RESEARCH ARTICLE

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KINETICS OF OXIDATION OF PHENYLEPHRINE BY CHLORAMINE-B IN $HClO_4$ MEDIUM - A MECHANISTIC APPROACH

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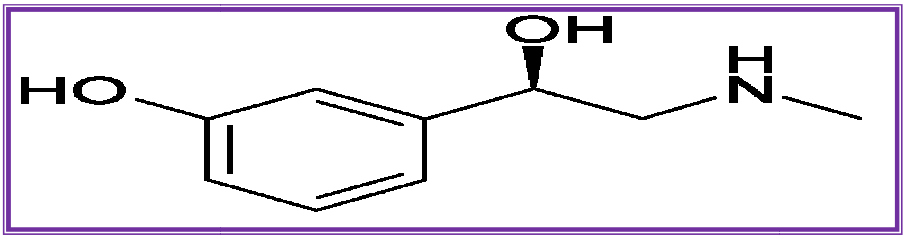
Abstract: Kinetics of oxidation of phenylephrine(PHE) by N-chlorobenzene sulphonamide or chloramine-B (CAB) has been carried out in $HClO_4$ medium at 303K. The reaction exhibits first order dependence of rate on chloramine-B and fractional order dependence of rate on both phenylephrine and [$HClO_4$]. The addition of halide ions and reduction product of CAB have no significant effect on the reaction rate. There is a negative effect of dielectric constant of the medium. The reaction rate remained unchanged with the variation of ionic strength of the medium indicating that non ionic species are involved in the rate determining step. The reaction fails to initiate the polymerization of acrylamide. Activation parameters have been computed from the Arrhenius plots. Michaelis-Menten type of kinetics has been proposed. The reaction stoichiometry and oxidation products were identified. The proposed mechanism and derived rate equation are consistent with the observed kinetic data.

Keywords: Kinetics, Oxidation, Chloramine-B, Phenylephrine

INTRODUCTION

Phenylephrine (3-[1-hydroxy-2-(methylamino)ethyl]phenol) is a powerful vasoconstrictor and is used to relieve nasal congestion and maintain blood pressure during anesthesia. Following oral administration, nasal decongestion may occur within 15 or 20 minutes and may persist for up to 4 hours. Phenylephrine's effectiveness as a decongestant stems from its vasoconstriction of nasal blood vessels, thereby decreasing blood flow to the sinusoidal vessels, leading to decreased mucosal edema[1].The structure of phenylephrine is as follows:



N-haloamines are mild oxidants and generally undergo a two electron change per mole in its reactions. They act as sources of halonium cations, hypohalite species and N-anions, which act both as bases and nucleophiles[2]. A prominent member of this class is chloramines-T (CAT), which is a byproduct during saccharin manufacture and is a well known analytical reagent for the determination of diverse substrates. Mechanistic aspects of many of these reactions have been documented. The other member of chloramines, chloramines-B(CAB, $C_6H_5SO_2NClNa.1.5H_2O$) is a stable compound and is found to be a better oxidizing reagent than its analogue CAT. There are many reports on N-halocompounds behaving as oxidizing agents[3-5]. However, a review of literature

shows that there are few reports on chloramine-B (CAB) as an oxidizing agent[6-8].

Literature survey shows that there is no information available on the kinetics and oxidation of PHE by any oxidizing agents from the mechanistic view point. There was a need for understanding the mechanism of oxidation of this drug. This study may throw some light on the metabolic conversions in the biological system. In the present communication we report our investigations of the kinetics and mechanistic aspects of the oxidation of PHE by chloramine-B in $HClO_4$ medium at 303K.

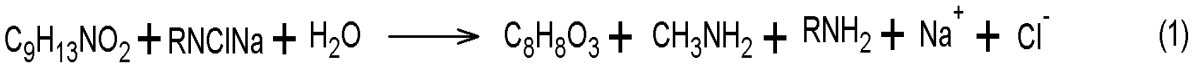
MATERIALS AND METHODS

An aqueous solution of CAB (E.Merck) was prepared[9], standardized iodometrically and stored in brown bottles to prevent any photochemical deterioration. The substrate phenylephrine (Biocon Ltd) was used as received. The aqueous solution of the substrate was prepared freshly each time. All the other chemicals used were of analytical grade. Doubly distilled water was used for all the measurements. The reactions were carried out under pseudo- first order conditions by keeping an excess of PHE over CAB. Appropriate amounts of the substrate, $HClO_4$ and water (to keep the total volume constant for all runs) were taken in a glass-stoppered pyrex boiling tube, and thermostated at 303K. A measured amount of CAB solution, also thermostated at the same temperature, was rapidly added to the mixture in the boiling tube. The progress of the reaction was monitored by iodometric estimation of unreacted CAB in a measured aliquot of the reaction mixture at different intervals of time. The course of the reaction was studied up to 75 to 80% completion. The rate constants were evaluated from the plots of log [CAB] against time. The

pseudo- first order rate constants (k') calculated were reproducible within + 4%.

Stoichiometry and Product Analysis

Varying ratios of phenylephrine and chloramine-B were equilibrated in the presence of 5.0 $x10^{-3}$ mol dm^{-3} $HClO_4$ for 24h at 303K. Determination of unreacted CAB in the reaction mixture showed that one mole of phenylephrine required one mole of CAB.



$$C_9H_{13}NO_2 + RNClNa + H_2O \longrightarrow C_8H_8O_3 + CH_3NH_2 + RNH_2 + Na^+ + Cl^- \quad (1)$$

(R = $C_6H_5SO_2$)

The reduction product of CAB, benzenesulphonamide was detected[10] by TLC using petroleum ether, chloroform and 1- butanol (2:2:1v/v/v) as the solvent and iodine as the reducing agent (R_f = 0.88). The reported R_f value is consistent with given R_f value in the literature. It was further confirmed by its melting point, IR & NMR spectral studies. The major oxidation product of phenylephrine, (2-hydroxy-2-(3-hydroxyphenyl)acetaldehyde) was detected by spot tests and further confirmed by IR spectral analysis which shows a strong peak at 1720 $cm^{-1}$and 3326cm^{-1}.The other oxidation product, methyl amine was identified by spot tests[11]. It was also observed that there was no further oxidation of these products under the present kinetic conditions.

RESULTS AND DISCUSSION

Effect of varying reactant concentrations

Under pseudo -first order conditions, with the substrate in excess, at constant [PHE], [$HClO_4$] and constant temperature, plots of log [CAB] versus time were linear indicating a first order dependence of the reaction rate on $[CAB]_0$. Values of pseudo-

first order rate constant ($k^{/}$) are given in Table 1. Further it was found these values are unaffected by a variation of $[CAB]_0$, confirming the first order dependence on [oxidant]. Under identical experimental conditions, an increase in $[PHE]_0$ increased the $k^{/}$ values (Table 1).A plot of log $k^{/}$ versus log [PHE] was linear (Fig 1) with unit slope, showing a first order dependence of the rate on $[PHE]_0$.

Effect of $[HClO_4]$

The rate of the reaction increases with the increase in $[HClO_4]$ (Table 1) and a plot of log $k^{/}$ versus log$[HClO_4]$ was linear (Fig 2) with a positive slope of 0.54 indicating a positive fractional order dependence of the rate on $[HClO_4]$.

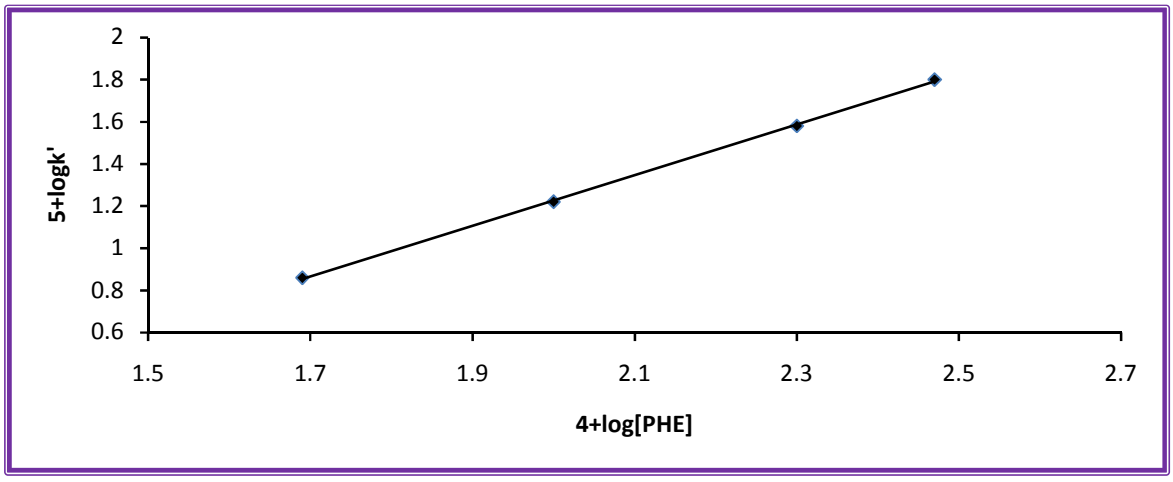


Fig 1 : Effect of [PHE] on the rate of the reaction

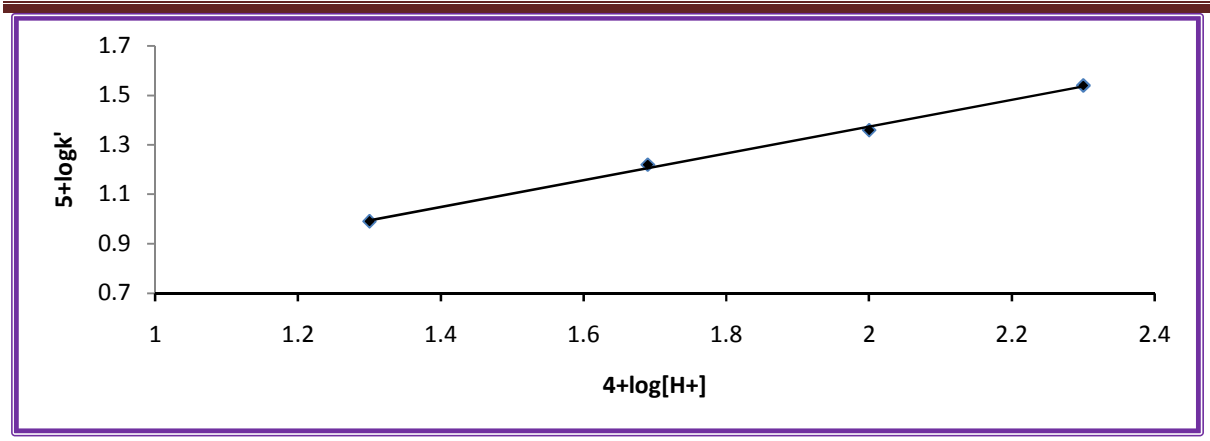


Fig 2 : Effect of [H^+] on the rate of the reaction

Effect of halide ions

The addition of NaBr and NaCl ($1.0x10^{-3}$ - $10.0x10^{-3}$ mol dm^{-3}) showed negligible effect on the rate of the reaction.

Effect of benzenesulphonamide

The addition of reduction product, benzenesulphonamide ($1.0x10^{-3}$-$10.0x10^{-3}$ mol dm^{-3}) had no significant effect on the reaction rate, indicating that it is not involved in the pre-equilibrium with the oxidant.

Effect of varying ionic strength and dielectric permittivity of the medium

The variation of ionic strength (I) of the medium using $NaClO_4$ solution ($1x10^{-3}$-$10x10^{-3}$ $moldm^{-3}$) did not influence the reaction rate, indicating the involvement of non-ionic species in the rate limiting step. The dielectric permittivity of the medium was varied by adding different proportions of methanol [0 – 30% v/v] to the reaction mixture. The rate was found to increase with decrease in methanol content (Table 2). A plot of $logk^{/}$ versus 1/D, where D is the dielectric permittivity of the medium (D values are taken from the literature[12]), gave a negative slope supporting a rate limiting step involving partial ionization. Blank experiments with methanol, indicated that the oxidation of methanol by CAB was

negligible (<3%) under the given experimental conditions. This was taken into account for the calculation of net reaction rate constant for the oxidation of phenylephrine.

Effect of Temperature

The reaction has been carried out at various temperatures (293- 323K) keeping other experimental conditions constant (Table 3). From the linear Arrhenius plots of log k/ versus 1/T (Fig 3) values of activation parameters have been computed. Table 3 summarizes the activation parameters.

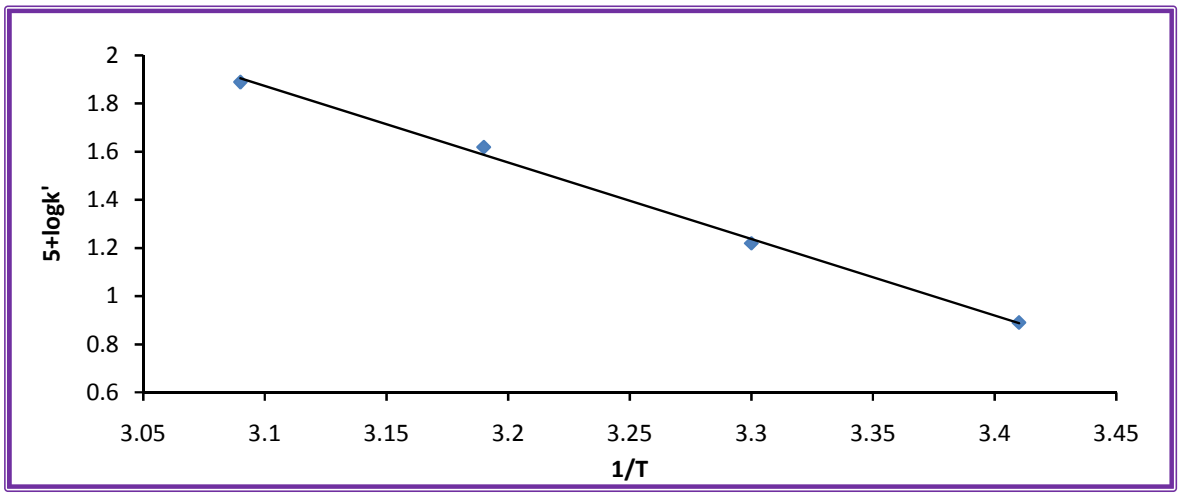


Figure 3 Effect of temperature on the rate of the reaction

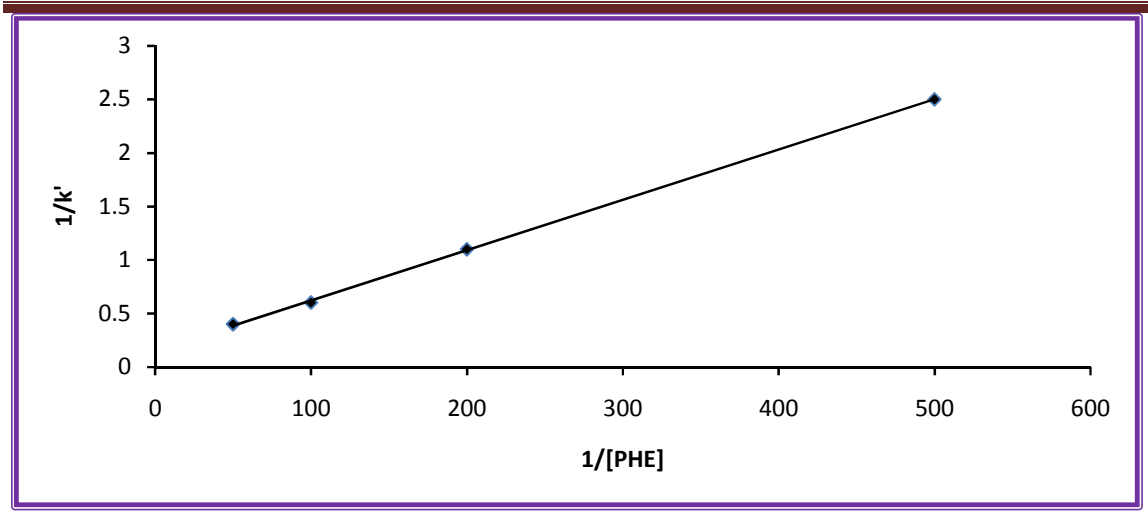


Figure 4 Double reciprocal plot of $1/k^{/}$ versus 1/[PHE]

Test for free radicals

Absence of free radical species in the reaction mixture was shown by the negative test with acrylamide , as no polymerization was initiated even after an hour.

Chloroamine-B is analogous to CAT and similar equilibria exist in acidified solutions. Depending on the pH of the medium CAB furnishes the following types of reactive species in solution[13,14].

$$RNClNa \rightleftharpoons RNCl^- + Na^+ \quad (2)$$

$$RNCl^- + H^+ \rightleftharpoons RNHCl \quad (3)$$

$$2RNHCl \rightleftharpoons RNH_2 + RNCl_2 \quad (4)$$

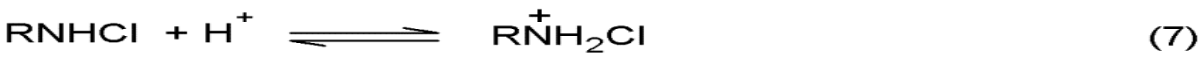
$$RNCl_2 + H_2O \rightleftharpoons RNHCl + HOCl \quad (5)$$

$$RNHCl + H_2O \rightleftharpoons RNH_2 + HOCl \quad (6)$$

Here (R= $C_6H_5SO_2$)

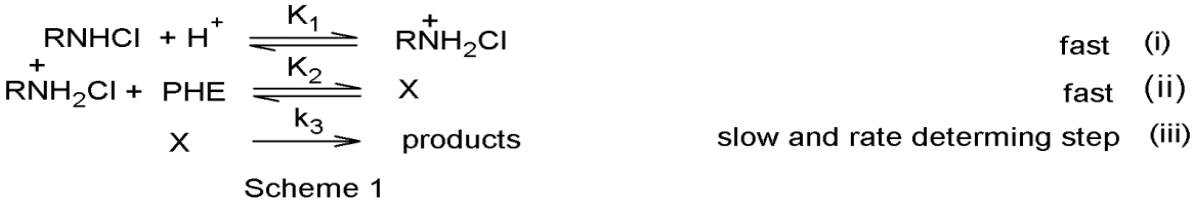
The possible oxidizing species in acidified CAB are RNHCl, $RNCl_2$ and HOCl. If $RNCl_2$ were to be the reactive species, the rate law should predict a second order dependence of the rate on [CAB] as seen from equation 4, which is contrary to the

experimental observations. If HOCl is primarily involved, a first order retardation of the rate by the added benzenesulphonamide is expected. Since no such effect is noticed, HOCl can be ruled out as the oxidizing species. It is therefore probable that RNHCl is the reactive species in acid medium. Monohalomines can be further protonated[15] at pH 2, as shown in equation 7.



$$RNHCl + H^+ \rightleftharpoons RNH_2^+Cl \qquad (7)$$

In the present investigations, the fractional order in $[H^+]$ indicates that the protonation of RNHCl results in the formation of RN^+H_2Cl, which is likely to be active oxidizing species involved in the mechanism of oxidation of PHE.



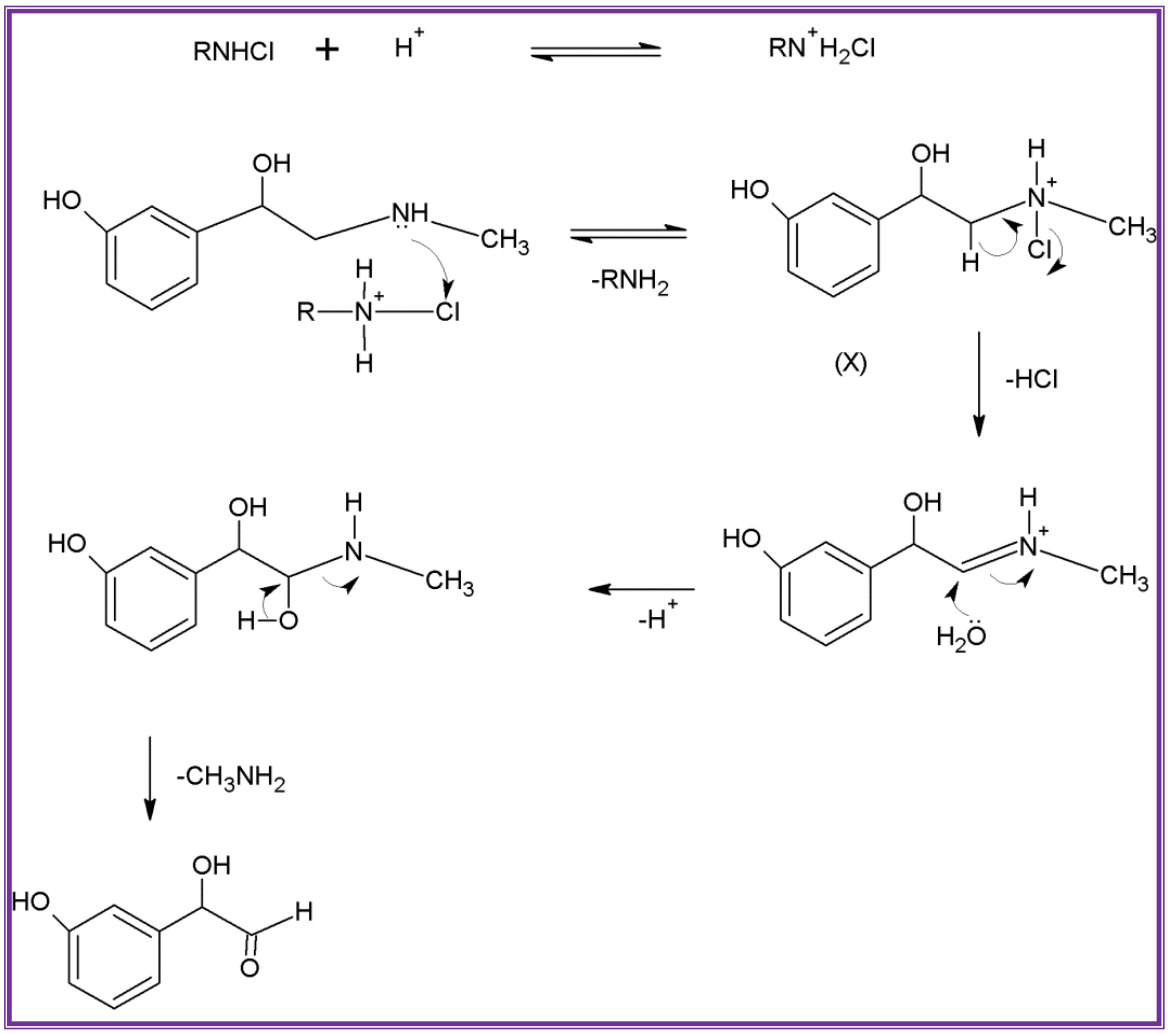
$$RNHCl + H^+ \overset{K_1}{\rightleftharpoons} RNH_2^+Cl \quad \text{fast} \quad (i)$$

$$RNH_2^+Cl + PHE \overset{K_2}{\rightleftharpoons} X \quad \text{fast} \quad (ii)$$

$$X \xrightarrow{k_3} \text{products} \quad \text{slow and rate determing step} \quad (iii)$$

Scheme 1

In Scheme 1, PHE and X represent the substrate and the complex intermediate species respectively. A detailed mechanistic interpretation of oxidation of phenylephrine is presented in Scheme 2. An initial equilibrium involves protonation of RNHCl forming an active oxidizing species of CAB (RN^+H_2Cl). In the next step, the electrophilic attack by RN^+H_2Cl at the nitrogen atom of the substrate results in the formation of intermediate complex (X) with the elimination of RNH_2. This complex decomposes in a rate limiting step to give the final products.



Scheme-2

From the slow step of Scheme 1,

$$\text{Rate} = k_3 [X] \quad (8)$$

If the total effective concentration of CAB is $[CAB]_t$, then

$$[CAB]_t = [TsNHCl] + [TsN^+H_2Cl] + [X] \quad (9)$$

By substituting [$TsNH_2Cl^+$] and [TsNHCl] from equilibrium steps (i) and (ii) of Scheme 1 in equation 9, the value of X obtained is,

$$[X] = \frac{K_1 K_2 [CAB]_t [PHE] [H^+]}{1 + K_1 [H^+] + K_1 K_2 [PHE] [H^+]} \quad (10)$$

By substituting [X] from equation 10 into equation 8, the following rate law is obtained,

$$rate = \frac{K_1 K_2 k_3 [CAB]_t [PHE] [H^+]}{1 + K_1 [H^+] + K_1 K_2 [PHE] [H^+]} \quad (11)$$

The rate law (equation 11) is in good agreement with the experimental results, wherein a first order dependence of rate on $[CAB]_0$, fractional orders on $[PHE]_0$ and $[H^+]$ was observed. Since rate = $k^/ [CAB]_0$, rate law can be transformed into equations 12 and 13

$$k^/ = \frac{K_1 K_2 k_3 [PHE] [H^+]}{1 + K_1 [H^+] + K_1 K_2 [PHE] [H^+]} \quad (12)$$

$$1/k^/ = \frac{1}{K_2 k_3 [PHE]} \left\{ \frac{1}{K_1 [H^+]} + 1 \right\} + \frac{1}{k_3} \quad (13)$$

Based on equation 13, plot of $1/k^/$ versus 1/[PHE] at constant $[H^+]$ and temperature has been found to be linear (Fig 4). From the slopes and intercepts of these plots, values of K_1, K_2 and k_3 were calculated. The decomposition constant k_3 was found to be 3.84×10^{-4} s^{-1}. Since the rate was fractional in [PHE], Michaelis-Menten type of kinetics[16] was adopted. The effect of [PHE] on the rate at different temperatures (293-323K) was examined. The reduction product of oxidant BSA does not influence the rate showing that it is not involved in a pre-equilibrium. The change in the ionic strength of medium does not alter the rate indicating that non-ionic species are

involved in the rate limiting step. The proposed mechanism is supported by the observed activation parameters. The moderate values of energy of activation support the proposed mechanism while low values of entropy of activation indicate the formation of rigid associative transition states.

CONCLUSION

Oxidation of PHE by CAB in $HClO_4$ medium has been studied at 303K. The stoichiometry of the reaction was found to be 1:1. Oxidation products have been characterized. $C_6H_5SO_2N^+H_2Cl$ were found to be the reactive oxidizing species. Thermodynamic parameters were computed from the Arrhenius plot. The observed results have been explained by a plausible mechanism and the related rate equation has been deduced.

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Table 1

Effect of varying reactant concentrations

10^4 $[CAB]_0$ (mol dm^{-3})	10^3 [PHE] (mol dm^{-3})	10^3 $[HClO_4]$ (mol dm^{-3})	$10^4k'$ (s^{-1})
5.0	10.0	5.0	1.66
10.0	10.0	5.0	1.65
15.0	10.0	5.0	1.60
20.0	10.0	5.0	1.62
10.0	5.0	5.0	0.73
10	10.0	5.0	1.66
10	20.0	5.0	3.81
10	30.0	5.0	6.31
10	10.0	2.0	0.98
10	10.0	5.0	1.66
10	10.0	10.0	2.30
10	10.0	20.0	3.47

I = 0.5 mol dm^{-3}, T= 303K

Table 2

Effect of varying dielectric constant of the medium

MeOH % v/v	D	$10^2/D$	$10^4k'$ (s^{-1})
0	76.73	1.3	1.66
10	72.37	1.38	1.48
20	67.38	1.46	1.32
30	62.71	1.60	1.13

$[CAB]_0$ =10×10^{-4}mol dm^{-3}, [PHE]=10×10^{-3} mol dm^{-3}, $[HClO_4]$ = 5×10^{-3}mol dm^{-3}, T=303K

Table 3

Effect of temperature and activation parameters

Temperature (K)	$10^4 k/$ (s^{-1})	Activation parameters	
		Parameter	Value
293	0.78(2.35)	Ea ($kJmol^{-1}$)	60.80 (68.31)
303	1.66(6.62)	$\Delta H^{\#}$ ($kJmol^{-1}$)	58.36 (65.79)
313	4.20(22.7)	$\Delta G^{\#}$ ($kJmol^{-1}$)	122.30 (138.05)
323	7.80(29.4)	$\Delta S^{\#}$ ($JK^{-1} mol^{-1}$)	-211.17 (-238.46)

Values in parenthesis are the decomposition constants and activation parameters for the rate determining step

REFERNCES

1. El-Hawary MB, Khayyall MT, and Z. Isaak: Hand Book of Pharmacology, The Scientific Book Center, S.O.P. Presee. Cairo. **1985**.

2. Kolvari A, Choghamarani AG, Salehi P, Shirini F and Zolfigol MA: Applications of N- halo reagents in organic synthesis. J Iran Chem Soc. 2007; 4(2): 126.

3. Puttaswamy and Ramachandrappa R: Kinetic and mechanistic studies on the oxidation of ninhydrin by N-bromo-p-toluenesulfonamide in perchloric acid medium. Indian J Chem 1999; 38A: 1272-1276.

4. Usha Joseph, Ramachandrappa R and Pushpa Iyengar: Kinetics of oxidation of pioglitazone by chloramine-T in HCl medium. International journal

of universal life sciences. 2012; 2(2): 85.

5. Ramachandrappa R, Usha Joseph and Pushpa Iyengar: Kinetics of oxidation of gabapentin by bromamine-B in NaOH medium. Research journal of pharmaceutical, biological and chemical sciences. 2012; 3(2):1186.

6. Puttaswamy and Anu Sukhdev: Oxidation of mephenesin and guaifenesin with chloramine-B in hydrochloric acid medium:

Design of kinetic model. Indian J Chem 2009; 48A: 339-345.

7. Ramachandrappa R: Kinetics of oxidation of salbutamol by chloramine-Bin NaOH medium. International research journal of pharmacy. 2012; 3(4): 170.

8. Gowda: Kinetics of oxidation of aliphatic primary amines by CAB in alkaline medium catalyzed by cyclodextrine. Int J Chem Res 2011; 2: 8-13.

9. Mythily CK, Mahadevappa DS and Rangappa KS: Oxidation of secondary alcohols by sodium N-chlorobenzenesulphonamide in aqueous solution. A kinetic study. Czech Chem Commun 1991; 56: 1671-1679.

10. Puttaswamy, Anuradha TM, Ramachandrappa R and Gowda NM: Oxidation of isoniazid by N-haloarenesulfonamidates in alkaline medium. A kinetic and mechanistic study. Int J Chem Kinet 2000; 32: 221-230.

11. Feigl F: Spot tests in organic analysis.5th ed. Elsevier, Amsterdam; **1956**: 376.

12. Akerl G: Dielectric constants of some organic solvent-water mixtures at various temperatures. J Am Chem Soc 1932; 54: 4125.

13. Meenakshisundaram SP and Sockalingam R: Os (VIII)-catalysed oxidation of sulfides by sodium salt of N-chlorobenzenesulfonamide. J Mol Catal A Chem 2000; 160: 269.

14. Mahadevappa DS, Ananda S, Murthy ASA and Rangappa KS: Oxidation of dimethyl sulphoxide by sodium-N-bromobenzene sulphonamide. A kinetic and mechanistic study. Tetrahedron 1984; 40(10): 1673-1682

15. Hardy FE and Johnston JP: Oxidation of p-nitrophenol by BAB. J Chem Soc Perkin Trans-II 1973; 2: 742-746.

16. Helfferich FG: Kinetics of multistep reactions, 2nd ed. Elsevier, Amsterdam; **2004**: 221-223