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KINETIC AND COMPARATIVE STUDY OF 3-METHYLINDOLE OXIDATION BY POTASSIUM BROMATE IN TWO SOLVENTS

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ABSTRACT
The study explored the oxidation of 3-Methylindole by potassium bromate ($KBrO_3$) in two different solvents of ethanol and acetone. It revealed that the reaction follows totally second-order kinetics and first order with respect to both 3-Methylindole and KBrO3. Interestingly, the rate remained unchanged when hydrogen ion concentration varied, and changes in ionic strength had no rate of effect. As the percentage of organic solvents increased, the rate of reaction also slowed down, and the absence of polymerization suggested the reaction did not proceed through a radical mechanism. Activation and thermodynamic parameters have been computed. A suitable kinetic mechanism based on these observations is proposed. The final product was confirmed through IR and NMR spectral analysis. The conclusion was that ethanol acts as a faster solvent for this oxidation compared to acetone.

KEYWORDS: Mechanism, Kinetics, 3-Methylindole, Potassium bromated, Ethanol, Acetone, Oxidation

Trial Registration: UMIN Clinical Trials Registry UMIN000056113 (registered November 11, 2024)

INTRODUCTION
Indoles are key precursors for substances produced within the human body and are widely used in lifestyle and medical applications. They also serve as candidates for the direct oxidation and reduction of biomolecules, along with other biological activities [1]. The oxidation of 2,3-dimethylindole by peroxodisulphate anions (PDS) to form 3-methylindole-3-carbaldehyde has been previously documented in the literature [2]. Indoles and bromoindoles possess significant potential across various fields, particularly in the electrochemical industry, where they function as electrocatalysts, anode materials in batteries, anticorrosion coatings, and fast-response potentiometric sensors [3]. In pharmacology, these compounds have drawn considerable interest due to their ability to act as antifungal and antibacterial agents. Due to the strong and diverse biological activities demonstrated by many indole derivatives, this heterocyclic system has gained substantial attention in chemistry, biology, and medicine [4-5].

Indoles serve as lead compounds and essential building blocks in numerous pharmaceuticals, which is not surprising given their importance. Indole derivatives are a significant class of therapeutic agents in medicinal chemistry, exhibiting activities such as antihypertensive, antiproliferative, antiviral, antitumor, analgesic, anti-inflammatory, and antimicrobial effects [6]. Among the various substituted indoles, Skatole or 3-Methylindole (3-MI) has been selected for investigation. Skatole is a microbial fermentation product of tryptophan found in the rumen of cattle [7, 8]. Although the indole moiety is small, it fascinates scientists due to the diverse biological activities exhibited by both indole and its various substituted derivatives. The indole moiety is present in many biologically occurring substances, with its metabolism often involving oxidative pathways [9].

The term "skatole" comes from the Greek word skato, meaning dung. This compound is present in mammalian feces and has a sharp odor; however, at low concentrations, skatole emits a flowery scent and is used in perfume manufacturing. Interestingly, skatole has been found to cause pulmonary edema in goats, sheep, and several rodents like mice and rats [10]. The oxidation of 3-Methylindole into 3-Methyloxindole has been carried out using peracetic acid [11]. Brominating agents oxidize skatole to yield bromo-substituted 3-methyloxindole [12]. Using the enzyme Pseudomonas, 3-Methylindole has been oxidized to indole-3-carboxaldehyde via indole-3-methanol [13]. Muniyappan et al. conducted kinetic studies of indole oxidation by PMS in various solvents such as ethanol [14], acetonitrile [15], and acetone [16]. Chandramohan et al. studied the oxidation of Indole-3-acetic acid (IAA) by PMS into 2-hydroxy indole-3-methanol in aqueous acetonitrile medium [17].

Periyasami et al. investigated the oxidation of 3-Methylindole by potassium bromate in acetic acid medium [18]. Skatole is a mildly toxic compound naturally occurring in feces and coal tar. It is also found in several flowers and essential oils, including orange blossoms, jasmine, and Ziziphus mauritiana. Additionally, the U.S. military uses skatole as a

malodorant in non-lethal weaponry [19]. This study presents the first report on the comparative kinetic and mechanistic investigation of the oxidation of 3-Methylindole by potassium bromate in ethanol and acetone solvents

EXPERIMENTAL

MATERIALS AND METHODS

High-purity 3-Methylindole (Skatole) and potassium bromate (≥99.9% purity) were used as received. Analytical-grade chemicals like sulfuric acid, acetic acid, sodium bisulphate, potassium iodide, starch, sodium thiosulphate, acetone, ethanol, and mercuric acetate (all ≥99.9% purity) were employed. Aqueous solutions of potassium bromate and sodium perchlorate (to maintain ionic strength) were prepared using double-distilled water, further purified by alkaline permanganate treatment. Reactions were conducted in a thermostat-controlled environment at ±0.1°C. Experiments varied substrate [3-MI] concentration while keeping oxidant, solvent, [H+], and ionic strength constant, and vice versa.

Kinetic studies

All reagents, including the substrate, were thermostated at 293-308 K to reach equilibrium. A measured volume of $KBrO_3$ solution, maintained at the same temperature, was quickly added to the reaction vessel. The reaction progress was monitored by iodometric assay of aliquots using starch as an indicator at specific time intervals. The unused bromate reacts with KI in acidic solution as follows:

$BrO_3^- + 6I^- + 6H^+ \rightarrow Br^- + 3I_2 + 3H_2O$

Reactions were conducted with a tenfold excess of 3-MI relative to bromate. Pseudo-first-order rate constants (s^{-1}) were determined from linear plots of log [bromate] versus time (r 2 0.98) up to 80% reaction completion. Rate constants were reproducible within 5%. Fresh 3-MI solutions in ethanol or acetone were used to prevent side reactions. Mercuric acetate (0.001 mol dm^{-3}) was added as a scavenger to remove bromine ions formed during the reaction. Duplicate runs showed reproducibility within ± 5% error.

RESULTS AND DISCUSSION

The factors affecting the oxidation rate of 3-Methylindole ([3-MI]) by potassium bromate were examined, including the effects of (i) [3-MI]. (ii) oxidant concentration. (iii) ionic strength (μ). (iv) hydrogen ion concentration [H^+] and (v) dielectric constant. Rate and activation parameters were also evaluated.

Effect of [3-Methylindole]: At 303 K, keeping oxidant, [H^+], μ, and solvent constant, the pseudo first-order rate constants increased linearly with [3-MI] (2.0×10^{-2} to 4.0×10^{-2} mol dm^{-3}), confirming first-order dependence on [3-MI]. This was supported by linear plots of k′ vs. [3-MI] passing through the origin (r = 0.999). Rate constants (k and k_2) were calculated over 293–308 K, with k_2 derived from the slope of k′ vs. [3-MI].

Effect of Oxidant ([$KBrO_3$]): The reaction rate showed first-order dependence on [$KBrO_3$], as log [$KBrO_3$] vs. time plots had constant slopes for concentrations ranging from 1×10^{-2} to 5×10^{-2} mol dm^{-3}.

Effect of Ionic Strength (μ): Varying μ (1×10^{-1} to 5×10^{-1} mol dm^{-3}) using sodium per chlorate had negligible effect on the rate, suggesting the reaction occurs between a neutral molecule (3-MI) and a mononegative ion (BrO_3^-).

Effect of [H^+]: Changing [H^+] from 0.5×10^{-2} to 9×10^{-2} mol dm^{-3} did not affect the reaction rate, indicating no protonation equilibrium under these conditions.

Effect of Dielectric Constant: The rate increased with decreasing solvent percentage (ethanol and acetone), i.e., with increasing medium polarity. This suggests charge development in the transition state involving a more polar activated complex, consistent with a polar (ionic) mechanism. The increasingly negative $\Delta S^{\#}$ with decreased solvent concentration hints at electrostriction due to greater charge at the activated complex.

Stoichiometry: Titrimetric analysis at room temperature with excess $KBrO_3$ showed a 1:2 stoichiometric ratio of 3-MI to oxidant.

Test for Free Radical Intermediates: The overall second-order rate, with first-order dependence on both reactants, and absence of polymer formation upon addition of acrylonitrile monomer, indicates a non-radical reaction pathway

Rate Law

In accordance with the above observations, the rate law for the disappearance of oxidant is given as follows:

$-d[Br(V)]/dt = k_2[Br(V)][3\text{-MI}]$

$rate/[Br(V)] = k'(s^{-1}) = k_2[3\text{-MI}]$

$k' = k_2[3\text{-MI}]$

where k′ = pseudo-first order rate constant and k_2 = second order rate constant.

Product Analysis: Reaction mixtures with a slight excess of oxidant (0.125 mol dm^{-3} $KBrO_3$) over substrate (0.06 mol dm^{-3} 3-MI) and other additives, using ethanol or acetone as solvents, were left at room temperature for about 48 hours to complete the reaction. Completion was confirmed by TLC analysis. The mixtures were then poured into double-distilled water, and the resulting solid products were filtered, washed, and dried.

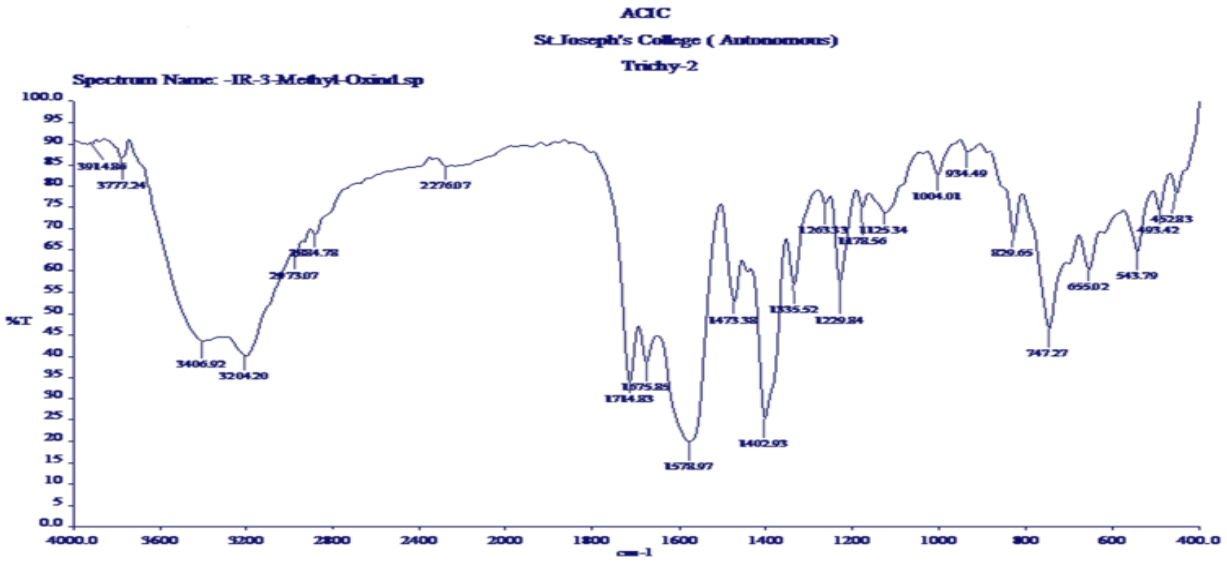


Fig. 1. FT-IR spectrum of product

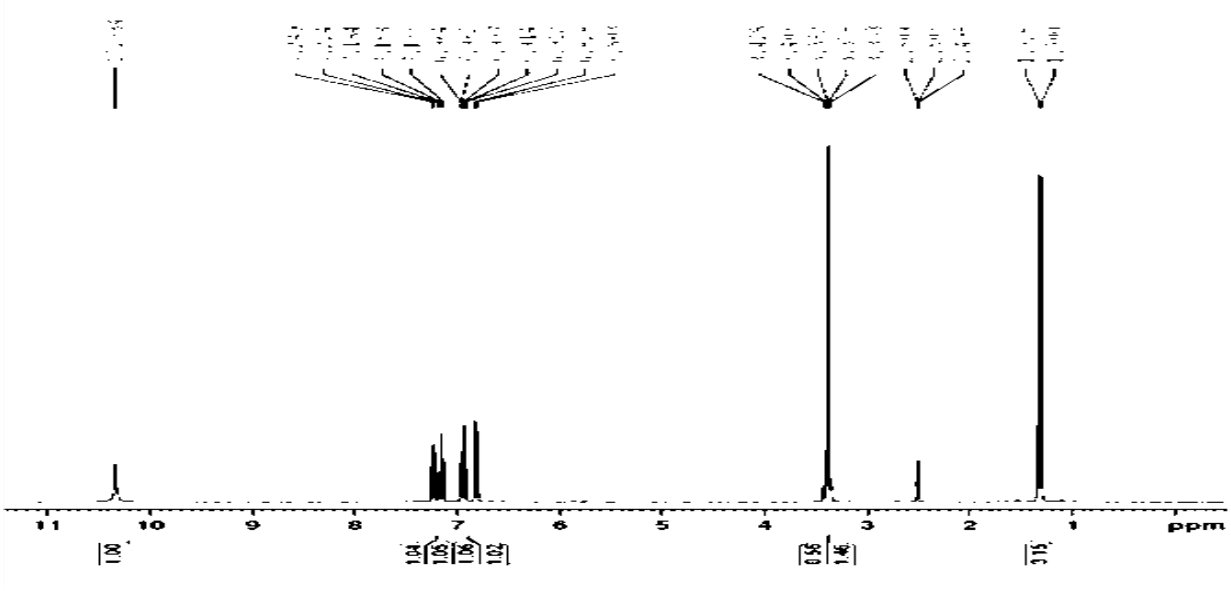


Fig. 2. NMR- spectrum of product

The identity of the product was further confirmed from its FT-IR spectra (Fig .I) and HMNR (Fig .II). FT-IR (KBr) 3406, 1714 and 1675 cm-1, HNMR (DMSO) ppm = 6.0-8.0 (m, 5H, ArH, NH), 3.3 (S, 3H, C-H).

Rate and Activation Parameters

The temperature effect on the rate constant k′ (s^{-1}) was studied between 293–308 K in ethanol and acetone solvent systems (Tables 2 & 3). The Arrhenius plots (log k_2 vs 1/T) were linear (Table 1 & Fig. V), allowing calculation of activation energy (Ea). The entropy of activation ($\Delta S^{\#}$), derived from the Eyring equation, showed a large negative value, indicating strong solvent molecule restriction around the transition state (Table 4).

Fig.1.Variation of [3-MI] @ 303 K

3-MI-$KBrO_3$-EtOH system **3-MI-$KBrO_3$-AC system**

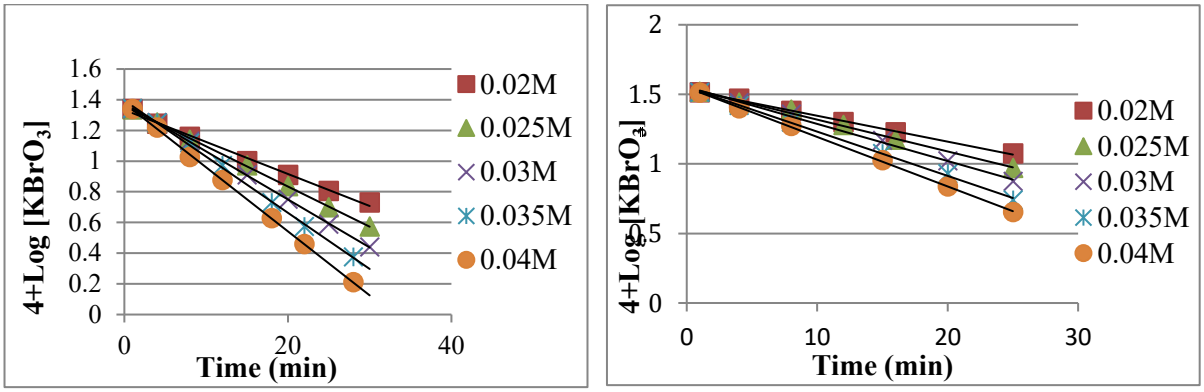


Fig. 2. Evaluation of k_2

3-MI-$KBrO_3$-EtOH system

3-MI-$KBrO_3$-AC system

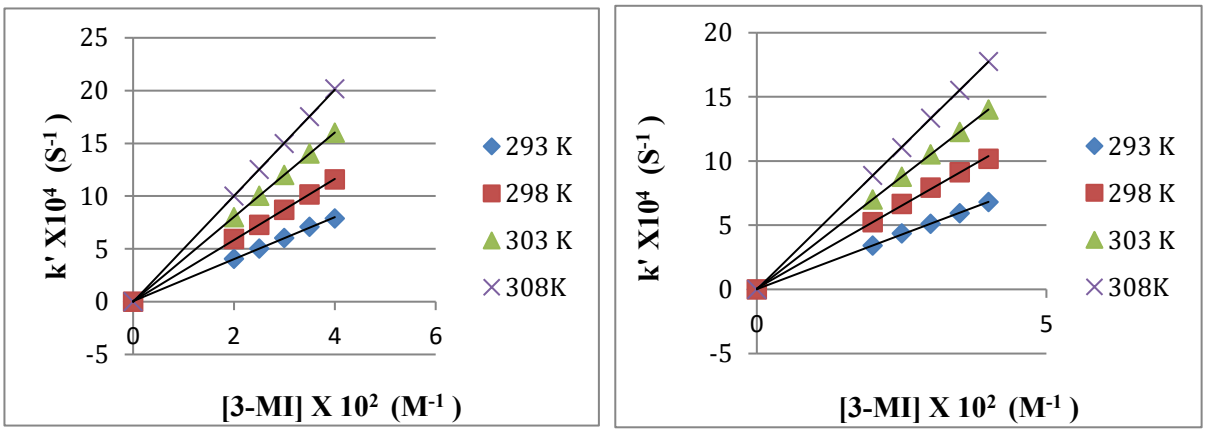


Table 3. Effect of temperature on the reaction rate

Temp (K)	k_2 (103 , s^{-1})	
	Ethanol Solvent	Acetone Solvent
293	2.01428	1.70926
298	2.92026	2.61425
303	4.01815	3.50550
308	5.01257	4.43452

Table 1.Pseudo-First Order Rate Constant for the oxidation of 3-MI by $KBrO_3$ in Ethanol Solvent

[3-MI] X10² (mol dm−3)	[$KBrO_3$] X10³ (mol dm−3)	[H^+] (mol dm−3)	[μ] (mol dm−3)	EtOH % (v/v)	k′ (104 s−1)			
			K 308K				293 K	298 K 303
2.0	2.0	0.02	0.3	50	4.08	5.95	8.01	10.01
2.5	2.0	0.02	0.3	50	5.04	7.27	10.05	12.52
3.0	2.0	0.02	0.3	50	6.05	8.72	12.01	15.00
3.5	2.0	0.02	0.3	50	7.09	10.17	14.04	17.52
4.0	2.0	0.02	0.3	50	7.87	11.59	16.01	20.16
3.0	1.0	0.02	0.3	50	-	-	12.44	-
3.0	1.5	0.02	0.3	50	-	-	12.55	-
3.0	2.0	0.02	0.3	50	-	-	12.01	-
3.0	4.0	0.02	0.3	50	-	-	12.02	-
3.0	5.0	0.02	0.3	50	-	-	12.15	-
3.0	2.0	0.005	0.3	50	-	-	12.54	-
3.0	2.0	0.02	0.3	50	-	-	12.01	-
3.0	2.0	0.05	0.3	50	-	-	12.26	-
3.0	2.0	0.09	0.3	50	-	-	12.28	-
3.0	2.0	0.02	0.1	50	-	-	12.14	-
3.0	2.0	0.02	0.2	50	-	-	12.37	-

3.0	2.0	0.02	0.3	50	-	-	12.01	-
3.0	2.0	0.02	0.5	50	-	-	12.22	-
3.0	2.0	0.02	0.3	40	12.00	16.11	20.19	25.43
3.0	2.0	0.02	0.3	45	9.87	12.61	16.06	21.14
3.0	2.0	0.02	0.3	50	6.81	8.01	12.01	17.82
3.0	2.0	0.02	0.3	55	3.18	4.21	8.12	13.61
3.0	2.0	0.02	0.3	60	0.98	1.61	4.46	9.881

Table 2.Pseudo-First Order Rate Constant for the oxidation of 3-MI by $KBrO_3$ in Acetone Solvent

[3-MI] $X10^2$ (mol dm−3)	$[KBrO_3]X10^3$ (mol dm−3)	[H+] (mol dm−3)	[μ] (mol dm−3)	Acetone % (v/v)	k′ (104 s^{-1}) 293 K	298 K	303 K	308K
2.0	2.0	0.02	0.3	50	3.41	5.22	7.00	8.88
2.5	2.0	0.02	0.3	50	4.35	6.65	8.78	11.04
3.0	2.0	0.02	0.3	50	5.11	7.92	10.51	13.33
3.5	2.0	0.02	0.3	50	5.93	9.13	12.27	15.50
4.0	2.0	0.02	0.3	50	6.80	10.18	14.01	17.76
3.0	1.0	0.02	0.3	50	-	-	10.54	-
3.0	2.0	0.02	0.3	50	-	-	10.51	-
3.0	3.0	0.02	0.3	50	-	-	10.47	-
3.0	4.0	0.02	0.3	50	-	-	10.46	-
3.0	5.0	0.02	0.3	50	-	-	10.11	-
3.0	2.0	0.005	0.3	50	-	-	10.46	-
3.0	2.0	0.02	0.3	50	-	-	10.51	-
3.0	2.0	0.05	0.3	50	-	-	10.48	-
3.0	2.0	0.09	0.3	50	-	-	10.44	-
3.0	2.0	0.02	0.1	50	-	-	10.52	-
3.0	2.0	0.02	0.2	50	-	-	10.82	-
3.0	2.0	0.02	0.3	50	-	-	10.51	-
3.0	2.0	0.02	0.5	50	-	-	10.20	-
3.0	2.0	0.02	0.3	40	12.88	15.10	17.64	19.33
3.0	2.0	0.02	0.3	45	9.98	11.82	13.60	15.21
3.0	2.0	0.02	0.3	50	6.28	8.14	10.51	12.95
3.0	2.0	0.02	0.3	55	3.14	5.61	8.24	10.62
3.0	2.0	0.02	0.3	60	1.84	2.98	5.60	7.74

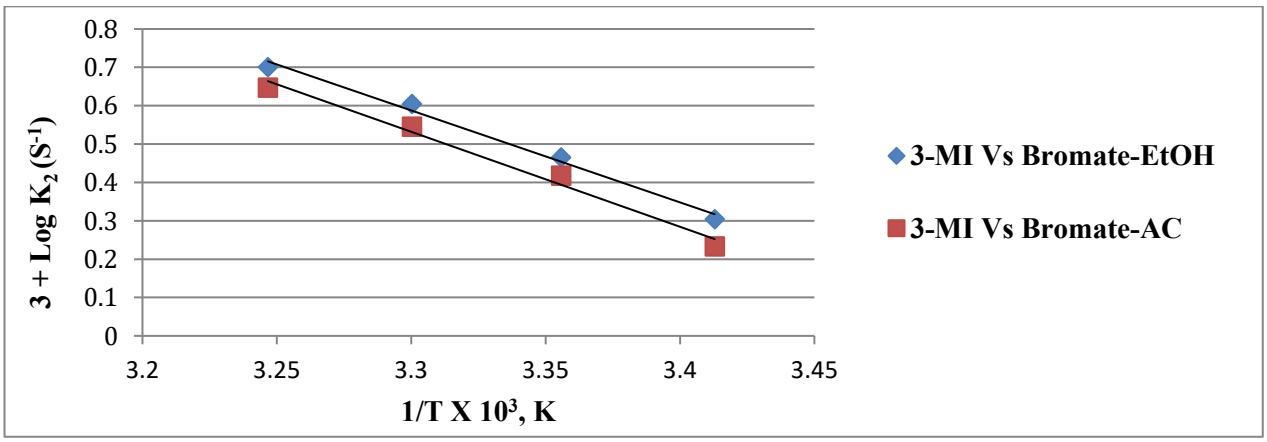


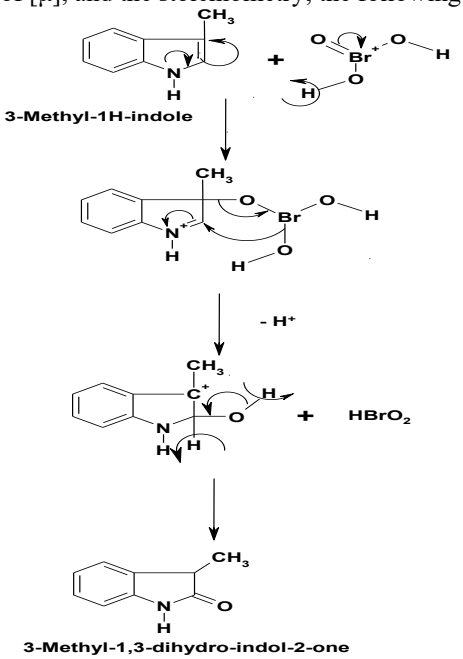
Fig. 3 Evaluation of Ea for Ethanol and Acetone solvent System

Table 4. Thermodynamic parameters

Thermodynamic parameters of Oxidation of 3-MI vs $KBrO_3$ in two solvent	Activation Parameters	
	Ethanol	Acetone
Energy of Activation (E_a) kJmol^{-1}	53.7387	47.4134
Enthalpy ($\Delta H^{\#}$) kJ mol^{-1}	51.2195	44.8962
Entropy ($\Delta S^{\#}$) J K-1 mol^{-1}	-284.4568	-284.3994
Free Energy ($\Delta G^{\#}$) kJ mol^{-1}	137.4099	131.0692

Mechanism

Based on the foregoing observations such as first-order dependence of rate each on [3-MI],[$KBrO_3$], zero-order dependence on [H^+], negligible effect of [μ], and the stoichiometry, the following mechanism is suggested:



The reaction proceeds via electrophilic attack by the bromate ion at the nucleophilic C-3 site of 3-Methylindole, forming a bromate ester intermediate. This intermediate rapidly decomposes to yield 3-Methyloxindole. The mechanism is supported by first-order kinetics in both oxidant and substrate, and second order in [H^+]. Increased solvent polarity enhances the reaction rate by facilitating nucleophilicity. The lack of effect from acrylonitrile, a radical scavenger, confirms no free radical involvement

CONCLUSION

The oxidation of 3-Methylindole by $KBrO_3$ proceeds through an ester intermediate that breaks down to form 3-Methyloxindole. The reaction follows first order with respect to both 3-Methylindole and $KBrO_3$, resulting in an overall second-order reaction. Ionic strength and [H^+] do not affect the rate. The dielectric effect shows that the rate increases as the percentage of solvents (ethanol and acetone) decreases.

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