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RESEARCH ARTICLE

KINETIC INVESTIGATION OF OXIDATION OF 3-METHYLINDOLE BY PEROXOMONOSULPHATE USING ETHANOL MEDIUM

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ABSTRACT

Kinetics of oxidation of certain substituted indole such as 2,3-Dialkyl indoles by Peroxomonosulphate (PMS) had been already reported. The present work is investigated the kinetic studies of oxidation of 3-methylindole (3-MI) by PMS using ethanol medium. Present work is investigating the order of the reaction follows a total second order, first order each with respect to [3-MI] and [PMS], effect of ionic strength, effect of [H⁺] and solvent effect. Absence of any polymerization indicated a nonradical pathway. Activation and thermodynamic parameters have been calculated from kinetic values. A suitable mechanism scheme based on these observations is proposed.

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INTRODUCTION

3-Methylindole (3-MI), a well known compound as Skatole is a microbial fermentation product of tryptophan in the rumen of cattle¹. 3-MI is also present in the feces of pigs, rats and man as a result of microbial fermentation of dietary tryptophan in the lower gastrointestinal tract^{3,4,5}. Another source of 3-MI is cigarette smoke. Each cigarette generates 4 to 50, µg of 3-MI as a result of pyrolysis of tryptophan in tobacco leaves⁶. The most prominent feature of 3-MI toxicity is its consistency in inducing a lung disease experimentally in ruminants with selective damage to specific lung cells. The oxidation of indole into oxindole was carried out by using various oxidants such as *N*-chloro-*N*-sodio-*p*-toluenesulphonamide in alkaline medium catalysed by osmium (VIII)⁷, chromium(VI)⁸ oxidation catalysed by ethylene diamine tetraacetic acid, oxalic acid, picolinic acid, peroxide oxidation of indole catalysed by chloroperoxidases⁹, oxidation of indole and indole derivatives catalysed by nonheme chloroperoxidases¹⁰ and oxidation of indole by cytochrome P450 enzymes¹¹. In view of this, the present work is significant as it involves the reaction of a peroxo linkage containing oxidant namely PMS with 3-MI. The oxidation of certain substituted indoles such as 2, 3-dialkyl indoles by peroxodisulphate¹², PMS¹², peroxomonophosphoric¹², peroxodiphosphoric acids¹² has been already reported in the literature. The oxidation of indole into isatin using PMS¹³ and oxidation of indole-3-acetic acid (IAA) into 2-hydroxy indole-3-methanol¹⁴ has been reported in the literature. The lack of kinetic and mechanistic investigation on the oxidation of 3-MI by PMS investigated us to carry out this work and is presented as a first report in this study.

EXPERIMENTAL

Materials

3-Methylindole and PMS under the other name Oxone[®] from Sigma aldrich of highest purity grade was used as such. Solutions of this salt were assayed iodometrically and by cerimetry¹⁵. Other chemicals and reagents such as sulphuric acid, methanol, sodium sulphate, and KI used were of analytical grade from Qualigens. All reagents and solutions were prepared using this doubly distilled water. All the reactions were carried out in a thermostat and the temperature was controlled to ± 0.1^oC. Various kinds of experiment were carried out varying the concentration of the substrate [3-MI] by keeping constant concentrations of Oxidant, Solvent, [H⁺], µ and vice-versa.

Kinetic Measurements

Kinetic studies were carried out in 50% (v/v) aqueous ethanol medium under pseudo first-order conditions with a large excess of 3-MI over PMS in the temperature range of 283–293 K. The reaction was followed by estimating the unreacted PMS as a function of time by using the iodometric method. The liberated iodine was titrated against standard sodium thiosulphate solution by using starch as indicator. From the titre values, plots of log [PMS] vs time were made and from the slope of such plots, the pseudofirst order rate constants, *k* (s⁻¹) were obtained. It was checked that the results were reproducible within ±5% error.

RESULTS AND DISCUSSION

Factors influencing the rate of oxidation of [3-MI] by PMS such as effects of (i) [3-MI], (ii) [PMS], (iii) ionic strength (µ), (iv) [H⁺], and

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(v) dielectric constant have been studied. Rate and activation parameters were evaluated.

Effect of [3-MI]

kinetic runs were carried out with various initial concentrations of [3-MI] at 293K by fixing constant [PMS], $[H^+]$, μ , and percentage of ethanol, which yielded [3-MI] dependent rate constants. The values of pseudofirst-order rate constants $k'(s^{-1})$ thus obtained were found to increase with [3-MI] (Table 1 & Fig. 1) over a range of [3-MI] used ($2.0 \times 10^{-2} - 4.0 \times 10^{-2} \text{ mol dm}^{-3}$). This shows that the reaction obeys first order with respect to [3-MI].

Table 1: Variation of [3-MI] @ 293 K

| Time (min) | [3-MI] x 10 ⁻² mol dm ⁻³ | | | | |
|---|--|--------|--------|---------|---------|
| | 4 + Log [PMS] | | | | |
| | 2.0 | 2.5 | 3.0 | 3.5 | 4.0 |
| 1 | 1.1808 | 1.1808 | 1.1808 | 1.1760 | 1.1760 |
| 4 | 1.1303 | 1.1947 | 1.0851 | 1.0479 | 1.0280 |
| 9 | 1.0669 | 1.0413 | 1.0000 | 0.9378 | 0.8846 |
| 14 | 0.9852 | 0.9461 | 0.8939 | 0.8129 | 0.7403 |
| 19 | 0.8846 | 0.8346 | 0.7659 | 0.6842 | 0.5835 |
| 24 | 0.8346 | 0.7132 | 0.6690 | 0.5642 | 0.4522 |
| 29 | 0.7533 | 0.669 | 0.5228 | 0.3979 | 0.3010 |
| $k' \times 10^4, (s^{-1})$ | 5.8899 | 7.3204 | 8.7026 | 10.1595 | 11.6398 |
| $k_2 \times 10^2$ (mol ⁻¹ dm ³ s ⁻¹) | 2.9449 | 2.9281 | 2.9008 | 2.9027 | 2.9099 |

[PMS] = $2 \times 10^{-3} \text{ mol dm}^{-3}$; $[H^+] = 0.02 \text{ mol dm}^{-3}$; $\mu = 0.3 \text{ mol dm}^{-3}$; Ethanol = 50 % (v/v);

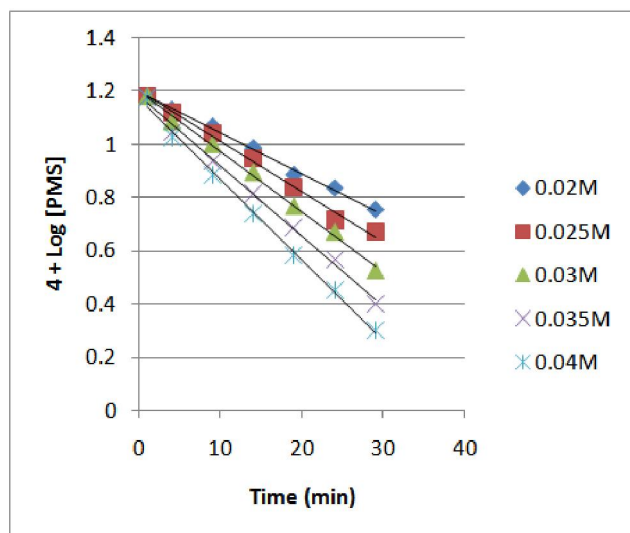


Fig. 1. Variation of [3-MI] @ 293 K

This was confirmed by the linear plots of $k'(s^{-1})$ vs [3-MI] passing through origin ($r = 0.999$) (Fig. 2). Such a kinetic behaviour indicates the absence of any self-decomposition of PMS¹⁶. The experiments were carried out at various temperatures 288 K and 283 K and the rate constant values of k' and k_2 were tabulated (Table 2). The value of k_2 (mol⁻¹ dm³ s⁻¹) was evaluated from the slope of $k'(s^{-1})$ vs [3-MI] plots. The k_2 (mol⁻¹ dm³ s⁻¹) values were calculated from the values of k' using the formula $k' (s^{-1})/[3-MI]$.

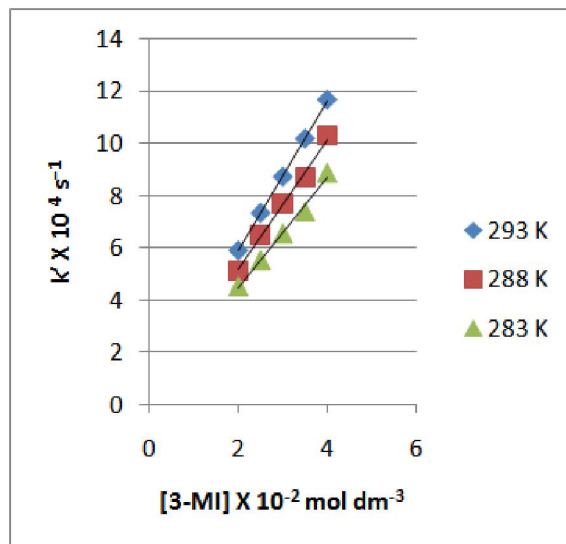


Fig. 2; Evaluation of k_2

Effect of [PMS]

It is observed that the reaction rate was unaffected as evident from the constant slopes of log [PMS] vs time plots for various [PMS] ($1.0 \times 10^{-3} - 4.0 \times 10^{-3} \text{ mol dm}^{-3}$) at fixed [3-MI]₀, $[H^+]_0$, μ , and percentage of ethanol (Table 3 & Fig. 3). This observation confirms the first-order dependence of rate on [PMS].

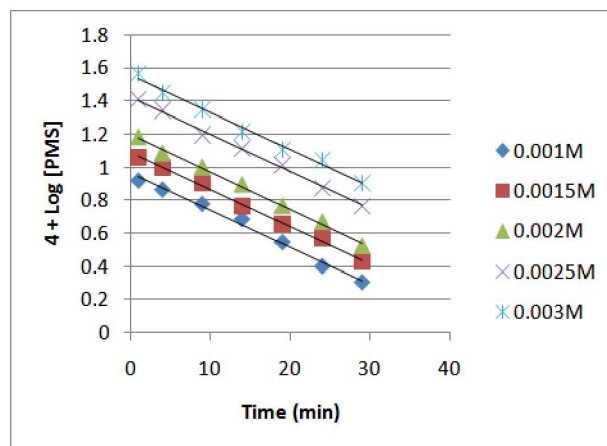


Fig.3; Variation of [PMS] @ 293 K

Table 2. Calculation of k' and k_2

| [3-MI]x10 ² , mol dm ⁻³ | 283 K | | 288 K | | 293 K | |
|--|--------------------------|--|--------------------------|--|--------------------------|--|
| | $k' \times 10^4, s^{-1}$ | $k_2 \times 10^2 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ | $k' \times 10^4, s^{-1}$ | $k_2 \times 10^2 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ | $k' \times 10^4, s^{-1}$ | $k_2 \times 10^2 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ |
| 2.0 | 5.8899 | 2.9449 | 5.3120 | 2.6560 | 4.5229 | 2.2614 |
| 2.5 | 7.3204 | 2.9281 | 6.5008 | 2.6003 | 5.5183 | 2.2073 |
| 3.0 | 8.7026 | 2.9008 | 7.6851 | 2.5617 | 6.5323 | 2.1774 |
| 3.5 | 10.1595 | 2.9027 | 9.2574 | 2.6449 | 7.3803 | 2.1086 |
| 4.0 | 11.6398 | 2.9099 | 10.2839 | 2.5708 | 8.8484 | 2.2121 |
| | Overall k_2 @283 K | 2.9173 | Overall k_2 @288 K | 2.6067 | Overall k_2 @293 K | 2.1934 |

[PMS] = $2 \times 10^{-3} \text{ mol dm}^{-3}$; $[H^+] = 0.02 \text{ mol dm}^{-3}$; $\mu = 0.3 \text{ mol dm}^{-3}$; Ethanol = 50 % (v/v);

Table 3. Effect of [PMS] at 293 K

| [PMS] (10^{-3} mol dm $^{-3}$) | k' (10^4 s $^{-1}$) |
|------------------------------------|-------------------------|
| 1.0 | 8.6991 |
| 1.5 | 8.6745 |
| 2.0 | 8.7026 |
| 2.5 | 8.6960 |
| 3.0 | 8.7057 |

[3-MI] = 3×10^{-2} mol dm $^{-3}$; [H $^{+}$] = 0.02 mol dm $^{-3}$;
 μ = 0.3 mol dm $^{-3}$; Ethanol = 50 % (v/v);

Effect of μ

The influence of ionic strength (μ) maintained by the addition of sodium sulphate on the reaction rate was found to be negligible (Table 4). This shows that the reaction occurs between a neutral species namely the 3-methylindole molecule and the mononegative ion HSO $_5^-$, the active species of the oxidant.

Table 4. Effect of [μ] and [H $^{+}$] at 293 K

| [μ] ^a (mol dm $^{-3}$) | k' (10^4 s $^{-1}$) | [H $^{+}$] ^b (10^{-2} mol dm $^{-3}$) | k' (10^4 s $^{-1}$) |
|--|-------------------------|---|-------------------------|
| 0.1 | 8.7380 | 0.5 | 8.7165 |
| 0.2 | 8.6661 | 1.0 | 8.6904 |
| 0.3 | 8.7026 | 2.0 | 8.7026 |
| 0.4 | 8.6819 | 3.0 | 8.7125 |

^a[3-MI] = 3×10^{-2} mol dm $^{-3}$; [PMS] = 2×10^{-3} mol dm $^{-3}$; [H $^{+}$] = 0.02 mol dm $^{-3}$;
 Ethanol = 50 % (v/v);

^b[3-MI] = 3×10^{-2} mol dm $^{-3}$; [PMS] = 2×10^{-3} mol dm $^{-3}$; μ = 0.3 mol dm $^{-3}$;
 Ethanol = 50 % (v/v);

Effect of [H $^{+}$]

The reaction rates measured at constant [3-MI], [PMS], μ , and percentage of ethanol but with various [H $^{+}$] (5×10^{-3} – 3×10^{-2} mol dm $^{-3}$) were found to be the same (Table 4). Such a kinetic behaviour indicates the nonexistence of any protonation equilibrium with respect to both PMS and 3-methylindole under the present experimental conditions employed.

Effect of Dielectric Constant

So as to determine the effect of dielectric constant (polarity) of the medium on rate, the oxidation of 3-MI by PMS was studied in aqueous ethanol mixtures of various compositions (Table 5). The data clearly reveals that the rate increases with decrease in the percentage of ethanol, i.e. with increasing dielectric constant or polarity of the medium, and lead to the inference that there is a charge development in the transition state involving a more polar activated complex than the reactants¹⁷, a neutral molecule (3-MI), and a mononegative ion (HSO $_5^-$) suggesting a polar (ionic) mechanism.

Table 5. Effect of EtOH percentage at 293 K

| % EtOH | k' (10^4 s $^{-1}$) |
|--------|-------------------------|
| 30 | 12.0730 |
| 40 | 9.5148 |
| 50 | 8.7026 |
| 60 | 6.7763 |

[3-MI] = 3×10^{-2} mol dm $^{-3}$; [PMS] = 2×10^{-3} mol dm $^{-3}$;
 μ = 0.3 mol dm $^{-3}$; [H $^{+}$] = 0.02 mol dm $^{-3}$;

Stoichiometry

Solutions of 3-MI containing an excess of PMS were kept overnight at room temperature. Titrimetric estimation of the concentration of PMS consumed and assuming that all the 3-MI taken had reacted, the stoichiometry of 3-MI: PMS was found to be 1:2.

Test for Free Radical Intermediates

The observed total second-order dependence of rate, beside first-order dependence each on both [3-MI] and [PMS], shows that the reaction involves a nonradical pathway. Moreover no polymer formation was observed when a freshly distilled acrylonitrile monomer was added to the deaerated reaction mixture indicating the absence of free radical intermediates.

Rate Law

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

$$-d[\text{PMS}]/dt = 2 k_2 [\text{PMS}][3\text{-MI}]$$

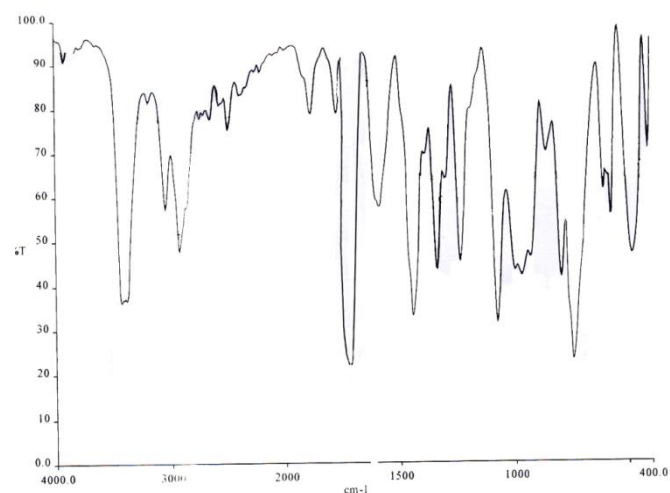
$$\text{rate} / [\text{PMS}] = k' (\text{s}^{-1}) = 2 k_2 [3\text{-MI}]$$

$$(i : e :) k^{-1} = 2 k_2 [3\text{-MI}]$$

where k' = pseudofirst order rate constant and k_2 = second order rate constant.

Product Analysis

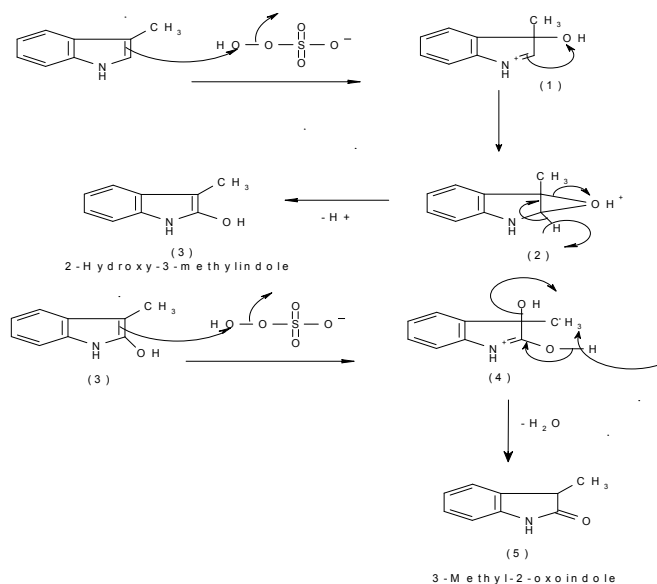
A reaction mixture containing slight excess of PMS and 3-MI dissolved in ethanol was kept aside at room temperature for a day, so that the substrate was completely converted into product. The mixture was extracted with ether. A resinous mass was obtained in the ether layer and it could not be identified. The aqueous layer was treated with acetone and then with methanol. The final product was obtained from the alcoholic solution and identified by IR (Fig. 4) and NMR spectra. The above product was identified as 3-methyloxindole from IR frequencies at 1720 cm^{-1} for C=O (str), at 3400 cm^{-1} for N-H (str). The proton NMR spectrum of the product obtained in our experiment showed distinctly different features from that of the starting material, 3-MI. That is the product spectrum exhibited signals at $\delta = 8.0$ corresponding to >NH, at $\delta = 6.8$ -7.3 corresponding to benzene aromatic ring and final signal at $\delta = 1.3$ corresponding to methyl group.



Mechanism

Based on the foregoing observations such as first-order dependence of rate each on [3-MI], [PMS], zero-order dependence on [H $^{+}$], negligible effect of [μ], and the stoichiometry, the following

mechanism is suggested: PMS exists as HSO_5^- ion in solution and the ion is weak nucleophile. It is suggested that the reaction proceeds through an electrophilic attack of the oxidant (PMS)¹⁴ at the nucleophilic site C3 of 3-MI by a mechanism involving displacement of sulphate ion to 3-hydroxy-3-methylindole (1) as the rate determining step. Compound (1) undergoes intramolecular rearrangement¹⁸ to give 2-hydroxy-3-methylindole (3) through a cyclic intermediate (2). The second attack of PMS ion on compound (3) gives 2,3-dihydroxy-3-methylindole (4) which finally loses H_2O to give 3-methyl-2-oxoindole (5) as the product.



Rate and Activation Parameters

The effect of temperature on k' (s^{-1}) was studied in the range of 283–293 K and the results are shown in (Table 2). The Arrhenius plot of $\log k_2$ vs $1/T$ was linear. From the above plot, the values of energy of activation (E_a) was calculated (Fig. 5). The value of ΔS^\ddagger was computed from Eyring equation. The large negative value of entropy of activation (ΔS^\ddagger) obtained is attributed to the severe restriction of solvent molecules around the transition state¹⁹.

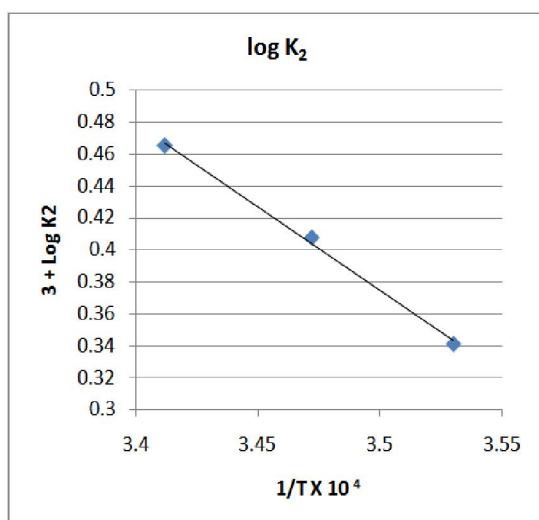


Fig. 5; Evaluation of E_a

| Thermodynamic parameters of Oxidation of 3-MI | | |
|---|-----------------------------------|---------|
| Energy of Activation (E_a) | kJ mol^{-1} | 20.088 |
| Enthalpy (ΔH^\ddagger) | kJ mol^{-1} | 17.652 |
| Entropy (ΔS^\ddagger) | $\text{J K}^{-1} \text{mol}^{-1}$ | -271.05 |
| Free Energy (ΔG^\ddagger) | kJ mol^{-1} | 97.070 |

Conclusion

3-MI and PMS reaction involves of a peroxo linkage, follows first order with respect to-3-MI and PMS and overall follows second order reaction. The results indicate that there is no effect of ionic strength and $[\text{H}^+]$. From the results of dielectric effect a suitable mechanism scheme from the observations is proposed.

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