IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
September 2018 Vol.:13, Issue:2

Kinetics and Mechanism of Uncatalyzed Oxidation of Omeprazole by Alkaline Potassium Permanganate

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ISSN 2349-7203
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Submission: 22 August 2018
Accepted: 29 August 2018
Published: 30 September 2018

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Kinetics, Oxidation, Omeprazole, Potassium permanganate, Mechanism.

ABSTRACT

The Kinetics of oxidation of Omeprazole by $KMnO_4$ in the aqueous alkaline medium was studied spectrophotometrically at constant ionic strength 0.01 moldm^{-3}. The reaction exhibits 1:1 stoichiometry. The reaction is a pseudo-first order with respect to Oxidant, fractional order with respect to reductant and medium. The activation parameters for the slow step were calculated. Effect of ionic strength and dielectric constant of the medium has been studied. The rate constant of the rate determining step was calculated and a suitable mechanism has been proposed.

1. INTRODUCTION:

Omeprazole(OMZ),5-methoxy-2[[(4-methoxy-3,5dimethyl-2-pyridinyl)methyl]sulphinyl]-1H-benz imidazole structural formula is shown in Fig.1 is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GORD/GERD), Laryngopharyngeal reflux (LPR) and Zollinger Ellison syndrome. It suppresses gastric acid secretion by specific inhibition of hydrogen-potassium adenosine triphosphate (H^+/K^+ ATP ase) enzyme system found at the secretory surface of parietal cells. Oxidative metabolism of omeprazole in human liver microsomes has studied by Chiba K *et al.* and others [1-5]. Electrochemical oxidation of OMZ at a carbon paste electrode was studied by cyclic and differential pulse voltammetry [6,7]. Kinetics of degradation of OMZ was studied by Maria Popilarz-Brzezi Ska [8]. Oxidation by cytochrome enzymes, stereoselective metabolism, pharmacokinetics, anti-oxidant properties, hydroxylation, and electrochemical redox behavior has been already revealed [9-11]. Copper-catalyzed oxidation of Omeprazole by hexacyanoferrate in the alkaline medium has been reported by Sateesh BC *et al.* [12].

Permanganate is a unique oxidizing agent in the neutral, alkaline and acidic medium. It oxidizes a greater variety of substances and finds extensive applications in organic synthesis. During oxidation by permanganate, it is evident that the Mn (VII) in permanganate reduced to various oxidation states depends on the medium used. In strongly alkaline media, the stable reduction product is manganate ion, MnO_4^{2-}. The oxidation product 6-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methane]sulfonyl}-1H-1,3-benzodiazole commonly known as omeprazole sulfone was isolated and identified by LC-MS spectra (Fig.2). Omeprazole sulfone belongs to the family of Sulfinylbenzimidazoles and used as single plasma sample as a probe for CYP3A4. There is limited research on oxidation of OMZ in the alkaline medium by inorganic oxidizing agents and hence in the present study, we have discussed the oxidation of OMZ with alkaline Potassium permanganate.

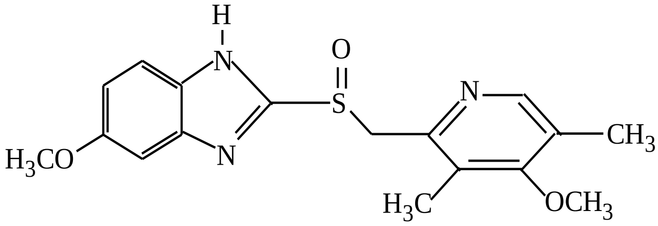


Fig. 1: Chemical structure of Omeprazole

2. MATERIALS AND METHODS:

2.1. Materials and reagents used

All Chemicals and reagents used Omeprazole, Permanganate (VII), NaOH, KNO_3, Na_2SO_4, KCl, $NaHCO_3$, CH_3OH were of analytical grade obtained from Merck and solutions were prepared using double distilled water, free from dissolved oxygen. Permanganate (VII) was prepared by dissolving the requisite amount of salt in doubly distilled water and the solution was standardized by oxalic acid. Omeprazole was prepared by dissolving the requisite amount of sample in NaOH and diluted using distilled water. NaOH, KNO_3 Na_2SO_4, KCl, $NaHCO_3$ were also prepared in doubly distilled water and standardized by standard methods. Absorbance was recorded using Systronic UV-Vis Spectrophotometer at wavelength 525nm**.**

All other reagents were of reagent grade and their solutions were prepared by dissolving the requisite amounts of sample in doubly distilled water.

2.2. Kinetic studies

The reaction of OMZ with $KMnO_4$ was studied under pseudo-first order condition where the concentration of OMZ is 10 times greater than the concentration of $KMnO_4$ at 25ºC$\pm$ 0.1. The reaction was initiated by mixing the $KMnO_4$ solution to omeprazole containing the required amount of NaOH and KNO_3. Extension of the reaction was observed spectrophotometrically by measuring the decrease in absorbance of $KMnO_4$ at wavelength 525 nm.

A graph of log [Absorbance] versus time was plotted for pseudo-first-order reaction and are linear up to 80% completion. Rate constants (k_{obs}) were calculated and are reproducible within $\pm$ 5% error.

3. RESULTS:

3.1. Stoichiometry and product analysis

The stoichiometry of reaction was determined by varying concentration of reactants at constant ionic strength 0.01 moldm^{-3} and at constant NaOH concentration. The reaction mixture was kept over 24 hours at room temperature and after the completion of reaction excess of Permanganate was measured spectrophotometrically at 525nm. The stoichiometry of the reaction was found as 1:1. The oxidative product was found to be Omeprazole sulphone formed by reacting 1mole of OMZ with 1mole of Permanganate. The reaction can be represented as follows. The product omeprazole sulphone was identified by LC-MS spectra Fig.2.

$$\mathbf{C_{17}H_{19}N_3O_3S \; + \; KMnO_4 + 2OH^- \longrightarrow C_{17}H_{19}N_3O_4S + MnO_4^{2-} + H_2O}$$

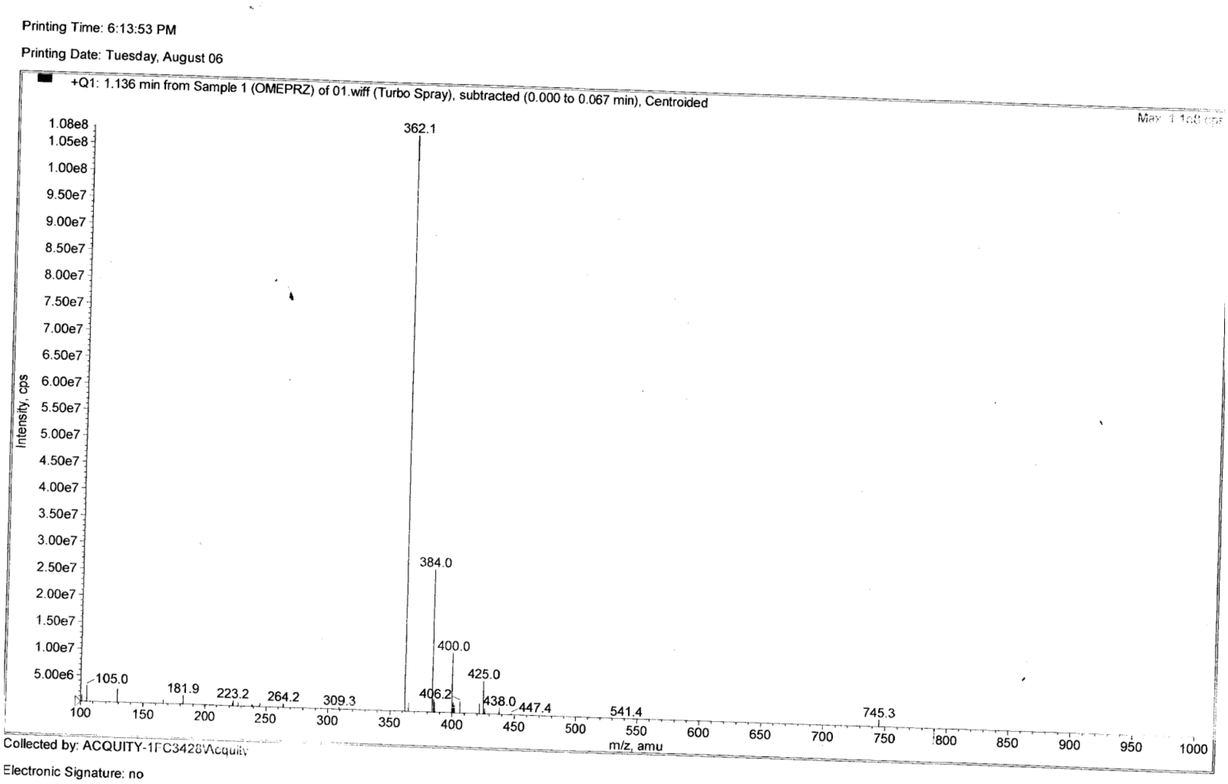


Fig.2: LC-MS of Omeprazole Sulphone gives molecular ion peak at 362.1 MHz.

3.2 Reaction order

3.2.1. Effect of variation of Permanganate concentration

Potassium permanganate concentration was varied from 0.25×10^{-4} to 3.0×10^{-4} $moldm^{-3}$ keeping concentrations of OMZ, NaOH, and KNO_3 as constant. The linearity of plots of log absorbance versus time up to 80% completion of the reaction (Fig.3) indicates the reaction is first order with respect to Permanganate. This is also confirmed by variation of Permanganate, which did not result in any change in pseudo-first-order rate constants (Table I).

3.2.2. Effect of variation of Omeprazole concentration

Effect of omeprazole on reaction rate was studied by varying its concentration from $0.25x10^{-3}$ to $3.0x10^{-3}$ moldm^{-3} and keeping the concentration of $KMnO_4$, NaOH and KNO_3 as constants. The plot log k_{Obs} versus log [OMZ] for the different initial concentration of OMZ is linear with fractional slope 0.74 which clearly indicates the fractional- order dependence on reaction rate (Fig.4).

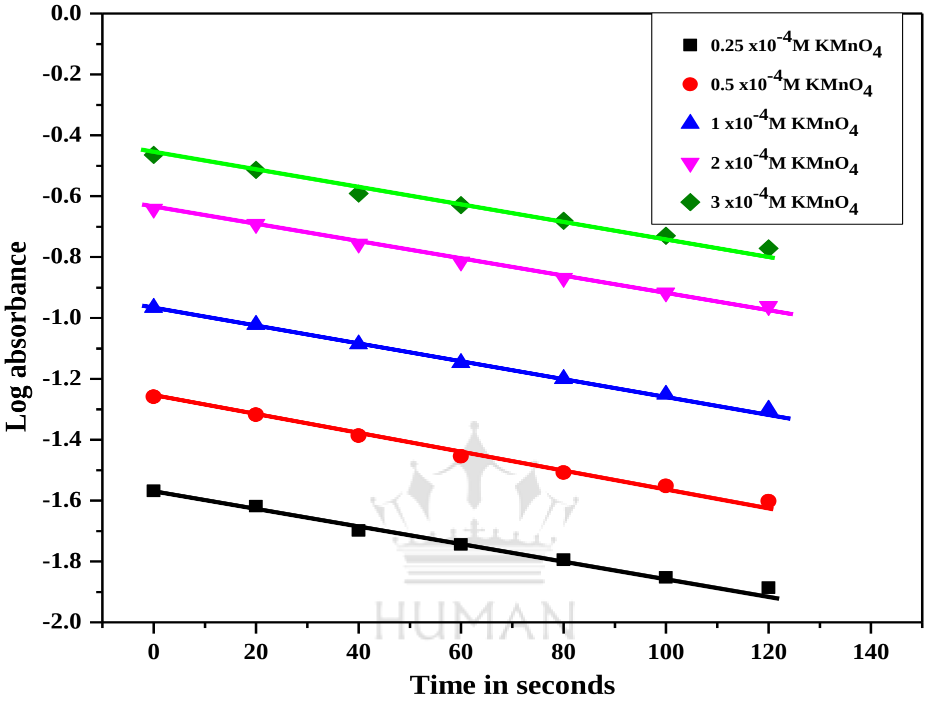


Fig.3: A graph of Log OD against time shows first order with respect to permanganate.

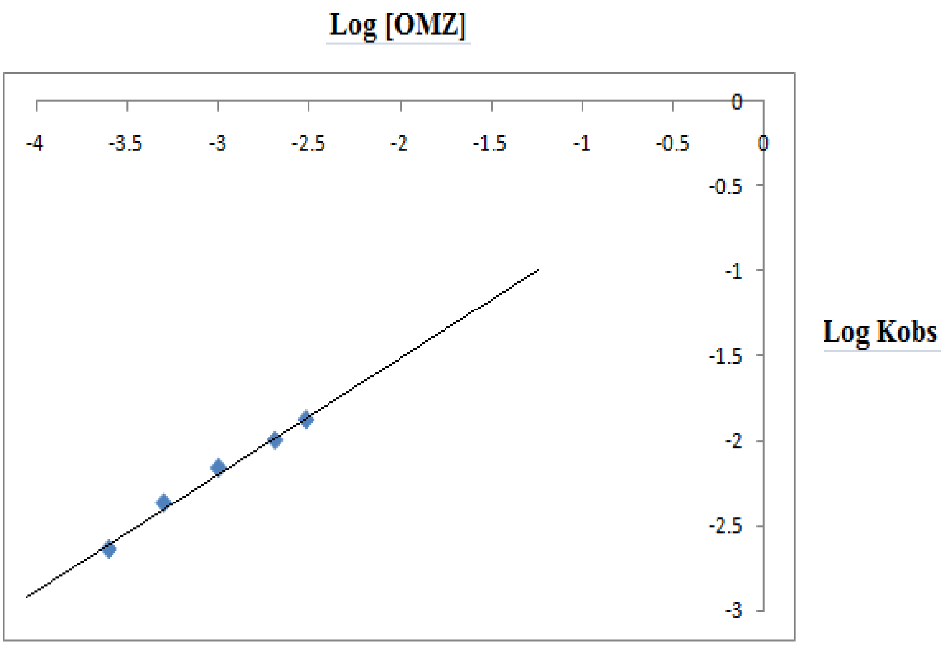


Fig.4: A graph of Log [OMZ] against Log Kobs shows fractional order with respect to omeprazole.

3.2.3. Effect of Dielectric constant and Ionic strength

The dielectric constant of the medium was studied by varying percentage of methyl alcohol and water like 1:2, 2:2, 3:2 and 4:2 in medium keeping all other conditions constant. Ionic strength was studied by varying concentration of KNO_3 from $0.25x10^{-2}$ to $3x10^{-2}$ $moldm^{-3}$ keeping the concentration of OMZ, $KMnO_4$, and NaOH as constants. It was found that dielectric constant of medium and ionic strength has no significant effect on reaction rate.

Table I: Effect of [OMZ], [KMnO4],[NaOH] and [KNO_3] on reaction rate at Temperature= 25 ±0.1ºC, μ=0.01 mol dm^{-3}.

[$KMnO_4$]x10^{-4} (moldm^{-3})	[OMZ]x10^{-3} (moldm^{-3})	[OH^-] (moldm^{-3})	[NO_3^-]x10^{-2} (moldm^{-3})	$K_{observed}$ (S^{-1}) x10^{-3}	$k_{calculated}$ (S^{-1}) x10^{-3}
0.25	1.0	0.025	1.0	7.12	6.98
0.5	1.0	0.025	1.0	7.10	6.98
1.0	1.0	0.025	1.0	6.94	6.98
2.0	1.0	0.025	1.0	6.84	6.98
3.0	1.0	0.025	1.0	6.97	6.98
1.0	0.25	0.025	1.0	2.30	2.35
1.0	0.5	0.025	1.0	4.31	4.29
1.0	1.0	0.025	1.0	6.94	6.98
1.0	2.0	0.025	1.0	10.1	10.3
1.0	3.0	0.025	1.0	13.4	12.9
1.0	1.0	0.012	1.0	5.75	5.62
1.0	1.0	0.025	1.0	6.94	6.98
1.0	1.0	0.05	1.0	7.53	7.92
1.0	1.0	0.1	1.0	8.63	8.52
1.0	1.0	0.2	1.0	9.10	8.86
1.0	1.0	0.025	0.25	6.88	6.98
1.0	1.0	0.025	0.5	6.83	6.98
1.0	1.0	0.025	1.0	6.94	6.98
1.0	1.0	0.025	2.0	6.70	6.98
1.0	1.0	0.025	3.0	6.82	6.98

3.2.5. Effect of Sodium hydroxide

The concentration of sodium hydroxide was varied from 0.0125 moldm^{-3} to 0.2 moldm^{-3} by keeping all other conditions constant. The rate constant increases with an increase in [alkali] (Table I) and shows fractional order dependence.

3.2.6. Effect of sulfate, chloride, Bicarbonate

Effect of sulfate, chloride, and bicarbonate on reaction rate was studied from 0.25x10^{-2} to 3x10^{-2} moldm^{-3} there is no significant effect on reaction rate.

3.2.7. Test for free radicals (Polymerization study)

Free radical involvement in the oxidation of omeprazole by permanganate (VII) was studied by adding acrylonitrile followed by methyl alcohol dilution which doesn't involve precipitate formation indicating that the reaction path is free from the radical mechanism.

3.2.8. Effect of Temperature

The reaction rate was measured at a different temperature, keeping the concentration of OMZ and other conditions constant. With the increase in temperature rate of reaction increases. The rate constants at different temperature K_{obs} were calculated [Table II]. A graph of log K_{obs} versus 1/T was plotted [Arrhenius plot Fig.5] and from the slope activation energy E_a($KJmol^{-1}$) was calculated. Different activation parameters $\Delta H^{\#}$ ($KJmol^{-1}$), $\Delta S^{\#}$($JK^{-1}mol^{-1}$) and $\Delta G^{\#}$ ($KJmol^{-1}$) were also calculated and tabulated [Table III].

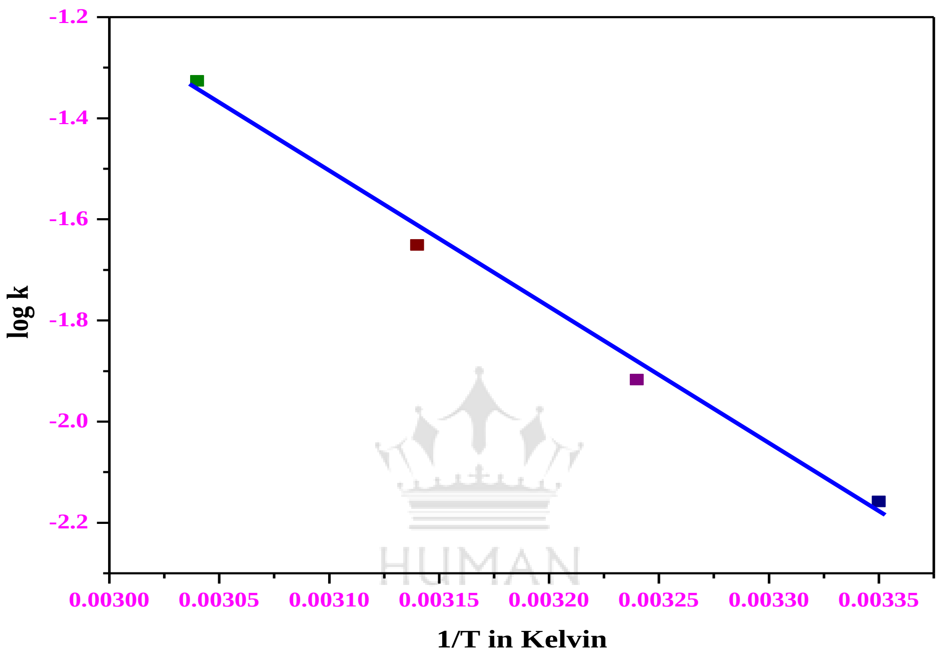


Fig.5: Arrhenius plot for variation of temperature.

Table II. Rate constants with respect to temperature.

Temperature in (K)	K_{obs} 10^{-3}(S^{-1})
298	6.94
308	12.1
318	22.3
328	47.1

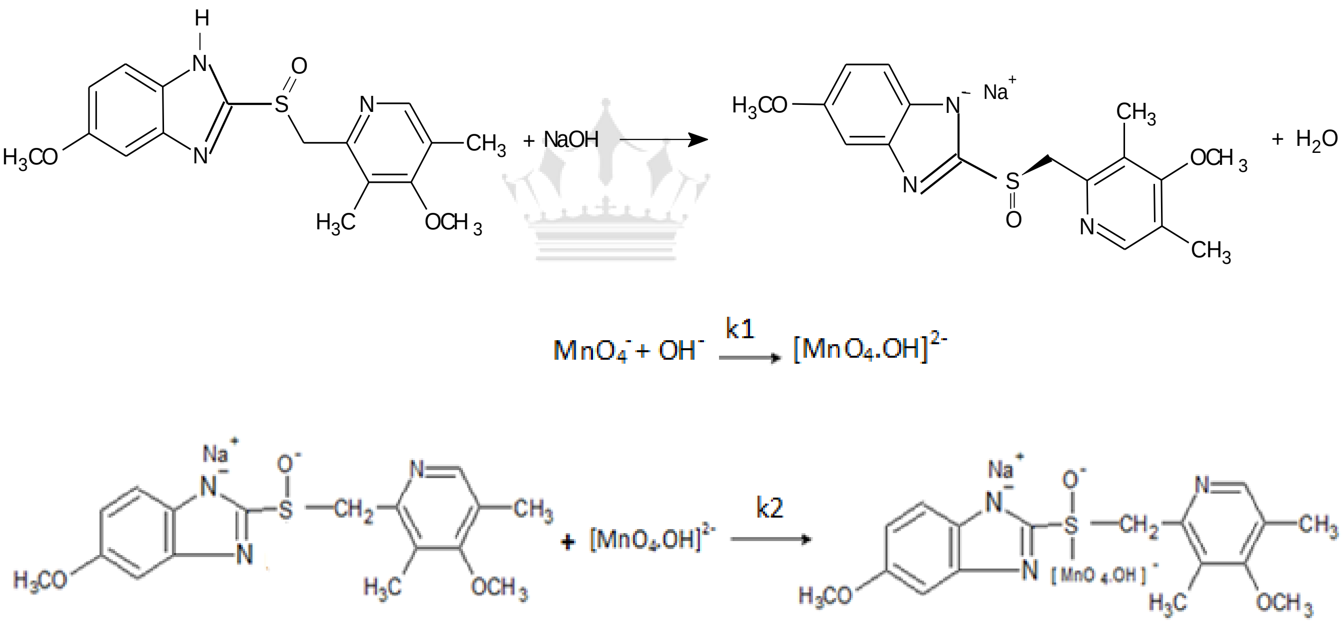
Table III. The activation parameters.

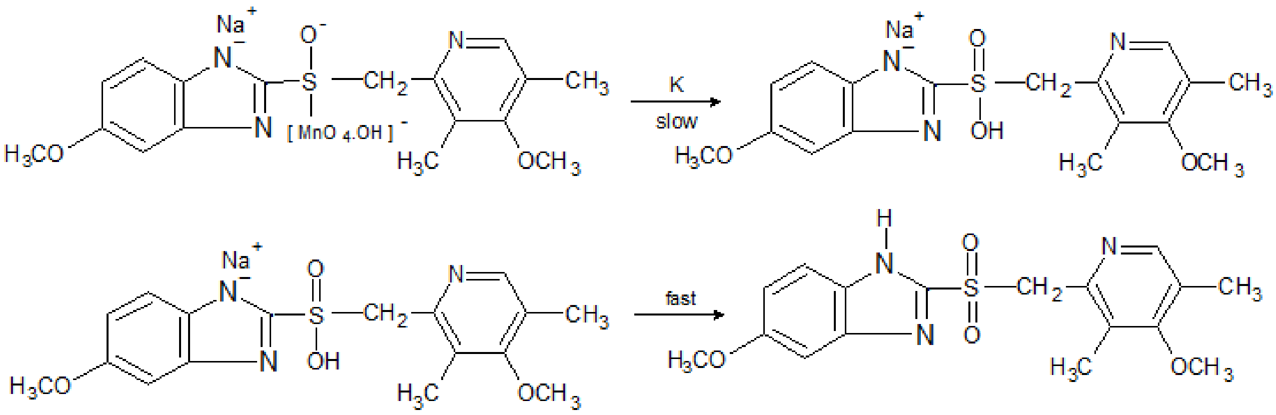
Parameters	Values
E_a (KJ/mol)	+44.03
$\Delta H^{\#}$(KJmol^{-1})	+41.52
$\Delta S^{\#}$ (JK^{-1}mol^{-1})	-270.28
$\Delta G^{\#}$ (KJmol^{-1})	124.57

4. DISCUSSION:

Omeprazole dissolved in sodium hydroxide result information of omeprazole sodium[13] which on reaction with alkaline permanganate forms a complex. The formed complex on further dissociation results in omeprazole sulphone which is confirmed by LC-MS.

SCHEME-1





Based on above scheme-I rate law can be derived as follows

Rate = $-d[MnO_4^-]/dt$ = k [complex-C]

Rate = kK_2 [OMZ-Na] $[MnO_4.OH]^{2-}$ ……………………………………(I)

$=kK_1K_2[\text{OMZ-Na}]_f\ [MnO_4^-]_f[OH^-]_f$

$[\text{OMZ-Na}]_T = [\text{OMZ-Na}]_f$ ……………………………………(II)

$[MnO_4^-]_T = [MnO_4^-]_f + [MnO_4.OH]^{2-} + [C]$

$[MnO_4^-]_T = [MnO_4^-]_f + K_1[MnO_4^-]_f[OH^-]_f + K_1K_2[\text{OMZ-Na}]\ [MnO_4^-][OH^-]$

$[MnO_4^-]_f = [MnO_4^-]_T / 1 + K_1[OH^-] + K_1K_2[\text{OMZ-Na}]\ [OH^-]$ …………………………………(III)

$[\text{OMZ-Na}]_T = [\text{OMZ-Na}]_f$

$[OH^-]_T = [OH^-]_f$

$Rate = kK_1K_2[\text{OMZ-Na}][MnO_4^-][OH^-]/1 + K_1[OH^-] + K_1K_2[\text{OMZ-Na}][OH^-]$
………………(IV)

$K_{obs} = Rate/[MnO_4^-] = kK_1K_2[\text{OMZ-Na}][OH^-] / 1 + K_1[OH^-] + K_1K_2[\text{OMZ-Na}][OH^-]$ ………(V)

On rearranging equation (5), we will get

$1/Kobs = 1/kK_1K_2[\text{OMZ-Na}][OH^-] + 1/kK_2[\text{OMZ-Na}] + 1/k$

By plotting graph of $1/K_{obs}$ versus 1/[OMZ] (Fig.6) and $1/K_{obs}$ versus $1/[OH^-]$ (Fig.7), from the slopes and intercepts k, K_1 and K_2 were Calculated and values are found to be 0.02, 66.85

and 854.7 respectively.

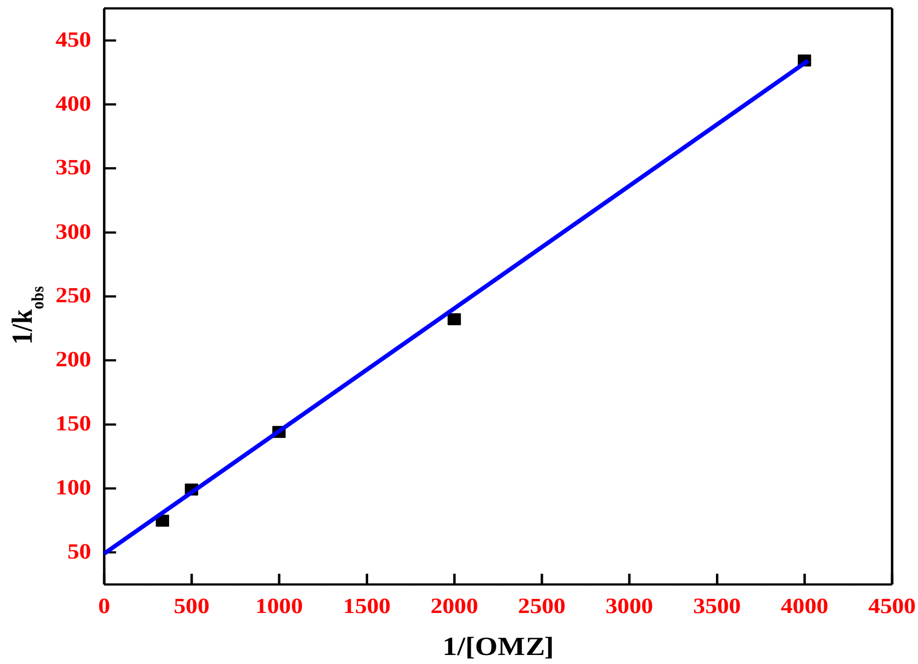


Fig.6: Plot of 1/Kobs against 1/[OMZ] for the verification of rate law

CONCLUSION:

The higher negative value of entropy of activation supports the formation of a complex in reaction. The overall mechanistic study described here explains clearly the product studies, mechanistic and kinetic studies. The proposed spectrophotometric method shows selective and simple, specific, and inexpensive analytical procedure for the oxidation of omeprazole drug by alkaline potassium permanganate. The change in color of $KMnO_4$ solution from violet Mn (VII) to dark green Mn (VI) which confirms the formation of MnO_4^{2-} in the reaction.

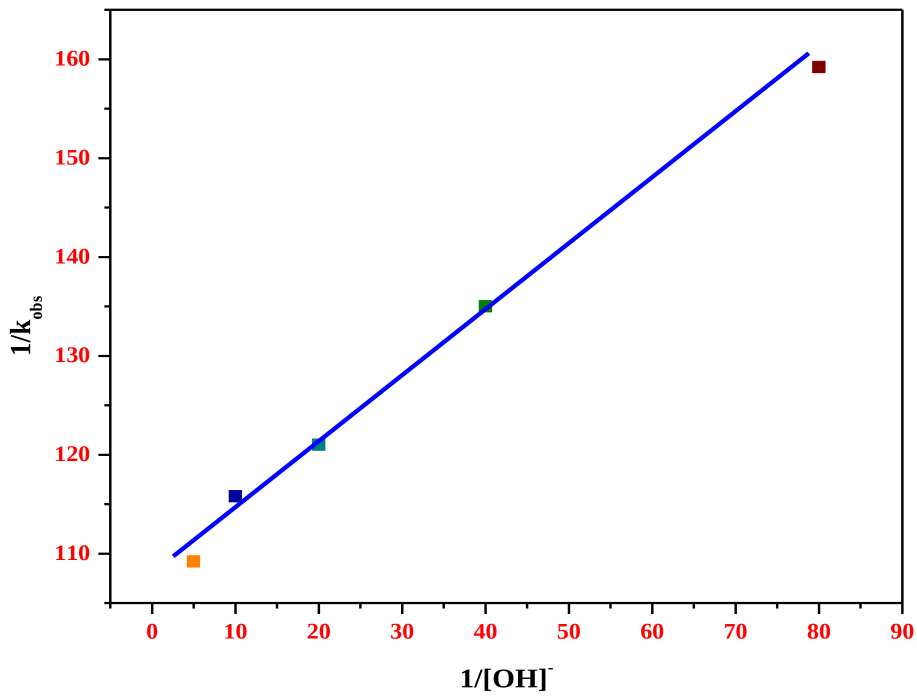


Fig.7: Plot of 1/Kobs against 1/[OH$^-$] for the verification of rate law

ACKNOWLEDGMENT:

The authors acknowledge the support and encouragement of principal and management of S. E. A. College of Engineering and Technology, Presidency University, Bangalore, India.

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