction mixture changes from violet Mn(VII) to dark green Mn(VI) through blue Mn(IV) were observed. It is plausible that blue colour originated from the violet of permanganate and the green from manganate, excluding the accumulation of hypomanganate. It is clear from Figure 8 that the concentration of MnO$_4^−$ decreases at wavelength 526 nm, while increases at 610 and 460 nm are due to Mn(VI). As the reaction proceeds, a yellow turbidity slowly develops, and after keeping for a long time the solution decolourises and forms a brown precipitate. This suggests that the initial products might have undergone further oxidation resulting in a lower oxidation state of manganese.

The results shows that OH$^-$ ions first combined with permanganate to form a basic permanganate reactive species [MnO$_4$OH]$^-$ (Thabaj et al., 2007), (Panari et al., 1998). Then [MnO$_4$OH]$^-$ reacts with NA to form a complex (C) (Intermediate).

The less than unit order with respect to NA may be due to the complex formation between the [MnO$_4$OH]$^-$ and NA before the rate determining step. A plot of 1/k$_{obs}$ versus 1/ [NA] (Figure 5) shows an intercept in agreement with complex formation. Further evidence for complex formation was obtained from the UV–VIS spectra of reaction mixtures. Two isosbestic points were observed for this reaction (Figure 8), indicating the presence of an equilibrium before the slow step of the mechanism (Chang, 1981; Sathyanarayana, 2001). Within the complex one electron is transferred from nalidixic acid to Mn(VII). The breaking of this complex (C) is assigned as the slowest step, leading to the formation of an NA radical intermediate and Mn(VI). The radical intermediate reacts with another Mn(VII) species, [MnO$_4$OH]$^-$, to give the final products (Scheme 2). The effect of ionic strength and dielectric constant on the rate explains qualitatively the involvement of a neutral molecule in the reaction. From the above mechanism the following rate law, eqn. (1) - (8) can be derived.

\[
\text{Rate} = \frac{d[MnO_4^-]}{dt} = kK_1[MnO_4^-][NA][OH^-]
\]

(1)

Total concentration of permanganate is given by

\[
[MnO_4^-] = [MnO_4^+] + [MnO_4 \cdot OH]^2 + [\text{Complex}]
\]

\[
= [MnO_4^+] + kK_1K_2[MnO_4^-][NA][OH^-]
\]

In view of low concentration of MnO$_4^-$ and nalidixic acid used, above equation can be written as:

\[
[OH^-]_1 = [OH^-], \quad \ldots 4
\]

Similarly,

\[
[NA] = [NA], \quad \ldots 5
\]

Substituting equation (2), (4) and (5) in equation (1) and omitting “i” and “f” subscripts

\[
\text{Rate} = \frac{kK_1K_2[MnO_4^-][OH^-][NA]}{1+ K_1[OH^-] + kK_1K_2[OH^-][NA]} \quad \ldots 6
\]

\[
\frac{[MnO_4^-]}{[MnO_4^-]} = \frac{kK_2[OH^-][NA]}{1 + K_1[OH^-] + kK_1K_2[OH^-][NA]} \quad \ldots 7
\]

Equation (7) can be rearranged as

\[
\frac{1}{k_{obs}} = \frac{1}{kK_1K_2[OH^-][NA]} + \frac{1}{kK_1K_2[NA]} + \frac{1}{k} \quad \ldots 8
\]

According to Eqn (8) the plot of $1/k_{obs}$ versus 1/ [NA] (Figure 5) is linear with positive intercept and slope at three different temperatures. The rate constant k, of the slow step, (Scheme 2) was obtained from the intercept of the plots $1/k_{obs}$ versus 1/ [NA] (Table 2). The energy of activation was determined by the plot of log k versus 1/T from which activation parameters were calculated (Table 2). The equilibrium constant (K$_1$) and the equilibrium constant of complex (K$_2$) in Scheme 2 were calculated from the intercept and slope of the plot $1/ k_{obs}$ versus 1/ [OH] (Figure 6) (Table 2).

The value of K$_1$ is in good agreement with earlier work (Thabaj et al., 2007) at 40°C. Van’t Hoff’s plots of log K$_1$ versus 1/T and log K$_2$ versus 1/T gave the values of enthalpy of reaction $\Delta H$, entropy of reaction $\Delta S$ and free energy of reaction $\Delta G$, calculated for the first, and second equilibrium steps (Table 2).

The values of $\Delta H^e$ and $\Delta S^e$ are both favourable for electron transfer process (Farokhi and Nandibewoor, 2004). The value of $\Delta S^e$ within the range of radical reaction has been ascribed (Wallin, 1957) to the nature of electron pairing and unpairing process. The negative value of $\Delta S^e$ indicates that complex is more ordered than the reactants (Rangappa et al., 2001; Bugarcic et al.,...
The observed modest enthalpy of activation and a relatively low value of the entropy of activation as well as a higher rate constant of the slow step indicate that the oxidation probably occurs via inner-sphere mechanism (Farokhi and Nandibewoor, 2003).

CONCLUSION

It is interesting that the oxidant species [MnO₄⁻] requires pH > 12, below which the system becomes disturbed and the reaction proceeds further to give a reduced oxidation product as manganese(IV), which slowly develops a yellow turbidity. Hence, the role of pH in the reaction medium is crucial. The oxidant, manganese(VII), exists in alkali media as alkali-permanganate species [MnO₄OH]²⁻, which takes part in the chemical reaction. Chemical oxidation using Mn(VII) has been widely used for treatment of pollutants in drinking water and waste water applications. The proposed mechanism is consistent with product, mechanism and kinetic studies.

ACKNOWLEDGMENT

We are grateful to Department of Science and Technology sponsored FIST laboratory of our institution for experimental work and Sophisticated Analytical Instrumentation Facility, CIL, Punjab University, Chandigarh for LC-MS measurements.

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Conflict of Interests: There are no conflicts of interest.

REFERENCES


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Oxidation of levofloxacin by acidic permanganate: a kinetic and mechanistic study

Jain A, Tazwar G, Devra V

ABSTRACT
The kinetic and mechanistic investigation of oxidation of levofloxacin (LF) has been studied by permanganate ion in aqueous sulphuric acid medium at 25°C. The reaction followed first-order kinetics with respect to [LF], and [H+] in their lower concentrations range, tending to zero-order at their higher concentrations. The effect of added products and dielectric constant of the medium was studied on the rate of reaction. Effect of varying salt electrolyte concentration was insignificant showing that the molecular species was involved in the rate determining step. The main products were identified by spot test, FT-IR, and LC-MS. A mechanism was proposed on the basis of experimental results. The activation parameters with respect to the slow step of the mechanism were evaluated, and the thermodynamic parameters were also determined and discussed. Potassium permanganate widely used as oxidizing agent in the kinetics of number of organic and biological active compounds. Permanganate is multi-electron oxidant, which can exist in various oxidation states, among which +7 is its highest oxidation state. In acidic medium it exists in different forms as HMnO4, HMnO4+, HMnO3, Mn2O7 and one depending on the nature of the reductant. Levofloxacin is a broad spectrum drug of activity against various bacteria, including gram-positive and gram-negative microorganisms. Kinetic measurements were performed on a Peltier accessory (temperature-Controlled) attached to a U.V.3000+ UV-Visible spectrophotometer (LABINDIA). The product analysis is characterized by LC-ESI-MS and FT-IR studies. The reaction stoichiometry indicates that 5 moles of levofloxacin require 2 moles of Mn(VII). The oxidation products were identified as 7-amino fluoroquinolone and Mn (II). The reaction shows first order kinetics with respect to MnO4- and fractional order with respect to levofloxacin and hydrogen ion concentration. The effect of added product, varying salt electrolyte were studied on the rate of reaction. The rate constant of the slowest step and other equilibrium constants involved in the mechanism are evaluated. Overall mechanistic sequence described here is consistent with product, mechanistic and kinetic studies.

INTRODUCTION

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 (Figure. 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.
Levofloxacin is a broad spectrum drug of activity against various bacteria, including gram-positive and gram-negative microorganisms. 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. 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. Since the metal ions cause fluorescence quenching of the drug, the spectrofluorimetric method for quantitative determination of the quinolone type drugs has been developed along with titrimetric, spectrophotometric, electrochemical, and chromatographic techniques. 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. Chemical oxidation of pollutant in drinking water and waste water by Chloramine-T has been widely done. A number of kinetic study on oxidation of levofloxacin in alkaline, aqueous and acidic medium have been reported. In view of potential pharmaceutical importance of levofloxacin and lack of literature on the oxidation of this drug and complexity of the reaction, a detail study of the reaction become important. Perkin-Elmer spectrophotometer was used throughout this study. Standard chemicals used were of analytical grade and doubly distilled water was used in permanganate concentration range (0.50 – 5.0) × 10⁻³ mol/dm³ at 525 nm. The molar absorptivity index of permanganate was found to be ε = 2260 ±50 dm⁴ mol⁻¹ cm⁻¹ as a function of time (compared to the literature, ε = 2200). The kinetics reactions were followed more than 85 % completion of the reaction. The pseudo-first-order rate constants kobs were calculated from the plots of the logarithm of absorbance versus time, which were linear. The values of kobs were reproducible within ±5%.

RESULTS AND DISCUSSION

Stoichiometry and Product Analysis

Different sets of concentration of reactants at constant concentration of sulphuric acid and ionic strength were kept over 24 hrs at 25°C in a closed container. When permanganate > levofloxacin, the remaining permanganate concentration was assayed by measuring the absorbance at 525 nm. Estimation of unreacted MnO₄⁻ indicates that 5 moles of levofloxacin consumed 2 moles of Permanganate; the Stoichiometry of the reaction is given in equation (1).

```
\[
\text{MnO}_4^{-} + 28\text{O}_{2} + 17\text{H}^+ \rightarrow 25\text{H}_2\text{O} + 25\text{O}_2 + 14\text{H}^+ \\
\] (1)
```
LC/MS analysis of levofloxacin oxidation reaction indicates the formation of product with molecular ions of m/z 279 (Figure 2). The molecular ion of levofloxacin is m/z 361.4. The m/z 279 corresponds to full dealkylation of the piperazine ring (i.e. the –NH₂ product). It is worth noting, that oxidation of piperazine moiety of levofloxacin between oxidized centres and nitrogen atoms lead to distinctive mass loss m/z = 69 and m/z = 83. This was attributed to ring opening, dealkylation and deamination process, which finally yielded 7-amino fluoroquinolone product. The product was also short written as M-69, indicating the net mass loss of the product from the parent levofloxacin. Infrared Spectroscopy analysis confirmed the presence of –NH₂ group in the oxidation product (Figure. 3). The Infrared spectrum shows a peak at 3412.70 cm⁻¹ which is due to –NH stretching of the –NH₂ group and the remaining peaks are of the parent compound (quinolone ring). The by-product formaldehyde was identified by spot test. The other product ammonia was detected by Nessler’s reagent test.

**Reaction Orders**
The reaction orders were determined from the slopes of log $k_{obs}$ versus log [concentration] plots by different concentration of levofloxacin, permanganate and acid in turn, keeping all other concentration and conditions constant.

**Dependence of Rate on the Concentration of Permanganate**
The oxidant permanganate [MnO₄⁻] concentration varied from $7.5\times10^{-5}$ to $6\times10^{-4}$ mol dm⁻³, and all other concentrations and conditions were constant. The plot of log absorbance versus time was linear (Figure. 4) indicating that the reaction is first order with respect to [KMnO₄]. The observed pseudo first order rate constant ($k_{obs}$) were independent of the concentration of KMnO₄ (Table 1).

**Table 1:** “Effect of variation of [MnO₄⁻], [LF] and [H⁺] on the oxidation of levofloxacin by acidic permanganate at 25°C and I = 0.02 mol dm⁻³

<table>
<thead>
<tr>
<th>S. No.</th>
<th>$10^4$MnO₄⁻ (mol dm⁻³)</th>
<th>$10^4$ [LF] (mol dm⁻³)</th>
<th>$10^4$ [H⁺] (mol dm⁻³)</th>
<th>$10^4$kobs (s⁻¹)</th>
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<tbody>
<tr>
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[LF]=1.0×10−3 mol dm−3,[H+] = 1.0×10−2 mol dm−3and I = 0.02 mol dm−3. [MnO4−]=10−4 mol dm−3 = (A) 0.75, (B) 1.0, (C) 2.0, (D) 3.0, (E) 4.0, (F) 5.0, (G) 6.0

Dependence of Rate on the Concentration of Levofloxacin

The effect of concentration variation of levofloxacin on the rate of reaction was studied in the range 2×10−3 to 7×10−3 mol dm−3 at constant concentration of permanganate, acid and ionic strength at three temperatures viz. 20°, 25°, 30°C respectively. The rate of reaction increases with increasing concentration of levofloxacin (Table 1). A plot of log kobs versus log [LF] was linear with a slope of 0.64, thus indicating a fractional-order dependence on levofloxacin concentration. This was confirmed by the plot of 1/kobs versus 1/ [LF] (Figure.5) which was also linear with a positive intercept.

Figure 5 - Plots of 1/kobs versus 1/ [LF] at three different temperatures. [KMnO4] = 2.0 × 10−4 mol dm−3, [H+] = 1.0 × 10−2 mol dm−3 and I = 0.02 mol dm−3.

Dependence of Rate on the Concentration of Sulphuric Acid

The effect of concentration variation of sulphuric acid on the rate of reaction was studied in the concentration range 5×10−3 to 2×10−2 mol dm−3 at fixed concentration of permanganate, levofloxacin and ionic strength at three temperatures viz. 20°, 25°, 30°C respectively. Pseudo first-order rate constant (kobs) was found to be increased with increase in [H+] (Table 1). A plot of log kobs versus log [H+] was linear with a fractional slope of 0.60. This was confirmed by the plot of 1/kobs versus 1/ [H+] (Figure.6) which was also linear with a positive intercept.

Figure 6 - Plots of 1/kobs versus 1/ [H+] at three different temperatures. [KMnO4] = 2.0 × 10−4 mol dm−3, [LF] = 2.0 × 10−3 mol dm−3 and I = 0.02 mol dm−3.

Dependence of Rate on Ionic Strength and Dielectric Constant

Effect of change in varying electrolyte concentration was monitored to establish the nature of intermediate species in the rate determining step by Na2SO4. It was observed that the change in an ionic strength of the medium does not alter the rate constant. The absence of salt effect indicates that the reaction does not take place between ionic species. The slope of plots between log kobs against 1/ [LF] was zero, which confirms the presence of the molecular species in the rate determining step. 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.

Neutral Salts Dependence

The effect of added neutral salt on the rate of reaction has been studied at varying concentration 1×10−2 - 4×10−2 mol dm−3 of NaNO3, CH3COONa and NaF at fixed concentration of other reactant and constant conditions. Addition of different sodium salts has no effect on the reaction rates.

Effect of Initially Added Products

The initial added products, Mn(II) was studied in the range of 5 × 10−3 to 5 × 10−2 mol dm−3 while other reactants concentration and conditions constant, does not change the rate of reaction.

Test for Free Radical

The reaction mixture (10ml) in which known quantity (2ml) of acrylonitrile has been added and kept in an inert atmosphere for 5 hours then diluted with methanol, white precipitate was formed, indicating the intervention of free radicals in the reaction. The blank experiment of reacting either KMnO4 or levofloxacin alone with acrylonitrile did not induce polymerisation under the same conditions. Permanganate ion, MnO4− ion is powerful oxidizing agent in acidic medium. The stable oxidation product of MnO4− in acid medium is Mn(II). Figure 7 illustrates the spectroscopic changes occurring in the oxidation of levofloxacin by acid permanganate at 25°C with scanning interval of 1minute. The literature survey reveals that43Mn(IV) ion absorbs in region 400-600 nm. Figure 7 shows no features in this wavelength area indicating that MnO2 is not a reaction product.

Figure 7 - Spectral changes during the oxidation of levofloxacin (LF) by permanganate in acidic medium at 25°C. [KMnO4] = 2.0 × 10−3 mol dm−3, [LF] = 2.0 × 10−3 mol dm−3, [H+] = 1.0 × 10−2 mol dm−3 and I = 0.02 mol dm−3.
The reaction between levofloxacin and permanganate in sulphuric acid has Stoichiometry 5:2, with first order dependence with permanganate and less than unit order with $\text{H}^+$ concentration and levofloxacin concentration. The fact that Mn(II) is the reduced product of Mn(VII) in the reaction might indicate that levofloxacin shows a strong reducing character in $\text{H}_2\text{SO}_4$ medium. In view of the presence of sulphuric acid in the reaction mixture, the oxidation of LF by sulphuric acid was checked, and it was found to be negligible compared to the oxidation of LF by permanganate. The active species of permanganate in aqueous acid solution may be deduced from the dependence of the rate on $[\text{H}^+]$, in the reaction medium. The order of $[\text{H}^+]$ is less than unity, which may indicate the formation of permanganate acid from permanganate ion. Permanganate acid $\text{HMnO}_4$ is more efficient oxidant species of Manganese (VII) then permanganate ion. It has been observed that the rate of reaction was tending to attain a limiting value at higher concentration of $[\text{H}^+]$ ion, which indicates that only the protonated form is active then acid permanganate. The negligible effect of ionic strength on the rate of reaction also confirms that $\text{HMnO}_4$ is the active species of $\text{MnO}_{4}^\cdot$, can be represented by equation-(2)

$$\text{MnO}_{4}^\cdot + \text{H}^+ \xrightarrow{K_f} \text{HMnO}_4$$

(2)

Where $K_f$ is the equilibrium constant of $\text{HMnO}_4$.

In view of increasing the rate with increase in $[\text{H}^+]$ ion, in the prior equilibrium step, $\text{H}^+$ reacts with $\text{MnO}_4^\cdot$ to form $\text{HMnO}_4$, which reacts with the one mole of levofloxacin to form a complex. Complex formed is dissociate in the rate determining step to give a free radical derived from levofloxacin and an intermediate Mn(VI). In further fast steps the intermediate Mn(VI) reacts with a free radical to produce the product 7-amino fluoroquinolone, $\text{NH}_2$, HCHO and intermediate Mn(V), subsequently reduced to the end product Mn(II). Although Mn(VI) and Mn(IV) are the final reduced species of $\text{MnO}_4^\cdot$ in alkaline and neutral media, it was observed that Mn(II) was the only reduced species of $\text{MnO}_4^\cdot$ in acid medium. Attempts were made to allow spectroscopic detection of intermediate Mn(V) and Mn(III) as the reaction proceeded in the oxidation of levofloxacin by permanganate. Unfortunately the low concentration of Mn(V) and Mn(III) intermediate obtained under our experimental conditions made the spectroscopic detection failure. However, the evidence for intermediate such as Mn(V) and Mn(III) are reported in the literature. The results are accommodated in the following mechanism (Scheme 1).

$$\text{MnO}_4^\cdot + \text{H}^+ \xrightarrow{K_f} \text{HMnO}_4$$

(3)

Here, $\text{AR} = \text{CH}_3\text{AR} \cdot \text{NN} + \text{Mn (VI)} + \text{H}^+$

Complex $\xrightarrow{k_{\text{Fast}}} \text{AR} \cdot \text{N} \cdot \text{CH}_3 + \text{Mn (VI)} + \text{H}^$

Scheme-1Proposed mechanism for the oxidation of Levofloxacin by acidic permanganate.

Following rate law can be derived from scheme 1:

Rate$= \frac{-d[\text{MnO}_4^\cdot]}{dt} = k[\text{Complex}]$

$=kK_2[\text{HMnO}_4][\text{LF}]$

$=kK_1K_2[\text{MnO}_4^\cdot][\text{H}^+]_i[\text{LF}]_i$ (3)

Total concentration of permanganate is given by

$[\text{MnO}_4^\cdot]_i = [\text{MnO}_4^\cdot]_i + [\text{HMnO}_4] + [\text{Complex}]$

$=[\text{MnO}_4^\cdot]_i + K_1[\text{MnO}_4^\cdot][\text{H}^+]_i + K_2[\text{HMnO}_4][\text{LF}]_i$

$=[\text{MnO}_4^\cdot]_i + K_1[\text{MnO}_4^\cdot][\text{H}^+]_i + K_1K_2[\text{MnO}_4^\cdot][\text{H}^+]_i[\text{LF}]_i$

$=[\text{MnO}_4^\cdot]_i \left[1 + K_1[\text{H}^+]_i + K_1K_2[\text{H}^+]_i[\text{LF}]_i\right]$ (4)

$[\text{MnO}_4^\cdot]_i$, and $[\text{MnO}_4^\cdot]_i$ are total free concentration of Mn (VII) respectively.

Total concentration of levofloxacin is given by:

$[\text{LF}]_i = [\text{LF}]_i + [\text{Complex}]$

$=[\text{LF}]_i + K_2[\text{LF}]_i[\text{HMnO}_4]$}

$=[\text{LF}]_i \left[1 + K_2[\text{HMnO}_4]\right]$
According to the rate determining step in Scheme 1, the change in the ionic strength and dielectric constant of the medium does not alter the reaction rate, which suggests the involvement of non-ionic species at the rate-determining step. The values of $\Delta H^\circ$ and $\Delta S^\circ$ are both favourable for electron transfer process. The value of $\Delta S^\circ$ within the range of radical reaction has been ascribed to the nature of electron pairing and unpairing process. The negative value of $\Delta S^\circ$ indicates that complex is more ordered than the reactants. The observed modest enthalpy of activation and a relatively low value of the entropy of activation as well as a higher rate constant of the slow step indicate that the oxidation presumably occurs via inner-sphere mechanism.

### Table 2: “Activation and thermodynamic quantities for the oxidation of levofloxacin by acidic permanganate from scheme 1”

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<tr>
<td>$\Delta H^\circ$ (kJ mol$^{-1}$)</td>
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</tr>
<tr>
<td>$\Delta S^\circ$ ± (J K$^{-1}$ mol$^{-1}$)</td>
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</tr>
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<td>$\Delta G^\circ$ ± (kJ mol$^{-1}$)</td>
<td>80.77</td>
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<table>
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<th>Equilibrium constants at different temperatures</th>
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<th>Thermodynamic quantities</th>
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<th>Using $K_2$ values</th>
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<td>$\Delta H$ (kJ mol$^{-1}$)</td>
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<td>$\Delta S$ ± (J K$^{-1}$ mol$^{-1}$)</td>
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</tr>
<tr>
<td>$\Delta G$ ± (kJ mol$^{-1}$)</td>
<td>-1.14</td>
<td>-1.0</td>
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</table>

### CONCLUSION

The oxidant MnO$_2$ exists in acid medium as H MnO$_2$, which takes part in the chemical reaction. The oxidation of levofloxacin by permanganate in acidic medium has a Stoichiometry of 5:2. The oxidation products were identified as Mn(II), 7-amino fluoroquinolone, NH$_3$ and HCHO. Dealkylated products of levofloxacin have antimicrobial activity. Since dealkylated products are obtained in the present study, it is evident that the products of the title reaction have antimicrobial activity after oxidation. So this study will be effectively used in waste water treatment at the sites contaminated by fluoroquinolone antibiotics. The rate constant of the slowest step and other equilibrium constants involved in the
mechanism are evaluated, and activation parameters with respect to slowest step were computed.

ACKNOWLEDGMENT

We are grateful to Department of Science and Technology sponsored FIST laboratory of our institution for experimental work and Sophisticated Analytical Instrumentation Facility, CIL, Punjab University, Chandigarh for LC-MS measurements and University Grants Commission, New Delhi for financial support through Junior Research Fellowship.

REFERENCES


Kinetics and Mechanism of Permanganate Oxidation of Ciprofloxacin in Aqueous Sulphuric Acid Medium

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P.G. Department of Chemistry, J. D. B. Govt. Girls P.G. College, University of Kota, Kota-324001, Rajasthan, India

ABSTRACT
The oxidation of ciprofloxacin (CIP) by permanganate ion in aqueous sulphuric acid medium at constant ionic strength (I = 0.05 mol dm⁻³) has been investigated spectrophotometrically at 525 nm. Order with respect to substrate, oxidant and acid concentrations were determined. Product characterization of reaction mixture indicates the formation of major product m/z 263 corresponding to dealkylation of the piperazine ring of ciprofloxacin. The piperazine moiety of ciprofloxacin is the predominant oxidative site to KMnO₄. Product analysis indicates that oxidation of permanganate results in dealkylation at the piperazine moiety of ciprofloxacin, with the quinolone ring essentially intact. The reaction constants involved in different steps of the mechanism were calculated at different temperatures. The activation parameters with respect to the slow step of the mechanism were computed and thermodynamic quantities were also determined.

Keywords: Permanganate, ciprofloxacin, sulphuric acid, oxidation, kinetics.

INTRODUCTION
Fluoroquinolones currently represent one of the most important classes of antibacterial agents worldwide, on the basis of annual global sales and therapeutic versatility. [1] They are a family of synthetic, broad spectrum antibacterial compounds, used in a multitude of human and veterinary applications. [2] Ciprofloxacin(CIP)[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(piperazine-1-yl)-quinolone-3-carboxylic acid] is a second generation fluoroquinolone antimicrobial agent with a wide spectrum of activity against many gram positive and gram negative aerobic and anaerobic bacteria. Ciprofloxacin has been use in the treatment of a wide range of infections. Due to their extensive usage, fluoroquinolones may enter in the environment via waste water effluent and bio solids from sewage treatment plants. There are studies on the modified pharmacological and toxicological properties of these drugs in the form of metallic complexes. [3-5] The structure of Ciprofloxacin is shown below which consist of piperazine and pyridone moieties. Potassium permanganate is widely used as an oxidizing agent as well as in analytical chemistry. These reactions are governed by the pH of the medium. Among six oxidation states of manganese from +2 to +7, permanganate, Mn(VII) is the most potent oxidant in acid as well as is alkaline media. Permanganate oxidation finds extensive applications in organic synthesis [6-7], especially since the advent of phase transfer catalysis. [8-9] In general, the reduction of
permanganate in slightly basic or neutral solution and in acid media goes through Mn(IV) and Mn(II) with reduction potentials \([10]\) of 1.695 V for Mn(VII)/Mn(IV) and 1.51V for Mn(VII)/Mn(II). In acid medium, permanganate exists in different forms namely Hmno_4 and H_2MnO_4^+ and depending on the nature of the reductant, the oxidant has been assigned both inner sphere and outer sphere mechanism pathways in their redox reactions.\([11-12]\)

A literature survey reveals that there are few study reports \([13-15]\) on the oxidation of ciprofloxacin in either alkaline or acidic medium. In view of the potential pharmaceutical importance of ciprofloxacin and lack of reported kinetic & mechanical data on the oxidation of this drug, a detailed oxidation study might elucidate the mechanism of conversion of such compounds. The present study deals to investigate the redox chemistry of permanganate in acid media and establishing a plausible mechanism for oxidation of ciprofloxacin by permanganate on the basis of experimental results.

**MATERIALS AND METHODS**

**Experimental**

All chemicals used were of analytical grade and doubly distilled water was used throughout this study. An aqueous solution of ciprofloxacin (KORES India Limited) was prepared by dissolving known amount of its hydrochloride salt in double distilled water. Permanganate solution was obtained by dissolving potassium permanganate (BDH Analar) in water and standardized by titrating against oxalic acid.\([16]\) Freshly prepared & standardized permanganate solutions were always used in kinetics experiments. The Mn(II) solution was made by dissolving manganese sulphate (BDH) in water. Na_2SO_4 (BDH) and H_2SO_4 (MERCK) were used to provide required ionic strength & acidity respectively.

For kinetic measurements, a Peltier accessory (temperature-Controlled) attached to a U.V. 3000+ UV-Visible spectrophotometer (LABINDIA) was used. For product analysis, an LC-ESI-MS, (Q-TOF Micromass, WATERS Company, UK), an alpha-T FTIR spectrophotometer (Bruker, Germany), and for pH measurements MSW-552 pH meter were used.

**Kinetic measurements**

All kinetic measurements were conducted under pseudo first order conditions, where the concentration of ciprofloxacin was much greater than permanganate ion concentration at constant temperature at 25 ± 0.1°C unless otherwise stated. The reaction was initiated by mixing thermostated solution of permanganate and ciprofloxacin with the required amount of sulphuric acid and sodium sulphate. The progress of the reaction was followed spectrophotometrically at 525nm. The Beer’s law verified in permanganate concentration range (0.50 - 5.0) × 10^-4 moldm^-3 at 525 nm. The molar absorptivity index of permanganate was found to 2260 ± 50 dm^3 mol^-1 cm^-1 as a function of time. The kinetics reactions were followed more than 85 % completion of the reaction. The pseudo first order rate constant \(k_{obs}\) were calculated from the plots of log(abs) versus time, which were linear. The values of \(k_{obs}\) were reproducible within ± 5%.

**Stoichiometry and product analysis**

Different sets of concentration of reactants in 0.01 mol dm^-3 sulphuric acid at constant ionic strength, 0.05mol dm^-3, were kept over 24 hours at 25°C in a closed container. When \([\text{permanganate}] > [\text{ciprofloxacin}]\), the remaining permanganate concentration was assayed by measuring the absorbance at 525 nm. Estimation of unreacted \([\text{MnO}_4^-]\) indicates that 5 moles of ciprofloxacin consumed 2 moles of Permanganate; the Stoichiometry of the reaction is given in equation (1).

\[
\text{MnO}_4^- + 5\text{NH}_3 + 20\text{HCHO} + 4\text{H}^+ \rightarrow \text{Mn}^{2+} + 5\text{N}_2 + 20\text{H}_2\text{O}.
\]

LC/MS analysis of ciprofloxacin reaction indicates the formation of product with molecular ions of m/z 263 (Fig. 1). The molecular ion of ciprofloxacin is m/z 332. The m/z 263 corresponds to full dealkylation of the piperazine ring (i.e. the -NH_2 product). It is worth noting, that oxidation of piperazine moiety of ciprofloxacin between oxidized centres and nitrogen atoms lead to distinctive mass loss m/z = 69 and m/z = 83. This was attributed to ring opening, dealkylation and deamination process, which finally yielded 7-amino fluoroquinolone product. The product was also short written as M-69, indicating the net mass loss of the product from the parent ciprofloxacin. This product was also identified previously as oxidation product of ciprofloxacin \([17]\) and IR Spectroscopy analysis confirmed the presence of -NH_2 group in the oxidation product (Fig. 2). The IR spectroscopy shows a peak at 3324 cm^-1 which is due to -NH stretching of the -NH_2 group and the remaining peaks of the parent compound (quinolone ring). The by-product formaldehyde was identified by spot test.\([18]\) The other product ammonia was detected by Nesseler’s reagent test.\([19]\)

**Fig. 1:** LC-ESI-MS spectra of oxidation product of ciprofloxacin. (a) Molecular ion peak of m/z 263 (M-69). (b) Fragmentation of (M-69) product.
RESULTS AND DISCUSSION

Permanganate dependence
The reaction orders were determined from the slopes of log k<sub>obs</sub> versus log [concentration] plots by different concentration of ciprofloxacin, permanganate and acid in turn, keeping all other concentration and conditions constant. The oxidant permanganate [MnO<sub>4</sub>⁻] concentration varied from 5 × 10⁻⁵ to 4 × 10⁻⁴ mol dm⁻³, and all other concentrations and conditions were constant (Fig. 3). The plot of log absorbance versus time was linear (Fig. 3) indicating that the reaction is first order with respect to [KMnO₄]. The observed pseudo first order rate constant k<sub>obs</sub> were independent of the concentration of KMnO₄.

Ciprofloxacin dependence
The effect of variation of ciprofloxacin on the rate of reaction was studied in the concentration range 1 × 10⁻³ to 7×10⁻³ mol dm⁻³ at constant concentration of permanganate, acid and constant ionic strength at 25°C. The rate of reaction increases with increasing concentration of ciprofloxacin. The value of slope of the plot of log k<sub>obs</sub> versus log [CIP] was found to be unity, which confirms the reaction is first order with respect to ciprofloxacin concentration. This was also confirmed by the plot of k<sub>obs</sub> versus ciprofloxacin concentration (Fig. 4) which is a straight line passing through the origin.

Hydrogen ion dependence
The effect of variation of sulphuric acid on the rate of reaction was studied in the concentration range 0.01 to 0.07 mol dm⁻³ at fixed concentrations of permanganate, ciprofloxacin and constant ionic strength at three temperatures viz. 25°C, 30°C, 35°C respectively and other conditions were constant. k<sub>obs</sub> was found to be increased with increase [H<sup>+</sup>] concentration (Table 1). The order with respect to [H<sup>+</sup>] was found to be less than unity (0.68).

Effect of ionic strength and dielectric constant
At constant concentration of reactants and other conditions constant, the ionic strength was varied by varying concentration of sodium sulphate 0.01 to 0.1mol dm⁻³. 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.

Table 1: Observed rate constants for the reaction of ciprofloxacin and permanganate at different hydrogen ion concentration at three temperatures. [CIP] = 2.0 × 10⁻³ mol dm⁻³, [KMnO₄] = 2.5 × 10⁻⁴ mol dm⁻³, I = 0.05 mol dm⁻³.

<table>
<thead>
<tr>
<th>[H&lt;sup&gt;+&lt;/sup&gt;] (mol dm⁻³)</th>
<th>25°C</th>
<th>30°C</th>
<th>35°C</th>
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<td>8.21</td>
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</table>

Effect of added products
At constant concentration of reactants and other conditions constant, the ionic strength was varied by varying concentration of sodium sulphate 0.01 to 0.1mol dm⁻³. 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.
The initial added products, Mn(II) was studied in the range of $5 \times 10^{-5}$ to $5 \times 10^{-4}$mol dm$^{-3}$ while other reactants concentration and conditions constant and aldehyde does not change the rate of reaction.

Test for free radical

The reaction mixture(10 ml) to which a known quantity (2 ml) of acrylonitrile has been added and kept in an inert atmosphere for 5 hours then diluted with methanol, white precipitate was formed, indicating the intervention of free radicals in the reaction. The blank experiment of reacting either KMnO$_4$ or ciprofloxacin alone with acrylonitrile did not induce polymerisation under the same conditions.

The expected oxidizing species of permanganate in acid media are HMnO$_4$, H$_2$MnO$_4^+$, HMnO$_3$ and Mn$_2$O$_7$. Among them MnO$_4^-$ ion is powerful oxidizing agent in aqueous alkaline as well as in acidic medium. The stable reduction product of MnO$_4^-$ in acid medium is Mn(II). Figure 5 illustrates the spectroscopic changes occurring in the oxidation of ciprofloxacin by acid permanganate at 25°C with scanning interval of 3 minutes. The literature survey reveals that [20] Mn(IV) ion absorbs in region 400-600 nm. Figure 5 shows no features in this wavelength area indicating that MnO$_2$ is not a reaction product.

The reaction between permanganate and ciprofloxacin in sulphuric acid has Stoichiometry 5:2, with first order dependence with permanganate and ciprofloxacin and less than unit order with H$^+$ concentration. The oxidation products were Mn(II), 7-amino fluoroquinolone, NH$_3$ and HCHO. On the basis of experimental results, the mechanism can be proposed. In view of increasing the rate with increase in [H$^+$] ion, in the prior equilibrium step, H$^+$ reacts with MnO$_4^-$ to form HMnO$_4$ which reacts with the one mole of ciprofloxacin in the rate determining step to give a free radical derived from ciprofloxacin and an intermediate Mn(VI). In further fast steps the intermediate Mn(VI) reacts with a free radical to produce the product 7-amino fluoroquinolone, NH$_3$, HCHO and intermediate Mn(V). In further fast steps Mn(V) subsequently reduced to the end product Mn(II). Although Mn(VI) and Mn(IV) are the final reduced species of MnO$_4^-$ in alkaline and neutral media, it was observed that Mn(II) was the only reduced species of MnO$_4^-$ in acid medium. Since none of the intermediate could be detected, scheme-1 is the only possible mechanism for the reaction in the presence of free radical. Attempts were made to allow spectroscopic detection of intermediate Mn(V) and Mn(III) as the reaction proceeded in the oxidation of ciprofloxacin by permanganate. Unfortunately the low concentration of Mn(V) and Mn(III) intermediate obtained under our experimental conditions made the spectroscopic detection failure. However, the evidence for intermediate such as Mn(V) and Mn(III) is as presented in the literature. [23-24] The results are accommodated in the following mechanism.

![Fig. 5: Spectral changes during the oxidation of ciprofloxacin (CIP) by permanganate in acidic medium at 25°C: [MnO$_4$] = 2.0 $\times$ 10$^{-5}$, [CIP] = 2.0 $\times$ 10$^{-3}$, [H$^+$] = 1.0 $\times$ 10$^{-2}$ and I = 0.05 mol dm$^{-3}$.](image)

The results are accommodated in the following mechanism.

Scheme 1. Proposed mechanism for the oxidation of ciprofloxacin by acidic permanganate.
From the scheme-1, the following rate law can be derived as follows:

\[
\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = k_i[\text{HMnO}_4][\text{CIP}]
\]

(3)

\[
= k_i K_i[\text{MnO}_4^-][\text{CIP}][H^+]
\]

(4)

The total concentration of permanganate is given by:

\[
[\text{MnO}_4^-]_i = [\text{MnO}_4^-] + [\text{HMnO}_4^-]
\]

(5)

\[
= [\text{MnO}_4^-] + K_i[H^+][\text{MnO}_4^-]
\]

\[
= [\text{MnO}_4^-] (1 + K_i[H^+])
\]

(6)

 Putting equation (5) and (6) in equation (4) and omitting “t” and “f” subscripts

\[
\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = \frac{k_i K_j[\text{MnO}_4^-][\text{CIP}][H^+]}{1 + K_i[H^+] + K_j[\text{MnO}_4^-] + K_i[H^+][\text{MnO}_4^-]}
\]

(7)

\[
K_j[\text{MnO}_4^-] \text{ and } K_i[H^+][\text{MnO}_4^-] \ll 1 \text{ or neglected due to low concentration of } [\text{MnO}_4^-] \text{ used in the experiment so equation (8) change to equation (9)}
\]

\[
\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = \frac{k_i K_j [\text{MnO}_4^-][\text{CIP}][H^+]}{1 + K_i[H^+]}\]

(9)

\[
\frac{[\text{MnO}_4^-]}{\text{Rate}} = \frac{k_i K_j[\text{CIP}][H^+]}{1 + K_i[H^+]}\]

(10)

(Where \(k_i = \text{First order rate constant}\))

\[
\frac{1}{k_i} = \frac{1}{k_i} + \frac{1}{k_i}
\]

Equation (11) can be rearranged as

(12)

According to equation (12) the plot of [CIP]/\(k_{obs}\) versus 1/ [H+] is linear with positive intercept and slope (Fig. 6) at three different temperatures. The rate constant \(k_i\) of the slow step, scheme-1 was obtained from the intercept of the plots [CIP]/\(k_{obs}\) versus 1/ [H+] (Table 2). The energy of activation was determined by the plot of log \(k_i\) versus 1/T from which activation parameters were calculated (Table 2). The equilibrium constant of HMK (K_i) was calculated from the intercept and slope of the plot [CIP] / \(k_{obs}\) versus 1/ [H+] (Table 2). The value of K_i is in good agreement with earlier work \(^{23}\) (literature value is 40 dm^3 mol^-1 at 25°C). Thermodynamic quantities were calculated from the Van’t Hoff plot (Table 2).

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ABSTRACT

The kinetics and mechanism of oxidation of ofloxacin by permanganate ion in acidic medium have been studied at 30 ±1°C. The Stoichiometry has been observed to be 2:5 in terms of mole ratio of permanganate ion and ofloxacin consumed. The reaction shows first order with respect to oxidant and fractional order in both the substrate and hydrogen ion concentration. The effect of added products and ionic strength has also been investigated. The main products identified were 7-amino quinolone and Mn(II). Investigation of the reaction at different temperature allowed the determination of the activation parameters with respect to the slow step of the proposed mechanism.

Keywords: Kinetics, Oxidation, Mechanism, Ofloxacin, Permanganate ion, Sulphuric acid medium.

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-benzoazine-6-carboxylic acid] belongs to the fluoroquinolone class of antibiotics. They are synthetic broad spectrum antibacterial drugs that exhibit significant activity against both gram-positive and gram-negative bacteria. [1] They act as specific inhibitors of the bacterial DNA-Gyrase, the enzyme responsible for converting double stranded DNA into a negative super-helical form. Ofloxacin possess two relevant ionisable functional groups: a basic piperazinyl group and a carboxylic group. The carboxylic group and the carbonyl groups are required for antimicrobial activity.
Potassium permanganate is widely used as an oxidizing, disinfectant and also as an analytical reagent. [2] The oxidation by Mn(VII) ions finds extensive applications in organic synthesis [3], especially since the advent of phase transfer catalysis. [4-6] Kinetic studies are important sources of mechanistic information on such reactions, as demonstrated by the results referring to unsaturated acids both in aqueous [4-7] and in non-aqueous media. [8] During oxidation by Mn(VII) it is evident that Mn(VII) is reduced to various oxidation states in acid, alkaline and neutral media. Among six oxidation states of manganese from +2 to +7, permanganate, Mn(VII) is the most potent oxidation state in acid medium with reduction potentials [9] 1.69V of Mn(VII)/Mn(IV) couple and 1.51V of Mn(VII)/Mn(II) couple. In acidic medium active species of Mn(VII) exists in different forms as HMnO₄, H₂MnO₄⁺, HMnO₃ and Mn₂O₇ depending on the nature of the reductant, the oxidant has been assigned both inner sphere and outer sphere mechanism pathways in their redox reactions [10, 11].

The literature survey reveals that there are few study reports [12, 13] on the oxidation of ofloxacin by MnO₂ followed by evaluation of the reaction kinetics and analysis of chemical structure of degradation products formed. Interaction of ofloxacin with various metal ions was studied for the determination of ofloxacin spectrophotometrically and polarographically in pharmaceutical formulation. [14-17] Hence, ofloxacin finds extensive application in pharmaceutical industry. It is noted that despite the importance of the drug, the literature survey reveals that there is no information about the oxidation kinetics. Thus prompted us to undertake the title reaction. The present study deals to investigate the redox chemistry of permanganate in acid media and establishing a plausible mechanism for oxidation of ofloxacin by permanganate on the basis of experimental results.

**MATERIALS AND METHODS**

**Chemicals**

All chemicals used were of analytical grade and doubly distilled water was used throughout this study. Standard solution of ofloxacin (KORES India Limited) was prepared by dissolving calculated quantity of pure drug in 0.1 M H₂SO₄. The acid present in the substrate solution is also taken into account in the calculation of the total acid present in each case of the present reaction. Permanganate solution was obtained by dissolving potassium permanganate (BDH Analar) in water and standardized by titrating against oxalic acid. [18] Freshly prepared & standardized permanganate solutions were always used in kinetics experiments. The Mn(II) solution was made by dissolving manganese sulphate (BDH) in water. Na₂SO₄ (BDH) and H₂SO₄ (MERCK) were used to provide required ionic strength & acidity respectively.
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), and for pH measurements MSW-552 pH meter were used.

Kinetic Measurements

All kinetic measurements were conducted under pseudo-first-order conditions, where the concentration of ofloxacin was much greater than permanganate ion concentration at constant temperature 30 ± 0.1°C unless otherwise stated. The reaction was initiated by mixing thermostated solution of permanganate and ofloxacin; in addition to that required quantities of H₂SO₄, Na₂SO₄ are added to provide required acidity and ionic strength of reaction. The progress of the reaction was followed spectrophotometrically at 525nm. The Beer’s law verified in permanganate concentration range (0.50 – 5.0) × 10⁻⁴ mol dm⁻³ at 525nm. The molar absorptivity index of permanganate was found to be ε = 2260 ±50 dm³ mol⁻¹ cm⁻¹ as a function of time. The kinetics reactions were followed more than 85 % completion of the reaction. The pseudo-first-order rate constants kobs were calculated from the plots of the logarithm of absorbance versus time, which were linear. The values of kobs were reproducible within ± 5%.

Stoichiometry and Product Analysis

Different sets of concentration of reactants in 0.01 mol dm⁻³ sulphuric acid at constant ionic strength, 0.02mol dm⁻³, were kept over 24 hrs at 30°C in a closed container. When [permanganate] > [ofloxacin], the remaining permanganate concentration was assayed by measuring the absorbance at 525 nm. Estimation of unreacted [MnO₄⁻] indicates that 5 moles of ofloxacin consumed 2 moles of Permanganate; the Stoichiometry of the reaction is given in equation (1).

\[
\begin{align*}
  &5 \overset{\text{OCH}_3}{\overset{\text{F}}{\overset{\text{NH}_2}{\text{N}}}} \overset{\text{O}}{\text{H}} + 2\text{MnO}_4^- + 17\text{H}_2\text{O} \\
  &\rightarrow 5 \overset{\text{OCH}_3}{\overset{\text{F}}{\overset{\text{NH}_2}{\text{N}}}} \overset{\text{O}}{\text{H}} + 2\text{Mn}^{2+} + 5\text{NH}_3 + 25\text{HCHO} + 14\text{H}^+
\end{align*}
\]

(1)

LC/MS analysis of ofloxacin oxidation reaction indicates the formation of product with molecular ions of m/z 279 “Fig.1”. The molecular ion of ofloxacin is m/z 362. The m/z 279 corresponds to full dealkylation of the piperazine ring (i.e. the –NH₂ product). It is worth
noting, that oxidation of piperazine moiety of ofloxacin between oxidized centres and nitrogen atoms lead to distinctive mass loss m/z = 69 and m/z = 83. This was attributed to ring opening, dealkylation and deamination process, which finally yielded 7-amino fluoroquinolone product. The product was also short written as M-69, indicating the net mass loss of the product from the parent ofloxacin. This product was also identified previously as oxidation product of ofloxacin \cite{19} and IR Spectroscopy analysis confirmed the presence of –NH₂ group in the oxidation produc “Fig.2”. The IR spectroscopy shows a peak at 3353.85 cm⁻¹ which is due to -NH stretching of the –NH₂ group and the remaining peaks are of the parent compound (quinolone ring).The by-product formaldehyde was identified by spot test \cite{20}. The other product ammonia was detected by Nesseler’s reagent test. \cite{21}

Fig. 1LC-ESI-MS spectra of oxidation product of ofloxacin. (a) Molecular ion peak of m/z 279 (M-69). (b) Fragmentation of (M-69) product.
RESULTS
The reaction orders were determined from the slopes of log $k_{obs}$ versus log [concentration] plots by different concentration of ofloxacin, permanganate and acid in turn, keeping all other concentration and conditions constant.

Permanganate Dependence
The oxidant permanganate $[\text{MnO}_4^-]$ concentration varied from $7.5 \times 10^{-5}$ to $6 \times 10^{-4}$ mol dm$^{-3}$, and all other concentrations and conditions were constant. The plot of log absorbance versus time was linear “Fig. 3” indicating that the reaction is first order with respect to $[\text{KMnO}_4]$. The observed pseudo first order rate constant ($k_{obs}$) were independent of the concentration of $\text{KMnO}_4$.

Fig. 3 First order plots of the variation of permanganate concentration at 30°C. $[\text{OFL}]=1.0 \times 10^{-3}$, $[\text{H}^+] = 1.0 \times 10^{-2}$ and $I = 0.02$/ mol dm$^{-3}$. $[\text{MnO}_4^-]\times 10^{-4}$ mol dm$^{-3} = (A) 0.75, (B) 1.0,(C) 2.0, (D) 3.0, (E) 4.0, (F) 5.0, (G) 6.0$
Ofloxacin Dependence
The effect of concentration variation of ofloxacin on the rate of reaction was studied in the range \(2 \times 10^{-3}\) to \(7 \times 10^{-3}\) mol dm\(^{-3}\) at constant concentration of permanganate, acid and ionic strength at 20\(^{\circ}\), 25\(^{\circ}\), 30\(^{\circ}\)C respectively. The rate of reaction increases with increasing concentration of ofloxacin (Table 1). A plot of \(\log k_{\text{obs}}\) versus \(\log [\text{OFL}]\) was linear with a slope of 0.63, thus indicating a fractional-order dependence on ofloxacin concentration. This was confirmed by the plot of \(1/k_{\text{obs}}\) versus \(1/ [\text{OFL}]\) “Fig.4” which was also linear with a positive intercept.

Hydrogen Ion Dependence
The effect of concentration variation of sulphuric acid on the rate of reaction was studied in the concentration range \(2 \times 10^{-3}\) to \(2 \times 10^{-2}\) mol dm\(^{-3}\) at fixed concentration of permanganate, ofloxacin and ionic strength at three temperatures viz. 20\(^{\circ}\), 25\(^{\circ}\), 30\(^{\circ}\)C respectively. Pseudo first-order rate constant \((k_{\text{obs}})\) was found to be increased with increase in \([H^+]\) (Table 1). A plot of \(\log k_{\text{obs}}\) versus \(\log [H^+]\) was linear with a fractional slope of 0.75. This was confirmed by the plot of \(1/k_{\text{obs}}\) versus \(1/ [H^+]\) “Fig.5” which was also linear with a positive intercept.

Table 1: Effects of variation of \([\text{MnO}_4^-]\), \([\text{OFL}]\) and \([H^+]\) on the oxidation of ofloxacin by acidic permanganate at 30\(^{\circ}\)C and \(I = 0.02\) mol dm\(^{-3}\).

<table>
<thead>
<tr>
<th>(10^4 [\text{MnO}_4^-]) (mol dm(^{-3}))</th>
<th>(10^4 [\text{OFL}]) (mol dm(^{-3}))</th>
<th>(10^4 [H^+]) (mol dm(^{-3}))</th>
<th>(10^3 k_{\text{obs}}) (s(^{-1}))</th>
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Effect of Ionic Strength and Dielectric Constant
At constant concentration of reactants and other conditions constant, the ionic strength was varied by varying concentration of sodium sulphate 0.01 to 0.1mol dm\(^{-3}\). 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.

Effect of Added Products
The initial added products, Mn(II) was studied in the range of 5 × 10\(^{-5}\) to 5 × 10\(^{-4}\) mol dm\(^{-3}\) while other reactants concentration and conditions constant and by-product aldehyde does not change the rate of reaction.

Test for Free Radical
The reaction mixture (10ml) in which known quantity (2ml) of acrylonitrile has been added and kept in an inert atmosphere for 5 hours then diluted with methanol, white precipitate was formed, indicating the intervention of free radicals in the reaction. The blank experiment of reacting either KMnO\(_4\) or ofloxacin alone with acrylonitrile did not induce polymerisation under the same conditions.

DISCUSSION
The expected oxidizing species of permanganate in acid media are HMnO\(_4\), H\(_2\)MnO\(_4^+\), HMnO\(_3\) and Mn\(_2\)O\(_7\). Permanganate ion, MnO\(_4^-\) ion is powerful oxidizing agent in acidic medium. The stable oxidation product of MnO\(_4^-\) in acid medium is Mn(II). The active species of permanganate in aqueous acid solution may be deduced from the dependence of the rate on [H\(^+\)], in the reaction medium. The order of [H\(^+\)] is less than unity, which may be indicate the formation of permanganate acid from permanganate ion. Permanganate acid HMnO\(_4\) is more efficient oxidant species of Manganese (VII) then permanganate ion \(^{[22]}\). It has been observed that the rate of reaction was tending to attain a limiting value at higher concentration of [H\(^+\)] ion, which indicates that only the protonated form is active then acid permanganate \(^{[23]}\).

Equilibrium can be represented by equation-(2)

\[
\text{MnO}_4^- + H^+ \rightleftharpoons K_{eq} \to \text{HMnO}_4
\] (2)
The reaction between ofloxacin and permanganate in sulphuric acid has Stoichiometry 5:2, with first order dependence with permanganate and less than unit order with H\(^+\) concentration and ofloxacin concentration. The oxidation products were Mn(II), 7-amino fluoroquinolone, NH\(_3\) and HCHO. In view of increasing the rate with increase in [H\(^+\)] ion, in the prior equilibrium step, H\(^+\) reacts with MnO\(_4\)\(^-\) to form HMnO\(_4\), which reacts with the one mole of ofloxacin to form a complex. Complex formed is dissociate in the rate determining step to give a free radical derived from ofloxacin and an intermediate Mn(VI). In further fast steps the intermediate Mn(VI) reacts with a free radical to produce the product 7-amino fluoroquinolone, NH\(_3\), HCHO and intermediate Mn(V). In further fast steps Mn(V) subsequently reduced to the end product Mn(II). Although Mn(VI) and Mn(IV) are the final reduced species of MnO\(_4\)\(^-\) in alkaline and neutral media, it was observed that Mn(II) was the only reduced species of MnO\(_4\)\(^-\) in acid medium. Attempts were made to allow spectroscopic detection of intermediate Mn(V) and Mn(III) as the reaction proceeded in the oxidation of ofloxacin by permanganate. Unfortunately the low concentration of Mn(V) and Mn(III) intermediate obtained under our experimental conditions made the spectroscopic detection failure. However, the evidence for intermediate such as Mn(V) and Mn(III) are reported in the literature.\(^{[24, 25]}\) The results are accommodated in the following mechanism (Scheme 1).

\[
\text{MnO}_4^- + H^+ \rightleftharpoons K_1 \text{HMnO}_4
\]

\[
\text{AR} \begin{array}{c} \text{N} \\ \text{CH}_3 \end{array} + \text{HMnO}_4 \rightleftharpoons K_2 \text{Complex}
\]

\[
\text{Complex} \xrightarrow{\text{Slow}} \begin{array}{c} \text{AR} \\ \text{N} \\ \text{CH}_3 \end{array} + \text{Mn (VI)} + H^+
\]

\[
\begin{array}{c} \text{AR} \\ \text{N} \\ \text{CH}_3 \end{array} + \text{Mn (VI)} \xrightarrow{\text{Fast} \text{5H}_2\text{O}} \begin{array}{c} \text{AR} \\ \text{N} \\ \text{CH}_3 \end{array} + \text{Mn (V)} + 5 \text{HCHO} + \text{NH}_3 + 6 \text{H}^+
\]

\[
2\begin{array}{c} \text{AR} \\ \text{N} \\ \text{CH}_3 \end{array} + 2 \text{Mn (V)} \xrightarrow{\text{Fast} \text{10H}_2\text{O}} 2 \begin{array}{c} \text{AR} \\ \text{N} \\ \text{CH}_3 \end{array} + 2 \text{Mn (III)} + 10 \text{HCHO} + 2 \text{NH}_3 + 12 \text{H}^+
\]

\[
\begin{array}{c} \text{AR} \\ \text{N} \\ \text{CH}_3 \end{array} + 2 \text{Mn (III)} \xrightarrow{\text{Fast} \text{5H}_2\text{O}} \begin{array}{c} \text{AR} \\ \text{N} \\ \text{CH}_3 \end{array} + 2 \text{Mn (II)} + 5 \text{HCHO} + \text{NH}_3 + 6 \text{H}^+
\]

Here, \(\text{AR} = \)

\[
\text{F} \begin{array}{c} \text{CH}_3 \\ \text{C} \\ \text{O} \\ \text{OH} \end{array}
\]
Scheme 1 Proposed mechanism for the oxidation of ofloxacin by acidic permanganate.

Following rate law can be derived from scheme 1:

\[
\text{Rate} = \frac{-d[MnO_4^-]}{dt} = k[\text{Complex}]
\]

\[
= kK_2[HMnO_4][OFL]
\]

\[
= kK_1K_2[MnO_4^-][H^+][OFL]
\]

Total concentration of permanganate is given by

\[
[MnO_4^-] = [MnO_4^-]_t + [HMnO_4] + [\text{Complex}]
\]

\[
= [MnO_4^-]_t + K_1[MnO_4^-]_t[H^+]_t + K_2[HMnO_4][OFL]
\]

\[
= [MnO_4^-]_t + K_1[MnO_4^-]_t[H^+]_t + K_2[MnO_4^-]_t[H^+]_t[OFL]
\]

\[
= [MnO_4^-]_t \{1 + K_1[H^+]_t + K_2[HMnO_4][OFL]\}
\]

\[
[MnO_4^-]_t = \frac{[MnO_4^-]_t}{1 + K_1[H^+]_t + K_2[HMnO_4][OFL]}
\]

Very low concentration of [MnO_4^-] were used in the experiment, so \(K_2 [HMnO_4] \ll 1\)

\[
[MnO_4^-] = [OFL]_t + [\text{Complex}]
\]

\[
= [OFL]_t + K_2[OFL]_t[HMnO_4]
\]

\[
= [OFL]_t \{1 + K_2[HMnO_4]\}
\]

\[
[OFL]_t = \frac{[OFL]_t}{1 + K_2[HMnO_4]}
\]

Total concentration of ofloxacin is given by:

\[
[OFL]_t = [OFL]_t
\]

Total concentration of \([H^+]\) is given by:

\[
[H^+] = [H^+]_t + [HMnO_4]
\]

\[
= [H^+]_t + K_1[MnO_4^-]_t[H^+]_t
\]

\[
= [H^+]_t \{1 + K_1[MnO_4^-]_t\}
\]

So, \([H^+]_t = [H^+]_t\)

Substituting equation (4), (5) and (6) in equation (3) and omitting “t” and “f” subscripts
Rate\(=\frac{-d[MnO_4^-]}{dt} = \frac{kK_1K_2[MnO_4^-][H^+][OFL]}{1+K_1[H^+]+K_1K_2[H^+][OFL]}\) \hspace{1cm} (7)

\[
\text{Rate}_{\text{obs}} = \frac{kK_1K_2[H^+][OFL]}{1+K_1[H^+]+K_1K_2[H^+][OFL]}
\]

Equation (8) can be rearranged as

\[
\frac{1}{k_{\text{obs}}} = \frac{1}{kK_1K_2[H^+][OFL]} + \frac{1}{kK_2[OFL]} + \frac{1}{k}
\]

According to equation (9) the plot of \(1/k_{\text{obs}}\) versus \(1/\text{[OFL]}\) “Fig.4” 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 \(1/k_{\text{obs}}\) versus \(1/\text{[OFL]}\) (Table 2). The energy of activation was determined by the plot of log \(k\) versus \(1/T\) from which activation parameters were calculated (Table 2). The equilibrium constant of HMnO\(_4\) (\(K_1\)) and the equilibrium constant of complex (\(K_2\)) in scheme-1 were calculated from the intercept and slope of the plot \(1/k_{\text{obs}}\) versus \(1/\text{[H}^+\text{]}\) “Fig.5” (Table 2). The value of \(K_1\) is in good agreement with earlier work \cite{24} at 30°C. Thermodynamic quantities were calculated from the Van’t Hoff plot (Table 2).

**Table 2: Activation and thermodynamic quantities for the oxidation of ofloxacin by acidic permanganate from scheme 1.**

<table>
<thead>
<tr>
<th>Temperature (Kelvin)</th>
<th>(10^2 k) (s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of temperature with respect to the slow step of Scheme 1.</td>
<td></td>
</tr>
<tr>
<td>293</td>
<td>4.0</td>
</tr>
<tr>
<td>298</td>
<td>4.34</td>
</tr>
<tr>
<td>303</td>
<td>4.76</td>
</tr>
<tr>
<td>Activation parameters</td>
<td>Value</td>
</tr>
<tr>
<td>(E_a) (kJ mol(^{-1}))</td>
<td>12.98</td>
</tr>
<tr>
<td>(\Delta H^\circ) (kJ mol(^{-1}))</td>
<td>10.47</td>
</tr>
<tr>
<td>(\Delta S^\circ) ± (J K(^{-1}) mol(^{-1}))</td>
<td>-171.74</td>
</tr>
<tr>
<td>(\Delta G^\circ) ± (kJ mol(^{-1}))</td>
<td>68.02</td>
</tr>
<tr>
<td>Equilibrium constants at different temperatures</td>
<td></td>
</tr>
<tr>
<td>Temperature (Kelvin)</td>
<td>$10^{-3} K_1$ (dm$^3$ mol$^{-1}$)</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>293</td>
<td>4.80</td>
</tr>
<tr>
<td>298</td>
<td>4.62</td>
</tr>
<tr>
<td>303</td>
<td>4.25</td>
</tr>
</tbody>
</table>

**Thermodynamic quantities Using $K_1$ values**

| $\Delta H$ (kJ mol$^{-1}$) | -10.3                              |
| $\Delta S \pm$ (J K$^{-1}$ mol$^{-1}$) | -31.0                              |
| $\Delta G \pm$ (kJ mol$^{-1}$) | -1.3                               |

<table>
<thead>
<tr>
<th>Temperature (Kelvin)</th>
<th>$10^{-2} K_2$ (dm$^3$ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>293</td>
<td>3.57</td>
</tr>
<tr>
<td>298</td>
<td>4.61</td>
</tr>
<tr>
<td>303</td>
<td>5.25</td>
</tr>
</tbody>
</table>

**Thermodynamic quantities Using $K_2$ values**

| $\Delta H$ (kJ mol$^{-1}$) | 29.75                              |
| $\Delta S \pm$ (J K$^{-1}$ mol$^{-1}$) | 100.4                              |
| $\Delta G \pm$ (kJ mol$^{-1}$) | -1.42                              |

**Fig. 4** Plots of $1/k_{obs}$ versus $1/ [OFL]$ at three different temperatures.
Fig. 5 Plots of 1/k<sub>obs</sub> versus 1/[H<sup>+</sup>] at three different temperatures.

The values of ΔH<sup>≠</sup> and ΔS<sup>≠</sup> are both favourable for electron transfer process<sup>[26]</sup>. The value of ΔS<sup>≠</sup> within the range of radical reaction has been ascribed<sup>[27]</sup> to the nature of electron pairing and unpairing process. The negative value of ΔS<sup>≠</sup> indicates that complex is more ordered than the reactants<sup>[28]</sup>. The observed modest enthalpy of activation and a relatively low value of the entropy of activation as well as a higher rate constant of the slow step indicate that the oxidation presumably occurs via inner-sphere mechanism.<sup>[29]</sup> The negligible effect of ionic strength and dielectric constant is consistent with reaction between two neutral molecules which supports the proposed mechanism.<sup>[30]</sup>

CONCLUSION

The study of oxidation of ofloxacin by permanganate in acidic medium, the results demonstrate the role of H<sup>+</sup> in the reaction medium is crucial. The literature<sup>[31]</sup> reports that dealkylated products of ofloxacin have antimicrobial activity. Since dealkylated products are obtained in the present study, it is evident that the products of the title reaction have antimicrobial activity after oxidation. So this study will be effectively used in waste water treatment at the sites contaminated by fluoroquinolone antibiotics. Chemical oxidation using Mn(VII) has been widely used for treatment of pollutants in drinking water and waste water applications. The proposed mechanism is consistent with product, mechanism and kinetic studies.

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REFERENCES


