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# KINETICS AND MECHANISTIC MODEL FOR OXIDATION OF PREGABALIN BY CHLORAMINE-B IN ACID MEDIUM

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## ABSTRACT:

The kinetics of oxidation of Pregabalin [PGB] by Sodium N–Chloro-Benzenesulfonamide [CAB] in HCl medium is studied spectrophotometrically at 298K. The reaction stoichiometry was found to be 1:3 and the oxidation products were identified by FTIR, $^{1}H$ NMR analysis. The reaction rate shows first order dependence on each [PGB] and [CAB] and negative fractional order dependence on [$H^+$]. The reaction constants involved in different steps of the mechanism were calculated. Addition of reduction product did not have any significant effect on reaction rate. The reaction was studied at different temperatures and various activation parameters have been evaluated. The proposed general mechanism and derived rate law are consistent with observations.

**KEYWORDS:** Kinetics, Oxidation, Sodium N –Chloro-benzenesulfonamide, Spectrophotometric, Pregabalin.

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## 1. INTRODUCTION

Anti-epileptic drugs are extensively used by the western population for chronic neurologic disorders. A new generation antiepileptic drug Pregabalin is a popular drug used in treating partial seizures of epilepsy. It is a Serotonin reuptake inhibitor which interacts with specific proteins at the nerve endings of the brain and spinal cord. This reduces the entry of calcium ions into nerve terminals and hinders the release of excess of neurotransmitter molecules in the spinal cord and brain. Pregabalin, chemically designated as (S)-3-(aminomethyl)-5-methylhexanoic acid is alpha 2-δ protein drug with a primary amine and a carboxyl group, found to be highly effective antiepileptic drug with a predictable pharmacokinetic path and a swift onset of action [1].

N-haloamines in acid medium are important organic oxidants used in the study of kinetic and mechanistic aspects of organic oxidation reactions [2-5]. A prominent analytical reagent of this class is N-Chloro benzene sulfonamide or Chloramine-B which is used in the interpretation of many organic reactions [6-9]. Literature survey reveals that recently Chloramine –T is used in exploring the kinetic model and selective oxidation of pregabalin drug molecule in alkaline medium [10] and in acidic medium [11]. However, no such investigations were found using N -Chloro-benzenesulfonamide as the oxidant. Hence, the present kinetic investigation of oxidation of Pregabalin has been carried out in acid medium using N–Chloro-benzenesulfonamide.

## 2. EXPERIMENTAL

### 2.1 Materials

Sodium N –Chloro-benzenesulfonamide was obtained by Merck, India. The compound purity was checked iodometrically and by IR spectrum. An aqueous solution of CAB was freshly prepared each day and its concentration was checked by iodometric titration against a standard thiosulphate solution using starch indicator near the end point. It was preserved in brown bottles to prevent its photochemical deterioration. PGB obtained from Apotex, India, was used without further purification. All other reagents namely double distilled water, hydrochloric acid, $NaClO_4$, benzene, ethanol, petroleum ether, chloroform, n-butyl alcohol and iodine were obtained from SD Fine-Chem Ltd. Potassium bromide used in making pellets of samples for obtaining IR spectra was heated to 120° C in oven and cooled down to lab temperature in a desiccator prior to its use. Double distilled water was used throughout the investigation.

### 2.2 Instrumentation

The progress of the reaction was monitored at 205nm using Shimadzu UV- 1700 PharmaSpc double beam UV-Vis Spectrophotometer. Fourier transform IR spectra were recorded on a Shimadzu FT-IR-8400S instrument, using KBr pellets.

$^1$H NMR spectra were recorded on a BRUKER DSX-300 solid state NMR spectrometer with Magnetic field: 7.04 Tesla and spinning speeds of 10-12 KHz at room temperature. The peaks are reported in ppm and referenced to tetra methylsilane (TMS) as internal standard.Coupling constants (J) are reported in Hz and processed using Linux & X-Winnmr Platform.

### 2.3 Kinetic measurements

Kinetic measurements were performed on Shimadzu UV 2401 PC UV-Vis Spectrophotometer. PGB exhibited an absorption maximum at 205 nm. The progress of the reaction was followed spectrophotometrically at 205nm by monitoring the decrease in absorbance of PGB. All kinetic measurements were performed under pseudo-first order condition where [oxidant]>> [substrate] in the presence of HCl at constant concentration of $NaClO_4$ (to maintain a constant ionic strength) at 298K. Reactions were carried out in glass stoppered Pyrex boiling tubes whose outer surfaces were coated black to prevent photochemical effects.The solutions were thermostatted and the reaction was initiated by rapid addition of a measured amount of oxidant to the stirred reaction mixture. Immediately, 4ml of the solution was pipetted in to a cuvette placed in the spectrophotometer. Absorbance measurements were made for two half-lives.

The absorbance readings at t = 0 and t = t is $A_0$ and $A_t$. Plots of log $A_0/A_t$ Vs time resulted in pseudo-first order rate constants ($k^l$)**(Table 1).**

Table 1.Effect of varying concentration of reactants on the reaction rate at 298K.

| $10^3$[CAB] (M) | $10^4$[HCl] (M) | $10^4$[PGB] (M) | $10^3$ $k^1$ ($s^{-1}$) |
|---|---|---|---|
| 1.00 | 1.00 | 0.20 | 6.58 |
| 1.00 | 1.00 | 0.50 | 6.58 |
| 1.00 | 1.00 | 1.00 | 6.58 |
| 1.00 | 1.00 | 2.00 | 6.59 |
| 0.20 | 1.00 | 1.00 | 1.83 |
| 0.50 | 1.00 | 1.00 | 3.84 |
| 1.00 | 1.00 | 1.00 | 6.58 |
| 2.00 | 1.00 | 1.00 | 15.4 |
| 1.00 | 0.20 | 1.00 | 10.1 |
| 1.00 | 0.50 | 1.00 | 7.90 |
| 1.00 | 1.00 | 1.00 | 6.58 |
| 1.00 | 2.00 | 1.00 | 5.02 |

### 2.4 Reaction Stoichiometry

Job's method of continuous variation [12] was employed where a plot of mole ratio between PGB and CAB Vs absorbance was drawn using standard equimolar solutions of drug and oxidant in 1:3mixture. A series of solutions consisting of fixed total number of moles of oxidant and drug but in which the complementary proportions (0.2:1.8, 0.3:1.7, 0.4:1.6…….) are varied and made up to 2ml calibrated flasks. The absorbance of the resulting solutions was measured at the end of 10 minutes when the reaction reached near completion, against reagent blank treated similarly. (Fig.1) displays a maximum absorbance of 3.45 (for the ratio 3.33:1.00) indicating the formation of 3:1 (CAB-PGB) oxidized product.

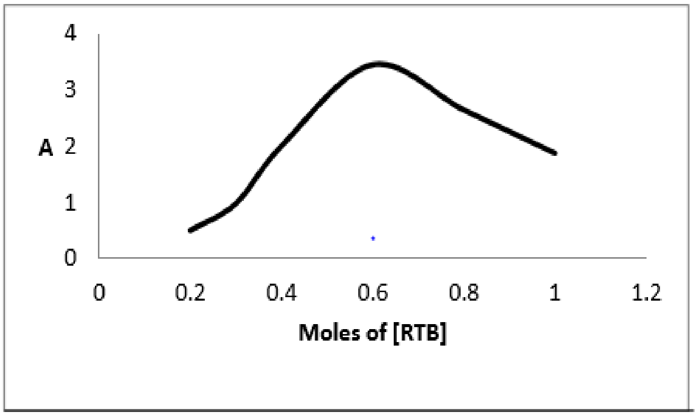


Fig-1. Job's plot of continuous variation graph for PGB - CAB reaction product

The results suggested that one mole of PGB reacted with three moles of CAB.

$C_7H_{15}NO_2 + 3C_6H_6NSO_2Cl$ $+ H_2OC_8H_{12}O_3$ $+$ $2C_6H_7SO_2N$ $+$ $N_2$ $+$ $C_6H_6SO_2H$ PGB
CAB $\longrightarrow$ Oxidized product Benzenesulphonamide Benzenesulfinic acid

### 2.5 Product Analysis

Keeping the concentration of PGB and CAB in 1:3 ratio, the two solutions were mixed and the reaction was allowed to progress for 24 hours under stirred conditions in the presence of HCl. After completion of the reaction, water insoluble and water-soluble products were observed. The water-soluble reduction products, was isolated from the reaction mixture by evaporating the water in vacuo. One of the products was identified to be Benzenesulphonamide, by TLC using a mixture of petroleum-ether, CHCl3 and ethanol (2:2:1 v/v) as the eluting solvent and iodine as spray reagent (Rf =0.88). Another product benzenesulfinic acid was extracted using ethyl acetate and identified by TLC using ethyl acetate and acetonitrile (2:2:1 v/v/v) as the mobile phase, and iodine as the detecting agent. Water insoluble product was filtered using whattman filter paper 40, and was identified by the following analytical data.

**UV-Vis Spectra** (200-400 nm)

The UV-Visible spectra were generated for a sample PGB, CAB and a mixture of both, (Fig-2). Absorption maxima of PGB appeared at 208 nm and for CAB at 223. The mixture exhibited two maxima, one small at 204 and another tall at 224nm. A hypsochromic shift of 4nm and bathochromic shift of 18 nm in the spectra generated by the mixture indicated the complex formation.

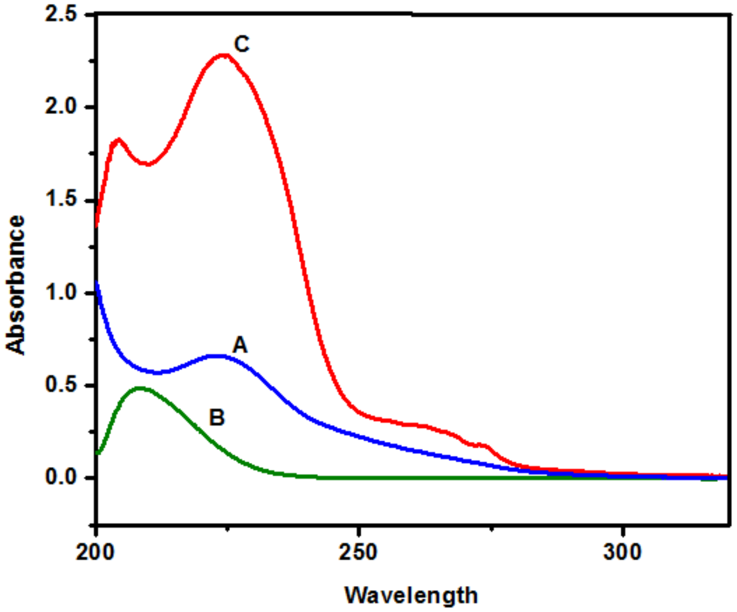


**Fig-2: UV-Visible spectra of (A) CAB (B) PGB (c) PGB + CAB complex**

**IR:** $\nu_{max/cm-1}$

A comparison of IR spectra of pure PGB (Fig-3) with IR spectra of oxidized product (Fig-4) indicates a clear structural change. Most characteristic vibrational peaks in the region 1600cm$^{-1}$ to 500cm$^{-1}$ show reproducible changes after treating PGB with CAB.

Pure PGB in Fig-3 shows a band at 1572.04 cm$^{-1}$ with a shoulder at 1624.12 cm$^{-1}$ which is the lowered value of C=O in COOH. A broad peak at 3412.19 cm$^{-1}$ because of O-H stretch of COOH is obscuring the C-H stretch bands and overlapping the primary amine stretching bands. The peak at 2955.04 cm$^{-1}$, 1396.51 cm$^{-1}$ and 1267 cm$^{-1}$ with small intensity indicates a C-H stretch, C-N stretch and a C-O stretch respectively of an amine. The peaks at 860.28 cm$^{-1}$ and 937.27 cm$^{-1}$ is because of out-of-plane bending absorption of N-H.

The oxidation product in Fig-4 shows a pair of sharp bands at 2949.26 $cm^{-1}$ and 2692.72 $cm^{-1}$ with 2603.99 $cm^{-1}$ because of O-H stretch and sp3 C-H stretch in CHO.This is overlapping and diminishing a broad peak of COOH at 3400.62 $cm^{-1}$. A strong band at 1552.75 $cm^{-1}$ and 1647.26 $cm^{-1}$ is because of C=O. Vanishing stretching bands of NH2 at 2692.72 $cm^{-1}$ and 2603.99 $cm^{-1}$ confirms the conversion of amine to aldehyde.

1572 $cm^{-1}$ (carbonyl in acid C=O)
3412 $cm^{-1}$(carboxyl O-H)
2955 $cm^{-1}$(C-H stretch),
1396 $cm^{-1}$(C-N stretch)
1267 $cm^{-1}$(C-O stretch)

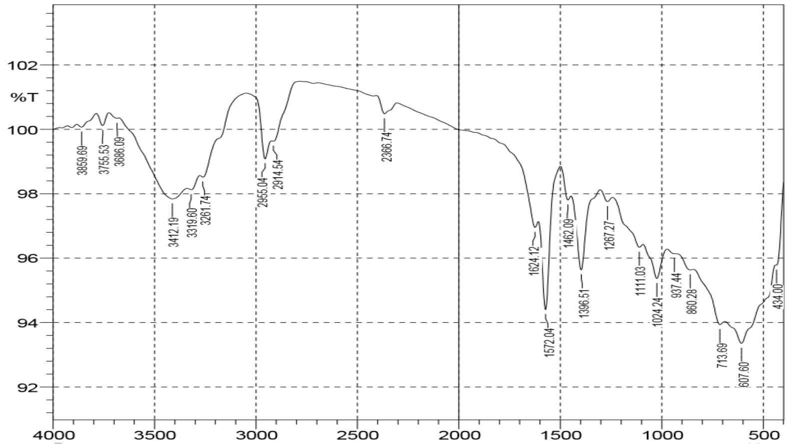


**Fig-3: IR spectrum of Pregabalin**

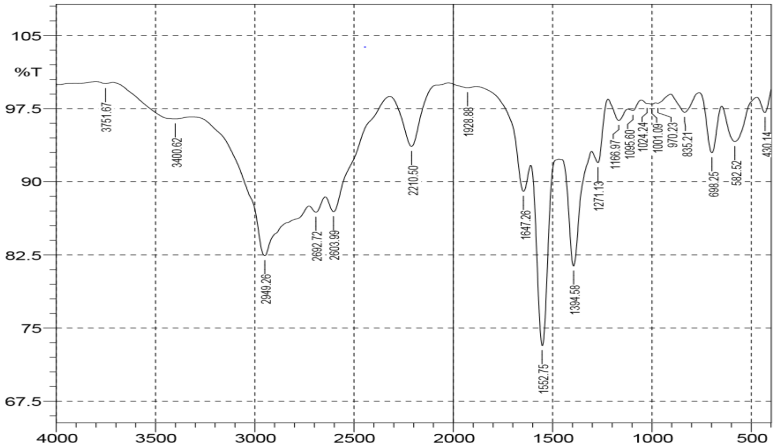


**Fig-4: IR spectrum of oxidized product**

**$^{1}$H NMR:** δ/ppm (600 MHz, DMSO, TMS)

**Fig-5(a) to 5(d)**shows 0.83-0.89 (n, 1H, CH, J=0.102 Hz), the methyne proton is influenced by 6 equivalent hydrogens in CH3 groups and 2 equivalent $CH_2$ groups and hence is split into nonet by 8 Hydrogen atoms.

2.36 (s, 6H, $CH_3$, J = 1.532) the terminal methyl groups are unaffected by neighboring protons.

2.49 (p, 1H, CH, J = 1.28) methyne proton is influenced by adjacent 2 methylene groups but unaffected by aldehydic proton.

7.36-7.34 (d, 2H, CH2, J = 0.925) methylene proton adjacent but unaffected by COOH split as a doublet due to methyneproton.

7.77 (d, 1H, J = 0.855) Aldehyde proton rarely split by adjacent proton

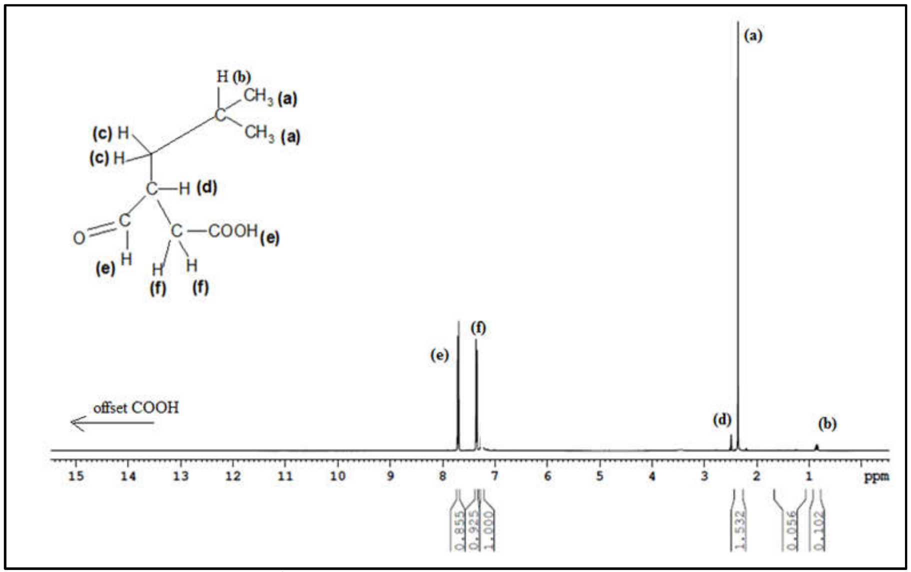


Fig-5 (a): $^1$H NMR spectrum of the oxidized product

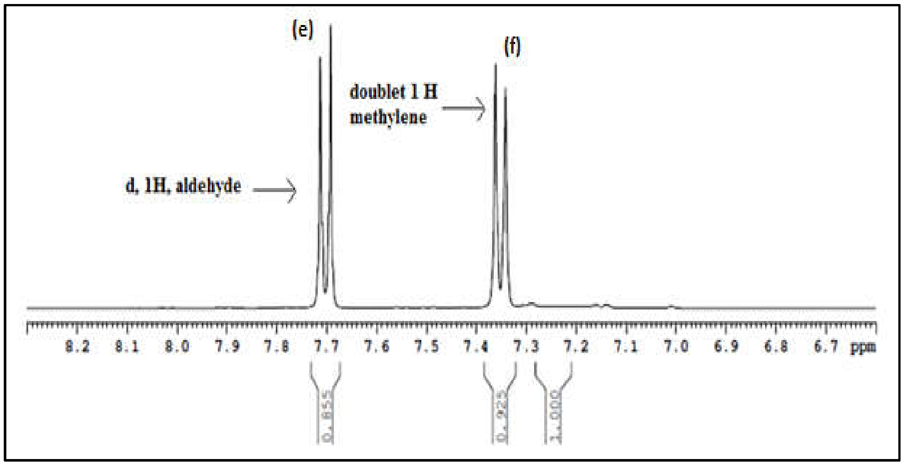


Fig-5 (b): Assignment of $^1$H NMR signals of the oxidized product (6.5-8.5ppm)

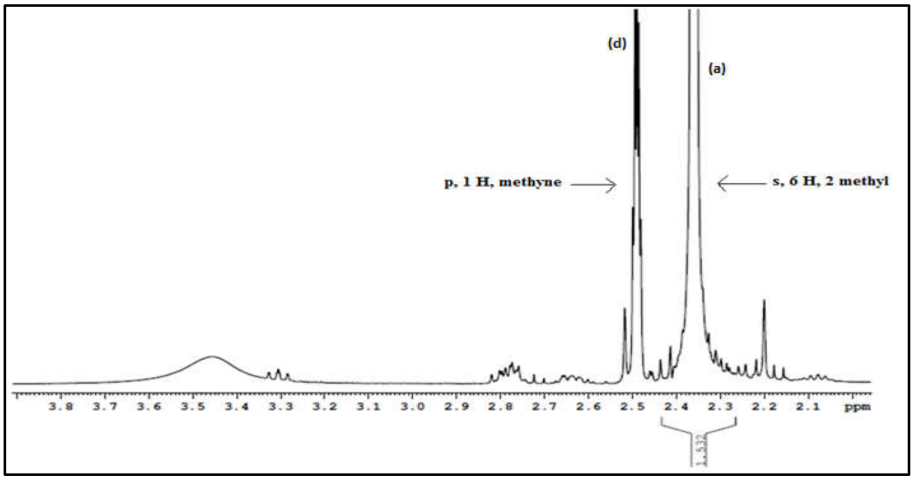


Fig-5 (c): Assignment of $^1$H NMR signals of the oxidized product (2.00- 4.00 ppm)

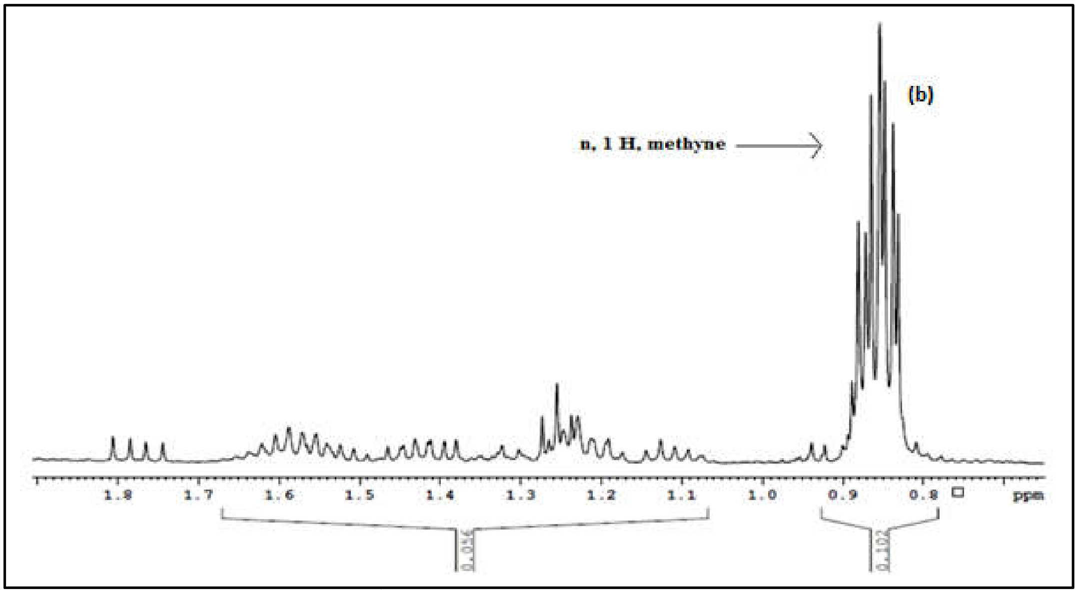


**Fig-5 (d): Assignment of $^1$H NMR signals of the oxidized product (0.5- 2.00 ppm)**

**Part II-** The water-soluble reduction products, was isolated from the reaction mixture by evaporating the water in vacuo. One of the products was identified to be Benzenesulphonamide, by TLC using an eluting solvent consisting of mixture of Petroleum-ether, $CHCl_3$ and ethanol (2:2:1 v/v) and iodine was used as the spraying reagent ($R_f$=0.88). Another product benzenesulfinic acid was extracted with ethyl acetate and identified by TLC using mobile phase composed of ethyl acetate and acetonitrile (2:2:1 v/v) with iodine sprayed as the detecting agent.

## 3. RESULTS

PGB exhibited an UV absorption peak at 205. The kinetic aspect of the oxidation reaction of PGB-CAB in HCl medium was examined spectrophotometrically by monitoring the decrease in absorbance of PGB. Pseudo-first order condition was maintained with [oxidant]>> [substrate] at constant concentration of HCl.

A mixture of PGB and HCl of known concentration was kept under stirred condition, and a measured amount of oxidant was rapidly added. Absorbance for two half-lives was measured, for the 4ml of the resulting mixture which was immediately transferred to a cuvette positioned in the spectrophotometer. The pseudo-first order rate constant 'k l' were determined from the log k Vs time plots. The course of the reaction was studied up to 75% completion. The pseudo-first order rate constant (Table 1) was evaluated and were reproducible within ±3% which facilitated the determination of the order, rate law and thereby the mechanism of the reaction.

### 3.1 Variation of concentration of oxidizing agent

Initially the concentration of PGB and HCl was maintained constant as 1.0 x 10-4 M and concentration of CAB was varied between $0.2 \times 10^{-3}$ and $2.0 \times 10^{-3}$. Plot of log [CAB] Vs log $k^l$were linear with unit slope (Fig-6) implying a first order dependency of rate on CAB.

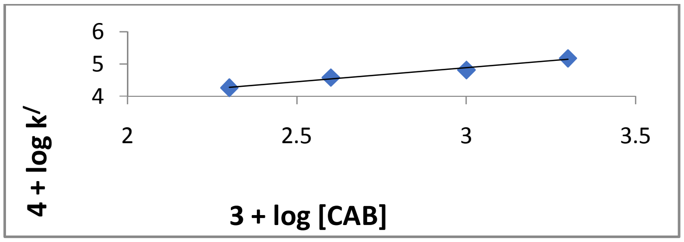


**Fig-6: Plot of log $k^/$ Vs log [CAB]**

### 3.2 Variation of concentration of PGB

The concentration of CAB and HCl was maintained to be constant as 1.0 x $10^{-3}$ M and 1.0 x $10^{-4}$ M respectively. The concentration of PGB was varied between 0.2 x $10^{-4}$ M and 2.0 x $10^{-4}$ M. It was found that the rate of the reaction inflated with the increments in the concentration of PGB. A plot of log $k^{l}$ versus [PGB] showed linearity with unit slope suggesting a pseudo-first order dependency on [PGB].

### 3.3 Variation of concentration of $[H^{+}]$

The concentration of CAB was maintained to be constant as 1.0 x 10-3 M and concentration of PGB as 1.0 x 10-4 M while varying the concentration of [H+] between 0.2 x 10-4 M and 2.0 x 10-4 M. It was found that the rate of the reaction inflated with the increments in the concentration of [H+]. A plot of log klVs [H+] showed linearity with negative slope (Fig-7) suggesting a negative fractional order dependency on [H+].

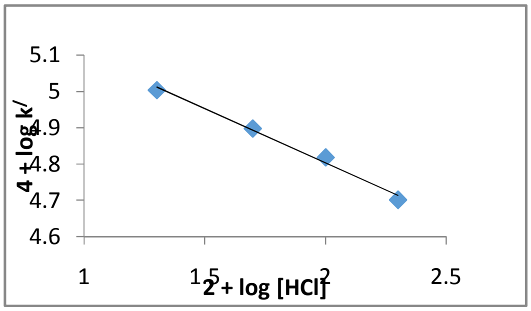


**Fig-7: Plot of log $k^{l}$ Vs log $[H^{+}]$**

### 3.4 Variation of concentration of halide ion

The rate was negligibly affected by the addition of NaCl in the concentration range 0.2 x $10^{-4}$ M and 2.0 x $10^{-4}$ M. This signifies that the independency of the rate on $[Cl^{-}]$.

### 3.5 Variation caused due to added reduction product

No variation in the rate was observed when the reaction product benzenesulphonamide was added.

### 3.6 Variation of concentration of solvent polarity and dielectric medium

The oxidation reaction was observed in mixture of methanol and water of various concentrations (% v/v) at 293K. The concentration of PGB and H+ was maintained to be constant as 1.0 x 10-4 M and concentration of CAB as 1.0 x 10-3 M. Reaction rate depleted with the increments in the concentration of methanol content in the medium **(Table-2).** The graph with log $k^{l}$ plotted on y-axis and 1/D (Fig.8) showed linearity with negative slope.

**Table-2: Influence of solvent composition on the reaction rate**

| MeOH (%) | D | $10^{3}$ $k^{l}$ ($s^{-1}$) |
|---|---|---|
| 0 | 76.73 | 6.58 |
| 5 | 74.55 | 6.22 |
| 10 | 72.37 | 5.45 |
| 20 | 67.48 | 4.88 |

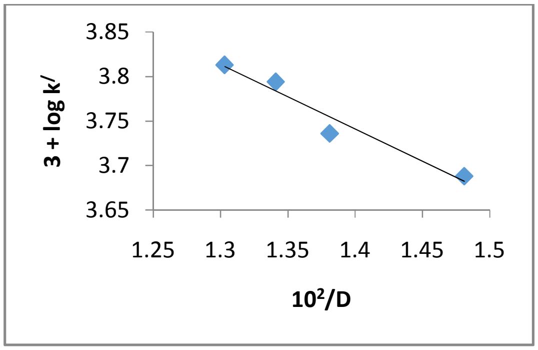


**Fig-8: Plot of log $k^{/}$ Vs 1/D**

### 3.7 Effect of ionic strength

$NaClO_4$ was added in the concentration range [1.0 x $10^{-4}$ – 1.0 x $10^{-3}$ M] but did not contribute to the change in rate of the reaction. Hence, no measure was undertaken to maintain a constant concentration of it during the study.

### Variation of temperature

The temperature was varied between 293-323 K from which Arrhenius plot where log k was plotted against 1/T to obtain activation parameters Ea, ΔH#, ΔS# and ΔG# (Table-3)

**Table-3: Rate constants at varying temperatures and activation parameters**

| Temperature (K) | $10^3$ $k^l$ ($s^{-1}$) | Activation parameter | Values |
|---|---|---|---|
| 293 | 4.35 | Ea(kJ $mol^{-1}$) | 47.72 |
| 298 | 6.58 | $\Delta H^{\neq}$ (kJ $mol^{-1}$) | 45.21 |
| 303 | 8.60 | $\Delta G^{\neq}$ (kJ $mol^{-1}$) | 90.25 |
| 313 | 13.0 | $\Delta S^{\neq}$ ($JK^{-1}$ $mol^{-1}$) | -150.4 |

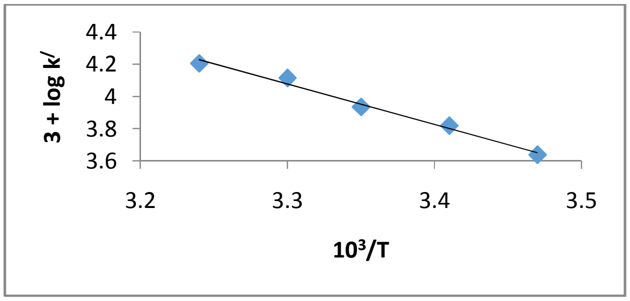


**Fig 9: Plot of log $k^/$ Vs 1/T**

## 4. DISCUSSION

Variation of the concentrations of each of the [CAB], [PGB] and [HCl] while keeping the others fixed, showed that the reaction exhibits first order in oxidant, substrate and negative fractional order acid concentration.

It is predicted that PhSO2NHCl, PhSO2NCl2 and HOCl are the possible oxidizing species of CAB by Bishop and Jennings [13], Morris et al [14] and Pryde and soper [15].

PhSO2NCl2 is excluded because the second order reaction rate with regard to oxidant is not observed in the present study. The reactions with HOCl as oxidant shows a first order retardation of rate on adding benzenesulphonamide. Such behavior was absent in this oxidation study. Hence PhSO2NHCl is considered as the oxidizing agent.

PhSO2NHCl has a great affinity to get protonated at conditions of pH<2

$$PhSO_2NHCl + H^+ \rightleftharpoons PhSO_2N^+H_2Cl$$

Since the present observations are carried at pH>3, it may be concluded that PhSO2NHCl is the oxidizing agent.

The following Scheme-1 can justify and describe all the observations.

$$PGB\,H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} PGB + H^+ \quad (fast)$$

$$PGB + CAB \xrightarrow{k_2} X \quad (slow)$$

$$X + CAB \xrightarrow{k_3} Products \quad (fast)$$

$$K_1 = \frac{[PGB][H^+]}{[PGB\,H^+]} \quad \text{---------------} \quad (i)$$

Total concentration of substrate is

$$[PGB]_t = [PGBH^+] + [PGB]$$

Substituting for $[PGBH^+]$ from (i)

$$[PGB]_t = \frac{[PGB]\,[H^+]}{K_1} + [PGB]$$

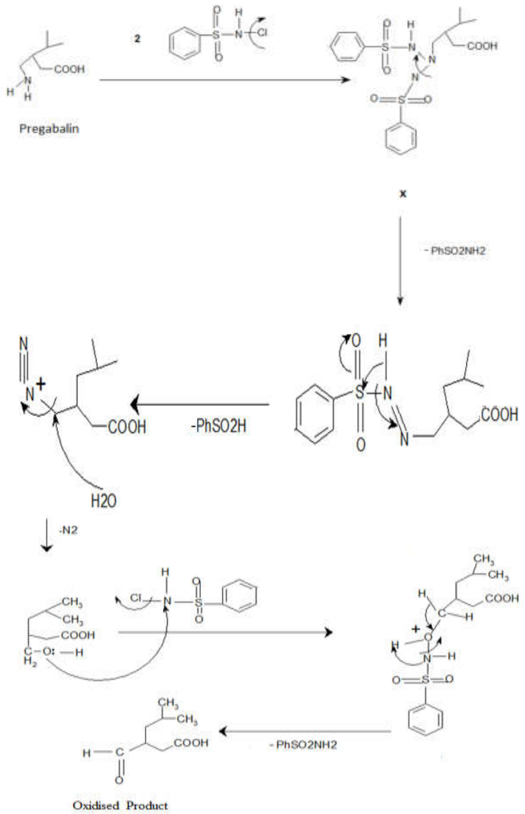
$$[PGB] = \frac{K_1\,[PGB]_t}{K_1 + [H^+]}$$

But rate $= k_2$ [PGB] [CAB]

$$rate = \frac{K_1\,k_2\,[PGB]_t\,[CAB]}{K_1 + [H^+]}$$

The rate law is in accord with all empirical results such as first order dependence of rate on [CAB] and [PGB], a negative fractional order dependence on [H+].

A detailed mode of oxidation of PGB by CAB in acid solutions is presented in **scheme 2.**



**Scheme II**

The negligible effect of added Benzenesulphonamide on the reaction rate, excludes the possibility of its involvement in the pre-equilibrium prior to the rate determining step and the decreased rate with increase in [$H^+$] could be traced to deprotonation of CAB.

The consequences of varying solvent composition and dielectric constant on the rate of reaction has been reported in many studies. In a restricted case where both dipoles or ions and dipole are drawn towards each other with zero angle, Amis [16] has proposed that a graph of log $k^l$and 1/D yields a linearity with decreasing slope for reaction between any two dipoles. However, the absence of the change due to varying dielectric constant on the rate cannot be explained by the Amis theory. Laidler has used Born equation and has presented the equation for a dipole-dipole interaction:

$$\ln k^l = \ln k^0 + 3/8kT\ (2/D - 1)\ [\mu 2A / r3_A + \mu 2_B / r3_B - \mu 2^{\neq} / r3^{\neq}]$$

Where 'k0' is the rate constant in a medium of infinite dielectric constant, 'μ' represents the dipole moment and 'r' refers to the radii of the reactants and activated complex. The rate of the reaction is always found to be more when a medium with low dielectric constant is used. This is due to the variation of charge scattering occurring in the transition state due to low dielectric constant. The extent of charge scattering is represented as $r3^{\#} = r3_A + r3_B$. On the contrary, the absence of influence of variation of dielectric constant on reaction rate implies that the size and charge distribution on the reactants and transition state do not differ and the charge scattering takes the form $r3 \approx r3_A + r3_B$.

The rate constant of a reaction is related to the dielectric constant [17] by the following expression

$$\ln k = \frac{\ln k_0 - NZ_AZ_Be^2}{DRTr\#}$$

where k0 signifies reaction rate constant of the medium with infinite dielectric constant, $Z_A$and $Z_B$ symbolizes the total charges on the ions A and B, r# refers to the radius of the activated complex, R, T and N have their usual meanings.

According the above equation, a linearity with negative slope for the graph of plot of log $k^l$ Vs 1/D represents a reaction between similarly charged ions whereas a positive slope indicates a reaction between oppositely charged ions.

The negative dielectric effect observed in the present studies **(Table-2)** clearly supports the involvement of two dipoles in the rate determining step of the mechanism considered in **(Scheme-II)**. A positive value of $\Delta G^{\neq}$ and $\Delta H^{\neq}$ specifies that a transition state which is greatly solvated is generated during the liberation of chlorine while a depleting entropy of activation implies the generation of a neatly packed and well-arranged transition state with a small number of degrees of freedom.

**Conclusion:** It is seen clearly from the obtained results that Pregabalin can be oxidized using a mild oxidant Chloramine-B in 1:3 ratio under pseudo-first order conditions and acidic medium. The characterization of the oxidized product, prediction of the mechanism and derivation of the rate law gives an insight into the biotransformation of the drug during its metabolism.

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