MECHANISTIC AND KINETIC STUDY OF OXIDATION OF TOPIRAMATE ANTI-EPILEPTIC DRUG BY PERMANGANATE IN AQUEOUS ALKALINE MEDIUM

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Abstract: The kinetics and mechanism of oxidation of antiepileptic drug Topiramate [TPM] was investigated in aqueous alkaline medium under pseudo first order condition. The experimental results indicated that the reaction exhibits fractional order concerning Topiramateand first order concerning potassium permanganate [$KmnO_4$]. The reaction stoichiometry shows one mole of Topiramate consumes one mole of potassium permanganate. The effect of temperature on the reaction rate is studied and the activation parameters are calculated and tabulated.A scheme is proposed based on which a reaction mechanism is proposed. LC-MS Technique was used to identify the oxidation product of topiramate. Based on the experimental results, a mechanism is proposed and constant K_1, K_2 and k_3 involved in the mechanism were evaluated. The observed rate constant values and the values calculated by substituting the value K_2 = 531.3k= 0.027and K_1 5.42 x $10^{-3}$are found to be in good accordance with K_{Cal} values.

Keywords: Oxidation, kinetics, Mechanism and Topiramate

Introduction:

Topiramate with chemical name 2,3;4,5-bis-O-(1-methylethylidene)-B-D-Fructopyranose isananti-epilepticdrug,itiswidelyuseddrugfortreatmentofepilepsywith efficacy in several type of seizures. Anti-epileptic drug suppress seizures but do not cure the disorder so lifelong treatment is required topiramate is currently gaining interest in the treatment of epilepsy. It is used for prevention of migraine. It decreases the frequency of attacks; other uses include treatment of obesity, anti-psychotic-induced weight gain and to treat post-traumatic stress disorder. Structurally topiramate does resemble a normal therapeutic agent as it presents a very high concentration of oxygen. The oxygen atom in the topiramate molecule is expected to function as acceptors for hydrogen-bond formation while it amide group serves as an important hydrogen donor[1-3]. Permanganate is a powerful oxidizing agent in acidic, alkaline and neutral medium. $KmnO_4$ is found to have large application in the oxidation of large biological molecule such as thiamine, nucleic acid, protein, Uracil, amino acid [4-5],it finds wide application in organic synthesis[6]. In a strongly basic solution, permanganate (VII) is reduced to the green +6 oxidation state. The permanganate ion can oxidize organic compounds through several pathways including hydrogen abstraction, electron-abstraction, and incorporation of oxygen atom into the structure. There is no literature of topiramate with potassiumpermanganate. Hence the present work aims to study the oxidation of topiramate with permanganate in alkaline medium.

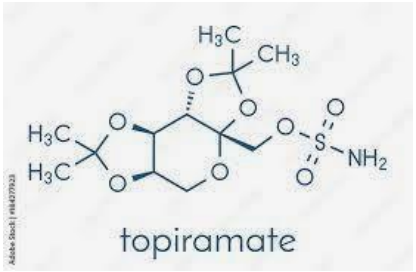


Fig.1: Chemical structure of Topiramate

Materials and Method:

The chemical reagent Topiramate used in this study was offered by CIPLA industries ltd. AR grade chemicals, Topiramate, $KmnO_4$, NaOH and ethanol were used in this study. The topiramate solution was prepared by dissolving a measured quantity of ethanol and made upto the desired mark with distilled water. $KmnO_4$ solution was prepared by dissolving in water. 0.1M solution of NaOH is used during this work.

'Kinetic measurements:

All kinetic measurements were conducted under pseudo-first order conditions where the concentration of drug was maintained in excess over the permanganate ion concentration at constant temperature. The reaction was initiated by mixing solutions of permanganate, topiramate which also contained the required amount of sulphuric acid and sodium hydroxide. The course of reaction was followed by monitoring the decrease in absorbance of permanganate ion at its absorption maximum at 525 nm as a

function of time.The kinetic runs were followed until completion of the reaction. The pseudo–first order rate constants, k_{obs}were calculated from the plots of log (absorbance) versus time plots which were linear.

Results and Discussions:

Stoichiometry:

The reaction mixture containing varying ratios of the topiramate to permanganate were mixed in the presence of NaOH maintaining to a constant ionic strength of 0.2moldm^{-3}and then the mixture is equilibrated for 24hours at room temperature. The concentration of excess permanganate was assayed by measuring the absorbance at 526nm; estimation of the unreacted permanganate showed that one mole of the topiramate consumed 1 mole of permanganate. The results indicate 1:1 stoichiometry as given in equation.

Product analysis:

The reaction mixture containing a required amount of topiramate 1.0 x10^{-3}mol dm^{-3}potassium permanganate 1.25 x 10^{-4} moldm^{-4} along with other reagents was kept for 24hours at room temperature, during this process; the substrate topiramate is converted entirely into a product. Using a separating funnel the product in the reaction mixture was extracted by washing it several times using CCl_4. The extracted product is separated from the aqueous phase. The separated organic phase is sent to LC-MS for product analysis. The LC-MS spectra show a molecular ion peak at 336 amu confirming the oxidation product.

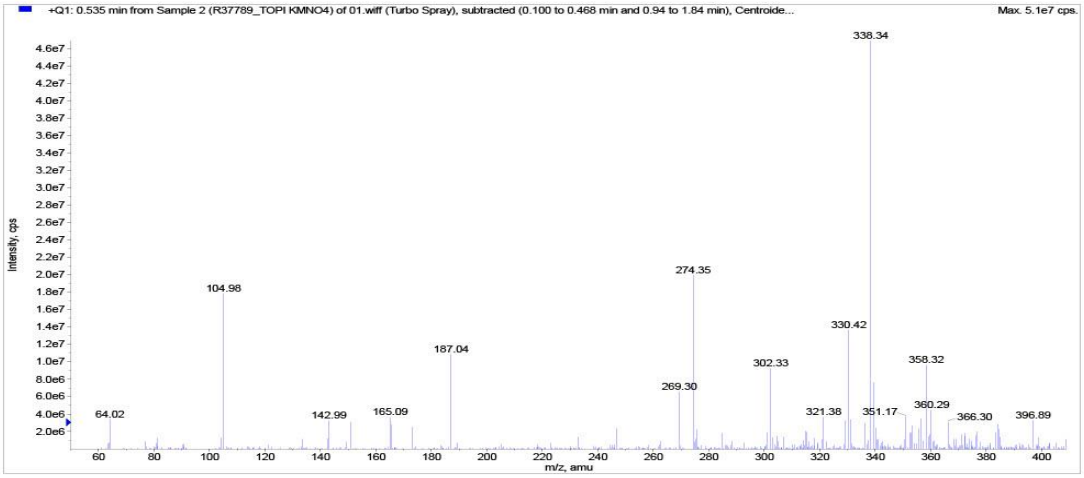


Fig:2 LC-MS spectra of the oxidation product of Topiramate

Reaction order:

Effect of Topiramate:

To determine the concentration concerning topiramate the concentration of TPM is varied from 1x 10^{-3} to 1.75 x 10^{-3}moldm^{-3} keeping constant concentration of $KmnO_4$1.25 x 10^{-4} moldm^{-3} and NaOH 1x10^{-2}moldm^{-3}. The value of k_{obs}increased with increase in topiramate concentration, and a plot of log K vs log [TPM] shows the reaction exhibits negative fractional order concerning substrate topiramate as shown in (Figure 5)

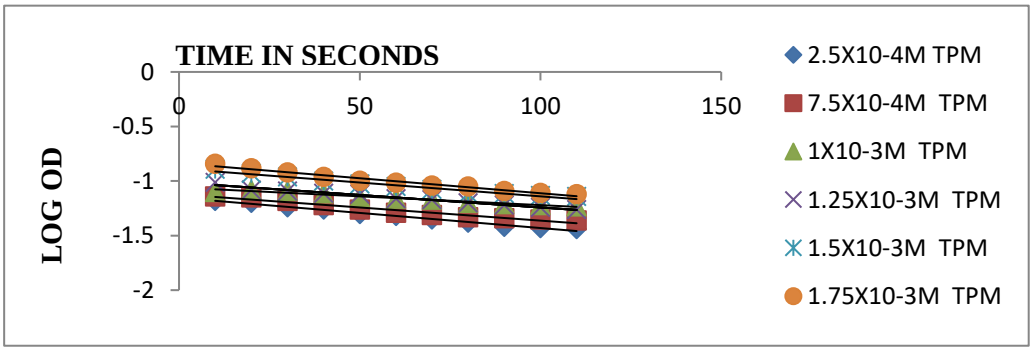


Fig.3: A plot of log OD vs time in seconds shows first order dependence w.r.to Topiramate:

Effect OF $KmnO_4$:

To determine the order concerning oxidant, study was conducted by varying the concentration of [kmnO$_4$]from1.0 x 10^{-4} moldm^{-3} to 2.25 × 10^{-3} moldm^{-4} at a constant concentration of [TPM] 1.0 × 10^{-3} moldm^{-3} and [NaOH] 1x10^{-2}moldm^{-3}. A plot of log K vs log Cshows first-order concerning KMnO$_4$.

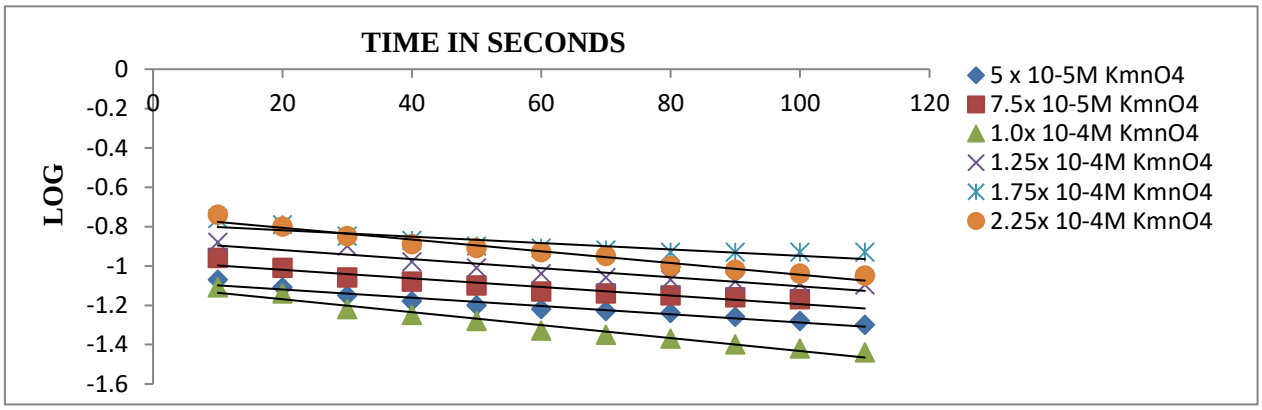


Fig-4.0 A plot of log OD vs time in seconds shows first order dependence w.r.to potassium permanganate.

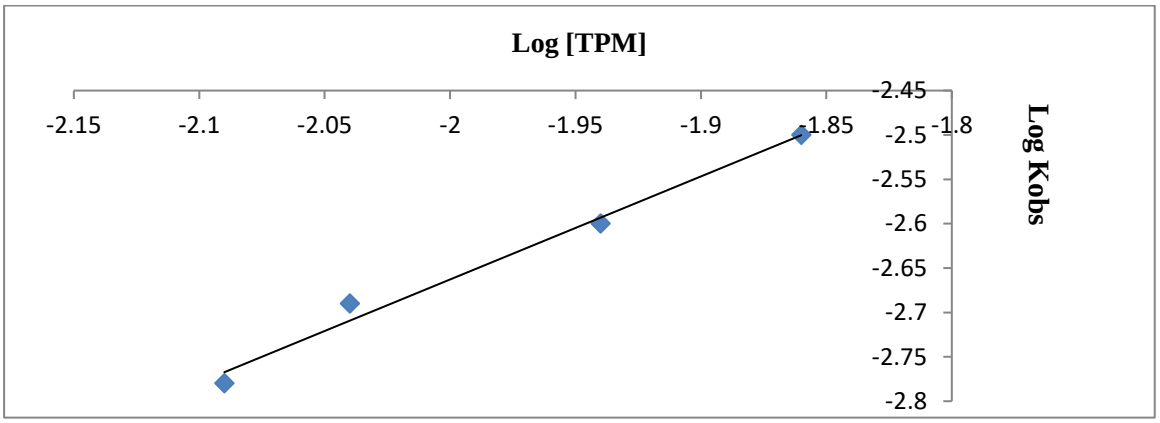


Fig 5.0 First order plot to study the variation of topiramate on the reaction rate at constant concentration of [KmnO$_4$] = 1.25 x 10^{-4}moldm^{-3},[NaOH] = 1 x 10^{-2}moldm^{-3}.

Effect of NaOH:

The concentration of sodium hydroxide was varied from 1.0 x 10^{-2} to 2.0 x 10^{-2} moldm^{-3} by keeping constant concentration constant of substrate 1x10^{-3}moldm^3, and oxidant concentration 1.25 x 10^{-4} moldm^3. There was an increase in rate with increase in NaOH concentration. A plot of initial rates vs concentration of sodium hydroxide shows the fractional order dependence with sodium hydroxide

Table -1: Sample run for oxidation of [Topiramate] = 1 x10^{-3}(moldm^{-3}) by [KmnO$_4$] = 1.75x10^{-4}(moldm^{-3}), [NaOH] = 0.1 (moldm^{-3}).

Time in (Seconds)	Absorbance at 528nm	Time in (Seconds)	Absorbance at 528nm
5	0.165	65	0.088
10	0.152	70	0.084
15	0.141	75	0.080
20	0.131	80	0.078
25	0.122	85	0.076
30	0.115	90	0.075
35	0.109	95	0.074
40	0.103	100	0.072
45	0.099	105	0.071
50	0.096	110	0.070
55	0.092	115	0.070
60	0.090	120	0.070

Table 2-Effect of varying concentrations of $KmnO_4$ [$1.25x10^{-4}$] ($moldm^{-3}$), Topiramate [1.0×10^{-3}]($moldm^{-3}$) and NaOH [1/20 X 0.1]($moldm^{-3}$) on the reaction rate at 303 K

$[KmnO_4]$ $x10^{-4}$ ($moldm^{-3}$)	[TOPI] $x10^{-3}$ ($moldm^{-3}$)	[NaOH] $\times 10^{-2}$ ($moldm^{-3}$)	K_{obs} $\times 10^{-3}$ s^{-1}	$K_{cal} \times 10^{-3}s^{-1}$
2.0	1.5	1.0	6.4	6.8
2.0	2.0	1.0	9.2	8.4
2.0	2.0	1.0	10.5	9.7
2.0	2.25	1.0	11.5	10.9
2.0	2.5	1.0	13.8	11.9
1.0	2.0	1.0	6.9	4.6
1.5	2.0	1.0	7.6	6.3
2.0	2.0	1.0	9.2	8.4
2.5	2.0	1.0	10.3	10.5
3.5	2.0	1.0	11.5	10.8
4.5	1.75	1.0	13.8	13.9
2.0	2.0	1.0	9.2	8.4
2.0	2.0	1.5	8.1	10.9
2.0	2.0	2.0	12.3	11.5

Effect of temperature:

At different temperature, the reaction rate was measured keeping constant concentration of topiramate, oxidant, and NaOH. The rate of a reaction increased with increase in temperature. The rate constants at different temperature Kobs were calculated in the table 3. A graph of log Kobs vs 1/T was plotted and from the slope the activation energy E_a was calculated. Different activation parameters, $\Delta H^{\#}$,$\Delta S^{\#}$ and $\Delta G^{\#}$were also calculated and tabulated in table 4.

Table : 3 Rate at different temperatures

Drug	**Rate at different temperatures**
301	9.2×10^{-3}
308	15.3×10^{-3}
313	$18.1x10^{-3}$
318	20.4×10^{-3}

Table 4 Activation Parameters

	Activation parameters
E_a $KJmol^{-1}$	56.0
$\Delta H^{\#}$ $KJmol^{-1}$	53.0
$\Delta S^{\#}$ $Jk^{-1}mol^{-1}$	-196.70
$\Delta G^{\#}$ $KJmol^{-1}$	107.5

Reaction Mechanism:

In the initial step MnO_4 reacts with OH to form $[MnO_4.OH]^2$ Intermediate complex and a linear positive intercept plot for $1/k_{obs}$ vs $1/[OH^-]$ [Michelis-Menten] plot also supports the formation of $[MnO_4.OH]$ in alkaline medium.

$$MnO_4 + OH^- \rightarrow [MnO_4.OH]^{2-}$$

The active species of permanganate reacts with $[MnO_4.OH]^2$reacts with topiramate leading to the formation of a complex and K_2 is the formation constant of the complex.

$$Topi + [MnO_4.OH]^{2-} \rightarrow Topi\text{-intermediate complex}$$

The decomposition of the complex lead to formation of products

$$Topi\text{-Intermediate} \rightarrow Products$$

The rate of disappearance of permanganate or the formation of the intermediate complex is expressed by the rate law

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

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

$= kK_1K_2[Topi]_f[MnO_4^-]_f[OH^-]_f$

$[Topi]_T=[Topi]_F$

$[MnO_4]_T=[MnO_4]_F[OH^-]_f + K_1K_2[Topi][MnO_4^-][OH^-]$

$[MnO_4]_f=[MnO_4]_T/ 1+ K_1 [OH^-]+ K_1K_2[Topi][OH^-]$

$[Topi]_T=[Topi]_F$

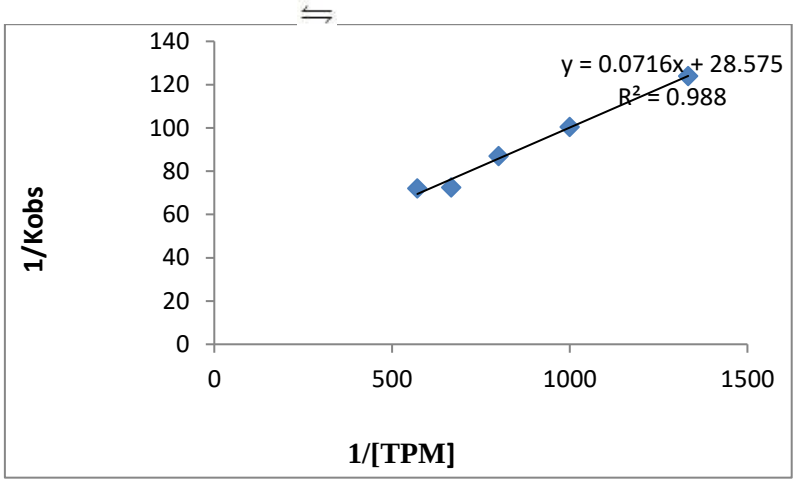
$[OH^-]_T = [OH^-]_f$

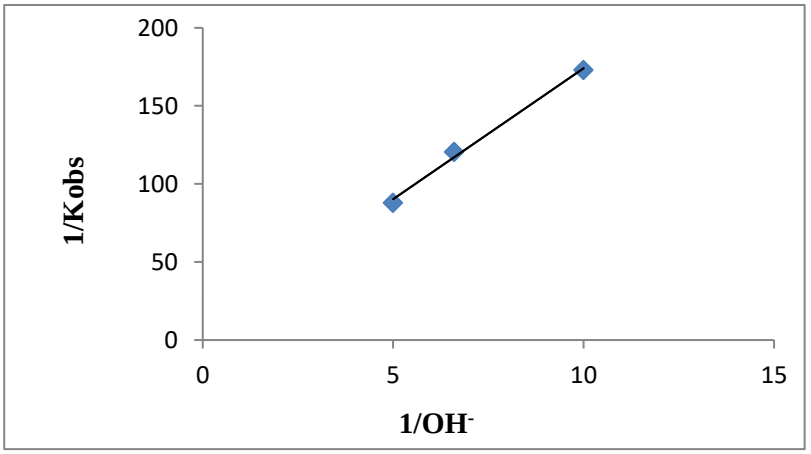
$Rate = kK_1K_2 [Topi][MnO_4^-][OH^-]/ 1+ K_1 [OH^-]+ K_1K_2[Topi][OH^-]$

On rearranging the above equation we have

$1/kobs=1/kK_1K_2[Topi][OH^-]+1/kK_2[Topi][OH^-]+1/]+1/K_1K_2[Topi]+1/k.$

According to the equation retaining other conditions constant, plots of 1/kobs vs 1/TPM and $1/k_{obs}$vs $1/[OH^-]$ are linear and the slopes and intercepts of these plots lead in the values of k K_1 and K_2. These constants were used to calculate the rate constants over different experimental conditions. The k_{exp} and k_{obs} values are in good agreement as shown in table-----.





Verification of rate law for oxidation of topiramate by potassium permanganate in aqueous alkaline medium

The rate law was verified by plotting the graph of $1/K_{obs}$ vs $1/ OH^-$. From the slopes of graph K_1K_2 were found and from the intercept k was found. Thus by substituting the value of K_1K_2 and k was found out. Thus by substituting the values of K_1, K_2 and k in the rate equation, the rate constant values are calculated.

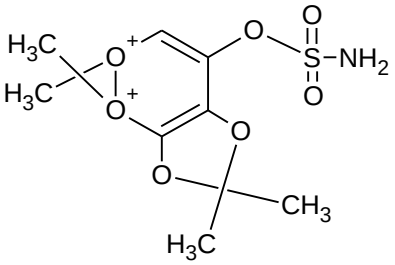
Scheme: 1:

An alkaline permanganate species $[MnO_4.OH]^{2-}$ is formed in a pre-equilibrium step. This is also confirmed from the fact that the reaction is fractional order in $[OH^-]$.

$MnO_4^- + OH^- \rightarrow [MnO_4.OH]^{2-}$

$K_1$is the equilibrium constant for the formation of alkaline species of oxidant $KmnO_4$.

The substrate topiramate reacts with oxidant to form an intermediate complex. K_2 is the formation constant of the complex.



$+ [MnO_4.OH]^{2-} \rightarrow [C_{12}H_{21}NO_8S.MnO_4.OH]^{2-}$

The complex formed dissociates into products.

$[C_{12}H_{21}NO_8S.MnO_4.OH]^{2-} \rightarrow C_{12}H_{19}NO_8S + MnO_4^{2-} + 2H_2O$

Conclusion:

Thus the spectroscopic investigation on oxidation of topiramate with powerful oxidizing agent potassium permanganate in aqueous alkaline medium has given ideas for proposing a mechanism for the reaction. The reactive species Permanganate was found to be $[MnO_4(OH)_2]^{2-}$, in alkaline medium the stable reduction product of $KmnO_4$ is manganate ion, MnO_4^{2-}. The stoichiometry of the reaction was observed to be 1:1. The product of oxidation was found by LC-MS. The fractional order confirmed the complex development between the substrate and the oxidant in the equilibrium step.The high negative value of $\Delta S^{\#}$ also supports the development of the complex. The evidence for complex formation between the topiramate and potassium permanganate was obtained by the plot of $1/K_{obs}$ vs 1/[TPM].

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