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

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ABSTRACT

The kinetics and mechanism of oxidation of nalidixic acid (NA) by permanganate ion in alkaline medium have been studied at 40 ± 1^{o}C. The Stoichiometry was observed to be 2:1 in terms of mole ratio of permanganate ion and nalidixic acid consumed. The reaction shows first order with respect to oxidant and fractional order in both the substrate and alkali concentration. The oxidation reaction proceeds via an alkali permanganate species that forms a complex with nalidixic acid and the complex then decomposes to give the product. The effects of added products and ionic strength have also been investigated. The main products identified were hydroxylated NA and Mn(VI). A mechanism was proposed on the basis of experimental results. Investigation of the reaction at different temperature allowed the determination of the activation parameters with respect to the slow step of the proposed mechanism.

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 MnO_4^-, Mn_2O_7, MnO_3F. Out of which MnO_4^- 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; Wiberg *et al.* 1973) 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, MnO_4^{2-}. MnO_2 appears only after long time, i.e., after the complete consumption of MnO_4^-.

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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 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 $C_{12}H_{12}N_2O_3$ (1-ethydm-3, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid) (Figure 1) is the first synthesized antimicrobial quinolone. NA is an ionizable, non-biodegradable 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).

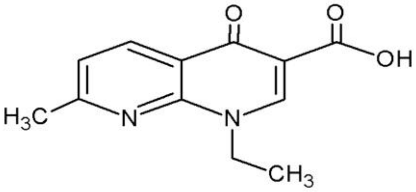


Fig. 1: Structure of Nalidixic acid.

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 $NaNO_3$ (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.

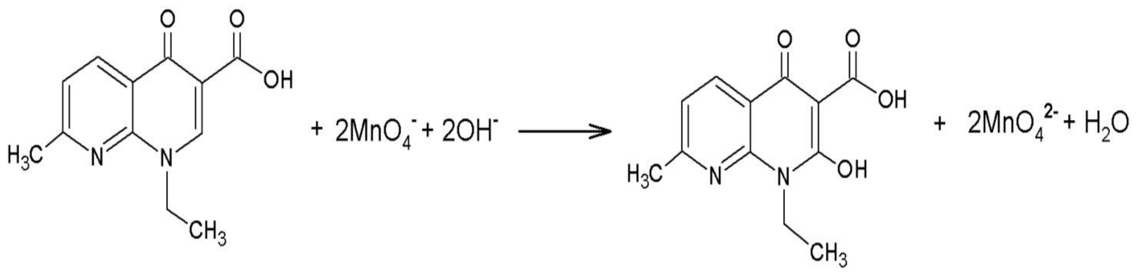
Kinetic Measurements

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^oC 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 $NaNO_3$ 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 $\varepsilon = 2260 \pm 50$ $dm^3\ mol^{-1}\ cm^{-1}$ as a function of time (compared to the literature, $\varepsilon = 2200$, Simandi *et al*., 1985). 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 ± 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^oC in a closed container. When [permanganate] > [nalidixic acid], the remaining permanganate concentration was assayed by measuring the absorbance at 525 nm. Estimation of unreacted $[MnO_4^-]$ 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.



Scheme 1: Formation of hydroxylated NA and Mn(VI).

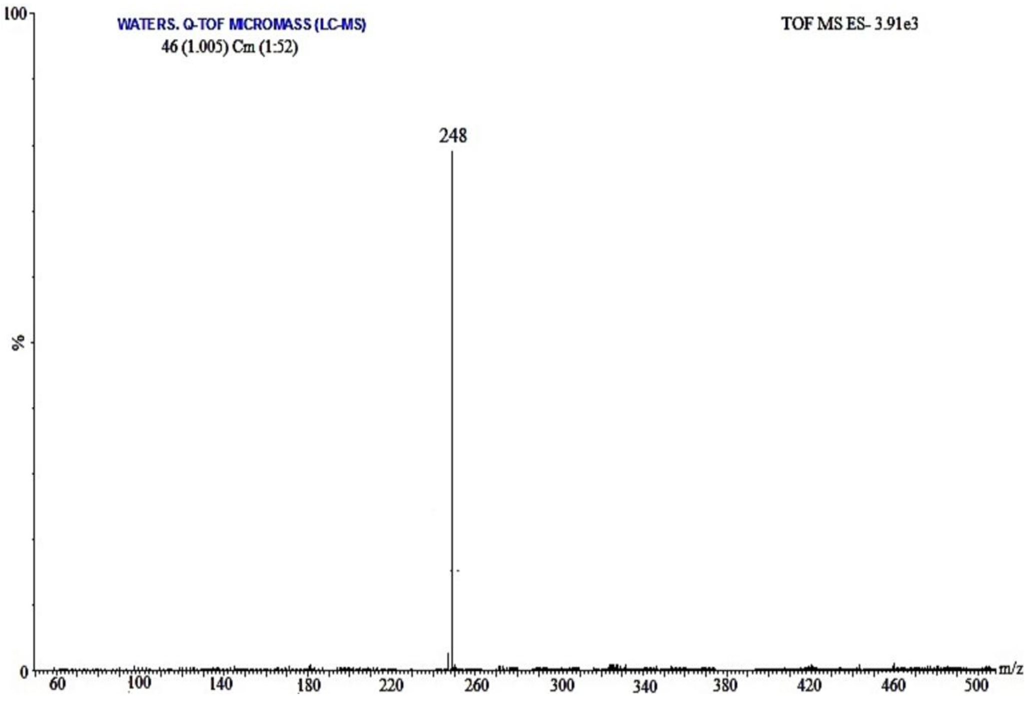


Fig. 2: LC-MS spectra of oxidation product of nalidixic acid.

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 1×10^{-4} to 7×10^{-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 2×10^{-3} to 10×10^{-3}mol dm^{-3} at constant concentration of permanganate, alkali and ionic strength at 35^o, 40^o, 45^oC 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 2.0×10^{-1} to 10×10^{-1}mol dm^{-3} at fixed concentration of permanganate, nalidixic acid and ionic strength at three temperatures viz. 35^o, 40^o, 45^oC 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 [MnO_4^-], [NA] and [OH^-] on the oxidation of nalidixic acid by alkaline permanganate at 40°C and I = 0.5 mol dm^{-3}.

10^4 [MnO_4^-] (mol dm^{-3})	10^3 [NA] (mol dm^{-3})	10^1 [OH^-] (mol dm^{-3})	$10^3 k_{obs}$ (s^{-1})
1.0	5.0	5.0	7.25
2.0	5.0	5.0	7.25
3.0	5.0	5.0	7.27
4.0	5.0	5.0	7.24
5.0	5.0	5.0	7.24
6.0	5.0	5.0	7.27
7.0	5.0	5.0	7.24
5.0	2.0	5.0	4.23
5.0	3.0	5.0	5.61
5.0	4.0	5.0	6.57
5.0	5.0	5.0	7.24
5.0	7.5	5.0	8.47
5.0	10.0	5.0	8.78
2.0	2.0	2.0	4.09
2.0	2.0	3.0	5.43
2.0	2.0	4.0	6.56
2.0	2.0	5.0	7.24
2.0	2.0	7.5	8.54
2.0	2.0	10.0	8.92

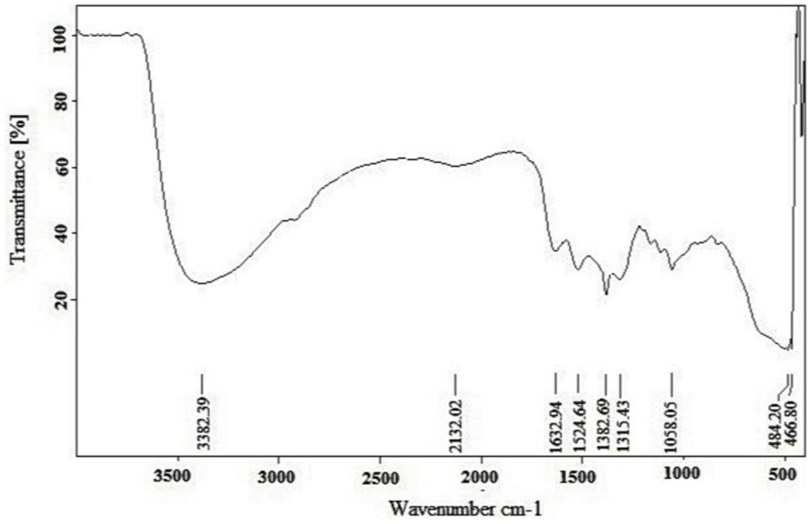


Fig. 3: FT-IR spectra of the product of oxidation of Nalidixic acid by permanganate.

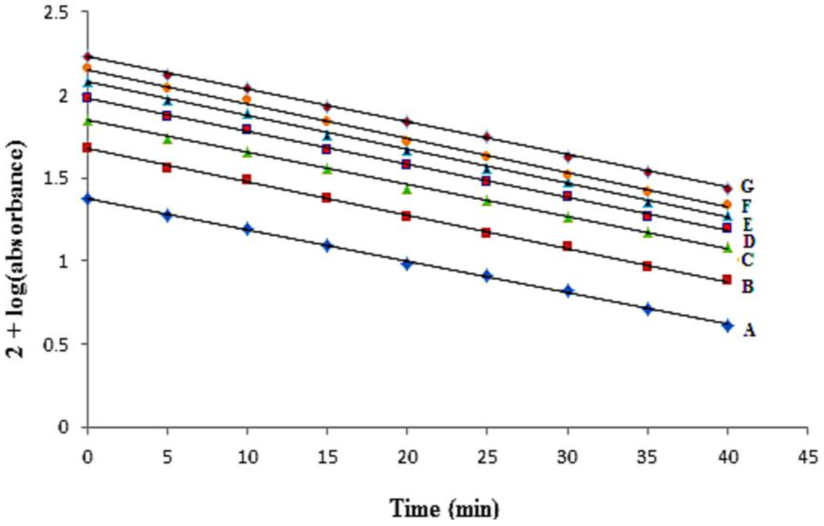


Fig. 4: First order plots of the variation of permanganate concentration at 40°C. [NA]=5.0×10^{-3}, [OH^-] = 0.5 and I = 0.5/ mol dm^{-3}. [MnO_4^-]×10^{-4} mol dm^{-3} = (A) 1.0, (B) 2.0,(C) 3.0, (D) 4.0, (E) 5.0, (F) 6.0, (G) 7.0

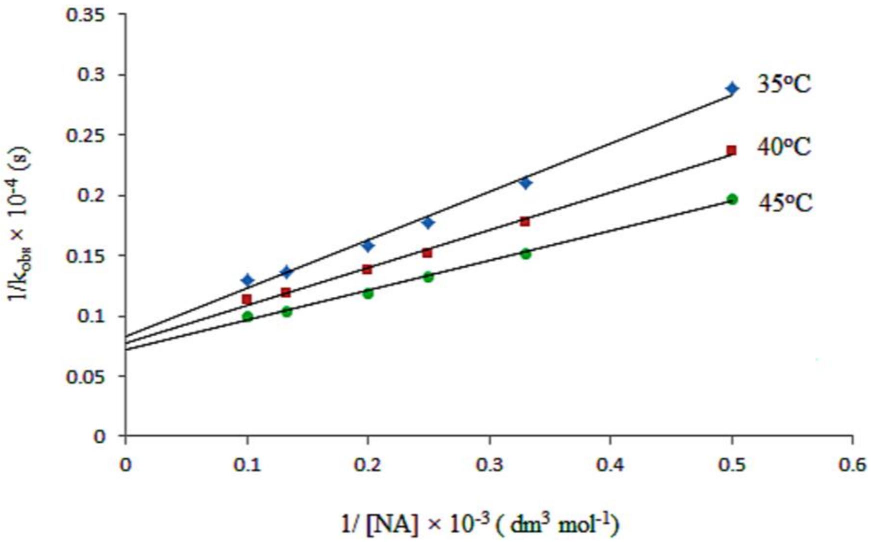


Fig. 5: Plots of $1/k_{obs}$ versus 1/ [NA] at three different temperatures.

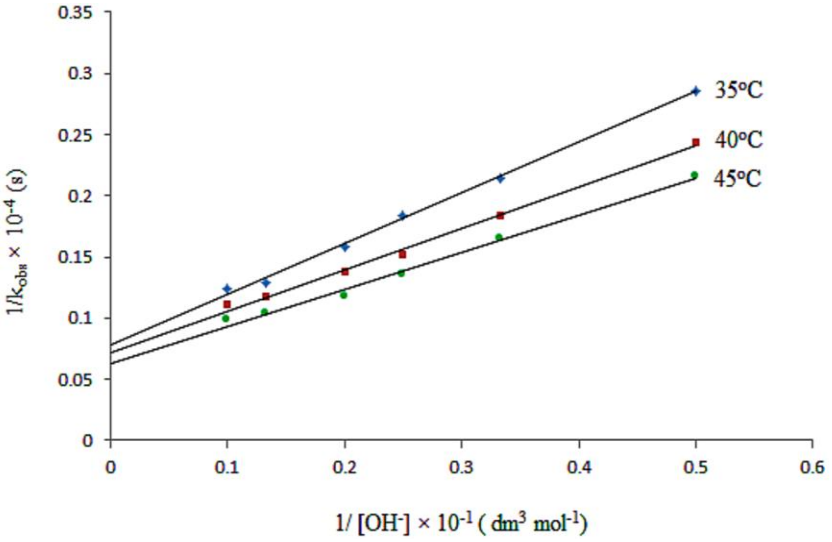


Fig. 6: Plots of $1/k_{obs}$ versus 1/ [OH^-] at three different temperatures.

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 4.0×10^{-5} to 4.0×10^{-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.

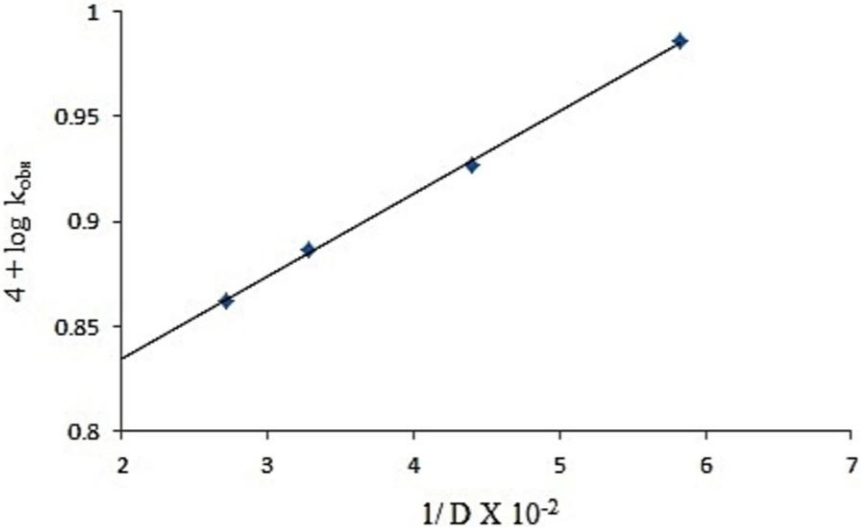


Fig. 7: Effect of dielectric constant on the oxidation of nalidixic acid by alkaline permanganate at 40°C.

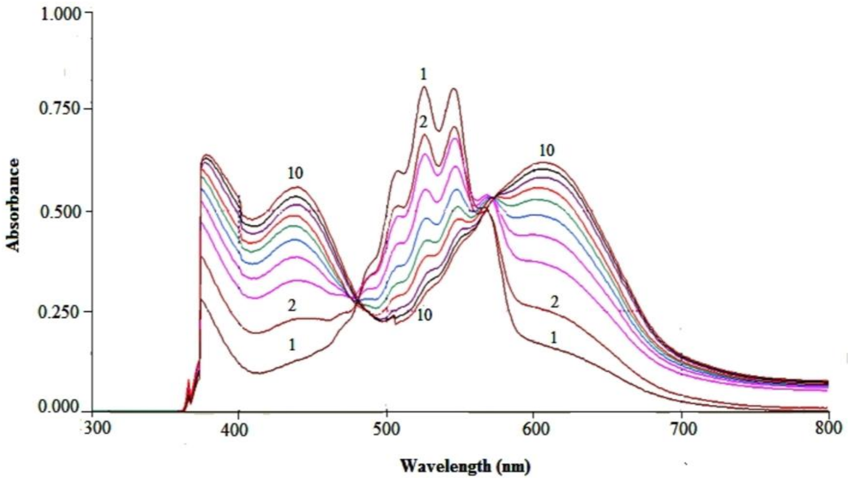


Fig. 8: Spectral changes during the oxidation of nalidixic acid (NA) by permanganate in alkaline medium at 40°C: $[MnO_4^-] = 5.0 \times 10^{-4}$, $[NA] = 5.0 \times 10^{-3}$, $[OH^-] = 5.0 \times 10^{-1}$ and $I = 0.5$/ mol dm^{-3}.

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

Temperature (Kelvin)	10^3 k (s^{-1})	
Effect of temperature with respect to the slow step of figure 10.		
308	1.22	
313	1.29	
318	1.40	
Activation parameters	Value	
E_a (kJ mol^{-1})	11.48	
$\Delta H^{\neq}$ (kJ mol^{-1})	8.88	
$\Delta S^{\neq}$ ± (J K^{-1} mol^{-1})	-289.27	
$\Delta G^{\neq}$ ± (kJ mol^{-1})	88.13	
Equilibrium constants at different temperatures		
Temperature (Kelvin)	$10^{-2}K_1$ (dm^3 mol^{-1})	$10^{-3}K_2$ (dm^3 mol^{-1})
308	12.09	3.30
313	16.77	2.81
318	29.76	1.69
Thermodynamic quantities	Using K_1 values	Using K_2 values
ΔH (kJ mol^{-1})	76.58	-55.52
ΔS ± (J K^{-1} mol^{-1})	256.04	-168.03
ΔG ± (kJ mol^{-1})	-3.64	-3.0

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 $[MnO_4{\cdot}OH]^{2-}$ (Thabaj *et al.*, 2007), (Panari *et al.*, 1998). Then $[MnO_4{\cdot}OH]^{2-}$ 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 $[MnO_4{\cdot}OH]^{2-}$ 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, $[MnO_4{\cdot}OH]^{2-}$, 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.

$$\text{Rate} = \frac{-d[MnO_4^-]}{dt} = kK_1K_2[MnO_4^-]_f[NA]_f[OH^-]_f \qquad (1)$$

Total concentration of permanganate is given by

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

$$= [MnO_4^-]_f + [MnO_4^-]\,[OH^-] + kK_1K_2[MnO_4^-]_f[NA][OH^-]$$

$$= [MnO_4^-]_f\,(1 + K_1[OH^-]_f + K_1K_2[OH^-]_f[NA])$$

$$[MnO_4^-]_f = \frac{[MnO_4^-]_t}{1 + K_1[OH^-] + K_1K_2[NA][OH^-]} \qquad ..2$$

$[MnO_4^-]_t$ and $[MnO_4^-]_f$ are total and free concentration of Mn (VII) respectively.

Total concentration of $[OH^-]$ is given by:

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

$$[OH^-]_f = \frac{[OH^-]_t}{1 + K_1[MnO_4^-] + K_1K_2[NA][MnO_4^-]} \qquad ..3$$

In view of low concentration of MnO_4^- and nalidixic acid used, above equation can be written as:

$$[OH^-]_f = [OH^-]_t \qquad \ldots 4$$

Similarly,

$$[NA]_f = [NA]_t \qquad \ldots 5$$

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

$$\text{Rate} = \frac{kK_1K_2[MnO_4^-][OH^-][NA]}{1 + K_1[OH^-] + K_1K_2[OH^-][NA]} \qquad \ldots 6$$

$$\frac{\text{Rate}}{[MnO_4^-]} = k_{obs} = \frac{kK_1K_2[OH^-][NA]}{1 + K_1[OH^-] + K_1K_2[OH^-][NA]} \qquad \ldots 7$$

Equation (7) can be rearranged as

$$\frac{1}{k_{obs}} = \frac{1}{k\,K_1K_2[OH^-][NA]} + \frac{1}{kK_2[NA]} + \frac{1}{k} \qquad \ldots 8$$

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 ΔH, entropy of reaction ΔS and free energy of reaction ΔG, calculated for the first, and second equilibrium steps (Table 2).

The values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are both favourable for electron transfer process (Farokhi and Nandibewoor, 2004). The value of $\Delta S^{\neq}$ within the range of radical reaction has been ascribed (Walling, 1957) to the nature of electron pairing and unpairing process. The negative value of $\Delta S^{\neq}$ indicates that complex is more ordered than the reactants (Rangappa *et al.*, 2001; Bugarcic *et al.*, 2006). 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 $[MnO_4^-]$ 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 $[MnO_4^{\cdot}OH]^{2-}$, 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.

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