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AN ANESTHETIC AGENT-ETOMIDATE, OXIDATION BY $KMNO_4$ USING ALKALINE MEDIUM: A KINETIC AND SPECTROSCOPIC APPROACH

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ABSTRACT

The anesthetic agent etomidate was oxidized by alkaline mediated potassium permanganate and the rate of oxidation was studied with the help of UV-VIS spectrophotometer at constant ionic strength 0.01 mol dm^{-3} which exhibited a stoichiometry of 1:1. With respect to oxidant and reductant it is pseudo first order and fractional order with respect to alkaline medium. Various activation parameters with respect to rate determining steps like E_a (kJ/mol), $\Delta H^\#$ (kJ/mol), $\Delta S^\#$ (J/K/mol) and $\Delta G^\#$ (kJ/mol) were calculated and thermodyanamic quantities are also calculated. The slow step is the rate determining step for which the rate constant was calculated and mechanism derived.

KEYWORDS: Kinetics, Oxidation, etomidate, Permanganate ion.

INTRODUCTION

$KMnO_4$ is a exclusive and broadly used oxidant in acid, alkaline and neutral medium.[1] Permanganate ions are wide application in synthetic and analytical chemistry.[2] It serves as its own indicator and has several advantages as an analytical reagent, according to Gour *et al*.[3] It is a good disinfectant.

The pH of the medium governs the reactions involving $KMnO_4$. Being a powerful oxidant in aqueous alkaline medium, manganese in $KMnO_4$ exhibits six oxidation state from +2 to +7, Mn(VII) has a major role in different medium. In strong alkaline medium, the stable reduction product[4,5] is, $MnO_4{}^{2-}$ the manganate ion.

Permanganates particles oxidizes more substrates and this has applications in natural combination.[6] The results of the kinetic study experiment referring to unsaturated acids in both non-aqueous and aqueous media provided the information for the prediction of mechanism of the reaction.[7]

A large number of organic synthesis has been carried out by permanganate ion.[8-13]

The permanganate oxidation of large biological molecule such as nucleic acid[14], protein[15], thymine[16], uracil[17] and several amino acid[18] have already been reported.

Etomidate is an IV (intravenous) anesthetic agent induced for general anesthesia and sedation for short term requirement of dislocated joints, cardioversion etc. Developed by Janssen Pharmaceutica[19] in 1964 was used in Europe and United states.

This was frequently used for emergency settings as sedative hypnotic agents and less likely to drop blood pressure as other induction agents. Etomidate likewise has intriguing qualities like for individuals with brain injury since it diminish intracranial pressure and keep up a typical blood vessel pressure.[20]

$KMnO_4$ reaction with etomidate shows the variation in the oxidation states of manganese. The final product have been separated using separating funnel, isolated and characterized. A mechanism for the reaction has been suggested. Various other studies like solvent effect, medium effect, temperature effect on such reaction has been investigated. In alkaline medium, potassium permanganate exists as an intermediate $MnO_4(OH)^{2-}$ species.[15] The active species ($MnO_4(OH)^{2-}$) reacts with the substrate and forms an intermediate complex and this complex decompose to form product.

Here, in the paper, the anesthetic agent, etomidate (Figure 1) has been oxidized in alkaline medium.

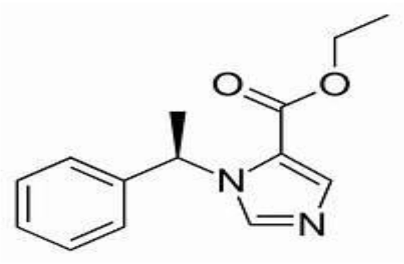


Figure 1: Structure of Etomidate.

EXPERIMENTAL

Materials and reagents used

All Chemicals and reagents used were AR grade and solutions were prepared using doubly distilled water, free from dissolved oxygen and were used without further purification. Accurately weighed $KMnO_4$ dissolved in doubly distilled water and it was standardized[21] by using 0.1 N oxalic acid also by measuring the absorbance using UV-visible spectrophotometer at 525 nm.

The drug, Etomidate was accurately weighed dissolved in 1ml NaOH and dissolved using distilled water. The requisite amount of NaOH, KNO_3 were also prepared and standardized with reference to Vogel book.[21] All the glassware used was washed by soaking in a HCl for more than 24 hrs and repeatedly washing and rinsing in deionized water. Absorbance was documented on UV-Vis Spectrophotometer at wave length 525 nm.

Kinetic Studies

The anesthetic etomidate was taken in large excess concentration than the oxidant and the kinetics of oxidation was considered spectrophotometrically, where {[etomidate]: [$KMnO_4$] > 10:1} at ionic strength (I = 0.01 mol dm^{-3}). The [etomidate] was changed from $5x10^{-4}$ to $6x10^{-3}$ mol dm^{-3} and [OH^-] was varied from $3.5x10^{-3}$ to 0.03 mol dm^{-3}.

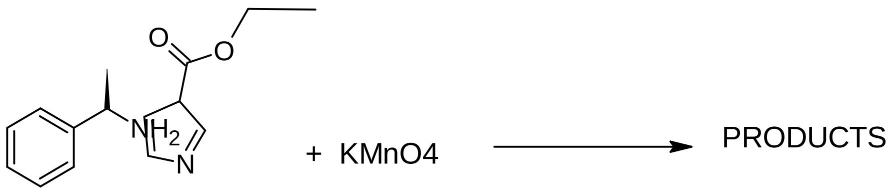
Beer's law was applied for $KMnO_4$ at a maximum wavelength of 525 nm verified[17], giving $\varepsilon = 2389 \pm 50$ dm^3 mol^{-1} cm^{-1} (Literature10 $\varepsilon = 2400$ dm^{-3} mol^{-1} cm^{-1}) as a function of time.

A conventional Systronic double beam UV-VIS spectrophotometer was used to record the decrease in colour fade for Mn (VII) at $\lambda_{max} = 525$ nm. A linear plot of log A versus time(s) were evaluated where slope gave the rate constant (k_{obs}).

RESULTS

Stoichiometry and product analysis

Spectrophotometric titration were performed. Different arrangements of the response blend containing various measures of reactants [MnO_4^-] >> [etomidate] but at constant alkali concentrations [OH^-] = 0.1 mol dm^{-3} and I=0.1 mol dm^{-3} of the reaction medium were allowed to react for 24 hrs until the reaction had gone to completion. The absorbance of the remaining MnO_4^- was analyzed spectrophotometrically. Thus single mole of MnO_4^- reacted with single mole of etomidate. This study helped in the calculation of the stoichiometry of the reaction is as shown below.



The final product of the oxidation reaction was obtained when 0.01 mol potassium permanganate and 0.01 mol of etomidate were made to react in a container and in an alkaline medium of 0.01 mol dm^{-3}. This was kept overnight at 298 K to complete its reaction. The product was identified by LC-MS. Figure 2.

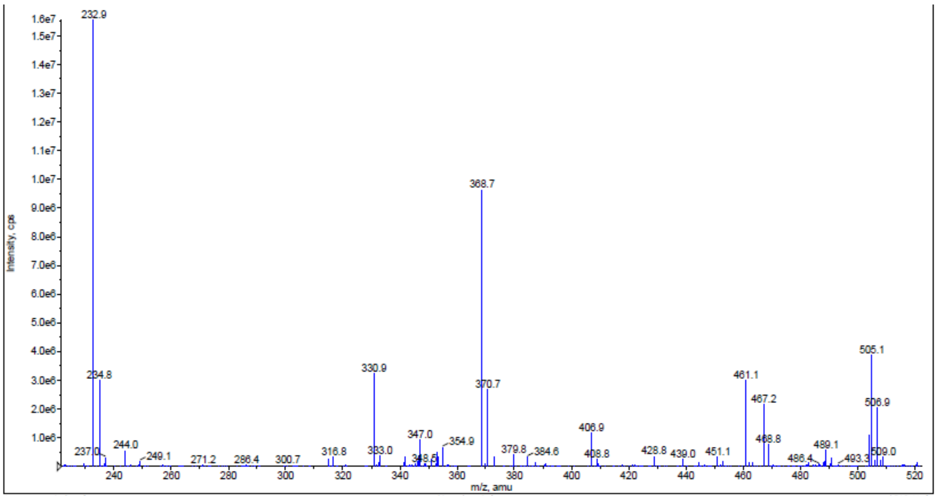


Figure 2: Product analysis- LC-MS method.

Reaction Order

The reaction between etomidate and oxidant Mn (VII) have been experimented in the range $5x10^{-4}$ to $6x10^{-3}$ mol dm^{-3} and $5x10^{-5}$ to $4.5x10^{-4}$ mol dm^{-3} respectively; [OH^{-}] over the range of $3.5x10^{-3}$ to 0.03 mol dm^{-3}; temperature from 298 K to 318 K.

In the plot log k_{obs} vs log [MnO_4^{-}] slopes were used to determine the reaction order by changing the concentrations of substrate and base maintaining other reactant concentration and other factors constant. With constant [etomidate] = $2.5x10^{-3}$ mol dm^{-3} and [alkali] = 0.01 mol dm^{-3} and I = 0.01 mol dm^{-3}, the [permanganate] varied from $5x10^{-5}$ to $5x10^{-4}$ mol dm^{-3}. Log (absorbance) vs time was linear, for various [$KMnO_4$] shows the order in Mn (VII) is unity. The etomidate concentration was varied from 5x10^{-4} to 6x10^{-3} mol dm^{-3} at 298 K. With increase in etomidate concentration a increase in k_{obs} values was noted.

Effect of used oxidant, potassium permanganate

[Potassium permanganate] was varied from 5x10^{-5} to 5x10^{-4} mol dm^{-3} at fixed concentration of all the other reactants in the study. A first order dependence with the oxidant was observed when plotted of initial rates versus concentration of potassium permanganate. (Figure: 3) The results and values of k presented in Table 1 indicates the unit order w. r. to $KMnO_4$.

Effect of the substrate, etomidate

[Etomidate] was changed between 5x10^{-4} to 6x10^{-3} mol dm^{-3} at fixed concentration of other involved reactants. The fractional order dependence with substrate presented Table 1.

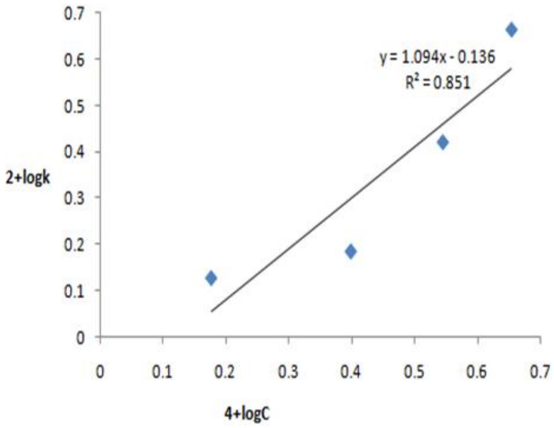


Figure 3: A plot of log k against log C showing first order dependence with the oxidant.

Effect of the medium, NaOH

[Sodium hydroxide] was varied from 3.5x10^{-3} mol dm^{-3} to 0.03 mol dm^{-3} with other reactant concentrations constant. Rate increased with NaOH concentration. Sodium hydroxide shows the fractional order dependence with sodium hydroxide presented Table 1.

Temperature effect

This study was done by varying the temperature. At four different T, from 298 K, 304 K, 309 K, 314 K and 319 K under varying [$KMnO_4$] and [substrate]. Form the slow step, rate constants (k) of the reaction mechanism were obtained. Reaction rate increases with rise of temperature.

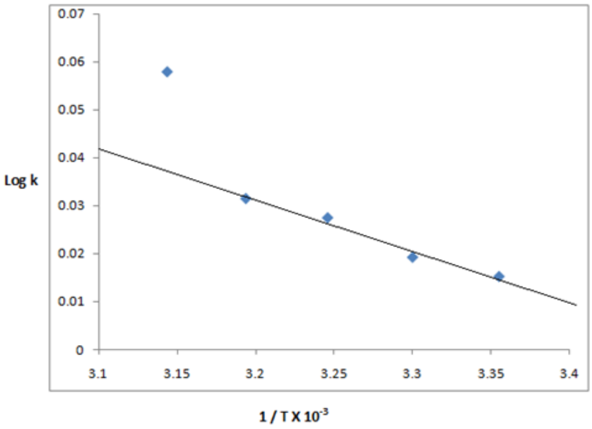


Figure 4: log k against 1/T (K^{-1}) for calculation of activation parameters.

Effect of KNO_3

[KNO_3] was varied from 2.5x10^{-3} mol dm^{-3} to 0.03 mol dm^{-3} and kept other reactants concentration constant. KNO_3 has shown the fractional order dependence with substrate, Table 1.

Table 1: Effect of etomidate, [$KMnO_4$], [OH^-] at T = 25 ± 0.1°C.

[$KMnO_4$] x 10^{-4} (mol dm^{-3})	[Etomidate] x 10^{-3} (mol dm^{-3})	[OH^-] x 10^{-1} (mol dm^{-3})	[NO^{3-}] x 10^{-2} (mol dm^{-3})	k_{obs}	k_{cal}
0. 5	2.5	0.1	0.1	0.0132	0.0101
1.5	2.5	0.1	0.1	0.0133	0.0170
2.5	2.5	0.1	0.1	0.0143	0.0193
3.5	2.5	0.1	0.1	0.0253	0.0209
4.5	2.5	0.1	0.1	0.0410	0.0299
2.5	0.5	0.1	0.1	0.0333	0.006
2.5	1.5	0.1	0.1	0.0355	0.016
2.5	2.5	0.1	0.1	0.0143	0.0193
2.5	3.5	0.1	0.1	0.0143	0.0307
2.5	4.5	0.1	0.1	0.0115	0.0379
2.5	2.5	0.025	0.1	0.0066	0.0068
2.5	2.5	0.05	0.1	0.0120	0.0138
2.5	2.5	0.1	0.1	0.0143	0.0193
2.5	2.5	0.15	0.1	0.0230	0.0342
2.5	2.5	0.2	0.1	0.4318	0.0388
2.5	2.5	0.1	0.25	0.0418	0.0397
2.5	2.5	0.1	0.5	0.0230	0.025
2.5	2.5	0.1	1	0.0153	0.0192
2.5	2.5	0.1	2	0.0085	0.0114
2.5	2.5	0.1	3	0.0080	0.0092

Table 2: Values of k, w. r. to Temperature for oxidation of etomidate by $KMnO_4$.

Temperature in (K)	k × 10^{-2}(s^{-1})
298	1.63
304	1.94
309	2.85
314	3.25
319	5.88

Table 3: The various Activation Parameters involved in the reaction between etomidate and $KMnO_4$.

Parameters	Values
Ea (kJ/mol)	20.84
$\Delta H^{\#}$(kJmol^{-1})	2568.92
$\Delta S^{\#}$ (J K^{-1}mol^{-1})	-175.0
$\Delta G^{\#}$ (kJmol^{-1})	85.273

Table 3: gives the activation parameters and thermodynamic quantities foe entomidate oxidation.

Scheme-I.

$$MnO_4^- + OH^- \xrightarrow{K1} [MnO_4(OH)]^{2-}$$

$$\text{Substrate} + [MnO_4(OH)]^{2-} \xrightarrow{K2} \text{Complex}$$

$$\text{Complex} \xrightarrow{k_{slow}} \text{Products} + H_2O$$

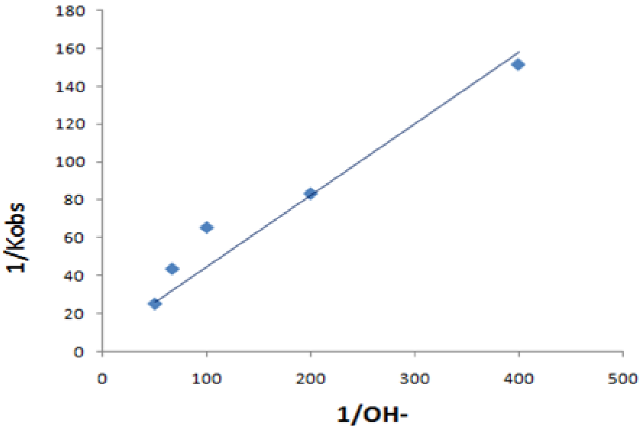


Figure 5: Rate law Verification.

Plot 1/K_{obs} Vs 1/OH^- (Figure 5) for rate law verification. Slopes of graph gave K_1K_2 value. Intercept equals k value. Thus, substituting the values of K_1K_2 and k in the rate equation,

Rate = k [Complex]

= kK2 [Etomidate] $[MnO_4OH]^{2-}$

$= kK1K2\ [\text{Etomidate}]\ [MnO^-_4]\ [OH^-]$ -------------- (1)

$[MnO_4]_T = [MnO_4]_f + K2[\text{Etomidate}]\ [MnO_4OH]^{2-}$

$= [MnO^-_4]_f + K1K2[\text{Etomidate}]\ [MnO^-_4]\ [OH^-]$

$= [MnO^-_4]_f\ \{1+K1K2[\text{Etomidate}]\ [OH^-]\}$

$[MnO_4]_f = [MnO_4]_T / 1+K1K2\ [\text{Etomidate}]\ [OH^-]$

$[OH^-]_T = [OH^-]_f + [MnO_4OH]^{2-} + [\text{Complex}]$

$= [OH^-]_f + K1[MnO_4^-]\ [OH^-] + K2[\text{Etomidate}]\ [MnO_4OH]^{2-}$

$= [OH^-]_f + K1[MnO^-_4]\ [OH^-] + K1\ K2\ [\text{Etomidate}]\ [MnO_4^-]\ [OH^-]$

$= [OH^-]_f\ \{1+K1\ [MnO_4^-] + K1\ K2\ [\text{Etomidate}]\ [MnO_4^-]\}$

$[OH^-]_f = [OH^-]_T / 1+K1[MnO_4^-] + K1\ K2[\text{Etomidate}]\ [MnO_4^-]$

$[OH^-]_f = [OH^-]_T$ since $[\text{Etomidate}] >> [MnO_4^-]$

Substituting in equation (1)

Rate = $kK1K2\ [\text{Etomidate}]\ [MnO_4^-]\ [OH^-] / 1+ K1\ K2\ [\text{Etomidate}]\ [OH^-]$

This is the rate law

$kobs = kK1K2\ [\text{Etomidate}]\ [MnO_4^-]\ [OH^-] / 1+ K1\ K2\ [\text{Etomidate}]\ [OH^-]$

$1 / kobs = 1 / kK1K2\ [\text{Etomidate}]\ [OH^-] + 1 / k$

DISCUSSIONS

This paper shows the oxidizing property of permanganate ion in alkaline medium. The importance of pH and medium is highlighted here. At pH > 12 reaction product is Mn (VII)) and it is stable. The reaction between etomidate and potassium permanganate in alkaline medium has been studied. The stoichiometry of the reaction is found to be 1:1. Observed first order reaction with oxidant and substrate and with alkali is fractional order dependence. Fractional order with OH^- indicates the formation of $[MnO_4(OH)]^{2-}$ in equilibrium step[24]. Michaeils Menton plot Figure 4 supports this, which is linear with positive intercept The $MnO_4(OH)^{2-}$ react with substrate to form intermediate complex which undergoes reaction with single mole of alkali permanganate species to form the products. The moderate values of activation parameters favors the electron transfer processes.

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