



RESEARCH ARTICLE

Kinetic Analysis of Oxidation of Ofloxacin by Permanganate Ion in Sulphuric Acid Medium: A Mechanistic Approach

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ABSTRACT

The Kinetic 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 Dielectric Constant and Ionic Strength has also been investigated. The main product identified were 7-amino quinolone and Mn(II). From the above experimental results the mechanism and rate law has been derived.

Keywords: Oxidation, Mechanism, Ofloxacin, Permanganate ion

INTRODUCTION

Ofloxacin (OFL) [9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido-[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid] belongs to the fluoroquinolone class of antibiotics. They are synthetic broad spectrum antibacterial drugs that exhibit significant activity against both gram-positive and gram-negative bacteria (Zhang, *et. al.*, 2005). 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 (Zhang, *et. al.*, 2008). The oxidation by Mn(VII) ions finds extensive applications in organic synthesis (Abbar, *et. al.*, 2011). Mn(VII) is the most potent oxidation state in acid medium with reduction potentials (Sunderland, *et. al.*, 1999) 1.69V of Mn(VII)/Mn(IV) couple and 1.51V of Mn(VII)/Mn(II) couple. HMnO₄, H₂MnO₄⁺, HMnO₃ and Mn₂O₇ are the active species of Mn⁺⁷ in the acidic medium (Kaur, *et. al.*, 2008; Wiberg, 1965).

The literature survey reveals that there are few study reports (Martinez, *et. al.*, 1996; Day, *et. al.*, 1985) on the oxidation of ofloxacin by MnO₂ followed by evaluation of the reaction kinetics and analysis of chemical structure of degradation products formed. It is noted that despite the importance of the drug, the literature survey reveals that there is no information about the oxidation kinetics.

MATERIALS AND METHODS

1. 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.

2. INSTRUMENTATION:

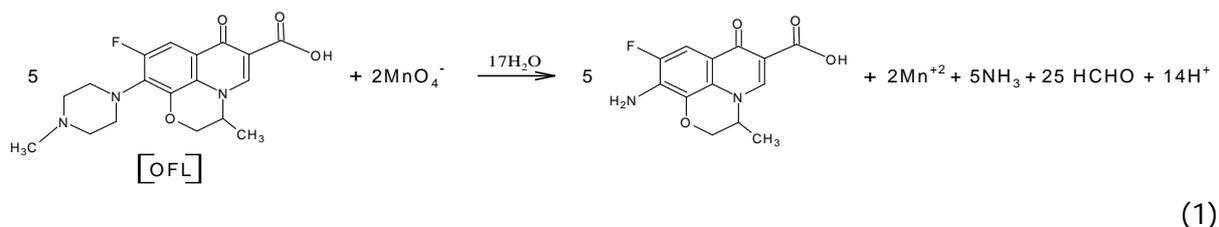
For kinetic measurements, a Peltier accessory (temperature-Controlled) attached to a U.V.3000+ UV-Visible spectrophotometer (LABINDIA) was used.

3. 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 $30 \pm 0.1^\circ\text{C}$ unless otherwise stated. The reaction was initiated by mixing thermostated solution of permanganate and ofloxacin; in addition to that required quantities of H_2SO_4 , Na_2SO_4 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 $(0.50 - 5.0) \times 10^{-4} \text{ mol dm}^{-3}$ at 525nm. The molar absorptivity index of permanganate was found to be $\epsilon = 2260 \pm 50 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ as a function of time. The kinetics reactions were followed more than 85 % completion of the reaction. The pseudo-first-order rate constants k_{obs} were calculated from the plots of the logarithm of absorbance versus time, which were linear. The values of k_{obs} were reproducible within $\pm 5\%$.

4. STOICHIOMETRY AND PRODUCT ANALYSIS:

Different sets of concentration of reactants in 0.01 mol dm^{-3} sulphuric acid at constant ionic strength, 0.02 mol dm^{-3} , were kept over 24 hrs at 30°C in a closed container. When $[\text{permanganate}] > [\text{ofloxacin}]$, the remaining permanganate concentration was assayed by measuring the absorbance at 525 nm. Estimation of unreacted $[\text{MnO}_4^-]$ indicates that 5 moles of ofloxacin consumed 2 moles of Permanganate; the Stoichiometry of the reaction is given in equation (1).



(1)

RESULTS

1. PERMANGANATE DEPENDENCE:

The oxidant permanganate $[\text{MnO}_4^-]$ concentration varied from 7.5×10^{-5} to $6 \times 10^{-4} \text{ mol dm}^{-3}$, and all other concentrations and conditions were constant. The plot of log absorbance versus time was linear 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 KMnO_4 .

2. OFLOXACIN DEPENDENCE:

The effect of concentration variation of ofloxacin on the rate of reaction was studied in the range 2×10^{-3} to $7 \times 10^{-3} \text{ mol dm}^{-3}$ at constant concentration of permanganate, acid and ionic strength at 20° , 25° , 30°C respectively. The rate of reaction increases with increasing concentration of ofloxacin. 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 $1/[\text{OFL}]$ which was also linear with a positive intercept.

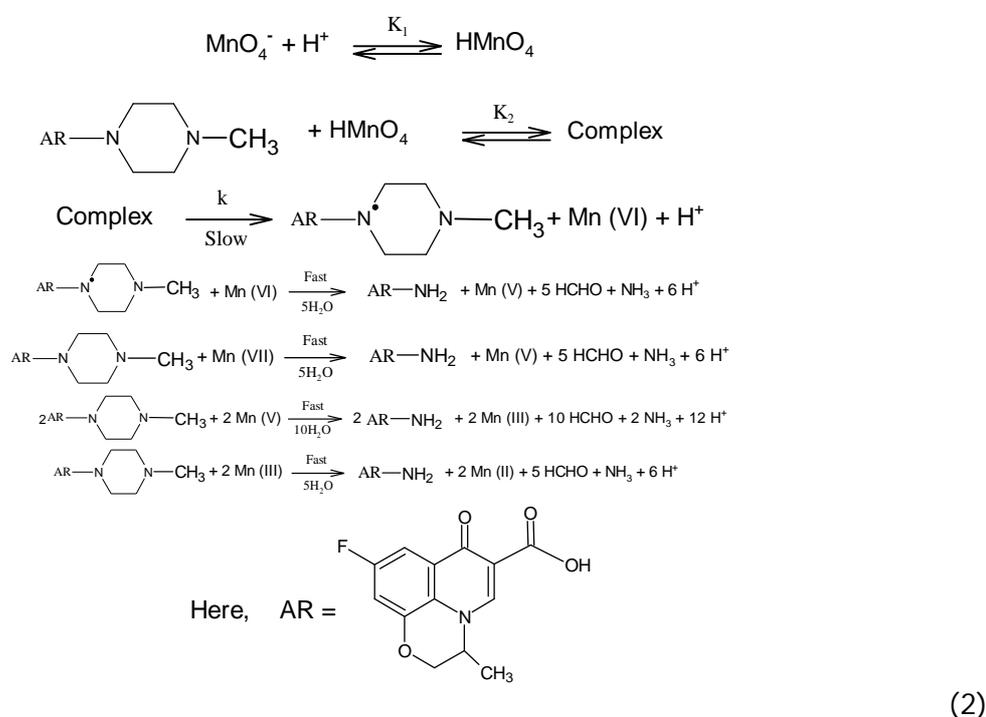
3. HYDROGEN ION DEPENDENCE:

The effect of concentration variation of sulphuric acid on the rate of reaction was studied in the concentration range 2×10^{-3} to $2 \times 10^{-2} \text{ mol dm}^{-3}$ at fixed concentration of permanganate, ofloxacin and ionic strength at three temperatures viz. 20° , 25° , 30°C respectively. Pseudo first-order rate constant (k_{obs}) was found to be increased with increase in $[\text{H}^+]$.

DISCUSSION

The stoichiometry of the reaction shows five molecules of ofloxacin oxidized by the two molecule of the permanganate in sulphuric acid. The reaction indicate first order dependence with permanganate and less than unit order with H^+ concentration and ofloxacin concentration.

The main oxidation product was 7-amino fluoroquinolone. The rate of reaction increase with increase in $[H^+]$ ion, in the prior equilibrium step indicates that H^+ reacts with MnO_4^- to form $HMnO_4$. The $HMnO_4$ reacts with the mole of ofloxacin and convert into the complex. Then complex in the rate determining step to give a free radical formed 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, and other products. 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 (Caron, *et. al.*, 2006; Sen, *et. al.*, 1995). The results are accommodated in the following mechanism (Scheme 1).



Scheme 1: Proposed mechanism for the oxidation of ofloxacin by acidic permanganate.

Following rate law can be derived from scheme 1:

$$\begin{aligned}
 \text{Rate} &= \frac{-d[MnO_4^-]}{dt} = k[\text{Complex}] \\
 &= kK_2[HMnO_4][OFL] \\
 &= kK_1K_2[MnO_4^-]_f[H^+]_f[OFL]_f
 \end{aligned}
 \tag{3}$$

Total concentration of permanganate is given by

$$\begin{aligned}
 [MnO_4^-]_t &= [MnO_4^-]_f + [HMnO_4] + [\text{Complex}] \\
 &= [MnO_4^-]_f + K_1[MnO_4^-]_f[H^+]_f + K_2[HMnO_4][OFL] \\
 &= [MnO_4^-]_f + K_1[MnO_4^-]_f[H^+]_f + K_1K_2[MnO_4^-]_f[H^+]_f[OFL] \\
 &= [MnO_4^-]_f \{ 1 + K_1[H^+]_f + K_1K_2[H^+]_f[OFL] \}
 \end{aligned}$$

$$[\text{MnO}_4^-]_f = \frac{[\text{MnO}_4^-]_t}{\{1 + K_1[\text{H}^+]_f + K_1K_2[\text{H}^+]_f[\text{OFL}]\}} \quad (4)$$

$[\text{MnO}_4^-]_t$ and $[\text{MnO}_4^-]_f$ are total and free concentration of Mn (VII) respectively.

Total concentration of ofloxacin is given by:

$$\begin{aligned} [\text{OFL}]_t &= [\text{OFL}]_f + [\text{Complex}] \\ &= [\text{OFL}]_f + K_2[\text{OFL}]_f[\text{HMnO}_4] \\ &= [\text{OFL}]_f \{1 + K_2[\text{HMnO}_4]\} \end{aligned}$$

$$[\text{OFL}]_f = \frac{[\text{OFL}]_t}{1 + K_2[\text{HMnO}_4]}$$

Very low concentration of $[\text{MnO}_4^-]$ were used in the experiment, so $K_2[\text{HMnO}_4] \ll 1$

$$[\text{OFL}]_f = [\text{OFL}]_t \quad (5)$$

Total concentration of $[\text{H}^+]$ is given by:

$$\begin{aligned} [\text{H}^+]_t &= [\text{H}^+]_f + [\text{HMnO}_4] \\ &= [\text{H}^+]_f + K_1[\text{MnO}_4^-]_f[\text{H}^+]_f \\ &= [\text{H}^+]_f \{1 + K_1[\text{MnO}_4^-]_f\} \end{aligned}$$

$$[\text{H}^+]_t = [\text{H}^+]_f \quad (6)$$

Substituting equation (4), (5) and (6) in equation (3) and omitting "t" and "f" subscripts

$$\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = \frac{kK_1K_2[\text{MnO}_4^-][\text{H}^+][\text{OFL}]}{1 + K_1[\text{H}^+] + K_1K_2[\text{H}^+][\text{OFL}]} \quad (7)$$

$$\frac{\text{Rate}}{[\text{MnO}_4^-]} = k_{\text{obs}} = \frac{kK_1K_2[\text{H}^+][\text{OFL}]}{1 + K_1[\text{H}^+] + K_1K_2[\text{H}^+][\text{OFL}]} \quad (8)$$

Equation (8) can be rearranged as

$$\frac{1}{k_{\text{obs}}} = \frac{1}{kK_1K_2[\text{H}^+][\text{OFL}]} + \frac{1}{kK_2[\text{OFL}]} + \frac{1}{k} \quad (9)$$

According to equation (9) the plot of $1/k_{\text{obs}}$ versus $1/[\text{OFL}]$ 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 $1/[\text{OFL}]$. The energy of activation was determined by the plot of $\log k$ versus $1/T$ from which activation parameters were calculated. 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 $1/[\text{H}^+]$. The value of K_1 is in good agreement with earlier work (Hassan, 1991) at 30°C.

CONCLUSION

The study of oxidation of ofloxacin by permanganate in acidic medium, the results demonstrate the role of H^+ in the reaction medium is crucial. The literature (Hassan, 1991) 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. The oxidation study by the Mn(VII) with fluoroquinolones drugs has been widely used for treatment of pollutants in waste water.

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