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

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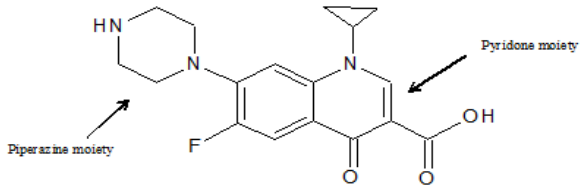
ABSTRACT

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 $KMnO_4$. 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

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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.

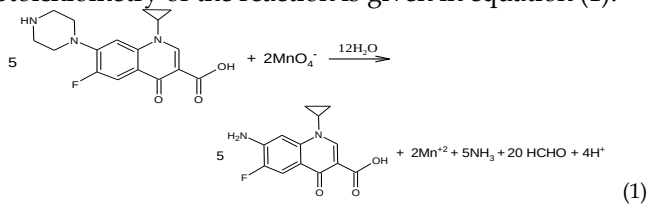
For kinetic measurements, a Peltier accessory (temperature-Controlled) attached to a U.V. 3000+ UV-Visible spectrophotometer (LABINDIA) was used.For product analysis, an LC-ESI-MS, (Q-TOF Micromass, WATERS Company, UK), an alpha-T FTIR spectrophotometer (Bruker, Germany), and for pH measurements MSW-552 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 $dm^3mol^{-1}cm^{-1}$ 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 [permanganate] > [ciprofloxacin], the remaining permanganate concentration was assayed by measuring the absorbance at 525 nm. Estimation of unreacted [MnO_4^-] indicates that 5 moles of ciprofloxacin consumed 2 moles of Permanganate; the Stoichiometry of the reaction is given in equation (1).



(1)

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]

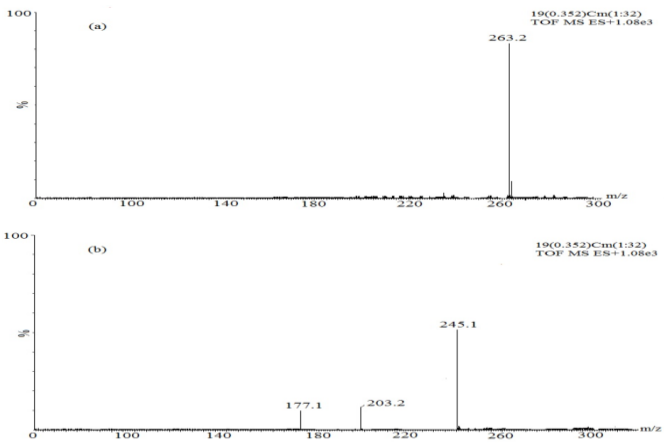


Fig. 1: LC-ESI-MS spectra of oxidation product of ciprofloxacin. (a) Molecular ion peak of m/z 263 (M-69). (b) Fragmentation of (M-69) product.

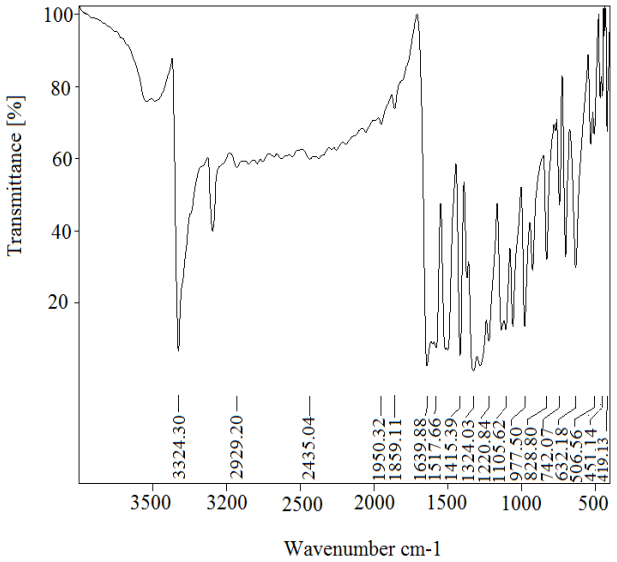


Fig. 2: FTIR spectra of the product of oxidation of ciprofloxacin by permanganate.

RESULTS AND DISCUSSION

Permanganate dependence

The reaction orders were determined from the slopes of log k_{obs} 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_4^-] 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 [$KMnO_4$]. The observed pseudo first order rate constant k_{obs} were independent of the concentration of $KMnO_4$.

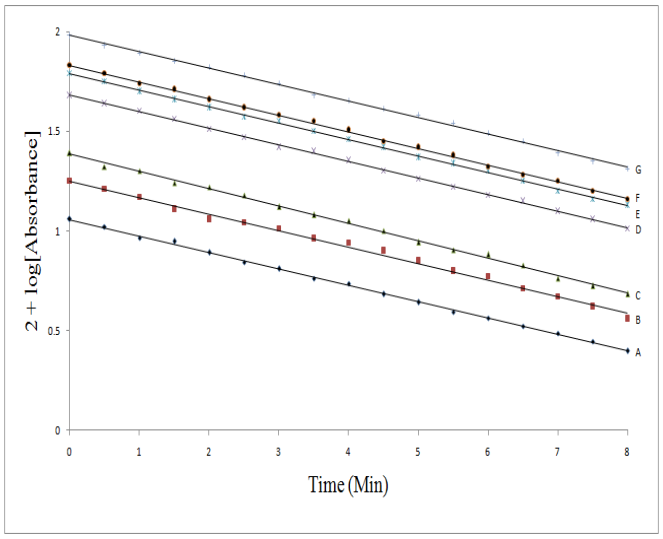


Fig. 3: First order plots of the variation of permanganate concentration at 25°C. [CIP] = 3.0×10^{-3}, [H^+] = 1.0×10^{-2}, I = 0.05/ mol dm^{-3}. [MnO_4^-] × 10^{-4} mol dm^{-3} = (A) 0.75, (B) 0.50, (C) 1.0, (D) 2.0, (E) 2.5, (F) 3.0, (G) 4.0.

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_{obs} 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_{obs} versus ciprofloxacin concentration (Fig. 4) which is a straight line passing through the origin.

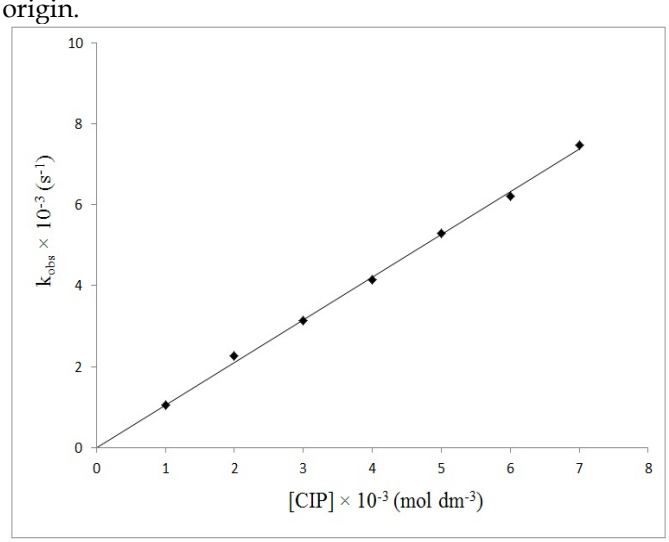


Fig. 4: Plot of [CIP] versus k_{obs}.
[$KMnO_4$] = 2.5×10^{-4}, [H^+] = 1.0×10^{-2}, I = 5×10^{-2}/mol dm^{-3} at 25°C.

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_{obs} was found to be increased with increase [H^+] concentration (Table 1). The order with respect to [H^+] was found to be less than unity (0.68).

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}, [$KMnO_4$] = 2.5×10^{-4} mol dm^{-3}, I = 0.05 mol dm^{-3}.

	$10^3 k_{obs}(s^{-1})$		
[H^+] (mol dm^{-3})	25°C	30°C	35°C
0.01	2.27	2.50	2.61
0.02	3.44	4.01	5.12
0.03	4.34	4.80	6.41
0.04	4.76	5.62	7.02
0.05	5.26	6.14	7.42
0.06	5.55	6.40	7.80
0.07	5.88	6.62	8.21

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 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 $HMnO_4$, $H_2MnO_4^+$, $HMnO_3$ and Mn_2O_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.

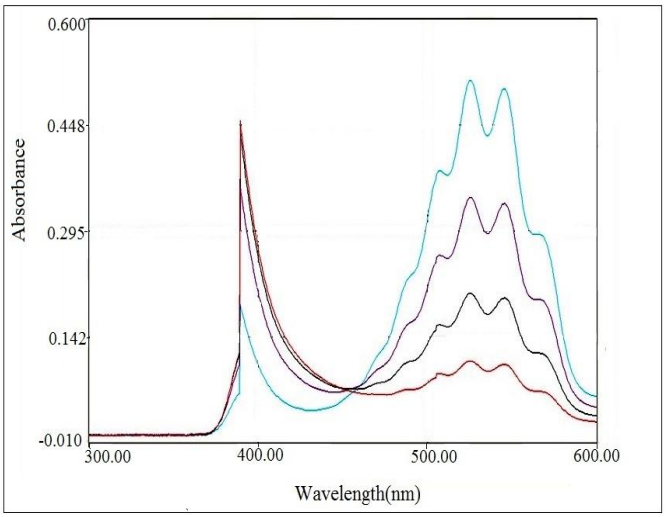
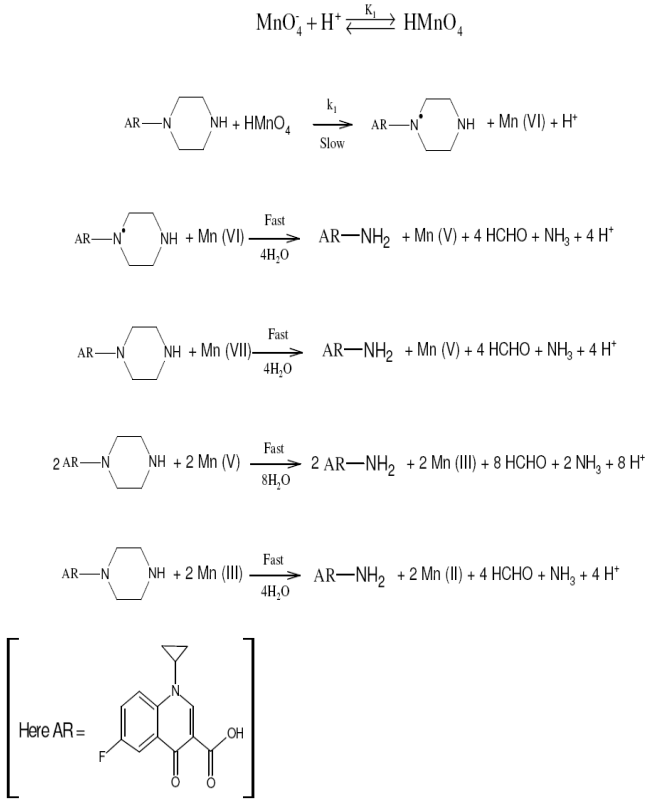


Fig. 5: Spectral changes during the oxidation of ciprofloxacin (CIP) by permanganate in acidic medium at 25°C: $[MnO_4^-] = 2.0 \times 10^{-4}$, $[CIP] = 2.0 \times 10^{-3}$, $[H^+] = 1.0 \times 10^{-2}$ and $I = 0.05$/ mol dm^{-3}.

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[21]. 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. [22] Equilibrium can be represented by equation-(2)

$$MnO_4^- + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} HMnO_4 \qquad (2)$$

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.



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:

$$\text{Rate} = \frac{-d[MnO_4^-]}{dt} = k_1[HMnO_4][CIP] \quad (3)$$

$$= k_1K_1[MnO_4^-]_f[CIP]_f[H^+]_f \quad (4)$$

The total concentration of permanganate is given by:

$$[MnO_4^-]_t = [MnO_4^-]_f + [HMnO_4]_f$$

$$= [MnO_4^-]_f + K_1[H^+][MnO_4^-]$$

$$= [MnO_4^-]_f\ (1 + K_1[H^+])$$

So

$$[MnO_4^-]_f = \frac{[MnO_4^-]_t}{(1 + K_1[H^+])} \quad (5)$$

Where "t" and "f" stands for total and free

$$[H^+]_f = \frac{[H^+]_t}{(1 + K_1[MnO_4^-])} \quad (6)$$

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

$$\text{Rate} = \frac{-d[MnO_4^-]}{dt} = \frac{k_1K_1[MnO_4^-]\,[CIP]\,[H^+]}{(1 + K_1[H^+])\,(1 + K_1[MnO_4^-])} \quad (7)$$

$$= \frac{k_1K_1[MnO_4^-]\,[CIP]\,[H^+]}{1 + K_1[H^+] + K_1[MnO_4^-] + K_1^2[H^+][MnO_4^-]} \quad (8)$$

$K_1[MnO_4^-]$ And $K_1^2[H^+][MnO_4^-]$ << 1 or neglected due to low concentration of $[MnO_4^-]$ used in the experiment so equation (8) change into equation (9)

$$\text{Rate} = \frac{-d[MnO_4^-]}{dt} = \frac{k_1K_1[MnO_4^-]\,[CIP]\,[H^+]}{1 + K_1[H^+]} \quad (9)$$

$$\frac{\text{Rate}}{[MnO_4^-]} = k_{obs} = \frac{k_1K_1[CIP]\,[H^+]}{1 + K_1[H^+]} \quad (10)$$

(Where k_{obs} = First order rate constant)

$$\frac{k_{obs}}{[CIP]} = \frac{k_1K_1\,[H^+]}{1 + K_1[H^+]} \quad (11)$$

Equation (11) can be rearranged as

$$\frac{[CIP]}{k_{obs}} = \frac{1}{k_1K_1\,[H^+]} + \frac{1}{k_1} \quad (12)$$

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_1, 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_1 versus 1/T from which activation parameters were calculated (Table 2). The equilibrium constant of $HMnO_4$ (K_1) was calculated from the intercept and slope of the plot [CIP] / k_{obs} versus 1/ $[H^+]$ (Table 2). The value of K_1 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).

Table 2: Activation and thermodynamic parameters for the oxidation of ciprofloxacin by acidic permanganate from scheme 1.

Temperature (Kelvin)	k_1 ($dm^3\ mol^{-1}\ s^{-1}$)
Effect of temperature with respect to the slow step of Scheme 1.	
298	3.88
303	4.81
308	7.29
Activation parameters	Value
E_a(kJ mol^{-1})	34.8
$\Delta H^{\neq}$ (kJ mol^{-1})	32.3
$\Delta S^{\neq}$ ± (J K^{-1} mol^{-1})	-116.6
$\Delta G^{\neq}$ ± (kJ mol^{-1})	69.6
Temperature (Kelvin)	Equilibrium constant K_1 ($dm^3\ mol^{-1}$)
298	40.6
303	34.6
308	22.8
Thermodynamic quantities	Value
ΔH (kJ mol^{-1})	-25
ΔS ± (J K^{-1} mol^{-1})	-81
ΔG ± (kJ mol^{-1})	-1.6

The moderate values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were favourable for electron transfer process. The value of $\Delta H^{\neq}$ was due to energy of solution changes in the transition state. The negative value of $\Delta S^{\neq}$ within the range of radical reaction has been ascribed [25] to the nature of electron pairing and electron unpairing process. The negligible effect of ionic strength and dielectric constant is consistent with reaction between two neutral molecules which supports the proposed mechanism. [26]

The study of oxidation of ciprofloxacin by permanganate in acidic medium, results demonstrate the role of pH in the reaction medium is crucial. The literature [27] reports that dealkylated products of ciprofloxacin have reduced antimicrobial activity. Since dealkylated products are obtained in the present study, it is evident that the products of the title reaction have reduced antimicrobial activity after oxidation. So this study will be effectively used in waste water treatment at the sites contaminated by fluoroquinolone antibiotics. The proposed mechanism is consistent with product, mechanism and kinetic studies.

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