International Journal of Pharmaceutical Chemistry

KINETICS AND MECHANISM OF *MESO*-TETRAPHENYLPORPHYRINIRON(III) CHLORIDE (TPP) CATALYSED OXIDATION OF INDOLE BY MAGNESIUMMONO PEROXYPHTHALATE

D. Kungumathilagam[a] and **K. Karunakaran**[b*]

[a] Department of Chemistry, VMKV Engineering College, Salem-636 308, India.
[*b]Department of Chemistry, Sona College of Technology, Salem-636 005, India.

Corresponding author*: thilagamchem@gmail.com

ABSTRACT:
Mechanistic study on *meso*- tetraphenylporphyriniron(III) chloride (TPP) catalysed oxidation of indole by magnesiummonoperoxyphthalate in aqueous acetonitrile medium have been carried out. The reaction follows a fractional order with respect to substrate and catalyst. The order with respect to oxidant was found to be one. Increase in percentage of acetonitrile and increase in the concentration of [H^+] decreased the rate.The reaction fails to initiate polymerization, and a radical mechanism is ruled out. Activation and thermodynamic parameters have been computed. A suitable kinetic scheme based on these observations is proposed. Significant catalytic activity is observed for the reaction system in the presence of TPP.

Keyword: Indole, magnesiummonoperoxyphthalate, *meso*- tetraphenylporphyriniron (III) chloride, kinetics, mechanism, oxidation.

1. Introduction

Indole, an electron-rich heteroaromatic nitrogen compound, is found in many naturally occurring compounds such as various plant alkaloids and fungal metabolites [1,2] usually as metabolites of tryptophan. Indole, on oxidation gives products which are involved in significant biological processes[3]. Indoles possess significant biological activity [4,5]. Lawson and Witkop have shown that N-bromosuccinimide can be used to convert indoles to

oxindoles[6,7]. Rangappa et al[8] have examined the kinetics of oxidation of indole by chloramines-T in the presence of Os(VIII) in alkaline medium. Peroxomonosulphate can also used to convert indoles to oxindoles[9]. Among the oxygen donors, towards oxidation, magnesium monoperoxyphthalate (MMPP) was recently found to be a very efficient oxidant [10].

Oxidation of organic compounds catalysed by synthetic metalloporphyrin complexes has been one of the hot areas in chemistry during the last decade[11]. The metalloporphyrins can catalyse the oxidation of a variety of organic substrates with many different terminal oxidants[11,12]. The catalytic properties of the transition metal porphyrins are due to the fact that an oxo-transition metal porphyrin intermediate is formed, which can transfer the oxygen atom to a substrate or can accept an electron from the substrate[11]. Many stable oxo-transition metal complexes are known and have been characterized, but several of these complexes are inert and non-reactive as oxygen transfer reagents. Groves and coworkers[13] described the use of *meso*-tetraphenylporphyriniron(III) chloride (TPP) in combination with the lipophilic iodosylbenzene, first used in vivo by Ullrich, for the epoxidation of olefins, and the hydroxylation of alkanes.

Literature survey reveals that no report was available on the kinetics of oxidation of *meso*-tetraphenylporphyriniron(III) chloride catalysed oxidation of indole, hence we have carried out this work with magnesiummonoperoxyphthalate (MMPP).

2. Experimental

2.1. Material: All the chemicals and solvents used were of analytical grade (Merck, India). Indole, magnesiummonoperoxyphthalate (MMPP) and TPP (Sigma Aldrich) were used as such. All the solutions used in the study were made by using doubly distilled water. All the reagents were prepared freshly and used in the reaction. All the reactions were carried out in a thermostat and the temperature was controlled to ± 0.1°C. Aqueous solution of magnesium monoperoxyphthalate was prepared fresh using double distilled water and standardized iodometrically.

2.2. Kinetic measurements: The kinetic studies were carried out in an aqueous acetonitrile medium. The reactions were performed by maintaining a large excess of [indole] over [MMPP]. The reaction mixture was homogeneous throughout the course of the reaction. The reaction's progress was monitored for atleast two half-lives by iodometric estimation of unchanged oxidant at regular time intervals. The rate constants (k_{obs}) were evaluated from the slopes of linear plots of log[titre] *versus* time. Replicate runs showed that the rate constants of oxidation reactions were reproducible within ± 3%.

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

2.4. Product analysis: The reaction mixture after 48 h, was extracted with chloroform, dried over anhydrous Na_2SO_4 and then evaporated. The residual brown solid obtained was subjected to column chromatography using silica gel and eluted with benzene and then evaporated. The melting point of the compound was found to be 116-118°C confirms oxindole (literature value is 118-120°C) as the main product of the reaction. The product was also confirmed by UV-Visible absorption spectra at λ_{max} of 407 nm (Fig. 6) which is in agreement with literature values[9].

2.5. Data analysis: Correlation studies were carried out using Microcal origin (version 6) computer software. The goodness of the fit was discussed using the correlation coefficient, r, in the case of simple linear regression and R in the case of multiple linear regressions.

3. Results and discussion

Factors influencing the rate of TPP catalysed oxidation of indole by magnesium monoperoxyphthalate such as [indole] , [MMPP], [TPP], [H^+] and dielectric constant have been studied. Rate and activation parameters were evaluated.

3.1. Effect of [indole]: At a constant [MMPP], [TPP], [H^+], and fixed percentage of acetonitrile, kinetic runs were carried out with various initial concentrations of indole, which yielded rate constants whose values depended on [indole]. The pseudo-first order rate constants (k_{obs}) thus obtained were found to increase with [indole] (Table 1) over a range of [indole] used (4.0 - 8.0 x 10^{-3} mol dm^{-3}). The plot (Fig. 1) of $\log k_{obs}$ *versus* log[indole] is linear with a slope of 1.57 showing that the reaction is fractional order in [indole]. The plot (Fig. 2) of $1/k_{obs}$ *versus* 1/[indole] is linear with definite intercept on the rate ordinate, which indicates the operation of Michalis-Menton mechanism, where K_3 is the equilibrium constant for the formation of Michalis-Menton complex, and k_4 the rate constant for the decomposition of Michalis-Menton complex. Usually first step is a fast pre-equilibrium and the electron transfer step is rate determining[14].

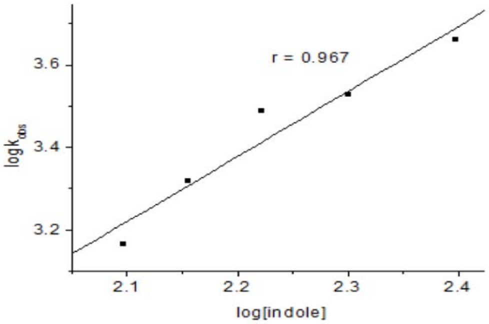


Figure. 1 Plot of $\log k_{obs}$ *versus* log[Indole] for TPP catalysed oxidation of indole by magnesium monoperoxyphthalate in acetonitrile medium.

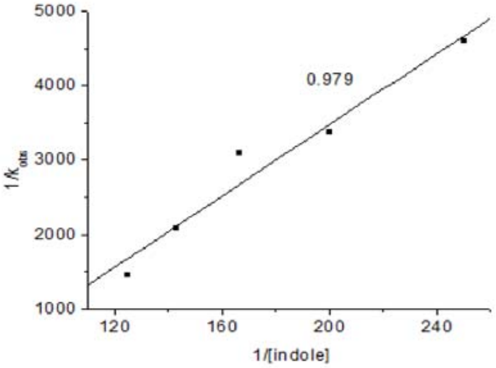


Figure. 2 Plot of $1/k_{obs}$ *versus* 1/[indole] for TPP catalysed oxidation of indole by magnesiummonoperoxyphthalate in acetonitrile medium.

3.2. Effect of [MMPP]: The order of the reaction with respect to MMPP was to be strictly unity as shown by the linearity of log[MMPP] *versus* time plots. The reaction rate was unaffected as evident from the constant slopes of log[MMPP] *versus* time plots for various [MMPP] (6.0 - 8.0 x 10^{-4} mol dm^{-3}) at fixed [indole], [TPP], [H^+] and fixed percentage of acetonitrile (Table 1) confirms the first order dependence of the reaction rate on MMPP.

3.3. Effect of [TPP]: At a constant [indole], [MMPP], [H^+] and fixed percentage of acetonitrile, kinetic runs were carried out with various initial concentrations of [TPP], which yielded rate constants whose values depended on [TPP]. The pseudo-first order rate constants (k_{obs}) thus obtained were found to increase with [TPP] (Table 1) over a range of [TPP] used (2.0 - 6.0 x 10^{-8} mol dm^{-3}). A linear plot was obtained between $\log k_{obs}$ and log[TPP] (Fig. 3) with a slope of 0.69, indicating that the order of the reaction with respect to catalyst was fractional.

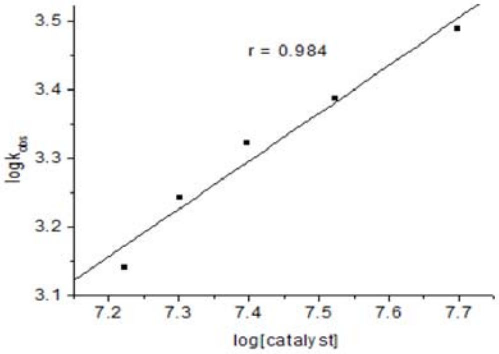


Figure. 3 Plot of $\log k_{obs}$ *versus* log [catalyst] showing the effect of catalyst concentration on reaction rate.

3.4. Effect of [H^+]: The reaction rates measured with various [H^+] (3.2 – 40.0 x 10^{-2} mol dm^{-3}) and were found to decrease with increase of [H^+] ion concentration (Table 2). This shows that added [H^+] retards the rate of reaction.

3.5. Effect of dielectric constant: In order to determine the effect of dielectric constant (polarity) of the medium on rate, the oxidation of indole by MMPP was studied in aqueous acetonitrile mixtures of various compositions (Table 3). The data clearly reveals that the rate increases with decrease in the percentage of acetonitrile, i.e. with increasing dielectric constant or polarity of the medium and leads to the influence that there is a charge development in the transition state involving a more polar activated complex than the reactants[15-17], a neutral molecule [indole], and a mono negative ion (HSO_5^-) suggesting a polar (ionic) mechanism.

3.6. Test for free radical intermediates: No turbidity was observed when a freshly distilled acrylonitrile monomer was added to the deaerated reaction mixture indicating the absence of free radical intermediates.

3.7. Rate and activation parameters: The effect of temperature was studied in the range of 283 – 323 K and the results were shown in Table 4. The Arrhenius plot of $\ln k_{obs}/T$ *versus* 1/T was found to be linear (Fig 4). The value of energy of activation(E_a) was found to be 12.75 kJ mol^{-1} K^{-1} and $\Delta H^\# = 10.23$ kJ mol^{-1}, $\Delta S^\# = -185.29$ J K^{-1} mol^{-1}, $\Delta G^\# = 66.37$ kJ mol^{-1}. The large negative value of entropy of activation ($\Delta S^\#$) obtained is attributed to the severe restriction of solvent molecules around
the transition state[18].

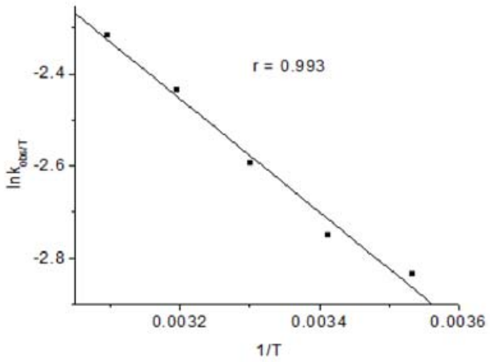


Figure. 4 Plot of $\ln k_{obs}$ / T *versus* 1/T showing the effect of temperature on reaction rate.

3.8. Rate law

$$\text{Rate} = k_4[C_2]$$

$$\frac{k_4K_3[\text{sub}]}{1 + K_3[\text{sub}]} = \frac{k_4K_3K_1[\text{sub}]\,[\text{cat}]\,[\text{oxi}]}{\{1 + K_3[\text{sub}]\}\,\{1 + K_1[\text{Cat}]\}}$$

Mechanism: In the present investigation no observed polymerization in the presence of acrylonitrile rules out a free radical process. Hence ionic mechanism was favoured in this study. Increase of [H^+] ion concentration decreased the rate. This showed that liberation of [H^+] during the reaction. The Michaelis-Menton dependence of the oxidation rate on [indole] confirms the formation of complex in a rapid pre-equilibrium. The first step is the formation of a complex between MMPP and TPP. This complex immediately decomposed and gives Por-Fe^v=O is in agreement with the literature study[19]. This Por-Fe^v=O may further react with the indole to form a complex (Fig. 5) at 602 nm, which would give the product in the next step (Fig. 6).This type of product was already reported[9]. The oxygen transfer step is associated with large negative value of entropies of activation and significant enthalpies of activation. The catalytic activity of TPP is significant, and this conversion exhibits fractional order. The plot of log [catalyst] *versus* $\log k_{obs}$ is found to be linear. In accordance with the above observations and stoichiometry of the reaction, the following reactions are involved to constitute the most probable mechanism of the reaction (scheme 1).

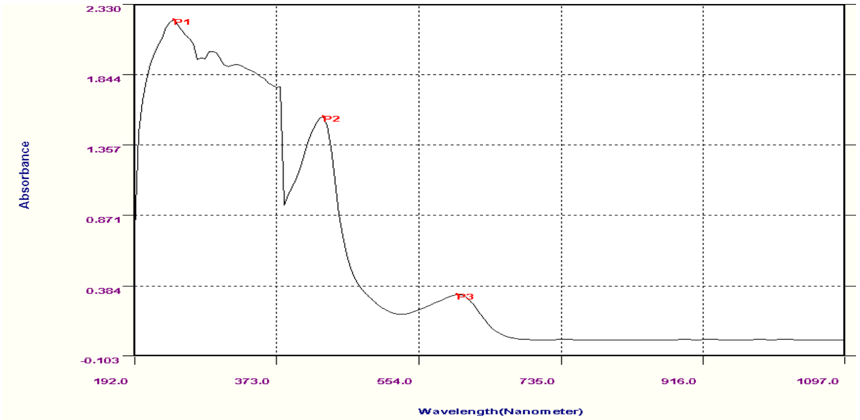


Figure. 5 UV spectrum showing formation of intermediate complex at 602 nm between indole and PorFe^{v}=O.

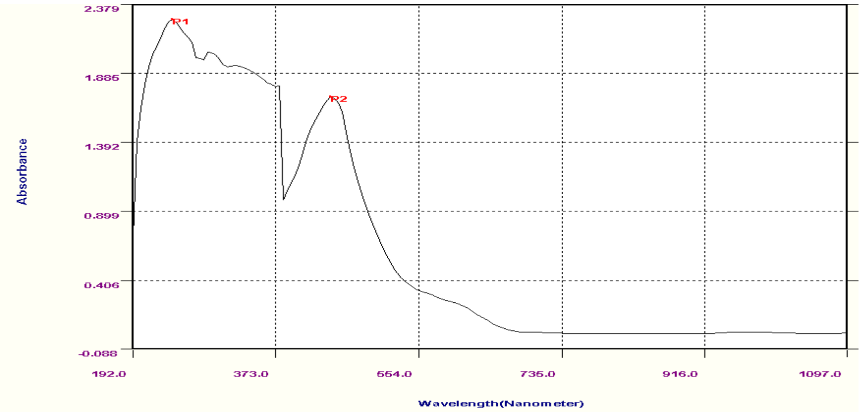
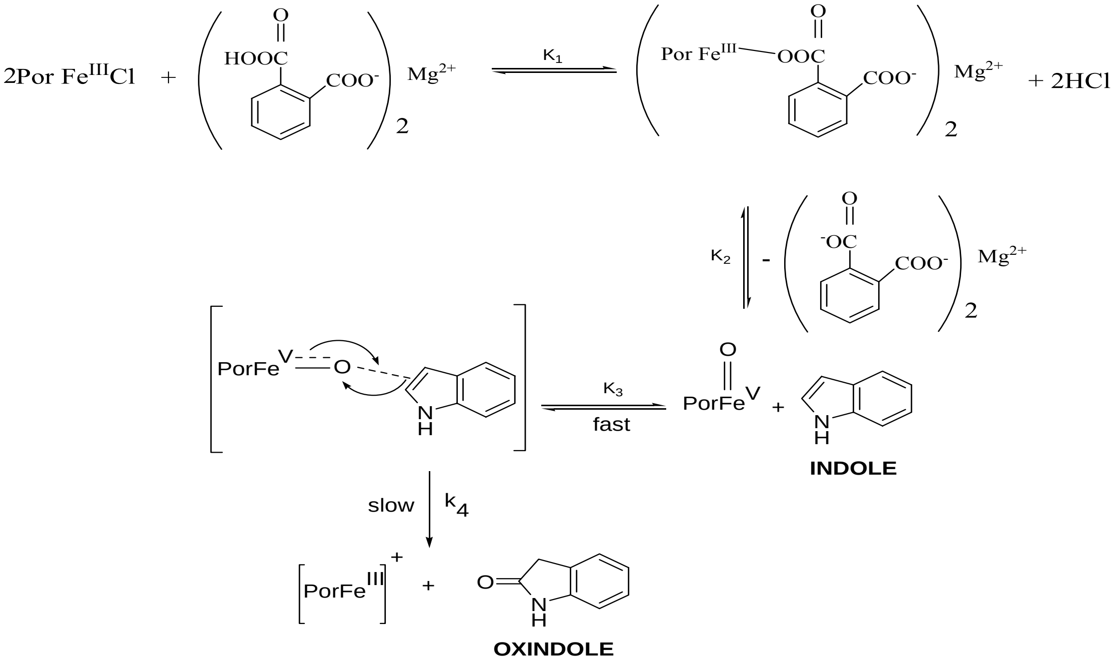


Figure. 6 UV spectrums showing the formation of product at 407 nm after the decomposition of intermediate complex at 602 nm.



Scheme 1. Probable mechanism for the *meso*-tetraphenylporphyriniron(III) chloride catalysed oxidation of indole by magnesiummonoperoxyphthalate

Table 1. Pseudo-first order rate constants for the TPP catalysed oxidation of indole by magnesium monoperoxyphthalate at 303K.

[indole] x 10^3 (mol dm^{-3})	[MMPP] x 10^4 (mol dm^{-3})	[TPP] x 10^8 (mol dm^{-3})	CH_3CN % (V/V)	k_{obs} x 10^4 (s^{-1})
4.0	6.0	2.0	80	2.18
5.0	6.0	2.0	80	2.96
6.0	6.0	2.0	80	3.24
7.0	6.0	2.0	80	4.81
8.0	6.0	2.0	80	6.85
6.0	6.5	2.0	80	3.51
6.0	7.0	2.0	80	3.13
6.0	7.5	2.0	80	2.97
6.0	8.0	2.0	80	3.17
6.0	6.0	3.0	80	4.11
6.0	6.0	4.0	80	4.76
6.0	6.0	5.0	80	5.73
6.0	6.0	6.0	80	7.22

Table 2. Effect of [H$^+$] concentration on the reaction rate.

[H$^+$] x 10^2 (mol dm^{-3})	k_{obs} x 10^4 (s^{-1})
3.2	7.76
6.4	6.96
9.6	5.28
12.8	4.96
40.0	4.13

[MMPP] = 6.0 x 10^{-4} mol dm^{-3}, [indole] = 6.0 x 10^{-3} mol dm^{-3}, [TPP] = 2.0 x 10^{-8}mol dm^{-3}, Acetonitrile:water = 40:10, Temperature = 303K

Table 3. Effect of dielectric constant on the reaction rate at 303K.

$CH_3CN:H_2O$	D^a	k_{obs} x 10^4 (s^{-1})
90:10	41.47	0.31
80:20	45.48	2.09
70:30	49.71	2.76
60:40	53.83	5.42
50:50	57.95	8.95

[MMPP] = 6.0 x 10^{-4} mol dm^{-3}, [indole] = 6.0 x 10^{-3} mol dm^{-3}, [TPP] = 2.0 x 10^{-8}mol dm^{-3},
[a] values are calculated from the values of pure solvent.

Table 4. Effect of temperature on reaction rate:

Temp. (K)	283	293	303	313	323
k_{obs} x 10^4 (s^{-1})	0.83	1.37	3.24	7.72	14.9

[MMPP] = 6.0 x 10^{-4} mol dm^{-3}, [indole] = 6.0 x 10^{-3} mol dm^{-3}, [TPP] = 2.0 x 10^{-8}mol dm^{-3}, Acetonitrile:water = 40:10.

References

1. Sundberg RJ, Kirk-othmer, Indole. Encyclopedia of Chemical Technology, Wiley, NewYork., 1995.
2. Goyal RN, Sangal A, *Electrochim Acta.,* 2005; 50: 2135.
3. Al- kazwini AT, O'Neill P, Adams GE, Cundall RB, Lang G, Junino A, *J. Chem.soc., perkin Trans 2.,* 1991; 1941.
4. Al-kazwini AT, O'Neill P, Adams GE, Cundall RB, Junino A, Maignan J, *J. Chem. Soc., Perkin Trans 2.,* 1992; 657.
5. Krylov SN, Dunford HB, *J. Phys. Chem.,* 1996; 100: 913.
6. Lawson WB, Witkop B, *J. Org. Chem.,* 1961; 26: 263.
7. Finch N, Taylor WE, *J. Am. Chem Soc.,* 1962; 84: 3871.
8. Rangappa KS, Esterline DT, Mythily CK, Mahadevappa DS, Ambedkar SY, *Polyhedron.,* 1993; 12: 1719.
9. Meenakshisundaram SP, Sarathi N, *Int. J. Chem. Kinet.,* 2007; 39: 46.
10. Baciocchi E, Lanzalunga O, Lapi A, *Tetrahedron lett .,* 1995; 36: 3547.
11. Meunier, *Chem Rev.,* 1992; 92: 1411.
12. Larsen J, Jorgensen KA, *J. Chem. Soc. Perkin Trans 2.,* 1992; 1213.
13. Groves JT, Nemo TE, Myers RS, *J. Am. Chem. Soc.,* 1979; 101: 1032.
14. Bhuvaneshwari DS, Elango KP, *J. Indian. Chem. Soc.,* 2009; 86: 242.
15. Laidler KJ, Chem. Kinet, Tata-Mcgraw Hill, New Delhi. 1965.
16. Ruff F, Kucsman A, *J. Chem. Soc, Perkin Trans 2.,* (1985); 683.
17. Meenakshisundaram SP, Sokalingam RM, *Collect. Czech. Chem. Commun.,* 2001; 66: 897.
18. Meenakshisundaram SP, Selvaraju M, Made gowda NM, Rangappa KS, *Int. J. Chem. Kinet.,* 2005; 37: 649.
19. Zhou XT, ji HB, Yuan QL, *J. Porphyr. Phthalocya.,* 2008; 12: 94.