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Spectrophotometric study of the oxidation of fosfomycin by potassium permanganate in aqueous perchloric acid medium _ a kinetic and mechanistic approach

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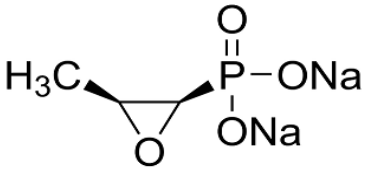
Abstract— The kinetics of oxidation of fosfomycin (FOS) by potassium permanganate in perchloric acid medium has been studied spectrophotometrically at 25 ^{o}C and at constant ionic strength of 3.60 mol dm^{-3}. The stoichiometry of the reaction is determined and found that one mole of permanganate requires one mole of FOS (1:1). The reaction shows first-order dependence in permanganate and apparently less than unit order in both fosfomycin and acid concentrations. The identified oxidation products are Mn^{2+}, formyl phosphonic acid and acetic acid. Reaction rate increases with increase in ionic strength. The increase in the acetic acid content in the reaction medium decreased the rate of the reaction. Based on the experimental results a mechanism involving complex formation between MnO_4^- and substrate has been proposed. The reaction constants involved in the different steps of mechanism are calculated and activation parameters with respect to thermodynamic quantities are computed and discussed. From this spectroscopic investigation we proposed suitable scheme of the experiment.

Keywords—*Fosfomycin, Permanganate, Kinetics and mechanism*

I. INTRODUCTION

Fosfomycin (FOS), [2R,3S)-3-methyloxiran-2-yl phosphonic acid] or (cis-1,2-epoxyphosphonic acid) [1] is an antibiotic drug produced by Streptomyces fradiae. It is used to treat urinary tract infections and to reduce nephrotoxicity and ototoxicity of platinum-containing anti-tumor agents. It is used for susceptibility studies of Klebsiella pneumonia and to study in vitro susceptibility testing procedures for fosfomycin tromethamine [2].

Epoxide displays the broad spectrum activity against various gram-positive and gram-negetive becteria by irreversibly blocking bacterial cell wall synthesis at an earlier stage. Fosfomycin is a broad spectrum antibiotic that concentrates in kidney and bladder. It is simple structure consist of the active bacterial epoxy group and a directly bonded carbon atom to the centrally positioned phosphorus[3, 4]. Fosfomycin is available in the market as the disodium calcium and tris(hydroxyl methyl)ammonium salts[5] and has the following structure.



[2R,3S)-3-methyloxiran-2-yl phosphonic acid]

Potassium permanganate is widely used as an oxidizing agent in synthetic as well as in analytical chemistry [6]. It is a strong oxidizing agent in a all pH range of the solution. In general, reduction of permanganate in acid medium goes to either Mn(IV) or Mn(II), where the reduction potentials [7] of the Mn(VII)/Mn(IV) couple is 1.695 V and the Mn(VII)/Mn(II) couple is 1.51 V respectively. Oxidations of permanganate finds extensive applications in organic synthesis [8]. In acidic medium permanganate exists in different forms $HMnO_4$, $H_2MnO_4^+$, $HMnO_3$, Mn_2O_7 and depending upon the nature of reductant, the oxidant has been assigned both inner and outer sphere mechanism pathway in their redox reactions [9]. The title reaction has been studied in detail and the suitable mechanism has been proposed, the $HMnO_4$ is active species. The reaction is outer sphere or inner sphere and to propose a suitable mechanism based on experimental results.

II. EXPERIMENTAL

Materials and Reagents

All chemicals used were of analytical reagent grade, and double distilled water was used throughout the work. The stock solution of fosfomycin disodium salt (FOS) (Himedia) was prepared in double distilled water. The purity of the drug was checked by comparing its IR spectrum. Permanganate stock solution was obtained by dissolving

potassium permanganate (Glaxo, Analar) in double distilled water and standardized by titrating against oxalic acid [10]. Manganese (II) solution was made by dissolving manganese sulphate (AR) in water. Perchloric acid (Glaxo, Excelar) and sodium perchlorate were used to provide the required acidity and ionic strength respectively.

Instruments Used

1. For kinetic measurements, a Peltier Acessory (Temperature controlled) attached to Varian CARY 50 BIO UV-vis spectrophotometer (Varian, Victoria-1370, Australia) was used.
2. For product analysis, a Shimaduzu 17A gas chromatograph with a Shimaduzu Qp-5050A mass spectrometer using the electron impact (EI) ionization technique, a Nicolet 5700 FT-IR spectrometer (Thermo Electron Corporation, Madison, WI), and an Elico *p*H meter model L1120 were used.

Kinetic Measurements

All kinetic runs were followed under pseudo first-order condition were the substrate fosfomycin concentration was maintained in excess over the permanganate ion concentration at constant temperature, 25.0 ± 0.1 ^{o}C. The reaction was initiated by mixing the thermally equilibrated solutions of permanganate and fosfomycin which also contained the required concentrations of $HClO_4$ and $NaClO_4$. The progress of the reaction was followed spectrophotometrically at 526 nm (i,e. λ_{max} = 526 nm) as a function of time by monitoring the decrease in the absorbance of permanganate in a 1 cm cell placed in the thermostatted compartment of Varian CARY 50 Bio UV-visible sphectrophotometer. Beer's law was verified for permanganate at 526 nm in the concentration range (0.5×10^{-4} - 5.0×10^{-4} mol dm^{-3}) and the extinction coefficient, ε, was found to be (2358±25 dm^3 mol^{-1} cm^{-1}). The kinetics was followed more than 80% completion of the reaction, and an good first order kinetics was observed. The pseudo first-order rate constant, $k_{obs,}$ were calculated from the slopes of the plots of log [MnO_4^-] versus time (Fig. 1). The pseudo first order plots were linear over 75% completion of the reaction. The k_{obs} values were reproducible within ± 5% and are average of least three independent kinetic runs (Table 1). The spectral changes during the oxidation reaction are shown in Fig. 2.

III. STOICHIOMETRY AND IDENTIFICATION OF PRODUCTS

Different sets of reaction mixtures containing excess permanganate with respect to fosfomycin in the presence of constant concentration of perchloric acid medium and at constant ionic strength, (3.60 mol dm^{-3}) at 25 ºC and were kept for 8h.The concentration of the unreacted permanganate

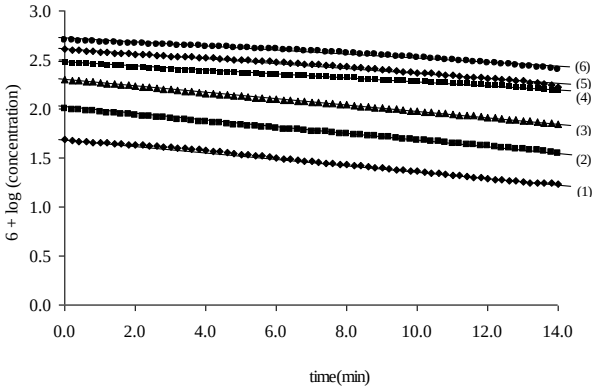
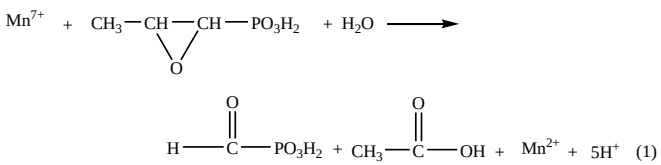


Fig. 1. The pseudo first order plots for the oxidation of fosfomycin by acid permanganate at 25^{o}C. [MnO_4^-] × 10^{-4} mol dm^{-3}: (1) 0.5, (2) 1.0, (3) 2.0, (4) 3.0, (5) 4.0 and (6) 5.0.

concentration was assayed sphectrophotometrically by measuring the absorbance at 526 nm. It showed that one mole of permanganate consumed one mole of fosfomycin. The results indicated 1:1 stoichiometry as given in Eq. (1).



After completion of the reaction, the reaction mixture was extracted by diethyl ether in acid medium. The ether layer was subjected to column chromatography and separated fractions were subjected to spectroscopic investigation. The main product was identified as formyl phosphonic acid and acetic acid as by-product [11]. The other reaction product was identified as Mn^{2+} at 310nm by UV-vis spectroscopy. IR spectrum showed C=O stretching for carbonyl group at 1628 cm^{-1}, while –OH stretching observed at 3500 cm^{-1} and C-PO_3H_2 stretching at 1252 cm^{-1} (Fig. 3). The mass spectrum showed the base peak at 44 amu consistent with molecular ion peak 108 amu. All other constituent peaks are observed in GC-MS (Fig. 4) are interpreted in accordance with the structure of formyl phosphonic acid.

Reaction Orders

The reaction orders were determined from the slopes of log k_{obs} versus log(concentration) plots constructed by varying the concentration of fosfomycin and perchloric

acid in turn, keeping all other concentration and condition constant.

Effect of the Concentration of Permanganate on Rate

The oxidant permanganate concentration was varied in the range of 0.50×10^{-4} mol dm^{-3} - 5.0×10^{-4} mol dm^{-3}, keeping all other conditions constant. At different permanganate concentrations, fairly constant k_{obs} values were obtained (Table 1). It indicates the unit order with respect to $[MnO_4^-]$. This was also confirmed by the linearity of the plots of log (concentration) versus time up to 75% completion of reaction (Fig. 1).

Effect of Concentration of Fosfomycin on Rate

The effect of the concentration of fosfomycin disodium salt on the rate of reaction was studied at constant concentration of permanganate and other constant conditions. It was varied in the range from 0.50×10^{-3} mol dm^{-3} - 5.0×10^{-3} mol dm^{-3} at 25 °C. The k_{obs} increased with increase in the concentration of fosfomycin (Table 1). The order with respect to fosfomycin concentration was obtained from the plot of log k_{obs} versus log [FOS] and was found to be less than unity (0.50).

Effect of Concentration of Perchloric acid on Rate

The effect of variation of perchloric acid on the first order rate of reaction was studied in the different concentration range 0.25 mol dm^{-3} - 2.5 mol dm^{-3} and other reaction conditions were kept constant at 25 °C. The rate constant was found to increase with increasing in the perchloric acid concentration (Table 1). The values from the slope of the plot of log k_{obs} versus log $[HClO_4]$, the reaction order with respect to $HClO_4$ concentration was found to be less than unity (0.59).

From the observed experimental results, the rate law for the reaction is given as, follows:

$$\text{Rate} = k_{obs}\,[MnO_4^-]^{1.0}[FOS]^{0.50}[H^+]^{0.39} \qquad (2)$$

Effect of Ionic Strength (I) and Dielectric Constant (D) on Rate

Effect of ionic strength was studied by varying the sodium perchlorate concentration from 1.5 mol dm^{-3} to 4.0 mol dm^{-3} at the constant concentrations of MnO_4^-, FOS and H^+ at 25 °C and found that increasing the ionic strength, increases the reaction rate. The plot of log k_{obs} versus √I was linear (Fig. 5, curve a). The effect of dielectric constant of the medium (*D*) was varied by varying the acetic acid–water (*v/v*) percentage with all other conditions kept constant. With increase in acetic acid content in the reaction medium, decreased the rate of reaction. The plot of log k_{obs} versus 1/*D* is linear (Fig. 5, curve b).

Effect of Initially Added Product

At constant concentrations of reactants and at other constant conditions initially added product, Mn(II), was studied in the concentration range 0.50×10^{-4} mol dm^{-3} - 5.0×10^{-4} mol dm^{-3}. The added product, Mn(II), did not show any significant effect on the rate of reaction.

Polymerization Study

The possible free radicals in the present reaction were investigated as follows: The reaction mixture, to which a known quantity of acrylonitrile (scavenger) monomer was initially added and kept for 2 h in an inert atmosphere. On diluting the reaction mixture with methanol a white precipitate was formed, it indicating the intervention of free radicals in the reaction. Blank experiments with either fosfomycin or permanganate alone with acrylonitrile did not induce any polymerization under the same condition as those induce for the reaction mixture. The added acrylonitrile also decreases the rate of reaction, indicating free radical invention in the reaction.

Effect of Temperature on Rate

The influence of temperature on the rate of reaction was studied at (15, 25, 35 and 45 °C), with varying the perchloric acid and fosfomycin disodium salt concentrations, keeping other conditions constant. The rate of the reaction found to be increase with increase in the temperature. The rate constant of the slow step (*k*), the formation constant of $HMnO_4$ (K_1), and the formation constant of complex (K_2) in Scheme 1 were obtained from the intercepts and slopes of the plots of $1/k_{obs}$ versus $1/[H^+]$ and $1/k_{obs}$ versus 1/[FOS] at four different sets of temperatures. The energy of activation, E_a, was evaluated from the slope of an Arrhenius plot, log*k* versus 1/*T* (Table 2). The enthalpy of activation $\Delta H^{\neq}$, the entropy of activation $\Delta S^{\neq}$ and the free energy of activation $\Delta G^{\neq}$ were obtained by using [12] the Eq (3).

$$\ln k = \ln A + \frac{E_a}{RT} = \left(\frac{-E_a}{T}\right)\left(\frac{1}{T}\right) + \ln A \qquad (3)$$

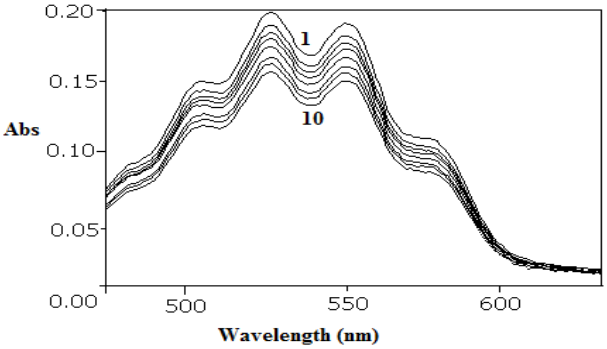


Fig. 2. UV-vis spectral changes during the oxidation of fosfomycin by acidic permanganate at 25°C $[MnO_4^-]$ = 1.0

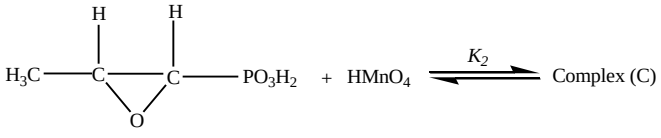
× 10^{-4} mol.dm^{-3}, [FOS] = 2.0 × 10^{-3} mol.dm^{-3}, [H^+] = 1.5 mol dm^{-3} and I = 3.60 mol dm^{-3} with scanning time interval of: (1) 0.5, (2) 1.0, (3) 1.5, (4)2.0 and (5) 2.5min.

IV. DISCUSSION

The active species of permanganate in acid medium may be deduced from the dependence of the reaction rate on [H^+]. The order of the reaction with respect to acid concentration is less than unity, it is the indication of the formation of permanganic acid from permanganate ion. In the acid media, permanganic acid, $HMnO_4$, is more effective oxidant species of manganese (VII) than the permanganate ion [13]. In addition the reaction rate increased with increase in [H^+]. At higher acidities [in the acid concentration range of 0.25 mol dm^{-3} to 2.5 mol dm^{-3}] protonation almost complete, leading to the limiting rate, which indicate that only the protonated from is active. The positive effect of the ionic strength on the rate of reaction also confirms that $HMnO_4$ is active species of MnO_4^- in acid medium. Thus the acid-permanganate equilibrium can be represented by equation 4.

$$MnO_4^- + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} \underset{[Mn(VII)]}{HMnO_4} \quad (4)$$

The stable oxidation product of MnO_4^- in acid medium is Mn(II). The spectral changes during the reaction are shown in Fig. 2. The reaction between fosfomycin and MnO_4^- has stoichiometry 1:1 with first-order dependence on the MnO_4^- concentration and less than-unity orders in both the FOS and $HClO_4$ concentrations. The oxidation products were formyl phosphonic acid, manganese (II) and acetic acid. The fact that, Mn(II) is reduced product of Mn(VII) in the reaction, might indicate that, fosfomycin shows a strong reducing character in $HClO_4$ medium. Based on the experimental results, a mechanism is proposed in the form of Scheme 1, in which all the observed orders in each constituent, [oxidant], [reductant] and [H^+] were accommodated.



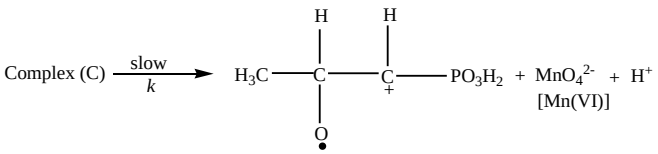
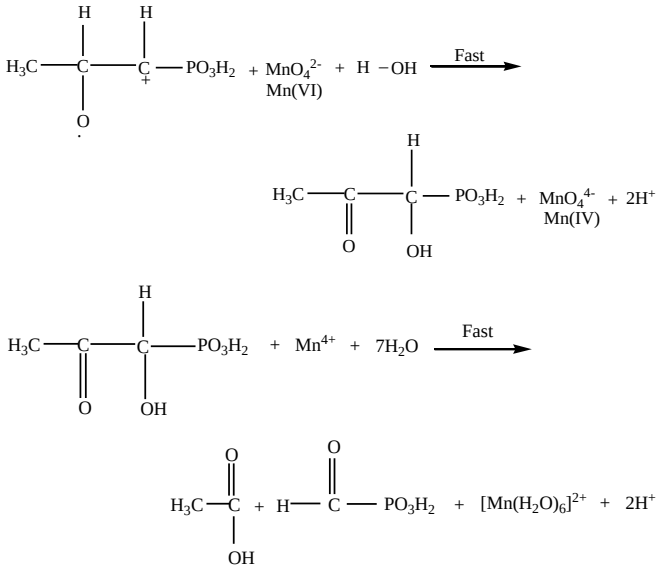


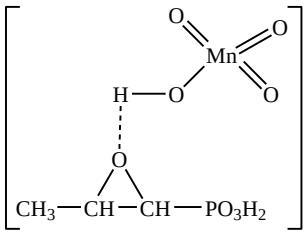
Table 1. Effect of variation of permanganate, fosfomycin and perchloric acid concentrations on the oxidation of fosfomycin by acidic permanganate at 25 °C and *I* =3.60 mol dm^{-3}

[MnO_4^-] × 10^4 (mol dm^{-3})	[FOS] × 10^3 (mol dm^{-3})	[$HClO_4^-$] (mol dm^{-3})	k_{obs} × 10^3 (s^{-1})
0.5	2.0	1.5	1.28
1.0	2.0	1.5	1.27
2.0	2.0	1.5	1.28
3.0	2.0	1.5	1.26
4.0	2.0	1.5	1.27
5.0	2.0	1.5	1.27
1.0	0.5	1.5	0.56
1.0	1.0	1.5	0.88
1.0	2.0	1.5	1.27
1.0	3.0	1.5	1.53
1.0	4.0	1.5	1.61
1.0	5.0	1.5	1.81
1.0	2.0	0.25	0.38
1.0	2.0	1.5	0.64
1.0	2.0	1.0	1.02
1.0	2.0	1.5	1.27
1.0	2.0	2.0	1.31
1.0	2.0	2.5	1.50



Scheme 1.

In the prior equilibrium step, acid (H^+) catalyses the reaction which reacts with MnO_4^- to form $HMnO_4$ active species as evidenced by literature [14]. In the second equilibrium step, fosfomycin reacts with the active species $HMnO_4$ to form a complex (C), which decomposes in a slow step to gives radical cation and an intermediate Mn(VI) species. It is known that most of the epoxides react in acidic medium to form a carbocation by breaking the epoxide ring [15]. In a fast step the intermediate Mn(VI) reacts with free radical cation to give 1-hydroxy 2-oxopropyl phosphonic acid and Mn(IV). Aqueous acid will open an epoxide under much milder conditions than an "ordinary" ether such as diethyl ether, because epoxides have considerable ring strain. Looking more closely at the reaction, the nucleophile attacks at the "more substituted" position of the epoxide, inversion of stereochemistry occurs at this position, but not at the other position [15]. In a further fast step intermediate Mn(IV) reacts with their formed 1-hydroxy 2-oxopropyl phosphonic acid, to give the final products formyl phoshonic acid, Mn(II), and the byproduct acetic acid satisfying the observed stoichiometry. The spectral evidence for a complex formation between the fofomycin and permanganate was obtained from UV-vis spectra of fosfomycin–MnO_4^- mixture in which hypsochromic shift (from 310 to 302nm) was observed (Fig. 6). The probable structure of the complex as follows:



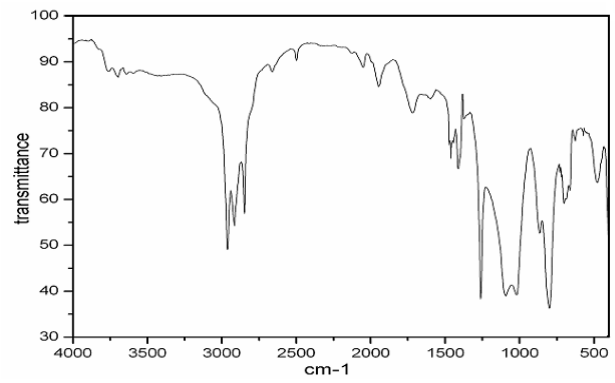


Fig. 3. IR spectrum of formyl phosphonic acid, a product obtained during the oxidation of fosfomycin by permanganate. C=O stretching at 1628 cm^{-1}, –OH stretching at 3500 cm^{-1} & C-PO_3H_2 stretching at 1252 cm^{-1}.

According to Scheme 1, the rate law (13) can be derived as follows,

$$\text{Rate} = -\frac{[MnO_4^-]}{dt} = k\,[\text{Complex}] \qquad (6)$$

$$[\text{Complex}] = K_2[FOS][HMnO_4^-] \qquad (7)$$

$$[HMnO_4^-] = K_1\,[MnO_4^-]\,[H^+] \qquad (8)$$

$$\text{Rate} = -\frac{d[MnO_4^-]}{dt} = kK_1K_2[FOS][MnO_4^-][H^+] \qquad (9)$$

$$[MnO_4^-]_t = [MnO_4^-]_f\{1 + K_1[H^+] + K_1K_2\,[FOS] + [H^+]\}$$

$$[MnO_4^-]_f = \frac{[MnO_4^-]_t}{1 + K_1[H^+] + K_1K_2\,[FOS] + [H^+]} \qquad (10)$$

$$[FOS]_f = \frac{[FOS]_t}{1 + K_2[HMnO_4^-]} \qquad (11)$$

$$[H^+]_t = [H^+]_f + K_1\,[MnO_4^-]\,[H^+]_f$$

$$= [H^+]_f\{1 + K_1[MnO_4^-]\} \qquad (12)$$

$$\frac{\text{Rate}}{[MnO_4^-]} = k_{obs} = \frac{k\,K_1\,K_2\,[FOS][H^+]}{1 + K_1\,[H^+]\,K_1\,K_2\,[FOS][H^+]} \qquad (13)$$

The rate law (13) to rearrange for the verification

$$\frac{1}{k_{obs}} = \frac{1}{k\,K_1\,K_2\,[FOS][H^+]} + \frac{1}{k\,K_1\,[FOS]} + \frac{1}{k} \qquad (14)$$

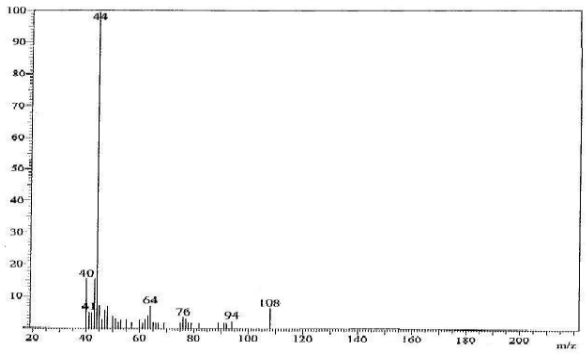


Fig. 4. Mass spectrum of the reaction product formyl phosphonic acid.

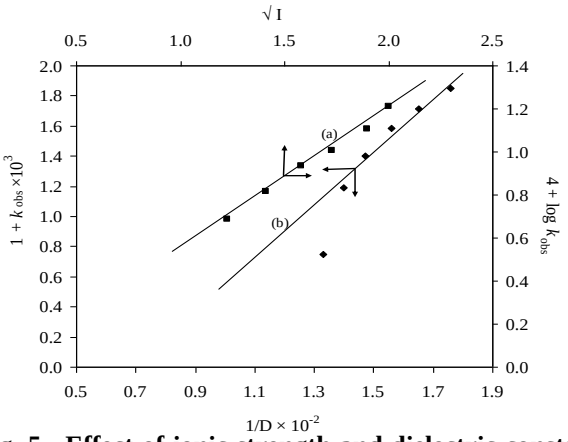


Fig. 5. Effect of ionic strength and dielectric constant of the medium on the oxidation of fosfomycin by acid permanganate at 25 °C.

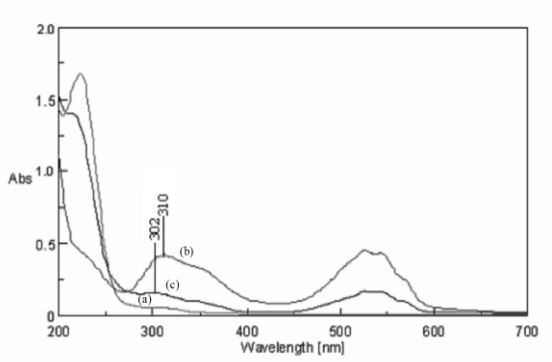


Fig. 6. Spectroscopic evidence for complex formation between permanganate and fosfomycin (a) fosfomycin, (b) permanganate and (c) a mixture of permanganate and fosfomycin. Condition: [MnO_4^-] = 2.0 × 10^{-4} mol.dm^{-3}, [FOS] = 2.0 × 10^{-3} mol dm^{-3}.

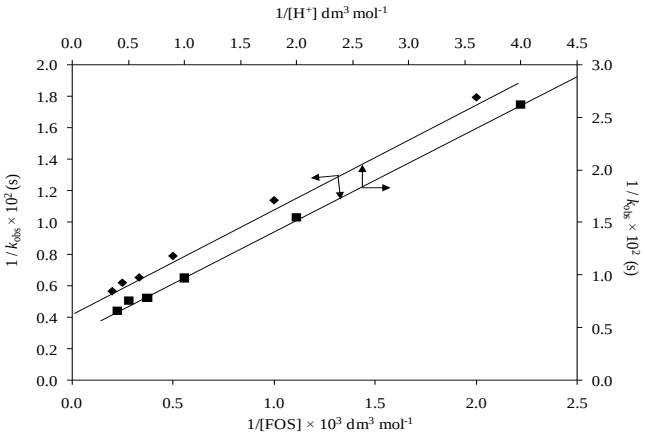


Fig. 7. The verification of rate law (14) in the form of eq. (14).

(a) Effect of temperature on the slow step of Scheme 1 and activation parameter

Temp. (K)	$k \times 10^3$ (s^{-1})	Activation Parameters	Values
288	0.38	Ea (k J mol^{-1})	80 ± 4
298	2.26	$\Delta H^{\neq}$ (k J mol^{-1})	78 ± 4
308	6.84	$\Delta S^{\neq}$ (J $K^{-1}mol^{-1}$)	-34 ± 3
318	8.59	$\Delta G^{\neq}$ (kJ mol^{-1})	88 ± 3
		log A	11

(b) Effect of temperature on first and second equilibrium steps of Scheme 1

Temp (*K*)	$K_1 \times 10^2$ (dm^3 mol^{-1})	$K_2 \times 10^{-3}$ (dm^3 mol^{-1})
288	0.9	56
298	2.2	18
308	10.6	4.7
318	15.7	1.2

(c) Thermodynamic quantities with respect to first and second steps of Scheme 1

Thermodynamic Quantities	Using K_1 values	Using K_2 values
ΔH (kJ mol^{-1})	78	-98
ΔS (J $K^{-1}mol^{-1}$)	204	-248
ΔG (kJ mol^{-1})	8	-23

Table 2. Effect of temperature on the oxidation of fosfomycin by permanganate in aqueous perchloric acid

According to equation (14), plots of $1/k_{obs}$ versus $1/[H^+]$ and $1/k_{obs}$ verses 1/[FOS] should be linear and that are found to be so (Fig. 7). The slopes and intercepts of such plots leads to values of K_1, K_2 and k the values are given in Table 2. The value of K_1 is in good agreement with the literature [16]. The reaction which supports the inner-sphere mechanism [8]. As the ionic strength increases, the rate of reaction also increases [17], it is contrary to that expected, in view of the high ionic strength (I =3.60 mol dm^{-3}) used in the experiment. A

decrease in the rate of reaction with decrease in dielectric constant may be due to stabilization of complex in less solvated than MnO_4^- at lower dielectric constant.

The thermodynamic quantities for the different equilibrium steps, of Scheme 1, can be evaluated as follows. The [FOS] and [H^+] as in (Table 1) were varied at four different temperatures. From the slopes and intercepts, K_1 and K_2 were calculated at four different temperatures. van't Hoff plot was made for the variation of K_1 and K_2 with temperature (log K_1 versus 1/T and log K_2 versus 1/T). The value of enthalpy of reaction, ΔH, entropy of reaction, ΔS and Gibbs energy of reaction, ΔG were calculated for the first and second equilibrium steps of Scheme 1. These values are given in the Table 2. The activation parameters with respect to slow step of Scheme 1 were also given in Table 2. These values are comparable where $\Delta H^{\#}$ = 59 k J mol^{-1}, $\Delta S^{\#}$ = -81 J K^{-1} mol^{-1}, $\Delta G^{\#}$ = 83 kJ mol^{-1}, and log A = 9, with earlier work [13]. The values of $\Delta S^{\neq}$ and $\Delta H^{\neq}$ are both favorable for electron transfer processes [18, 19]. The observed modest enthalpy of activation and higher rate content for the slow step indicates that the oxidation probably occurs via on inner sphere mechanism. This conclusion is supported by earlier literature [20].

V. CONCLUSIONS

The oxidation of potassium permanganate by fosfomycin in acid perchlorate solutions have been investigated, spectrophotometrically. The oxidation process was found to proceed through the formation of 1:1 stoichiometry. The reaction was found to be acid-inhibition where the oxidation rates were increased with increasing the hydrogen ion concentration. The kinetic evaluated value of the ionization constant of fosfomycin was found to be in good agreement with that reported elsewhere. The oxidation product of fosfomycin was identified as formyl phosphonic acid. It noticed that the entropy of activation tends to be more positive for outer-sphere types, whereas the reactions of negative $\Delta S^{\neq}$ values are mainly preceded via inner-sphere mechanism.

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