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Kinetic Studies of Oxidation of Ethambutol in Basic Media

Sandipsingh Gour¹, R.P. Phase², B R Agarwal³, Mazahar Farooqui^{4*}

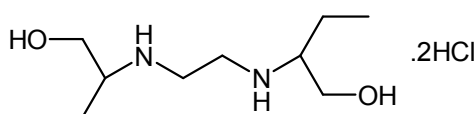
1. Sant Ramdas College, Ghansawangi, Dist Jalna (MS) India.
2. Lal Bahadur Shastri College, Partur, Dist. Jalna (MS) India.
3. J E S College, Jalna (MS) India.
4. Rafiq Zakaria College for Women, Aurangabad(MS) India.
[E-mail: mazahar_64@rediffmail.com]

The oxidation of pyrazinamide in acidic media is carried out using potassium permanganate as a oxidizing agent. The reaction was monitored using UV-Visible spectrophotometer at 525 nm. It was found to be zero order with respect to oxidant,, fractional order with respect to hydrogen ion concentration and first order with respect to substrate. The thermodynamic parameters(were determined. The average (ΔG^\ddagger) was found to be 86.508 KJ/mol. The values ΔS^\ddagger was found to be -0.1354 KJ/mole and energy of activation was found to be 46.7709 KJ/mole. A suitable mechanism is proposed based on the experimental conditions.

Keyword: Ethambutol, Kinetic Studies, Oxidation.

1. Introduction

The IUPAC name of ethambutol is N N1 – Ethylene bis (2-amino butan-1-ol) dihydrochloride. Its molar mass is 277.23 g/mol. The structure of ethambutol is shown as follow



The physical properties of Ethambutol is given in the table 1

Table 1: Physical properties of Ethambutol

S.No.	Name of property	Value
1	Mol. Formula	C ₁₀ H ₂₆ N ₂ O ₂ Cl ₂
2	Mol. Weight	277.23 g/mol
3	R.I	1.477
4	Density	0.987 g/cm ³
5	Flash Point	113.7
6	Melting point	201 °C
7	Boiling point	345.3 0 c 760 mm Hg
8	Water solubility	15 mg/ml

Ethambutol (EMB) is an important component of multidrug treatment regimen for Mycobacterium avium complex lung disease [1]. The adverse effect of ethambutol is visual impairment which includes irreversible blindness. Ethambutol is distributed into most body tissues including the lung, kidneys and saliva [2]. Ethqambutol is a first –line anti MTB (mycotuberculosis) drug with abroad spectrum of activity. The most series adverse effect of ethambutol is optic neuritis which leads to blindness.

2. Kinetic Procedure

The reactions were allowed to occur in glass stopper Erlenmeyer flask of corning make. These flasks were suspended in a water bath with a temperature sensitivity of 0.1 °C. The reaction mixture except substrate was prepared by taking all reaction ingredients. The temperature preequilibrated solution of substrate was added into the reaction mixture and the time of initiation of the reaction was recorded when half of the contents of pipette were released [3-5]. The reaction mixtures were shaken and aliquot (1ml) was taken out at different time intervals and

absorbance of remaining KMnO_4 was noted at $\lambda_{\text{max.}} = 525 \text{ nm}$. The reaction rates were calculated by drawing pseudo first order plot, $[\text{substrate}] \gg [\text{KMnO}_4]$ condition. Good straight lines were obtained and pseudo first rate constant were calculated in the usual manner [6-8]. These rate constants exhibit reproducibility within to 5 %.

3. Product Analysis

Known volume of 0.1 M substrate and 0.01M KMnO_4 in 1 M H_2SO_4 solution were taken in 250ml beaker and kept the reaction mixture for 4-5 days for completion of the reaction. The diethyl ether was added into the reaction mixture and then it was shaken for an hour before separating two layers ether and water by employing separating funnel. The ethereal layer was taken on the watch glass; latter was left for some time for evaporation of ether. The residue left on the watch glass was air drying before identification. The solid mass was identified by M.P. and IR Spectra. The IR spectra of EMB and the product obtained was compared. It gives values for EMB

IR (KBr, Cm^{-1}) 3312 (—OH stretching), 3410 ($\text{N}-\text{H}$ stretching)

The product obtained was 2-(2-(1-carboxypropylamino) ethyl amino) butanoic acid with melting point 322°C and shows IR frequencies

IR (KBr, Cm^{-1}) 2975 (—OH stretching broad), 1700 ($\text{C}=\text{O}$ stretching)

4. Experimental kinetic results

4.1 Dependence of Permanganate Concentration

To study the effect of dependence of permanganate concentration, the concentration of KMnO_4 was varied from 1×10^{-4} to 9×10^{-4} M, keeping constant concentration of other reaction ingredients such as substrate and acid. Since reaction has been studied under pseudo first orders were calculated. These results are given in the table 2 From the perusal of the results, it is clear that pseudo first rate constant do not change with change in concentration of permanganate confirming the first order dependence with respect to oxidant [9].

Table 2: First order rate constant

S.No.	[EMB]	[KMnO_4]	[NaOH]	$k(\text{s}^{-1})$
1	1×10^{-3}	1×10^{-4}	1	0.0384
2	1×10^{-3}	2×10^{-4}	1	0.0407
3	1×10^{-3}	3×10^{-4}	1	0.0394
4	1×10^{-3}	4×10^{-4}	1	0.0376
5	1×10^{-3}	5×10^{-4}	1	0.0334
6	1×10^{-3}	6×10^{-4}	1	0.033
7	1×10^{-3}	7×10^{-4}	1	0.0294
8	1×10^{-3}	8×10^{-4}	1	0.0349
9	1×10^{-3}	9×10^{-4}	1	0.0344

The least square method for linear fit between $\log k_{\text{obs}}$ and $\log [\text{KMnO}_4]$ gives negative correlation with fractional order. The $\log [\text{rate}]$ against $\log [\text{C}]$ also confirmed the fractional order closed to one with respect to KMnO_4 [10].

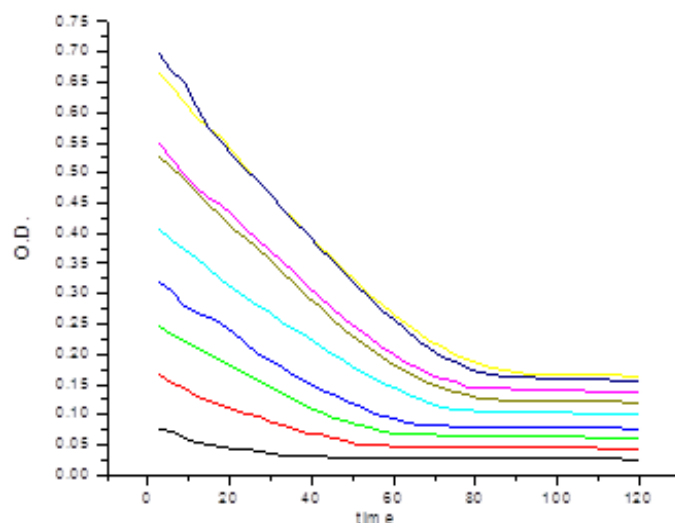


fig. 7 (a) variation of KMnO_4 with time at constant EMB ($1 \times 10^{-3} \text{ M}$) & NaOH (1M)

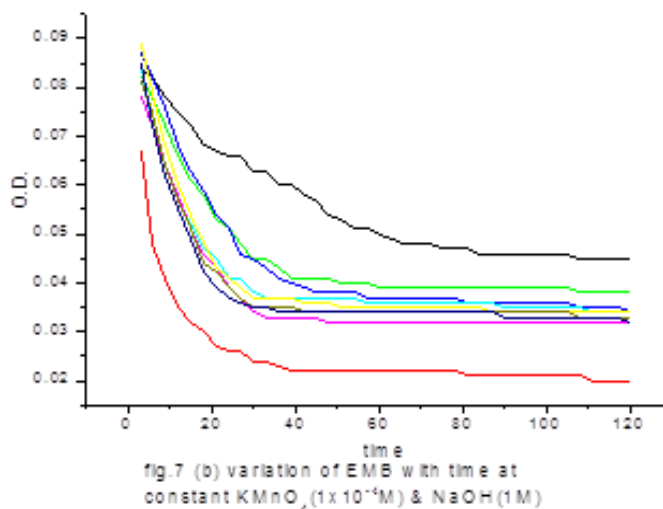
4.2 Dependence of Substrate Concentration

The concentration of substrate was varied from 1×10^{-3} to 9×10^{-3} M and fixed concentration of $[\text{MnO}_4^-] = 1 \times 10^{-4}$ M and $[\text{H}_2\text{SO}_4] = 1$ M The pseudo first order rate constant were calculated see table 3 in this variation were plotted against concentration of substrate, a straight line passing through origin was obtained. This shows that order with respect to substrate is also one.

Table 3: first order rate constant

S.No	[EMB]	[KMnO ₄]	[NaOH]	k(s ⁻¹)
1	1 x10 ⁻³	1 x10 ⁻⁴	1	0.0313
2	2 x 10 ⁻³	1 x10 ⁻⁴	1	0.0469
3	3 x10 ⁻³	1 x10 ⁻⁴	1	0.0469
4	4 x10 ⁻³	1 x10 ⁻⁴	1	0.0417
5	5 x10 ⁻³	1 x10 ⁻⁴	1	0.0548
6	6 x10 ⁻³	1 x10 ⁻⁴	1	0.0715
7	7 x10 ⁻³	1 x10 ⁻⁴	1	0.0676
8	8 x10 ⁻³	1 x10 ⁻⁴	1	0.0604
9	9 x10 ⁻³	1 x10 ⁻⁴	1	0.0574

From the least square method the $\log k_{\text{obs}}$ shows good co-relation with $\log [\text{EMB}]$ i.e. $r = 0.8611$. The order is found to be in fraction. The order of reaction was further confirmed from $\log [\text{rate}]$ against $\log [C]$

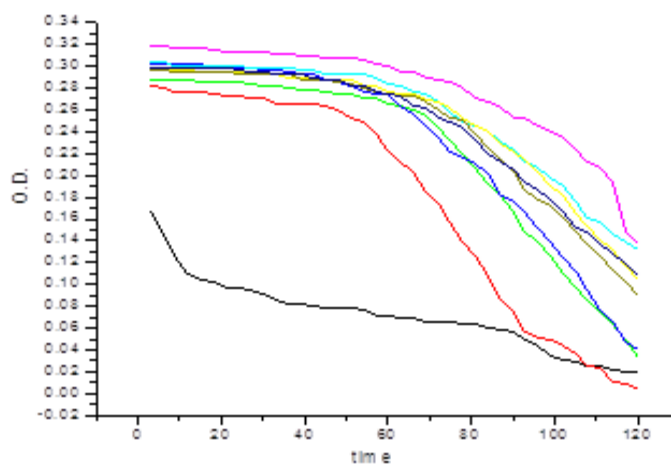


4.3 Dependence of Base Concentration

The hydroxyl ion concentration dependence was studied by employing H₂SO₄ at fixed [MnO₄⁻] and [substrate] respectively. The pseudo first plot were made and the plot of these rate constant against [H⁺] shows fractional order with respect to acid. Since rate decrease with increase in [H⁺] ion, the deprotonated species of oxidant or substrate must involve in the reaction mechanism. The results are given in the table 4.

Table 4: First order rate constant

S.No.	[EMB]	[KMnO ₄]	[NaOH]	k(s ⁻¹)
1	1x10 ⁻³	1x10 ⁻⁴	0.1	0.0225
2	1x10 ⁻³	1x10 ⁻⁴	0.2	0.0088
3	1x10 ⁻³	1x10 ⁻⁴	0.3	0.0046
4	1x10 ⁻³	1x10 ⁻⁴	0.4	0.0065
5	1x10 ⁻³	1x10 ⁻⁴	0.5	0.0051
6	1x10 ⁻³	1x10 ⁻⁴	0.6	0.0034
7	1x10 ⁻³	1x10 ⁻⁴	0.7	0.0057
8	1x10 ⁻³	1x10 ⁻⁴	0.8	0.0059
9	1x10 ⁻³	1x10 ⁻⁴	0.9	0.005



4.4 Effect of Added Salts

In the present investigation effect of salt on the rate of reaction is carried out. The salts selected are KCl, KBr, and KI. These will give effect of anion particularly halides on the rate of reaction. The divalent and trivalent cationic salts were also used such as CaCl₂, Ca (NO₃)₂, MgCl₂, AlCl₃, Al (NO₃)₃ and K₂SO₄. The experiments was carried out under pseudo first order condition taking 1x10⁻³ M EMB, 1 M H₂SO₄, 1x10⁻⁴ M KMnO₄ and varying the concentration of salts from 1x10⁻² M to 9x10⁻² M. These results were used to determine first order rate constant. The time curved obtained for these experiments were used to determined initial rate. The initial rate and rate constants for the oxidation of EMB in presence of different salts is given in the table 5.

Table 5: Effect of added salt on first order rate constant

Conc. of salt	Rate constants (S ⁻¹)								
	KCl	KBr	KI	K ₂ SO ₄	CaCl ₂	Ca(NO ₃) ₂	MgCl ₂	AlCl ₃	Al(NO ₃) ₃
1x10 ⁻²	0.0337	0.0284	0.0301	0.0409	0.0518	0.0141	0.0321	0.0233	0.0145
2x10 ⁻²	0.0231	0.0285	0.0283	0.0425	0.0204	0.0228	0.0251	0.0391	0.156
3x10 ⁻²	0.0288	0.0399	0.0429	0.0503	0.0224	0.0219	0.0399	0.0324	0.0223
4x10 ⁻²	0.0271	0.0387	0.0402	0.0449	0.0203	0.0234	0.0353	0.0382	0.031
5x10 ⁻²	0.0273	0.0423	0.0336	0.0438	0.0143	0.0221	0.0267	0.0258	0.0147
6x10 ⁻²	0.0309	0.0467	0.0217	0.04	0.0221	0.0204	0.0211	0.0432	0.0188
7x10 ⁻²	0.0274	0.0408	0.0324	0.0374	0.0238	0.0215	0.0246	0.0494	0.0229
8x10 ⁻²	0.0234	0.0496	0.027	0.0437	0.0224	0.022	0.0276	0.0519	0.0221
9x10 ⁻²	0.0309	0.0474	0.0412	0.0455	0.0246	0.0136	0.0167	0.0715	0.0238

The result reveals that there was no regular trend observed for rate constant with change in concentration of added salts. But among these salts the constant for the oxidation of EMB in presence of Ca-salt was more and the trend will be KI < KBr < KCl < K₂SO₄ < Ca (NO₃)₂ < CaCl₂ < MgCl₂ < Al (NO₃)₃ < AlCl₃

4.5 Effect of Temperature

The effect of temperature was also studied keeping constant concentration of all other reaction ingredients such as [MnO₄⁻], [substrate]

and [H⁺]. The temperature variation was at 25 to 60o C. The energy of activation was calculated by plotting graph between logk verses 1/T, a straight line was obtained. The entropy of activation also calculated in the usual manner by employing bimolecular rate equation

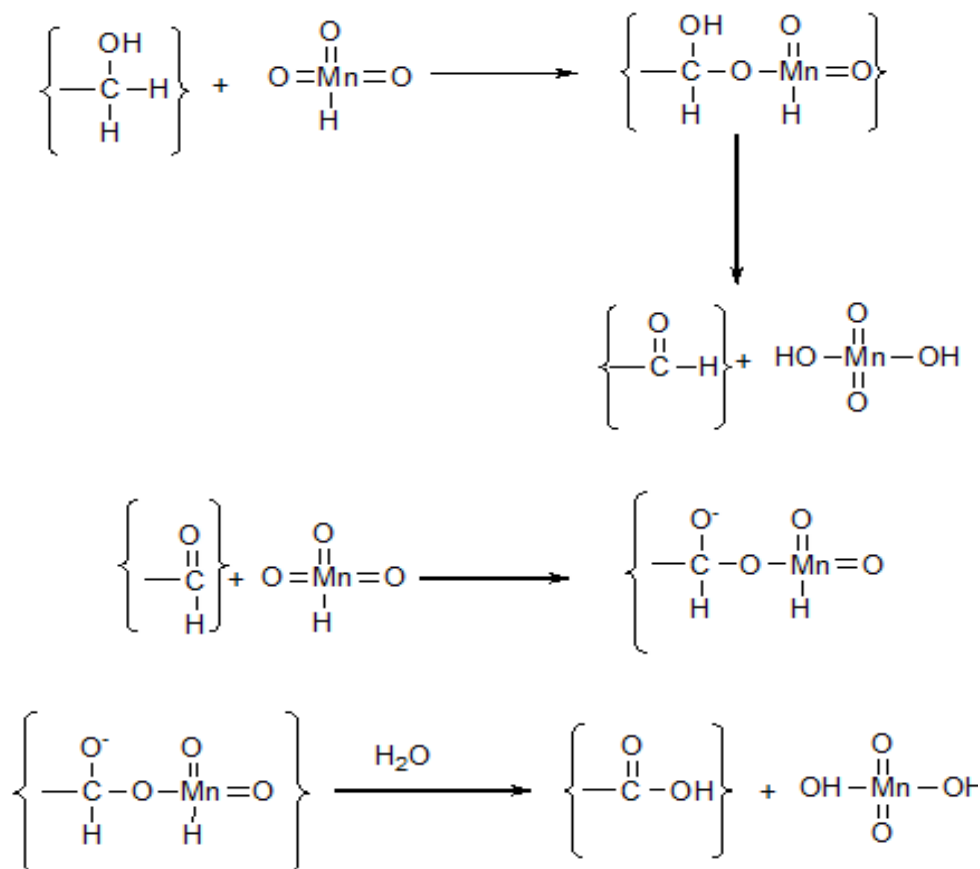
$$k = k_B T/h e^{-\Delta E_a^\ddagger/RT} e^{\Delta S^\ddagger/R}$$

The moderate values of ΔH^\ddagger and the negative ΔS^\ddagger support a rigid transition state of the complex from the reactants [3]. The plot ΔH^\ddagger and ΔS^\ddagger gives a linear relationship with slope 0.00391. The slope of this line is nothing but isokinetic temperature.

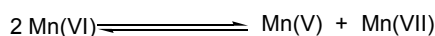
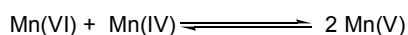
Table 6: Thermodynamic parameter Activation energy Ea =46.7709366 KJmol⁻¹

S.No.	Temp.(K)	ΔH^\ddagger (KJmol ⁻¹)	ΔS^\ddagger (KJmol ⁻¹)	ΔG^\ddagger (KJmol ⁻¹)
1	293	44.334935	-0.134350001	83.69948538
2	298	44.2933646	-0.134720457	84.44006064
3	303	44.2517946	-0.13736428	85.87317155
4	308	44.2102246	-0.139282755	87.10931311
5	313	44.1686546	-0.136761151	86.97489494
6	318	44.1270846	-0.134657356	86.94812375
7	323	44.0855146	-0.136674278	88.23130636
8	328	44.0439446	-0.136424587	88.7912091
9		44.18394658	-0.135476284	86.5084456

4.6 Mechanism



The MnO_4^- formed in alkaline media as intermediate, it may go further decomposition as per the scheme



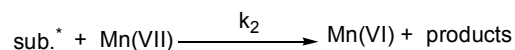
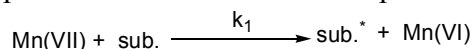
The color of the reaction mixture as the reaction proceed, changes from purple –pink Mn (VII) to the blue Mn(V) to green Mn(VI) to yellow Mn(IV), may suggest the formation of short lived various intermediates in alkaline media.

The yellow color persists even after completion of the reaction while the disappearance of the MnO_4^- ions suggests the formation of stable soluble Mn (IV) as a final product [5].

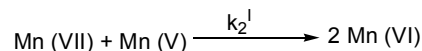
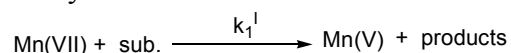
The pH of the solution is greater than 12, under such high alkalinity the formation of Mn (V) is ruled out. Since in strong alkaline condition Mn

(VI) is most stable and further reduction of Mn (VI) might be stopped.

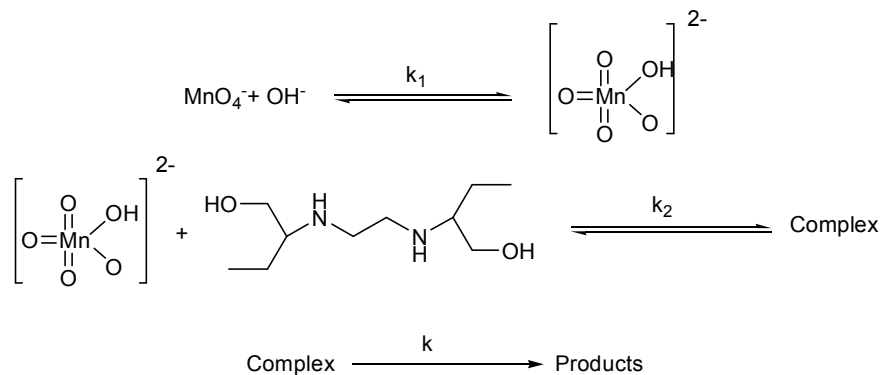
The probable mechanisms can be predicted as



Alternately



4.7 Kinetic:



$$\text{Rate} = \frac{k k_2 [\text{MnO}_4^-] [\text{EMB}]}{1+k_1 [\text{OH}^-]}$$

$$\frac{\text{Rate}}{[\text{MnO}_4^-] [\text{EMB}]} = \frac{k k_2}{1+k_1 [\text{OH}^-]}$$

$$[\text{MnO}_4^-]_{\text{T}} = [\text{MnO}_4^-] + \left[\begin{array}{c} \text{O} \\ \parallel \\ \text{O}=\text{Mn}-\text{OH} \\ \parallel \\ \text{O} \end{array} \right]^{2-}$$

$$= [\text{MnO}_4^-] + k_1 [\text{MnO}_4^-] [\text{OH}^-]$$

$$= [\text{MnO}_4^-] \{1+k_1 [\text{OH}^-]\}$$

$$k_{\text{obs}} = \frac{k k_2}{1+k_1 [\text{OH}^-]}$$

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k k_2} + \frac{k_1}{k k_2} [\text{OH}^-]$$

5. References

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