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RESEARCH ARTICLE

KINETIC AND MECHANISTIC INVESTIGATION OF OXIDATION OF 3-METHYLINDOLE BY PEROXODISULPHATE USING ETHANOL MEDIUM

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ABSTRACT

The kinetic studies of oxidation of 3-methylindole (3-MI) by Peroxodisulphate (PDS) has been carried out in ethanol medium. A total second order, first order first order each with respect to [3-MI] and [PDS] has been observed. The reaction was unaffected by increase of $[H^+]$. Increase of percentage of ethanol decreases the rate. Variation of ionic strength had no influence on the rate. Activation and thermodynamic parameters have been calculated from kinetic values. A suitable mechanism scheme based on these observations is proposed.

INTRODUCTION

Indoles possess significant biological activity (Shyadligeri and Gadaginamath 1995). Oxidation of indoles has received much attention due to the involvement of their resulting products in significant biological processes (Al-Kazwini *et al.,* 1991). 3-MI a degradation product of tryptophan formed in the rumen of cattle and goats and in the large intestine of humans is well-known as a highly selective pulmonary toxicant for ruminants (Carlson *et al.,* 1972). Metabolism and bioactivation of 3-MI by human liver microsomes have been reported that a total of eight oxidized metabolites were detected in human liver microsomes. Five of the metabolites were confirmed as 3-methyloxindole, 3-hydroxy-3-methylindolenine, 3-hydroxy-3-methylindole, 5-hydroxy-3-methylindole and 6-hydroxy-3-methylindole. Among the three newly identified metabolites, one is either 4- or 7-hydroxy-3-methylindole and the other two were derived from subsequent oxidation on the phenyl ring of 3-methyloxindole (Zhengyin Yan *et al.,* 2007). We have recently reported oxidation of 3-MI by peroxomonosulpahte to 3-methyl-2-oxindole (Stephen *et al.,* 2013). The oxidation of 2,3-dimethylindole by peroxodisulphate anions (PDS) to give 3-methylindole-3-carbaldehyde have been already reported in the literature (Balon *et al.,* 1993). In view of this, the present work is significant as it involves the reaction of a peroxo linkage containing oxidant namely PDS with 3-MI. The lack of kinetic and mechanistic investigation on the oxidation of 3-MI by PDS investigated us to carry out this work and is presented as a first report in this study.

MATERIALS AND METHODS

3-Methylindole from Sigma alrdich and Peroxodisulphate under the other name potassium persulphate from Qualigens of highest purity grade was used as such. Solutions of this salt were assayed iodometrically and by cerimetry (Maruthamuthu and Neta 1997). Other chemicals and reagents such as sulphuric acid, ethanol, 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^{0}C. 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 PDS in the temperature range of 303-323 K. The

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reaction was followed by estimating the unreacted PDS 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.

$S_2O_8^{2-}{}_{(aq)} + 2I^{-}{}_{(aq)} \rightarrow 2SO_4^{2-}{}_{(aq)} + I_{2(aq)}$

From the titre values, plots of log [PDS] vs time were made and from the slope of such plots, the pseudo first 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 PDS such as effects of (i) [3-MI], (ii) [PDS], (iii) ionic strength (μ), (iv) [H^+], and (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 303K by fixing constant [PDS], [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 (2.0×10^{-2} – 4.0×10^{-2} mol dm^{-3}). This shows that the reaction obeys first order with respect to [3-MI]. 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 PDS (Montgomery 1979). The experiments were carried out at various temperatures 313 K and 323 K and the rate constant values of **k′** and **k_2** were tabulated (Table 2). The value of **k_2** (mol^{-1} dm^3 s^{-1}) was evaluated from the slope of **k′**(s^{-1}) vs [3-MI] plots. The **k_2** (mol^{-1} dm^3 s^{-1}) values were calculated from the values of **k′** using the formula **k′** (s^{-1})/[3-MI].

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

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

[3-MI] x 10^{-2} mol dm^{-3}									
2.0		2.5		3.0		3.5		4.0	
Tim (min)	4+log [PDS]	Tim (min)	4+log [PDS]	Tim (min)	4+log [PDS]	Tim (min)	4+log [PDS]	Tim (min)	4+log [PDS]
1	1.7841	1	1.7841	1	1.7841	1	1.7829	1	1.7817
10	1.7805	10	1.7757	10	1.7708	10	1.7403	10	1.6857
20	1.6989	20	1.6812	20	1.6674	20	1.6384	20	1.5740
30	1.6266	30	1.5965	30	1.5603	30	1.5378	30	1.4286
60	1.4795	60	1.4259	60	1.3921	60	1.1949	60	1.1461
90	1.3256	90	1.2430	90	1.1249	90	0.8346	90	0.8346
180	0.8450	180	0.6020	180	0.3679	180	0.1760	150	0.1760
*k'*x10^4,s^{-1}	2.0472		2.5595		3.0717		3.5797		4.1048
k_2x10^2mol dm^{-3}	1.0236		1.0238		1.0239		1.0235		1.0262

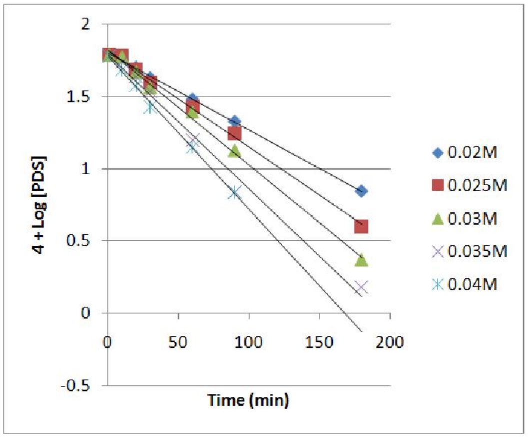


Fig. 1. Variation of [3-MI] @ 303 K

Table 2. Calculation of k′ and k_2

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

[3-MI]x10^{-2}, mol dm^{-3}	303 K		313 K		323 K	
	k′ x10^4,s^{-1}	k_2x$10^2$$mol^{-1}$$dm^3$$s^{-1}$	k′x10^4, s^{-1}	k_2x$10^2$$mol^{-1}$$dm^3$$s^{-1}$	k′x10^4, s^{-1}	k_2x$10^2$$mol^{-1}$$dm^3$$s^{-1}$
2.0	2.0472	1.0236	2.9805	1.4902	4.2013	2.1006
2.5	2.5595	1.0238	3.7260	1.4904	5.2547	2.1018
3.0	3.0717	1.0239	4.4726	1.4908	6.3092	2.1030
3.5	3.5822	1.0227	5.2173	1.4906	7.3525	2.1007
4.0	4.1048	1.0262	5.9636	1.4909	8.4022	2.1005
	Overall *k_2* @303 K	1.0240	Overall *k_2* @313 K	1.4906	Overall *k_2* @323 K	2.1013

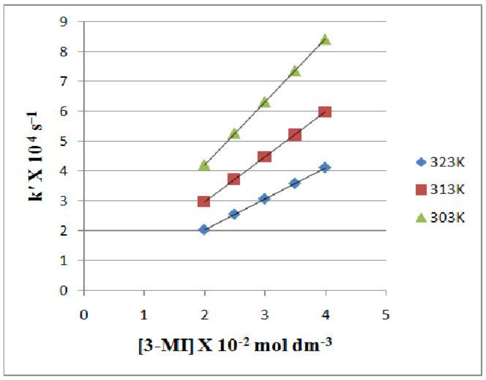


Fig. 2. Evaluation of *k_2*

Effect of [PDS]

It is observed that the reaction rate was unaffected as evident from the constant slopes of log [PDS] Vs time plots for various [PDS] ($1.0 \times 10^{-2} - 4.0 \times 10^{-2}$ mol dm^{-3}) at fixed [3-MI], [H$^+$], μ, and percentage of ethanol (Table 3 & Fig. 3). This observation confirms the first-order dependence of rate on [PDS].

Table 3. Effect of [PDS] at 303 K

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

[PDS] (10^{-2} mol dm^{-3})	k ' (10^4 s^{-1})
1.0	3.0766
1.5	3.0709
2.0	3.0717
2.5	3.07522
3.0	3.07194

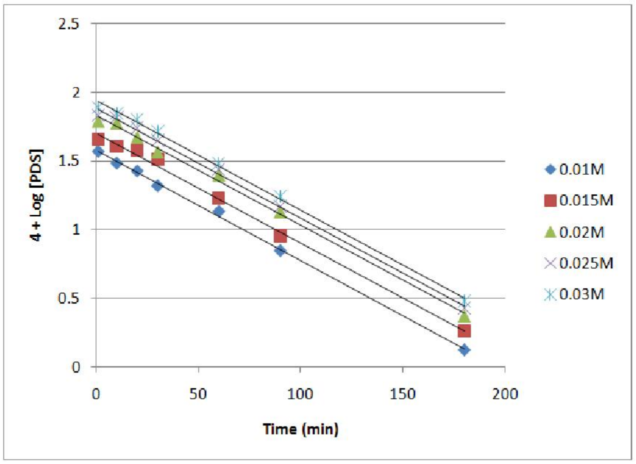


Fig. 3. Variation of [PDS] @ 303 K

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 negative ion $S_2O_8^{2-}$, the active species of the oxidant.

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

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

[μ] (mol dm^{-3})[a]	k ' (10^{4}s^{-1})	[H$^+$] (10^{-2} mol dm^{-3})[b]	k ' (10^{4}s^{-1})
0.1	3.0707	0.5	3.0752
0.2	3.0707	1.0	3.0704
0.3	3.0717	2.0	3.0717
0.4	3.07039	3.0	3.0738

Effect of [H$^+$]

The reaction rates measured at constant [3-MI], [PDS], μ, and percentage of ethanol but with various [H$^+$] (5×10^{-3} - 3 x 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 PDS and 3-methyindole 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 PDS 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 reactants (Laidler 1965), a neutral molecule (3-MI), and a dinegative ion ($S_2O_8^{-2}$) suggesting a polar (ionic) mechanism.

Table 5. Effect of EtOH percentage at 293 K

[3-MI] = 3 x 10^{-2} mol dm^{-3}; [PDS] = 2 x 10^{-2} mol dm^{-3}; μ = 0.3 mol dm^{-3}; [H+] = 0.02 mol dm^{3}

% EtOH	k ' (10^4 s^{-1})
30	3.8527
40	3.1948
50	3.0717
60	3.0020

Stochiometry

Solutions of 3-MI containing an excess of PDS were kept overnight at room temperature. Titrimetric estimation of the concentration of PDS consumed and assuming that all the 3-MI taken had reacted, the stoichiometry of 3-MI: PDS 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 [PDS], 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 PDS is given as follows:

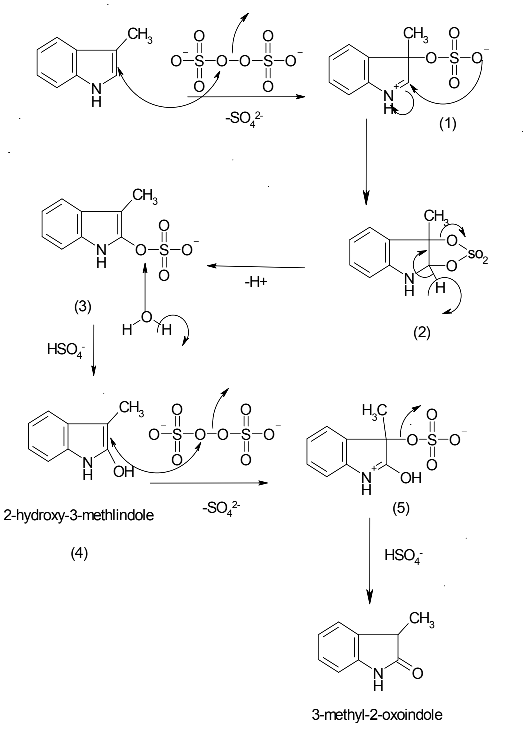
$-d[PDS]/dt = \boldsymbol{k_2}\,[PDS][3\text{-}MI]$
$\text{rate} / [PDS] = k'(s^{-1}) = \boldsymbol{k_2}[3\text{-}MI]$
(i : e :) $k^{-1} = \boldsymbol{k_2}[3\text{-}MI]$
where **k′** = pseudo-first order rate constant and $\mathbf{k}_2$ = second order rate constant.

Product Analysis

A reaction mixture containing slight excess of PDS 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 resinuous 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 and NMR spectra. The above product was identified as 3-methyloxoindole from IR frequencies at 1720 cm^{-1} for C=O (str), at 3400 cm^{-1} for N-H (str).

Mechanism

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



Our result suggest that the reaction proceeds through an electrophilic attack of the oxidant (PDS) exists as $S_2O_8^{-2}$ ion in solution at the nucleophilic site C3 of 3-MI by a mechanism involving displacement of sulphate ion to form compound (1) as the rate determining step. Compound (1) undergoes intramolecular rearrangement **(**Jackson and Lynch 1987**)** to give 2-hydroxy-3-methylindole (4) through a cyclic intermediate (2). The second attack of PDS ion on compound (4) gives Compound (5) which finally loses HSO_4^- to give 3-methyl-2-oxoindole as the product.

Rate and Activation Parameters

The effect of temperature on **k′** (s^{-1}) was studied in the range of 303 – 323 K and the results are shown in (Table 2). The Arrhenius plot of log $\mathbf{k}_2$ vs 1/**T** was linear. From the above plot, the values of energy of activation ($\mathbf{E}_a$) was calculated (Fig. 5). The value of $\Delta \mathbf{S}^{\#}$ was computed from Eyring equation. The large negative value of entropy of activation ($\Delta \mathbf{S}^{\#}$) obtained is attributed to the severe restriction of solvent molecules around the transition state **(**Anis 1992**).**

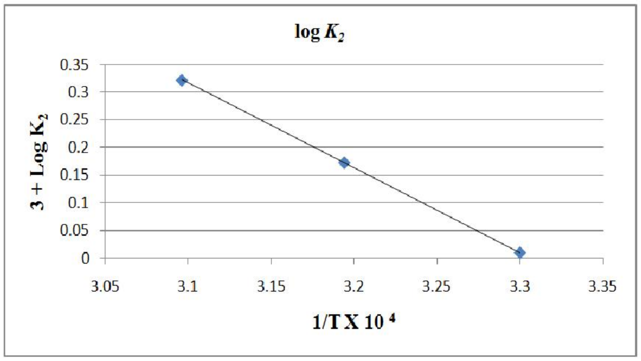


Fig. 5.Evaluation of Ea

Thermodynamic parameters of Oxidation of 3-MI		
Energy of Activation (Ea)	$kJmol^{-1}$	29.302
Enthalpy ($\Delta H^{\#}$)	$kJ\ mol^{-1}$	26.782
Entropy ($\Delta S^{\#}$)	$J\ K^{-1}\ mol^{-1}$	-194.74
Free Energy ($\Delta G^{\#}$)	$kJ\ mol^{-1}$	85.79

Conclusion

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

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