ABSTRACT. A kinetics pathway of oxidation of Cefpodoxime Proxetil by permanganate in alkaline medium at a constant ionic strength has been studied spectrophotometrically. The reaction showed first order kinetics in permanganate ion concentration and an order less than unity in cefpodoxime acid and alkali concentrations. Increasing ionic strength of the medium increase the rate. The oxidation reaction proceeds via an alkali-permanganate species which forms a complex with cefpodoxime acid. The latter decomposes slowly, followed by a fast reaction between a free radical of cefpodoxime acid and another molecule of permanganate to give the products. Investigations of the reaction at different temperatures allowed the determination of activation parameters with respect to the slow step of proposed mechanism and follows first order kinetics. The proposed mechanism and the derived rate laws are consistent with the observed kinetics.

Keywords: Cefpodoxime proxetil, Permanganate, Kinetics, Thermodynamics
upper respiratory tract and urinary tract infections. In the biological system, CFP undergoes ester hydrolysis and is converted into CFA to exhibit its antibiotic activity. \(^1\)\(^{–}\)\(^2\) CFP has an asymmetric carbon at position 4 and is supplied as racemic mixture of R- and S-enantiomers. Few methods are reported to quantify CFA. \(^3\)\(^{–}\)\(^4\) The β-lactum antibiotic is known to degrade by hydrolysis in alkaline solution (Fig. 2). \(^5\) Hydrogen peroxide is used for degradation study in the development of pharmaceuticals. The HCl, NaOH, NH\(_2\)OH and H\(_2\)O\(_2\) at appropriate concentration were evaluated as degradation agents for cleaning or decontamination. \(^6\) Permanaganate ion oxidizes a larger variety of substrate and finds extensive application in organic synthesis. \(^7\)\(^{–}\)\(^12\) During oxidation permanaganate is reduced to various oxidation states in acidic, alkaline and neutral media. The mechanism of oxidation depends on the substrate and medium. \(^13\) The process Mn(VII) to Mn(IV) can be divided into a number of partial steps and examined discretely. The MnO\(_2\) appears only a after the complete consumption of MnO\(_4^–\). No mechanistic information is available to distinguish between a direct one-electron reduction of Mn(VII) to Mn(IV) or a hypopermanaganate ion is formed in a two-electron reduction followed by a quick reaction. \(^14\)\(^{–}\)\(^15\) In this paper a simple and sensitive kinetic spectrophotometric method has been developed to establish the thermodynamic parameters of Cepfodoxime acid. The method is based on the oxidation of the drug by permanaganate in alkaline medium. The present studies is aimed at checking the reactivity of CFA toward permanaganate, at determining the redox chemistry of the Mn(VII) in such media, and at arriving at a plausible mechanism.

**EXPERIMENTAL**

**Apparatus**
A Shimadzu UV-visible 1601 spectrophotometer was used for all spectral measurements, pH-metric measurements were done with Elico-LI 120 pH meter and a water bath shaker NSW 133, India was used to control the temperature.

**Materials**
The Cepfodoxime Proxetil was obtained from (Lupin pharmaceutical Ltd, India). Pharmaceutical preparations containing the studied compounds were purchased from commercial sources in the local market. The permanganate solution was prepared and standardized against oxalic acid. \(^16\) Potassium permanganate solution was prepared as described by Carrington and Symons. \(^17\) NaOH (Merck Ltd, Mumbai, India) and NaClO\(_4\) (Ranbaxy fine chem. Ltd, India) were employed to maintain the required alkalinity and ionic strength, respectively.

**Reagents**
Double distilled, de-ionized water was used throughout. The chemicals used were of analytical grade. Stock solutions of the compounds were wrapped with carbon paper to protect them from photodecomposition.

**Kinetic procedure**
The oxidation of (CFA) by permanaganate ion was followed under pseudo- first order conditions where CFA concentration was greater than manganese (VII) at 25 °C. The reaction was initiated by mixing...
previously thermostated solutions of MnO$_4^-$ and (CFA), which also contained required quantities of NaOH and NaClO$_4$ to maintain alkaline medium and ionic strength, respectively. The temperature was maintained at 25 °C: The reaction was monitored by a the decrease in absorbance of MnO$_4^-$, at its absorption maximum of 525 nm. Earlier it was verified that there is no interference from other reagents at this wavelength. Application of Beer’s Law for permanganate at 525 nm had earlier been verified, giving $\varepsilon$, was found to be 2083 ± 50 dm$^3$ mol$^{-1}$ cm$^{-1}$. The reaction was followed more than three half lives. The first order rate constants $k_{obs}$ were evaluated by plots of log [MnO$_4^-$] vs. time. The first order plots in almost all cases were linear up to 85% of the reaction and $k_{obs}$ were reproducible at 525 nm and an increasing absorbance of Mn(VI) at 610 nm during the course of the reaction (Fig. 5). The effect of dissolved oxygen on the rate of reaction was checked by preparing the reaction mixture and following the reaction in nitrogen atmosphere. No significant difference between the results obtained under nitrogen and in the presence of air was observed. Added carbonate had also no effect on the reaction rate. Regression analysis of experimental data to obtain the regression coefficient $r$ and the standard deviation S of points from the regression line was performed using a Microsoft excel-2007 program.

**RESULTS**

The absorption spectrum of CFP was exhibited two peaks at 270 and 345 nm (Fig. 3). After addition of potassium permanganate in the same medium is oxidized the (CFA) and exhibits a green colour of manganate ion, appears which absorbs at 610 nm. It was empirically found that the blue colour originated from a mixture of violet MnO$_4^-$ and green colour MnO$_4^{2-}$ rather than form the formation of hypopermanganate. The formation of Mn (VII) was also evidence by the decrease of the absorbance of Mn(VII) at 525 nm and the increase of that of Mn(VI) at 610 nm during the course of reaction (Fig. 5). The intensity of the colour increases with time and hence a kinetic method based on the spectrophotometric measurement was developed.

**Stoichiometry of the reaction**

The reaction mixture containing an excess of permanganate over (CFA) were mixed in the presence of $5.0 \times 10^{-2}$ mol dm$^{-3}$ NaOH and at constant ionic strength $I = 0.10$ mol dm$^{-3}$ were kept in a closed container under a nitrogen atmosphere at 25 °C. After 1 h the manganese (VII) concentration was assayed by measuring the absorbance at 610 nm. The results indicated that 2 mols of manganese (VII) consumed 1 mol of (CFA). Therefore, the reaction mechanism is proposed on the basis of the literature background and our experimental study as shown in eq 1.

**Reaction order**

The reaction order were evaluated from the slope of log $k_{obs}$ versus log concentration plots by the varying concentration of (CFA) and alkali keeping other factors constant.
Effect of Concentration of Manganese (VII)

At constant concentration of (CFA), $1.0 \times 10^{-3}$ mol dm$^{-3}$, and alkali, $5.0 \times 10^{-2}$ mol dm$^{-3}$, and at constant ionic strength, $0.10$ mol dm$^{-3}$, the oxidant KMnO$_4$ concentration was varied in the range of $6 \times 10^{-5}$ to $6 \times 10^{-4}$ mol dm$^{-3}$. All kinetic runs exhibited identical characteristics. The linearity of plots of log (absorbance) vs. time, for different concentrations of permanganate, indicates order in manganese(VII) concentration as unity ($\text{Fig. 4}$). This was also confirmed by the constant values of pseudo first order rate constants, $k_{obs}$, for different manganese(VII) concentrations ($\text{Table 1}$).

Effect of NaOH Concentration

The effect of increasing cone of alkali on the reaction was examined at constant concentration of drug and permanaganate ion at $25$ °C. The alkali concentration was varied in the range of $0.6 \times 10^{-2}$ to $1.0 \times 10^{-1}$ mol dm$^{-3}$. The $k_{obs}$ values increased with increase in concentration of alkali.

Effect of [CFA]

The effect of (CFA) concentration on the reaction was studied at constant concentrations of alkali and permanganate and at a constant ionic strength of $0.10$ mol dm$^{-3}$ at $25$ °C. The substrate, (CFA) was varied in the range of $5.0 \times 10^{-4}$ to $5.0 \times 10^{-3}$ mol dm$^{-3}$. The $k_{obs}$ values increased with increase in concentration of (CFA) ($\text{Table 1}$).

Effect of Ionic Strength

The effect of ionic strength was studied by varying the NaClO$_4$ concentration from $0.01$ to $0.10$ mol dm$^{-3}$ at constant concentrations of permanganate,

Table 1. Effect of variation of [KMnO$_4$], [CFA] and [OH] on the oxidation of cefpodoxime acid by alkaline [KMnO$_4$] at $25$ °C and ionic strength $I = 0.10$ mol dm$^{-3}$.

<table>
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<tr>
<th>$10^3$ [KMnO$_4$] mol dm$^{-3}$</th>
<th>$10^3$ [CFA] mol dm$^{-3}$</th>
<th>$10^3$ [OH] mol dm$^{-3}$</th>
<th>$10^3 k_{obs}$ (S$^{-1}$)</th>
<th>$10^3$ kcal (S$^{-1}$)</th>
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$\text{Fig. 4.}$ First order plots for the oxidation of CFA by alkaline MnO$_4^-$ at $25$ °C; [CFA] = $1.0 \times 10^{-3}$; [OH] = $2 \times 10^{-3}$; $I = 0.10$ mol dm$^{-3}$. [Mn(VII)] × 10$^4$ mol dm$^{-3}$: (1) 0.6, (2) 0.8, (3) 1.0, (4) 2.0, and (5) 3.0.

$\text{Fig. 5.}$ Spectral changes during the oxidation of [CFA] by alkaline MnO$_4^-$ at $25$ °C; [Mn(VII)] = $1.0 \times 10^{-4}$, [CFA] = $1.0 \times 10^{-3}$, [OH] = $2 \times 10^{-2}$, $I = 0.10$ mol dm$^{-3}$. 

$\text{Table 1.}$ Effect of variation of [KMnO$_4$], [CFA] and [OH] on the oxidation of cefpodoxime acid by alkaline [KMnO$_4$] at $25$ °C and ionic strength $I = 0.10$ mol dm$^{-3}$. 

The effect of increasing cone of alkali on the reaction was examined at constant concentration of drug and permanaganate ion at $25$ °C. The alkali concentration was varied in the range of $0.6 \times 10^{-2}$ to $1.0 \times 10^{-1}$ mol dm$^{-3}$. The $k_{obs}$ values increased with increase in concentration of alkali.
(CFA), and alkali. It was found that increasing ionic strength had no effect on the rate of reaction.

**Effect of temperature**

The kinetics was studied at four different temperatures under varying concentrations of (CFA), and alkali, keeping other conditions constant. The rate constants were found to increase with increase in temperature. The rate constant (k) of the slow step of Scheme 1 were obtained from the slopes and intercepts of $\frac{1}{k_{obs}}$ versus $\frac{1}{[CFA]}$ and $\frac{1}{k_{obs}}$ versus $\frac{1}{[OH^-]}$ plots at four different temperatures. The energy of activation corresponding to these rate constants was evaluated from the Arrhenius plot of $\log k$ versus $\frac{1}{T}$ and from which other activation parameters were obtained (Table 2).

**Polymerization Study**

The possibility of free radicals was examined as follows: the reaction mixture, to which a the reaction mixture with methanol, precipitate resulted, suggesting that there was participation of free radicals in the reaction.

**DISCUSSION**

At the observe experimental condition at pH > 12 the reductant product of Mn(VII) might be stopped. Although During our study the colour of the solution undergoes a series of change from blue to green. It is probable that green color originated from the permanganate ion. The spectrum of green solution was identical to that of MnO$_4^{2-}$. It is probable that the blue color originated from the violet of permanganate and the green from manganate, excluding the accumulation of hypomanganate. It is evident from the (Fig. 5) that the concentration of MnO$_4^{4-}$ decreases at 525 nm due to Mn(VII) and increases at 610 nm due to Mn(VI). As the reaction proceeds, slowly yellow turbidity develops, and after keeping for a long time the solution decolorizes and forms a brown precipitate. This suggests that the products formed might have undergone further oxidation resulting in a lower oxidation state of manganese. The results imply that first the alkali combines with permanganate to give an alkali-permanganate species [MnO$_4$·OH]$^{2-}$ in a prior equilibrium step, which is in accordance with literature and also experimentally observed order.
in OH⁻ ion concentration. In the second step [MnO₄²⁻·OH]₂⁻ combines with CFA to form an intermediate complex. The fractional order with respect to CFA presumably results from the complex formation between oxidant and substrate prior to the slow step. The reaction between permanganate and CFA is supported by Michaelis-Menten plot which is linear with positive intercept which is in agreement with complex formation. Within the complex one-electron is transferred from CFA to Mn(VII). Then this complex (C) decomposes in a slow step to form a species derived from CFA. All the results indicate a mechanism as given in Scheme 1.

\[
\text{Rate} = -\frac{d[MnO_4^-]}{dt} = kK_1K_2[MnO_4^-][CFA][OH^-] \quad (2)
\]

The total [MnO₄⁻] can be written as

\[
[MnO_4^-]_t = [MnO_4^-]_f + [MnO_4^-·OH]^2 + [\text{Complex}]
= [MnO_4^-]_f + [MnO_4^-][OH^-] + K_1K_2[MnO_4^-][CFA][OH^-] = [MnO_4^-]_f + 1 + K_1[OH^-] + K_1K_2[OH^-]
\]

\[
[MnO_4^-]_t = \frac{[MnO_4^-]_f}{1 + K_1[OH^-] + K_1K_2[OH^-]} \quad (3)
\]

where “t” and “f” stand for total and free. Similarly, total [OH⁻] can be calculated as

\[
[OH^-]_t = [OH^-]_f + [MnO_4^-·OH]^2 + [\text{Complex}]
[OH^-]_t = \frac{[OH^-]_f}{1 + K_1[MnO_4^-] + K_1K_2[CFA][MnO_4^-]} \quad (4)
\]

In view of the low concentrations of MnO₄⁻ and CFA used in the experiment, in eq 4 the terms \(K_1[MnO_4^-]\) and \(K_1K_2[MnO_4^-][CFA]\) can be neglected in comparison with unity.

Thus,

\[
[OH^-]_f = [OH^-]_t \quad (5)
\]

Similarly,

\[
[CFA]_f = [CFA]_t \quad (6)
\]

Substituting equation 3, 5, and 6 in equation 2 and omitting the subscripts, we get

\[
\text{Rate} = \frac{kK_1K_2[MnO_4^-][CFA][OH^-]}{1 + K_1[OH^-] + K_1K_2[CFA][OH^-]} \quad (7)
\]

Equation 7 confirms all the observed orders with respect to different species, which can be verified by rearranging to eq 8.

\[
\frac{1}{k_{obs}} = \frac{1}{kK_1K_2[CFA][OH^-]} + \frac{1}{kK_2[CFA]} + \frac{1}{k} \quad (8)
\]

According to eq 8, other conditions being constant, plots of \(1/k_{obs} \text{ versus } 1/[CFA] \) and \(1/k_{obs} \text{ versus } 1/[OH^-] \) should be linear and are found to be so (Figs 6a and 6b). The slopes and intercepts of such plots lead to the values of \(K_1, K_2, \) and \(k \) (Table 2). The value of \(K_1 \) is in good agreement with the literature. Using these constants, the rate constants were calculated over different experimental conditions, and there is a reasonable agreement between the calculated and the experimental values, which for the proposed mechanism (Table 1). The thermodynamic quantities for the first and second equilibrium step of Scheme 1 can be evaluated as follows: The [CFA] and [OH⁻] as in Table 1 were varied at four different temperature. The spectral evidence of the complex formation was obtained from UV-Vis spectral study. It is also proved kinetically by the non zero intercept of the plots of \(1/k_{obs} \text{ versus } 1/[CFA] \) \((r > 0.9997, S < 0.0148) \) (Fig. 6b). According to the rate law the plots of \(1/k_{obs} \text{ versus } 1/[OH^-] \) \((r > 0.9987, S < 0.0124) \) and \(1/k_{obs} \text{ versus } 1/[CFA] \) \((r > 0.9998, S < 0.0151) \) should be linear (Figs 6a and b) from the slope and intercept, the value of \(k, K_1 \) and \(K_2 \) could be derived as \(2.87 \times 10^{-3}, 13.8 \text{ dm}^3 \text{ mole}^{-1}, \) and \(22.36 \text{ dm}^3 \text{ mole}^{-1} \) respectively. The rate constant were calculated from these values (Table 1) which supports the proposed mechanism. The reaction rate of CFA increased with increasing intensity of the complex. The kinetics was studied at four different temperature and concentration of CFA and NaOH keeping all other conditions constant. The rate constant was found to increase with increasing...
The rate constant $k$ of the slow step of Scheme 1 were obtained from the slope and intercept of $1/k_{obs}$ versus $1/[CFA]$ and $1/k_{obs}$ versus $1/\text{[OH]}^-$ plots at four different temperatures. The activation parameters corresponding to these constant were evaluated from the Arrhenius plot of $\log k$ versus $1/T$ and are listed in Table 2. The experimental value of $\Delta H^\circ$ and $\Delta S^\circ$ were both favorable for electron transfer process. The high negative value of $\Delta S^\circ$ indicate that interaction of the reaction ions of similar charges form an activated complex and is more ordered than the reactants due to loss of degree of freedom. The hydroxyl ion concentration i.e. Table 1 was verified at four different temperature and the $K_1$ value were determined from a (Fig. 6a) as shown in Table 2. Similarly CFA concentration as in Table 1 was varied at four different temp and $K_2$ values were determined at each temp (Fig. 6b) as listed in Table 2. The effect of temp on reaction rate is well known and important in the various activation parameters of the reaction product. A Arrenhius plot was made for the variation of $K_1$ with temperature (i.e. $\log K_1$ versus $1/T$). The values of the enthalpy change of the first equilibrium step $K_1$ of the reaction ($\Delta H$), enthalpy of the reaction ($\Delta S$) and free energy of reaction ($\Delta G$) were calculated as listed in Table 2. Similarly thermodynamic parameters for second step $K_2$ are calculated such as enthalpy; entropy and free energy of activation of the reaction product were calculated using Eyring equation.

$$\log K/T = \left[ \log k_b/h + S/2.302R \right] - \Delta H/2.303R1/T$$

The plot of $\log K_2/T$ versus $1/T$ was linear with correlation coefficient of -0.9996 $\Delta H^\circ$ was evaluated from the slope (- $\Delta H/2.303R1/T$) and $\Delta S^\circ$ from the intercept [log $k_b/h + S/2.302R$] of the compiled Eyring plot. The Gibbs free energy of activation was determined by $\Delta G^\circ = -2.303 RT \log K$ at room temperature. These values are given in Table 2. The proposed mechanism supported by the above thermodynamic parameter. A comparison of the later values (from $K_2$) with those obtained for the slow step of the reaction shows that these values mainly refer to the rate-limiting step, supporting the fact that the reaction before rate determining step is fairly fast and involves low activation energy. The negative value of indicate that the complex (C) is more ordered than the reactant. A detailed mechanistic explanation is given in Scheme 2.

CONCLUSION

It is interesting to note that the oxidant species $[$MnO$_4^-$] required a pH $> 12$ below which the system becomes anxious and the reaction proceeds to Mn(IV) which slowly develops yellow turbidity. The oxidant, manganese(VII), exists in alkali media as alkali-permanganate species $[$MnO$_4$·OH$]^{2-}$, which takes part in the chemical reaction. The role of hydroxyl ions is essential to the chemical reaction.

2009, Vol. 53, No. 6
Scheme 2. Mechanistic Interpretation for the Oxidation of CFA by Alkaline Permanganate

The given mechanism is consistent with all the experimental evidence. The rate constant of slowest step involved in the mechanism are evaluated and activation parameters with respect to slowest step of reaction were computed. The overall mechanistic sequence described here is consistent with the final product, mechanistic and kinetic studies.

REFERENCES