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A Kinetic Study of Oxidation of Esomeprazole by Potassium Permanganate

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***Abstract*: The kinetics and mechanism of oxidation of Esomeprazole (ESM) by Potassium permanganate have been studied. The stiochiometry has been observed to be 1:1 ratio of permanganate ion and ESM consumed. First order kinetics with respect to $KMnO_4$ was observed for the oxidation of ESM. The effect of halide ions, ionic strength has been studied on the rate of reaction. The reaction products were identified and characterized by LCMS. The product was identified. Activation parameters were calculated.**

***Keywords*: Esomeprazole, Kinetics, Oxidation, Permanganate.**

1. Introduction

Esomeprazole(ESM) is a medication which reduces stomach acid. Esomeprazole is a proton pump inhibitor used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome. Esomeprazole, the S-enantiomer of omeprazole, shows improved effectiveness of this single enantiomer product over the racemic mixture of omeprazole. ESM is a proton pump inhibitor, which reduces acid secretion through the inhibition of ATPase in gastric parietal cells, by inhibiting the operation of this enzyme, so the drug prevents formation of gastric acid. The primary uses of esomeprazole are for gastroesophageal reflux disease, treatment of duodenal ulcers caused by H. pylori, prevention of gastric ulcers in those on chronic NSAID therapy, and treatment of gastrointestinal ulcers associated with Crohn’s disease. Esomeprazole is widely metabolized by CYP3A4 and CYP2C19 isoenzyme in the liver [2].

Molecular weight:345.4 g/mol

Molecular formula:$C_{17}H_{19}N_3O_3S$

Esomeprazole is a

5-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl}-1H-benzimidazole that has S configuration at the sulfur atom.

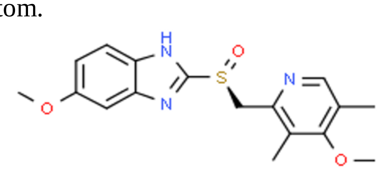

Fig. 1. Structure of esomeprazole

Permanganate ions are widely used as oxidizing agent in synthetic and analytical chemistry [3]. Permanganates ions oxidize a greater variety of substrates and find extensive applications in organic syntheses [4]. During oxidation by permanganate, it is evident that the Mn(VII) in permanganate is reduced to various oxidation states in acidic, alkaline and neutral media [5].

2. Experimental Details

A. Materials and methods

All chemicals were of Analytical Grade. The solutions was prepared by dissolving requisite amount of ESM in NaOH and Potassium permanganate is prepared in distilled water. NaOH, KCl and were also prepared in doubly distilled water and standardized by standard methods.

B. Kinetic measurements

Reaction of Esomeprazole was studied under pseudo first order condition where the [Esomeprazole] is ten times greater than permanganate. The reaction was initiated by mixing permanganate to esomeprazole containing required amount of NaOH, and KCl. The progress of reaction was observed spectrophotometrically by measuring decrease in absorbance of Mn(VII) at 525 nm wavelength. Graphs of log [Mn(VII)] versus time were plotted for pseudo first order reaction linear upto 80% completion of reaction and the rate constants (kobs) were calculated.

3. Result and Discussion

A. Stoichiometry and product analysis

Stoichiometry of the reaction was determined by equilibrating reaction mixture of various [Mn(VII)] and [Esomeprazole] at 298K for 24 hrs, keeping all other reagents constant. The unreacted potassium permanganate was estimated spectophotometrically at 525 nm, which reveals that one mole of esomeprazole requires one mole of Mn(VII) for oxidation. The oxidative products were identified as Ufiprazole shown in figure 2, (2-{[(3,5-Dimethyl-4-methoxy-2-pyridinyl)-methyl]-thio}-5-methoxy-1H-benzimidazole), which gives molecular ion peak at 329 MHz as shown in Fig. 3.

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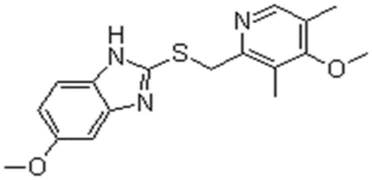

Fig. 2. Ufiprazole

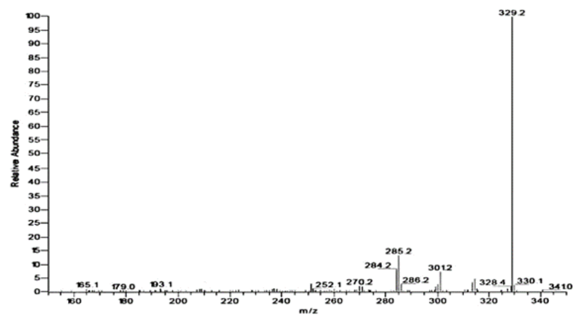

Fig. 3. LCMS Product of esomeprazole

Table 1
Effect of varying concentration of esomeprazole, potassium permanganate, sodium hydroxide, potassium chloride on the rate of the reaction

$[MnO_4] \times 10^4$ (mol dm^{-3})	$[ESM] \times 10^3$ (mol dm^{-3})	$[OH^-]$ (mol dm^{-3})	kobs X 10^3 (s^{-1})
0.5	2	0.05	0
1	2	0.05	1
2	2	0.05	1
3	2	0.05	1.1
5	2	0.05	1.2
2	0.5	0.05	0.2
2	1	0.05	0.6
2	2	0.05	1.0
2	3	0.05	2.0
2	5	0.05	3.0
2	0.02	0.5	0.5
2	0.04	0.7	0.7
2	0.05	1.0	1.0
2	0.10	1.2	1.2
2	0.20	1.8	1.8

4. Reaction orders

A. Effect of permanganate

The potassium permanganate concentration was varied in the range of 5.0 x 10^{-5} to 5.0 x 10^{-4} mol dm^{-3}, and the linearity of plots of log (absorbance) versus time indicated a reaction order of unity in $[MnO_4^-]$. This was also confirmed by variation of $[MnO_4^-]$, which did not result in any change in the pseudo-first order rate constants kobs.

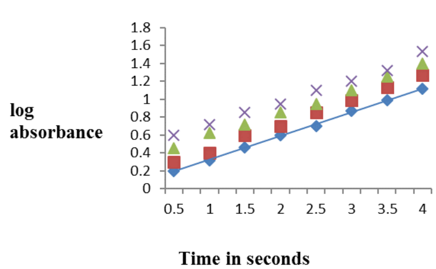

Fig. 4. A graph of log OD versus time shows first order with respect to permanganate

B. Effect of Esomeprazole

The esomeprazole concentration was varied in the range 0.5 x 10^{-4} to 5.0 x 10^{-3} mol dm^{-3} while keeping all other reactant concentrations and conditions constant.

C. Effect of sodium hydroxide

The effect of alkali on the reaction has been studied in the range 0.02 to 0.20 mol dm^{-3} at constant concentrations of esomeprazole and potassium permanganate. The rate constants increased with increasing [alkali].

D. Effect of temperature

The effect of temperature was also studied at different temperature like 298, 302, 308, 312K at fixed concentration of esomeprazole and potassium permanganate, sodiumhydroxide, potassium chloride were at constant condition. Rate of reaction increased with increase in temperature. The rate constant 'k' is at different temperature was tabulated in table 2. From fig. 4 arrehnius plots of Log k v/s 1/T, the activation parameters $\Delta H^{\#}$, $\Delta S^{\#}$ were calculated and tabulated in table 3.

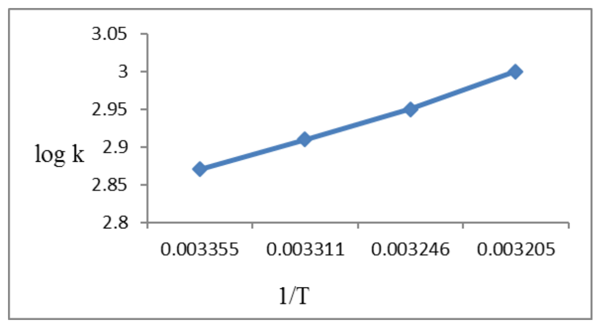

Fig. 5. Graph of log k v/s 1/T

Table 2
Rate constant with respect to temperature

T(K)	kx10^3
298	1
302	1.1
308	1.21
312	1.34

Table 3
Activation parameters

Parameters	Values
Ea	40
$\Delta H^{\#}$	40
$\Delta G^{\#}$	69
$\Delta S^{\#}$	-115

E. Effect of ionic strength

At constant concentration of reactants, the ionic strength was varied [KCl]. Ionic strength had insignificant effect on the rate of reaction.

F. Discussion

$$Rate = \frac{-d[MnO_4^-]}{dt} = k[complex\text{-}C]$$

$$Rate = kK_2[ESM][MnO_4.OH]^{2-}$$

$=k\, K_1K_2[ESM]_f\, [MnO_4]_f\, [OH^-]_f$ (1)

$[ESM]_T = [ESM]_f$ (2)

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

$[MnO_4^-]_T = [MnO_4^-]_f + K_1[MnO_4^-]_f[OH^-]_f + K_1K_2[ESM][MnO_4][OH^-]$

$[MnO_4^-]_f = \frac{[MnO_4^-]_T}{1+K_1[OH-]+K_1K_2[ESM]\,[OH^-]}$ (3)

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

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

$Rate = \frac{kK_1K_2[ESM][MnO_4^-][OH^-]}{1+K_1[OH^-]+K_1K_2[ESM][OH^-]}$ (4)

$K_{obs} = \frac{Rate}{[MnO_4^-]} = \frac{kK_1K_2[ESM][OH^-]}{1+K_1[OH^-]+K_1K_2[ESM][OH^-]}$ (5)

Rearranging 5, we get

$\frac{1}{Kobs} = \frac{1}{kK_1K_2[ESM][OH^-]} + \frac{1}{kK_2[ESM]} + \frac{1}{k}$ (6)

Kinetics of the oxidation of esomeprazole by potassium permanganate in basic medium is governed by the rate law.

G. Verification of rate law

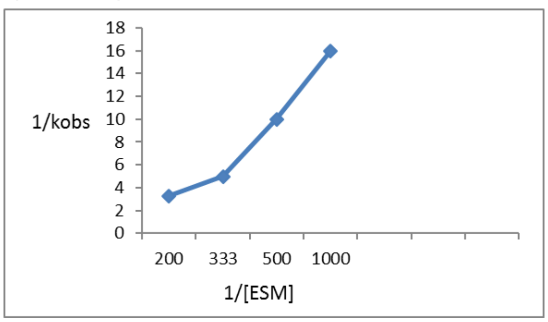

Fig. 6. 1/kobs v/s 1/[ESM]

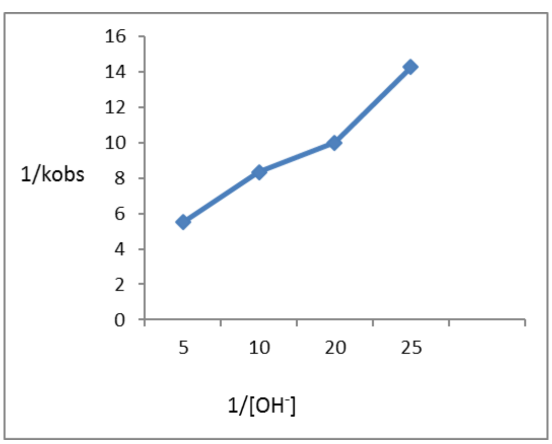

Fig. 7. 1/kobs v/s $1/[OH^-]$

The plots of 1/kobs v/s 1/[ESM] and 1/kobs v/s $1/[OH^-]$ should be linear as shown in figure.From slopes and intercepts k, K_1 and K_2 were calculated and they are substituted in rate equation, K_{obs} and K_{cal} show excellent agreement with each other.

5. Conclusion

Kinetics and oxidation of Esomeprazole by potassium permanganate in alkaline medium has been studied. The stiochiometry of oxidation esomeprazole was found to be 1:1. The oxidation product was found to ufiprazole. The arrehnius plot shows how activation energy and temperature affect the sensitivity of the reaction rate. The negative value of $\Delta S^{\#}$ suggests that intermediate complex is more ordered than the reactants [6].

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References

[1] Palavai Sripal Reddy, Kishore Kumar Hotha, and Shakil Sait, Complexity in Estimation of Esomeprazole and its Related Impurities' Stability in Various Stress Conditions in Low-Dose Aspirin and Esomeprazole Magnesium Capsules, Sci Pharm, 81(2): 475–492, April-June 2013.

[2] Andersson T, Hassan-Alin M, Hasselgren G, Röhss K, Drug interaction studies with esomeprazole, the (S)-isomer of omeprazole. Clin Pharmacokinet, 40:523–37, September 2001.

[3] O. A. Babatunde, A Study of the Kinetics and Mechanism of Oxidation of L -Ascorbic Acid by Permanganate Ion in Acidic Medium, World Journal of Chemistry, vol. 3, November, 27-31, 2008.

[4] Rahamatalla M. Mulla, Gurubasavaraj C Hiremath and Sharanappa T Nandibewoor, "Kinetic, mechanistic and spectral investigation of ruthenium (III) catalysed oxidation of atenolol by alkaline permanganate (stopped-flow technique), J. Chem. Sci., Vol. 117, 33–42, January 2005.

[5] K. G. Pujeri, S. D. Lamani and S.T. Nandibewoor, "Oxidation of tricyclic antidepressant agent, amitriptyline, by permanganate in sulphuric acid medium: kinetic and mechanistic approach," IJPSR, vol. 3, pp. 4856-4865, November 2012.