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CHEMICAL OXIDATION OF PHENYLEPHRINE BY USING CHLORAMINE-T IN ACID MEDIA: A KINETIC AND MECHANISTIC STUDY

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Keywords:

Phenylephrine, Chloramine-T, Oxidation, Spectroscopic technique

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ABSTRACT: The kinetics and mechanism of oxidation of Phenylephrine (PHE) by Chloramine-T (CAT) in acid media have been investigated by spectroscopic technique at the temperature of 298 K. It is found that the reaction is of first order with respect to PHE, fractional order with respect to CAT & inverse order with respect to H^+. The reaction rate remained unchanged with the variation of ionic strength of the medium indicating that the non ionic species are involved in the rate determining step. The rate of reaction decreases with increase in concentration of dielectric constant. Addition of chloride ions had no effect on rate of reaction. The stoichiometric ratio was found to be 1:1(PHE: CAT) ratio. The major oxidation product of PHE has been identified by an UV, Cyclic voltammetry (CV), IR, H^1 NMR and Mass spectroscopy. On the basis of the experimental results, a suitable mechanism has been proposed. The rate constants of the rate-determining step together with the activation parameters were evaluated and also thermodynamic quantities were determined.

INTRODUCTION: Phenylephrine hydrochloride [PHE, (R)-1-(3-hydroxyphenyl)-2-(methylamino) ethanol hydrochloride, $C_9H_{13}O_2N{\cdot}HCl$, (**Fig.1**)], is a white crystalline powder and belongs to the group of medicines called sympathomimetics. It acts stimulating the alpha receptors in certain areas of the body. It is a non-sedative antihistamine, used in the treatment of seasonal rhinitis, hay fever, running nose, control sneezing of allergic origin. It is used locally, as decongestant, allergic conjunctivitis, sinusitis and nasopharyngitis. The medicine exhibit vasoconstrictor effects similar to nor epinephrine, but the vasopressor effect of phenylephrine is less pronounced, but longer.

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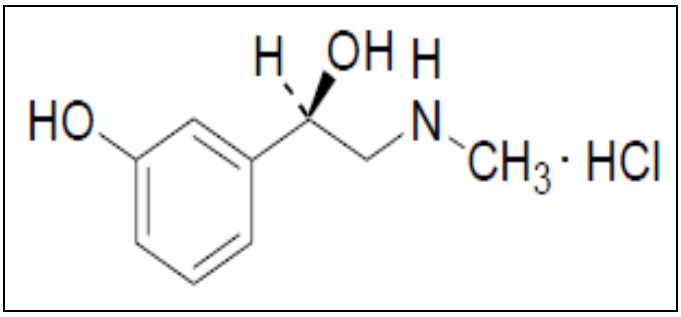


FIG. 1: (R)-1-(3-HYDROXYPHENYL)-2-(METHYLAMINO) ETHANOL HYDROCHLORIDE

It is the world's only non-prescription agonists since in the mean therapeutic doses it almost does not show a significant stimulatory effect on the central nervous system and is part of many drugs used in emergency treatment, ophthalmology and the treatment of infectious diseases [1-3].

Literature reveals that many analytical methods are specified for the determination of PHE as individual and combined dosage form with other combination of drugs and also in biofluid viz., spectrophotometry [4-8], spectrophotometry with chromogenic reagent [9], multiwavelength spectroscopic method [10], and chromatography [11,12], High-performance liquid chromatography [13-16], micellar liquid chromatography [17], micellar electrokinetic chromatography [18], capillary zone electrophoresis [19, 20], spectro-fluorimetric and derivative spectrophotometric methods [21].

Aromatic sulfonylhaloamines such as chloramine-T (CAT), chloramines-B (CAB), and bromamine-T (BAT) contain a polar N-halo bond, which is capable of forming a halonium (X^+) ion in solutions. This electrophilic species can function as an oxidizing and halogenating agent in solutions. Inorganic chloramines are the byproducts formed in drinking water due to chlorination [22]. Chloramine-T (CAT) is the most important member of organic halo-amine family and behaves as an oxidizing agent in both acidic and alkaline media. It is versatile oxidizing agent and has shown a variety of kinetic results due to formation of its various oxidizing species depending upon pH of the medium [21].

CAT is widely used in chemistry to study the oxidation reaction mechanisms for a variety of substrates. Veeraiah, M.K *et al.,* [22], Wadhwani Meena *et al.,* [23], Anu Sukhdev *et al*., [24] Ajaya Kumar Singh *et al.,* [25], K. B. Sudha Rani *et al.,* [26], P.A. Prasanth *et al.,* [27], R.J.D. Saldanha *et al.,* [28], *M. S.* Veena *et al.,* [29], have shown the oxidation of drugs by using CAT as oxidising agents in various methods. Literature shows oxidation of methyl vinyl ketone and isopropyl methyl ketone, ketoglutaric acids, formic acids, substituted trans-cinnamic acids, methionine, substituted and unsubstituted imidazole and benzimidazoles done by using CAT as an oxidising agent [30].

Studies on PHE oxidation involving many oxidants have been reported. In the past decades, Roopa K. Papanna *et al.,* [31] determined the PHE drug based on oxidation by using Ce(IV) ammonium sulphate and N-Bromosuccinamide, R. Ramchandrappa *et al.,* [32] investigated oxidation of PHE by using CAT & CAB in acidic medium at 303K by titrimetric method. As no one used the spectrophotometric method to determine the rate laws for PHE, our aim is to present the same work at room temperature by spectrophotometric method using UV-Visible light and also the oxidised product along with drug is determined by CV. Hence, the present work is to report the UV-visible spectrophotometrically monitored kinetics of oxidation of PHE by CAT in acidic medium at 298K in order to find out the rate law and to elucidate the reaction mechanism.

EXPERIMENTAL:

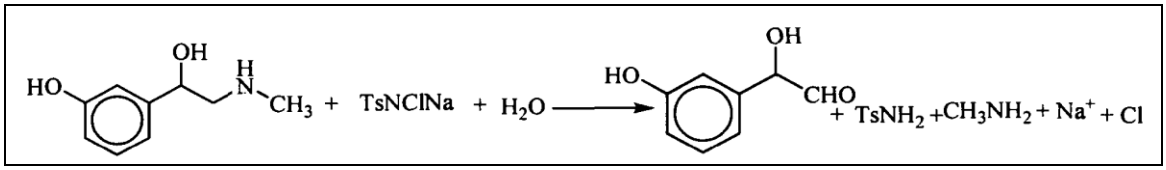
Apparatus: All the spectrophotometric measurements were performed using an Ocean optics Model UV-visible digital Spectrophotometer provided with 1-cm matched quartz cells.

Reagents and Materials: All chemicals used were of analytical grade. Chloramine-T (CAT) (S.D. Fine Chem Ltd.) was used without further purification by freshly preparing their solution in double distilled water and standardized iodometrically. Sodiumperchlorate monohydrate (NaClO4) (Hi Media) was used without further purification by preparing solution appropriate in double distilled water. PHE borrowed from Dr. B.K Jayanna & the solubility of PHE was checked which is soluble in water. Double distilled water was used for preparing aqueous solutions.

Kinetic measurement: Kinetic runs were followed under pseudo-first order conditions with the CAT concentration in excess over PHE. Solutions containing appropriate amounts of PHE, HCl, $NaClO_4$ and water (to keep the total volume constant for all the runs) were taken in a conical flask and kept on water bath at 298K. A measured amount of CAT solution was taken in another conical flask and kept on the same water bath. After few minutes the CAT solution rapidly added to the reaction mixture and shaken well for uniform concentration.

The progress of reaction was followed spectrophotometrically at 275 nm by monitoring the changes in absorbance. It was verified that there is a negligible interference from other species present in the reaction mixture at this wavelength. The reaction was followed to more than 80% completion of the reaction. Plot of log (absorbance) versus time leads to first order rate constant (k).

Stoichiometry and product analysis: Different sets of reaction mixtures containing different concentrations of PHE and CAT in presence of HCl were equilibrated at 273 K for 24 hr. The unreacted concentration of CAT in the reaction mixture was estimated by titrimetric method. The results indicated that 1:1 stoichiometry (PHE: CAT) is represented by equation,



The products in the reaction mixture were extracted several times with diethyl ether. The oxidized form of PHE was identified as 2-hydroxy-2-(3-hydroxyphenyl) acetaldehyde. The nature of the product was confirmed by its UV, Cyclic voltammetry, IR, H^1 NMR and mass spectra. The UV absorbance (**Fig. 2**) of CAT seen at λ_{max} = 225 nm and 260 nm, absorbance of PHE showed at λ_{max} = 275 nm & 214 nm and the absorbance after completion of reaction showed in two region 220 and 275 nm due to conjugation in the structure. The LC-MS spectra showed a molecular ion peaks at 150 amu (**Fig. 3**) confirming the above product. Further confirmed by IR spectral analysis which shows a strong peak at 1693 cm^{-1} for –C=O group, medium peak at 2921 cm^{-1} for –CHO group, strong peak at 1153 cm^{-1}& 1093 cm^{-1} for Ar-OH, -CH-OH groups.

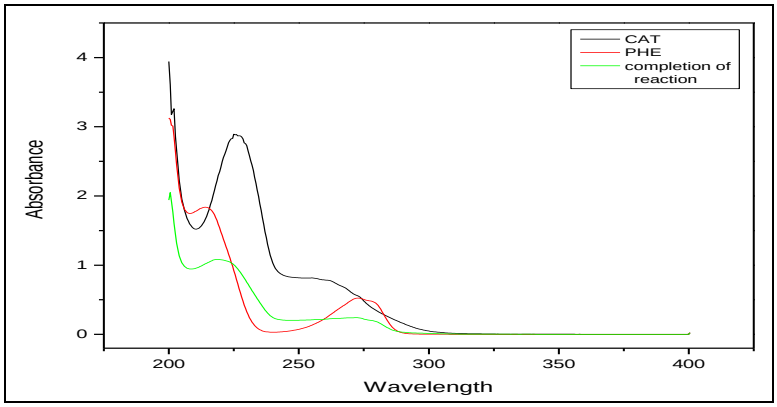


FIG. 2: UV SPECTRUM OF THE CAT, PHE AND PRODUCT

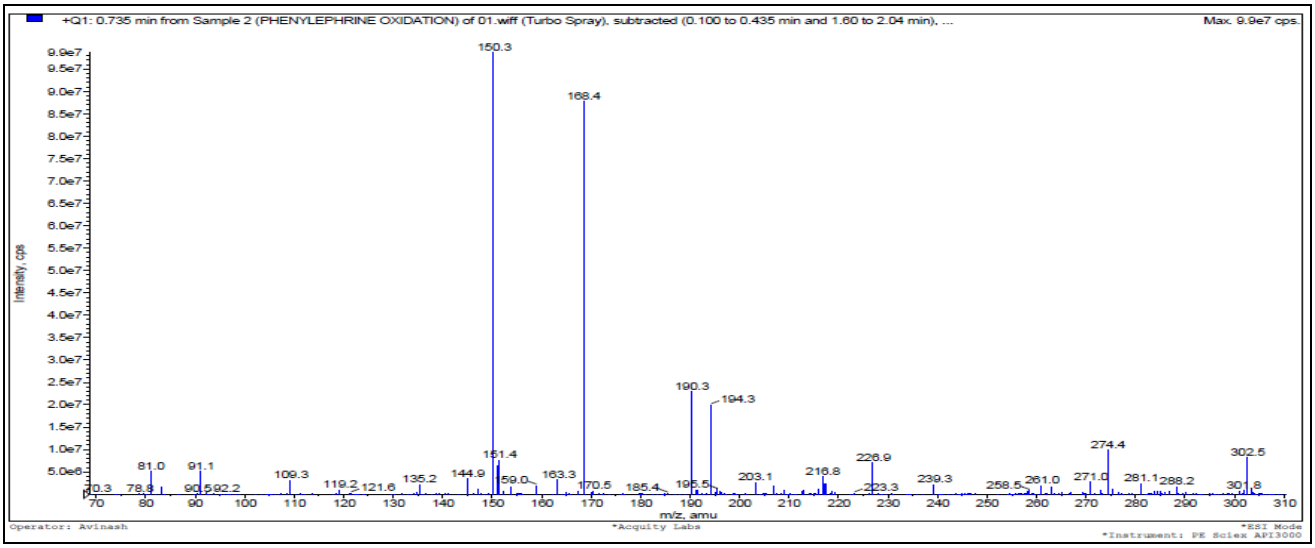


FIG. 3: LCMS SPECTRUM OF THE PRODUCT SHOWS MOL. ION PEAK AT 150 AMU

Voltammetric method was used for determination of PHE at carbon paste electrode (CPE). Cyclic voltammogram obtained for electrochemical oxidationt of 0.5 mM PHE in phosphate buffer (pH 7) on CPE are shown in **Fig. 4.** The Oxidation peak of Phenylehrine at 0.82 V showed that the drug undergoes oxidation and there is no oxidation peak at this region for the product hence we can conclude that the drug is completely oxidised in presence of CAT.

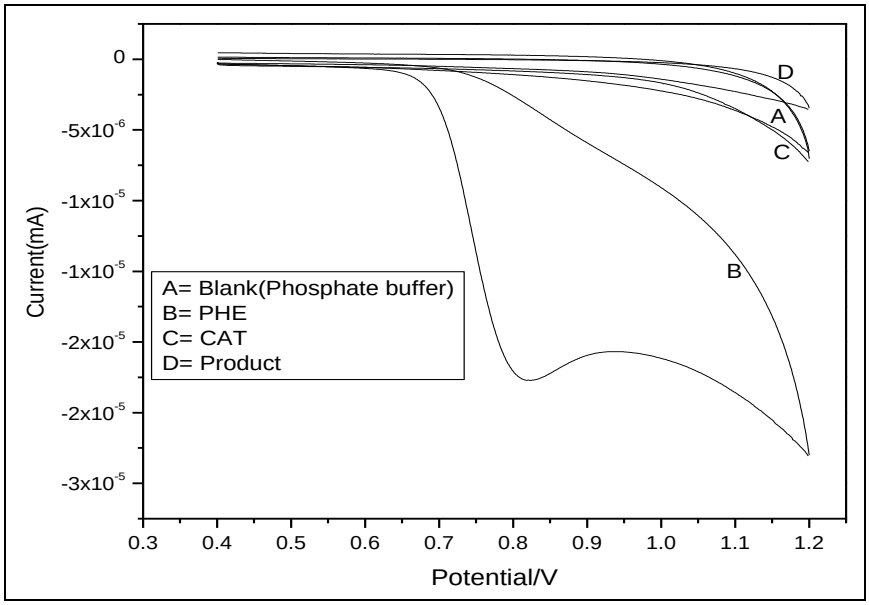


FIG. 4: CYCLIC VOLTAMMOGRAM, A= 0.1 M PHOSPHATE BUFFER, B= 0.5mM PHE, C= 0.5mM CHLORAMINE-T AND D= 0.5mM PRODUCT, pH= 7.0, SCAN RATE AT 0.1 V/s ON CARBON PASTE ELECTRODE

RESULTS:

Effect of varying reactant concentrations on the reaction rate: The oxidation of PHE by CAT was kinetically investigated at different initial concentrations of reactants in HCl medium at 273K. Under pseudo-first order conditions, with the Oxidation in excess, at constant [PHE], [HCl] and temperature, plots of log [CAT] versus log k were linear with a slope of 0.731 (**Fig. 5**), indicating a fractional order dependence of the reaction rate on [CAT]. Under identical experimental conditions, an increase in [PHE] leads to an increase in the k values **(Table 1**). A plot of log [PHE] versus log k was linear with a slope of 0.953 (**Fig. 6**) showing a first order dependence of the reaction rate on [PHE].

TABLE 1: EFFECT OF VARYING CONCENTRATIONS OF THE REACTANTS

10^4[PHE] (mol dm^{-3})	10^3[CAT] (mol dm^{-3})	$10^1[H^+]$ (mol dm^{-3})	10^3k (s^{-1})
3.0	3.0	3.0	2.76
3.0	3.5	3.0	3.24
3.0	4.0	3.0	3.32
3.0	4.5	3.0	3.68
3.0	5.0	3.0	3.90
2.0	4.0	3.0	4.74
2.5	4.0	3.0	5.69
3.0	4.0	3.0	6.45
3.5	4.0	3.0	7.34
4.0	4.0	3.0	7.98
3.0	4.0	2.0	3.79
3.0	4.0	2.5	3.27
3.0	4.0	3.0	3.24
3.0	4.0	3.5	3.17
3.0	4.0	4.0	3.01

I= 9 $x10^{-2}$mol dm^{-3}; T = 273K

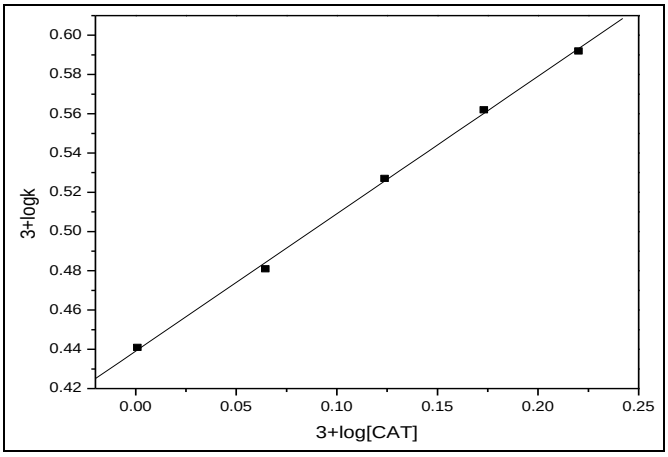


FIG. 5: EFFECT OF VARIATION OF [CAT] ON THE OXIDATION OF PHE BY CAT IN HCL AT 273 K

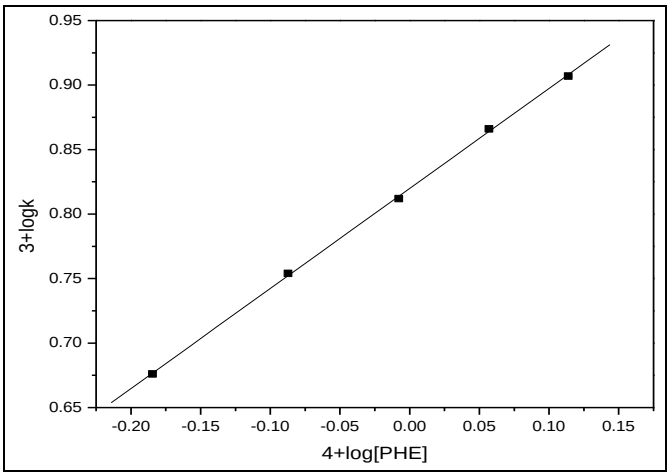


FIG. 6: EFFECT OF VARIATION OF [PHE] ON THE OXIDATION OF PHE BY CAT IN HCL AT 273 K

Effect of varying [H^+] ion the reaction rate: The reaction rates were measured with varying [HCl] with all other reaction conditions kept constant. The rate of the reaction decreased with increase in [H^+]. A plot of log k versus [H^+] was linear with a negative slope of 0.27 (**Table 1**, **Fig. 7)** indicating an inverse fractional order dependence on [H^+].

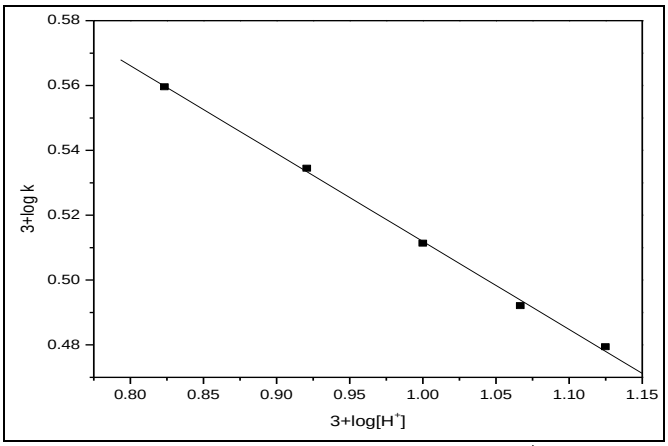


FIG. 7: EFFECT OF VARIATION OF [H^+] ON THE OXIDATION OF PHE BY CAT IN HCL AT 273 K

Effect of PTS: During the oxidation reaction, oxidizing agent CAT gets reduced. The reduction product of CAT is p-toluenesulfonamide (PTS). In order to study the effect of reduction product during the oxidation reaction of PHE by CAT, the reduction product of CAT was added to the reaction mixture. The rate constants for different PTS concentrations are shown in (**Table 2**). The data showed that the rate constant remains same in the range of studied PTS concentration which indicates that the rate constants on the oxidation of PHE by CAT does not depend on PTS concentration and hence PTS has no effect on the rate of the reaction (**Fig. 8**).

TABLE 2: EFFECT OF VARYING CONCENTRATIONS OF THE PTS

10^5[PTS]	10^3 k (s^{-1})
6.66	2.57
8.33	2.27
10.0	2.24
11.6	2.10

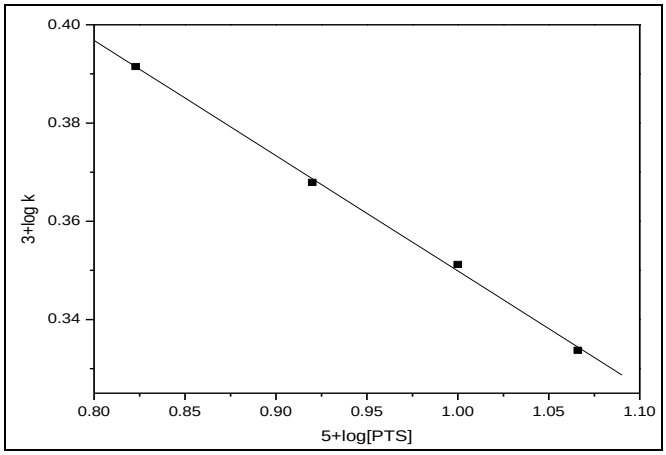


FIG. 8: EFFECT OF VARIATION OF [PTS] ON THE OXIDATION OF PHE BY CAT IN HCL AT 273 K

Effect of Ionic strength on the reaction rate: Increase in concentration of $NaClO_4$ doesn't affect much on reaction rate (**Table 3**). A plot of log k versus log [NaClO4] was linear with a negative slope of 0.59 (**Fig. 9)** indicating that non-ionic species being involved in the rate determining step.

TABLE 3: EFFECT OF VARYING CONCENTRATIONS OF [$NaClO_4$]

10^3[$NaClO_4$]	10^3 k (s^{-1})
0.66	4.81
0.833	4.49
1.0	4.44
1.16	3.98
1.33	3.13

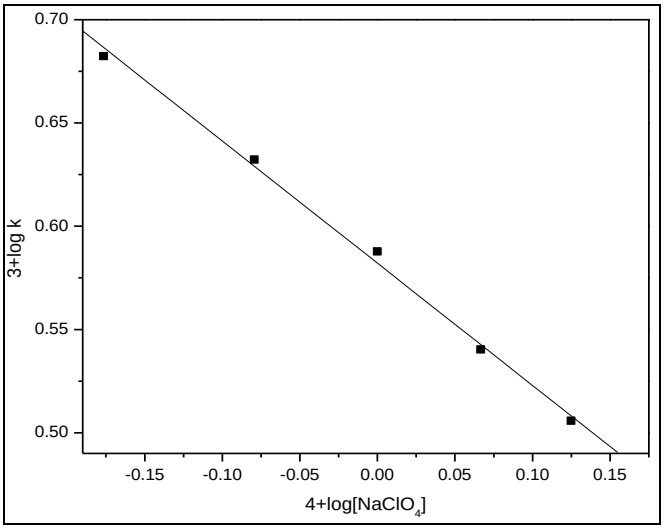


FIG. 9: EFFECT OF VARIATION OF [$NaClO_4$] ON THE OXIDATION OF PHE BY CAT IN HCL AT 273 K

Effect of Dielectric constant of Medium: The dielectric constant (D) of the medium was studied by the addition of Ethanol to the reaction medium. The results obtained indicated that the increase in the concentration of Ethanol decreases the rate of the reaction. Plots of log k vs. [1/D] shown in (Fig. 10). The slope of the plot is negative with a value of 0.654.

TABLE 4: EFFECT OF DIELECTRIC CONSTANT OF THE MEDIUM: [PHE] =3.0×10^{-4} mol dm^{-3}; [CAT] = 4.0×10^{-3} mol dm^{-3}; [H^+] =1.0×10^{-3} mol dm^{-3}; [NaClO4] = 9×10^{-2} mol dm^{-3}

[EtOH] % v/v	D	10^2/D	10^3k(S^{-1})
0	80.1	1.24	6.07
5	77.32	1.29	5.64
10	74.54	1.34	5.36
15	71.76	1.39	4.79
20	68.98	1.44	4.46

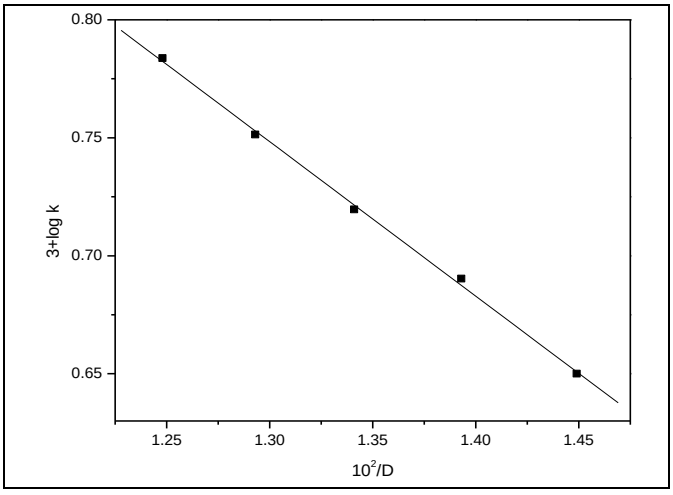


FIG. 10: EFFECT OF DIELECTRIC CONSTANT [ETOH] ON THE OXIDATION OF PHE BY CAT IN HCL AT 273K

Effect of chloride ions: The addition of chloride ions in the form of NaCl (2.0×10^{-3} to 6.0×10^{-3} M) showed a slight increase in the reaction rate. This shows an approximately zero order dependence on Cl^- & rate constants of the oxidation of PHE by CAT does not depend on halide ions concentration, hence halide ions showed no effect on the rate of the reaction.

Effect of temperature: The rate constants for the oxidation of PHE with CAT at different temperature ranges from 298 K to 318 K was measured by keeping the other experimental conditions constant. It was observed that the rate constant of the reaction increases with increase in temperature. The energy of activation corresponding to these constants was evaluated from the Arrhenius plot of log k versus 1/*T* (**Fig. 11**), and other activation parameters were also obtained as reported in **Table 5**.

TABLE 5: EFFECT OF VARYING TEMPERATURE; [PHE] =3.0×10^{-4} mol dm^{-3}; [CAT] =4.0×10^{-3} mol dm^{-3}; [H^+] =1.0×10^{-3} mol dm^{-3}; [NaClO4] = 9×10^{-2} mol dm^{-3}

Temperature(K)	10^3 k(s^{-1})
298	1.95
303	2.01
308	2.03
313	2.06
318	2.80

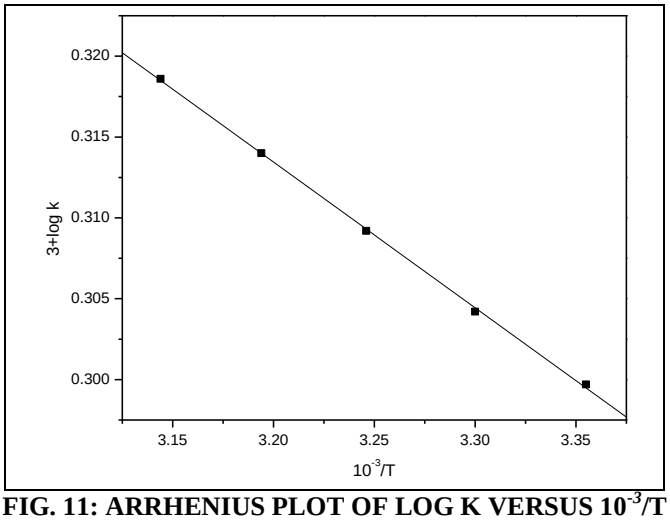


FIG. 11: ARRHENIUS PLOT OF LOG K VERSUS 10^{-3}/T

TABLE 6: VALUES OF ACTIVATION PARAMETERS

Parameter	Value
Ea(kJ^{-1} mol^{-1})	44.781
$\Delta H^{\#}$(kJ^{-1} mol^{-1})	42.210
$\Delta G^{\#}$ (kJ^{-1} mol^{-1})	73.546
$\Delta S^{\#}$ (JK^{-1} mol^{-1})	-160.283
Log A	14.766

DISCUSSION: Chloramine-T behaves as strong electrolyte in aqueous solutions. Depending on pH of the medium, CAT furnishes different types of reactive species in solution. Many researchers have shown the existence of similar equilibria in acid and alkaline solutions of *N* metallo-*N*- hallo-aryl sulphonamides [31]. CAT behaves as a strong electrolyte in aqueous solutions, forming different species as shown in equations (1.1) to (1.6)

$TsNClNa \longrightarrow TsNCl^- + Na^+$ (1.1)

$TsNCl^- + H^+ \longrightarrow TsNHCl$ (1.2)

$TsNHCl + H_2O \longrightarrow TsNH_2 + HOCl$ (1.3)

$2TsNHCl \longrightarrow TsNH_2 + TsNCl_2$ (1.4)

$HOCl + H^+ \longrightarrow H_2OCl^+$ (1.5)

$HOCl \longrightarrow H^+ + OCl^-$ (1.6)

In the present case, the fractional order dependence on $[H^+]$ indicates that the protonation of TsNHCl results in formation of $TsNH_2Cl^+$ which is likely to be the active species involved in the formation mechanism of reaction of Phenylephrine. In view of the preceding discussion and experimental facts, **Scheme 1** is proposed to explain the reaction mechanism for oxidation of PHE by CAT in acid medium.

$TsNHCl + H^+ \underset{}{\overset{k_1}{\rightleftharpoons}} TsNH_2Cl$ .... (i) fast

$TsNH_2Cl + PHE \xrightarrow{k_2} X$ ..... (ii) slow (rds)

$X \xrightarrow{k_3} product$ ..... (iii)

Scheme 1:

Total effective concentration of PHE is,

$[PHE]_t = PHE + X$ eq.1

From steps (i) and (ii) of Scheme 1

$k_1 = \frac{[TsNH_2Cl]}{[TsNHCl][H^+]}$ eq.2

$[TsNH_2Cl] = k_1 [TsNHCl][H^+]$ eq.3

$k_2 = \frac{X}{[TsNH_2Cl][PHE]}$ eq.4

Substituting eq.3 in eq.4

$[PHE]_t = \frac{X}{k_1 k_2 [TsNHCl][H^+]}$ eq.5

Equating 5 in 1 we get,

$X = \frac{k_1 k_2 [CAT][H^+][PHE]t}{1 + k_1 k_2 [CAT][H^+]}$ eq.6

From the slow and rate-determining step (iii) of Scheme 1

$Rate = k_3[X]$ eq.7

By substituting for [X], from eq.6 into eq.7, the following rate law is obtained

$Rate = \frac{k_1 k_2 k_3 [CAT][H^+][PHE]t}{1 + k_1 k_2 [CAT][H^+]}$ eq.8

Rate law in eq.8 is in good agreement with the experimental results, wherein a first-order dependence of rate on [PHE], fractional-order dependence each on [CAT] and an inverse-fractional order on $[H^+]$ was observed.

Since rate = $k'[PHE]$

$k' = \frac{k_1 k_2 k_3 [CAT][H^+]}{1 + k_1 k_2 [CAT][H^+]}$

$\frac{1}{k'} = \frac{1}{k_1 k_2 k_3 [CAT][H^+]} + \frac{1}{k_3}$ eq.9

Based on eq. 9, plot of 1/k versus 1/[PHE] at constant $[H^+]$ and temperature has been found to be linear (**Fig. 5**). 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}

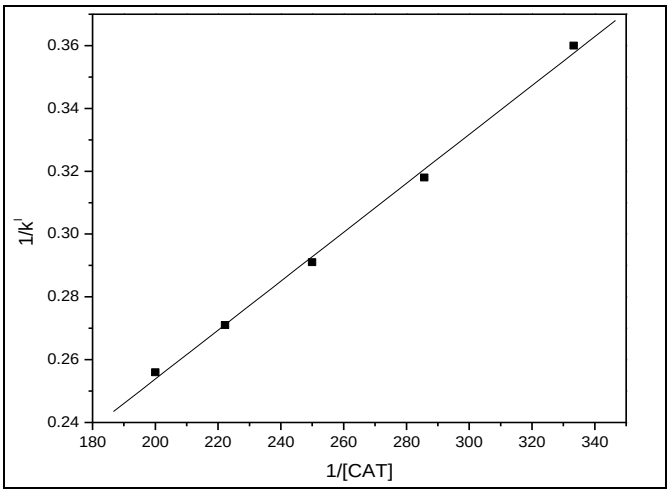
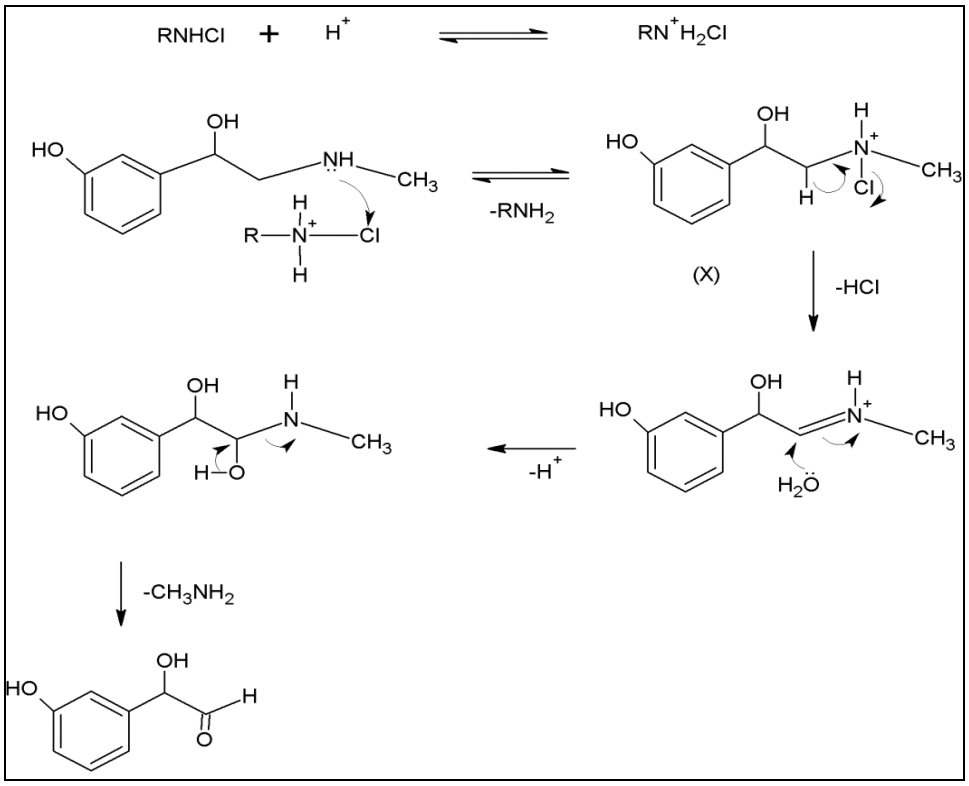


FIG. 12: DOUBLE RECIPROCAL PLOT OF 1/k VERSUS 1/[CAT]

Addition of halide ions had no effect on the rate, indicating that no inter halogen compound or free chlorine was formed.

The reduction product PTS had no influence on the rate showing that it was not involved in pre-equilibrium. The change in the ionic strength of the medium did not alter the rate indicating that non-ionic species were involved in the rate determining step. Ramachandrappa [32] has shown that a plot of log k versus 1/D was linear. with a negative slope for a reaction between the cations and dipole. The negative dielectric effect, in the present studies (**Fig.12**), supports the interaction of dipolar species in the rate limiting step. The proposed mechanism (**Scheme 2**) is also supported by the moderate value of energy of activation. The fairly high positive value of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the negative entropy of activation suggests the formation of the compact activated complex.



SCHEME: 2

CONCLUSION: Oxidation of PHE by CAT in HCl medium by spectrophotometrically has been studied at 298K. The stoichiometry of the reaction was found to be 1:1. The oxidation product identified was 2-hydroxy-2-(3-hydroxyphenyl) acetaldehyde and 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 the mechanism and the related rate equation has been deduced.

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