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The kinetic and mechanistic study of levetiracetam oxidation with chloramine-B in acid medium

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Abstract

The medicine levetiracetam, marketed under the brand name Keppra, is approved by the Food and Drug Administration, used to treat seizures. It belongs to a class of drug known as anticonvulsants. The current work uses sodium-*N*-chloro-benzene sulfonamide or chloramine-B to evaluate the kinetics and mechanistic of levetiracetam at 308 K in HCl medium. (CAB). The reaction has a first-order dependence on $[CAB]_0$ and $[substrate]_0$, as well as a fractional-order dependence on the concentration of [HCl]. Changes in ionic strength or the adding of benzene sulfonamide have no effect on the rate. We looked at the effect at five temperatures. The Arrhenius plots were used to evaluate the thermodynamic parameters. The reaction stoichiometry was found 1:2, and chromatographic and spectroscopic studies anticipated the oxidation product imine. The probable mechanism back up the above-mentioned findings. The relevant rate law has been determined because of all these discoveries.

Keywords: Acid medium; Levetiracetam; Chloramine-B; Kinetics; Oxidation

1. Introduction

The *N*-halo-aryl sulphonamide, commonly known as *N*-halo amines, is interesting because it may behave as halonium cations, hypo halites, and *N*-anions, which act as nucleophiles and bases. As a result, these compounds react with a diverse spectrum of functional groups, resulting in a variety of molecular changes[1,2,3]. Sulfonamides and NaCl or HCl are reduction products when monohaloamines suffer two electron changes and dihaloamines undergoes four electron variations. The most well-known member of this family of compounds is chloramine-T (p-$CH_3C_6H_4SO_2NClNa.3H_2O$ (CAT), whereas chloramine-B (sodium *N*-chlorobenzene sulfonamide) has been used to oxidise a range of organic and inorganic molecules, and the kinetics of their oxidation have been carefully characterised[4,5,6,7,8].

LVT is a white powder with the molecular weight of 170.20 g/mol and the chemical formula $C_8H_{14}N_2O_2$. It is soluble in methanol, water, ethanol, chloroform, and acetonitrile, but not in n-hexane. Levetiracetam (LVT) is a new antiepileptic medication with a well-known pharmacokinetic profile. Epilepsy is a long-term disorder marked by two or three recurring seizures of unknown aetiology. It's currently used to help those with partial seizures. It is the most common nerve disorder after headaches. Epilepsy is separated into partial and global seizures based on the aetiology of the seizure[9,10]. Negative symptoms include agitation, despair, memory loss, double vision, and depression[11,12].

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2. Material and methods

TCI Chemicals Pvt, Ltd, India, provided chloramine-B ACS reagent (>85.0 percent purity). Jubilant Bioscience, Ltd., India sent me a gift sample of Levetiracetam (purity > 95.0 percent as determined by HPLC Fig.1). When a drug's desired strength is necessary, it is administered. We used double distilled water and analytical grade chemicals throughout the experiment. We used an fx-991 MS scientific calculator for all calculations, and the regression coefficient r was obtained using the MS Excel application. According to the literature[13], a Shimadzu LC-2010 was used for HPLC analysis. With a length of 5 metres, a C_{18} column with just a diameter of 250 mm and a width of 4.6 mm was used. Waters Synapt Q-TOF and FT-IR mass spectrometer The IR Affinity-1S MIRacle 10 from Shimadzu was used.

2.1. General procedure

For the kinetic runs, the measurements were carried out in pseudo-first-order conditions. The needed amount of Levetiracetam, HCl, was mixed in a stoppered brown bottle to avoid the photochemical reaction. The amount of water added to keep the overall volume constant. In a water bath at 308 K for 30 minutes, a tube thermostat (Techno-ST-405, India) was employed to maintain the desired temperature. The reaction was started by adding a pre-equilibrated quantity of CAB to the mixture, and the course of the reaction was tracked using an iodometric titration of unreacted CAB in a measured aliquot (5.0 mL) of the mixture at various time intervals. We looked at the progression of two half-live' reactions. The linear plots were used to compute the rate constant (k's-').

2.2. Stoichiometry and product analysis

In an aqueous acid medium, we equilibrated excess concentrations of CAB with LVT at 308 K for 18 hours. According to the iodometric study's residual oxidant, one mole of LVT consumes two moles of chloramine-B. Under stirring conditions, a stoichiometric reaction mixture in the presence of an acid medium might progress for 24 hours at 308 K. After the reaction was completed, thin layer chromatography[14] was used to monitor it. The reaction product was extracted using hexane. TLC was used to monitor the reaction (Toluene: methanol: acetone 6:2:2), and LC-MS was used to validate the reaction, which revealed a molecular ion peak with a m/z of 186.12 amu (Fig. 3). ATR analysis reveals a peak of C=O aldehyde stretching frequency at 1700 cm-1, N-H stretching at 3250 cm^{-1}, amide C=O IR peak at 1630 cm^{-1}, and a sharp strong peak of C-O stretching at 1190 cm^{-1}, all supporting the production of N-(1-amino-oxobutan-2-yl) -4-oxobutanamide.

3. Results

3.1. Effect of reactants concentration on reaction rate

The kinetic oxidation of LVT by CAB was investigated at 308 K under pseudo-first-order conditions at various starting reactant concentrations. The plot of log $[CAB]_0$ versus time was linear at constant [HCl] and temperature, showing that the reaction rate was first order dependent on $[CAB]_0$. The values of the pseudo-first-order rate constant (k') were unaffected by changes in $[CAB]_0$ (Table 1). The rate rises as $[LVT]_0$ grows, as shown in Table 1, and the plot of log k' vs log $[LVT]_0$ was linear (R=0.993) with a first order slope of 1.01, suggesting a first order reaction on $[LVT]_0$.The rate of reaction increases as $[HCl]_0$ increases, and the plot of log k' vs log $[H^+]$ was linear (R=0.970) with a fractional slope of 0.39, indicating that the rate is fractionally dependent on $[H^+]$, Table 1. Figure 5.

3.2. Impact of ionic strength, solvent, and benzene sulphonamide on rate

Adding sodium perchlorate (0.1-0.2 mol dm^{-3}) to increase the ionic strength of the medium had no influence on the reaction rate, showing that non-ionic species are engaged in the rate-determining phase. The dielectric permittivity of the medium was adjusted at various concentrations of acetonitrile (0-20%), but no substantial increase in the rate was observed, as shown in Table 2.

3.3. Effect of altering $[H^+]$ and $[Cl^-]$ on rate

The effect of halide ions (H^+ and Cl^-) on reaction rate was also looked at. By modifying the concentration of one ion while keeping the concentration of the other ion constant at constant $[H^+]$, adding NaCl did not affect the rate much. As a result, the rate's dependence on [HCl] solely represented the influence of $[H^+]$, and the reaction rate is proportional to $[H^+]$ ion concentration. The rate was unaffected by adding reactant and product Benzene sulfonamide (2.0×10^{-4} - 8.0×10^{-4} mol dm^{-3}) to the mixture.

3.4. Impact of temperature on rate

We investigated the reaction at various temperatures using the Arrhenius plot log k' versus 1/T (R=0.985) (302-314K). The values of activation parameters, such as energy of activation Ea, enthalpy-of-formation H#, Gibbs free energy G #, and entropy S #, log A, are shown in Table 3.

Table 1 The effect of altering the concentrations of oxidant, substrate, and HCl on the rate of reaction at 308 K

10^4 [CAB] (Mol dm^{-3})	10^3 [LVT] (Mol dm^{-3})	10^2 [HCl] (Mol dm^{-3})	10^4 k' ($s^{-'}$)
2.0	6.0	3.0	6.29
4.0	6.0	3.0	6.39
6.0	6.0	3.0	6.59
8.0	6.0	3.0	6.61
4.0	2.0	3.0	4.93
4.0	4.0	3.0	5.48
4.0	6.0	3.0	6.39
4.0	8.0	3.0	6.85
4.0	10.0	3.0	7.35
4.0	6.0	1.0	4.79
4.0	6.0	2.0	5.44
4.0*	6.0	3.0	6.39
4.0	6.0	4.0	6.93
4.0	6.0	5.0	7.46
4.0**	6.0	3.0	6.28

*In presence of Benzenesulfonamide; ** At ionic strength 0.2 mol/dm^{-3}

Table 2 Effect of varying dielectric constant of the medium

% of CH_3CN	10^{-4} K (k's-')	D
0	6.39	70.08
5	6.30	69.0
10	6.19	67.3
15	6.38	65.7
20	6.28	64.2

$[CAB]_0 = 4.0\times10^{-4}$ mol dm^{-3} ; $[LVT]_0 = 6.0\times10^{-3}$ mol $dm^{-3;}$ $[HCl]_0 = 3.0\times10^{-2}$ mol dm^{-3}

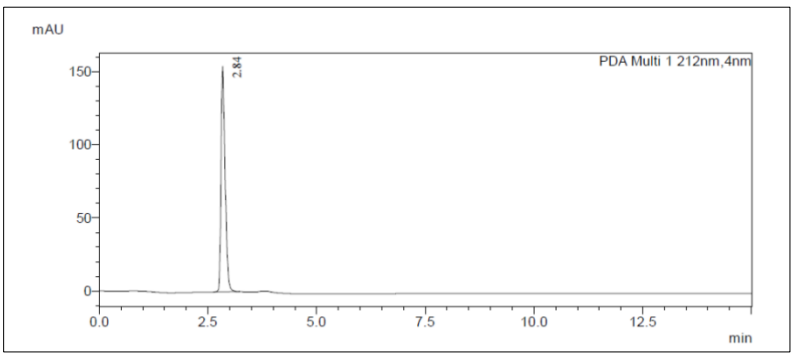

Figure 1 HPLC Chromatogram of LVT RT at 2.84 min

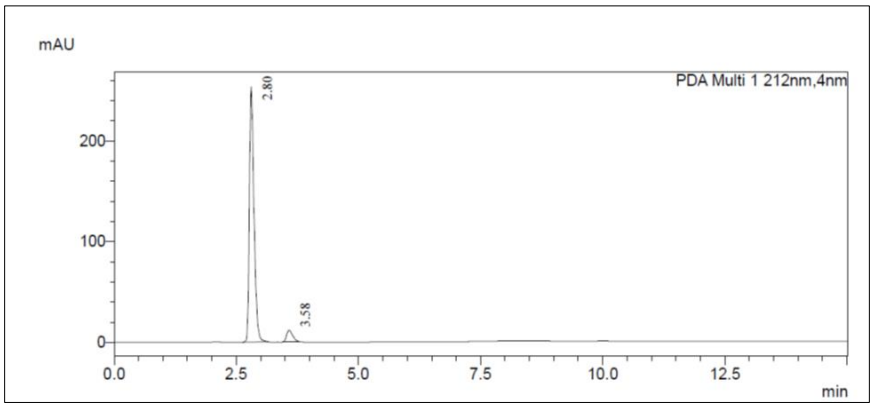

Figure 2 HPLC Chromatogram of LVT oxidation products RT at 3.58 min

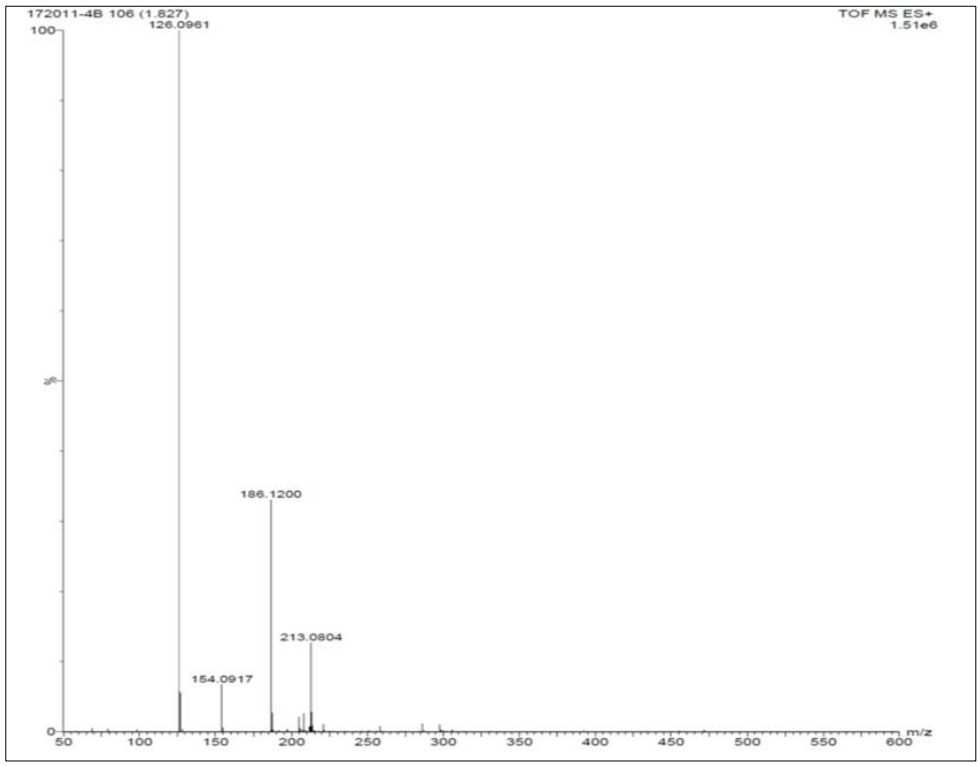

Figure 3 LC-MS Spectrum of *N*-(1-amino-oxobutan-2-yl)-4-oxobutanamide molecular ion peak at 186.12 amu

3.5. Chromatographic Conditions:

- Solutions should be prepared freshly.
- Column : $C_{18,}$ 4.6 mm X 250 mm, 5μ
- Wavelength : 212 nm
- Run time : 15 minutes
- Flow rate : 1.0 mL/min
- Mobile Phase : Methanol: Water: Acetonitrile (30:60:10)
- Column Temp : 40 ^{0}C
- Injection Volume : 20 µL
- Retention Time : 2.84 & 3.58 min

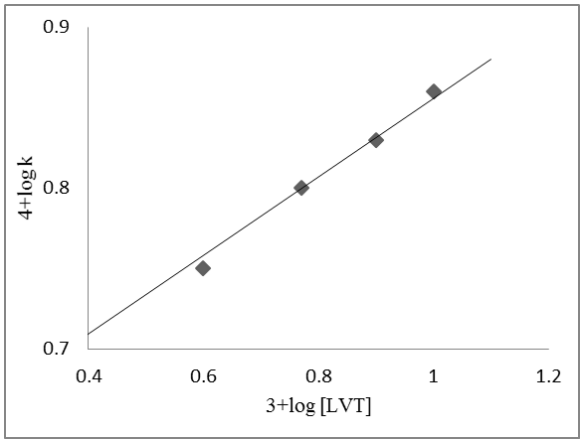

Figure 4 Plot 4+lok k' versus 3+log [LVT]

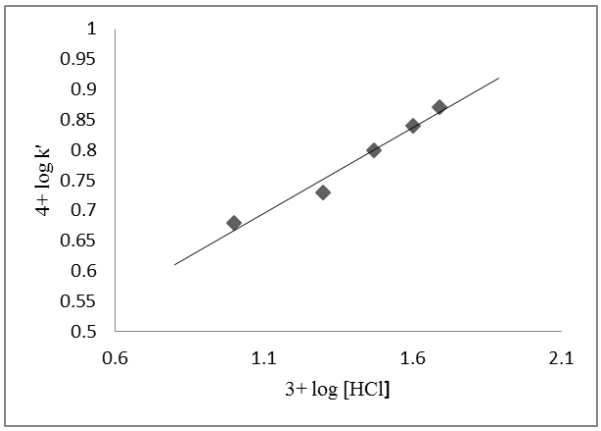

Figure 5 Plot4+lok k' versus 3+log [HCl]

Table 3 Effect of varying temperature on the rate of reaction & activation parameters for oxidation of LVT by CAB in acid medium

Temp (K)	**10^4 k' (s^{-1})**
302	4.66
305	5.59
308	6.39
311	7.09
314	7.67
Ea kJ/mol^{-1}	30.44
$\Delta H^{\#}$ kJ/mol^{-1}	27.87
$\Delta G^{\#}$ kJ/mol^{-1}	98.69
$\Delta S^{\#}$ Jk^{-1}/mol^{-1}	-229.96

$[CAB]_0 = 4.0\times10^{-4}$ mol dm^{-3} ; $[LVT]_0 = 6.0\times10^{-3}$ mol $dm^{-3;}$ $[HCl]_0 = 3.0\times10^{-2}$ mol dm^{-3}

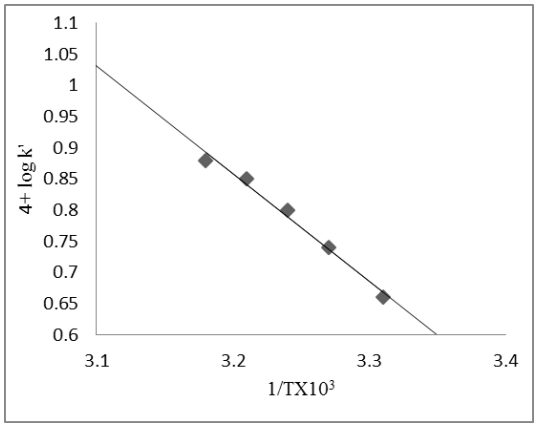

Figure 6 Plot 4+lok k' versus $1/T\times10^3$

3.6. Reactive species of Chloramine-B

In acidic and basic aqueous solutions, CAB is similar to CAT in that it has the same equilibrium. CAB undergoes a two-electron change in the reduction process, generating benzene sulphonamide (BSA; $PhSO_2NH_2$) and sodium chloride as reduction products (NaCl). The oxidation potential of the CAB-BSA redox pair varies depending on the pH of the medium. In aqueous solutions, CAB works as a strong electrolyte. Depending on the pH, CAB creates a range of reactive species [15,16,17].

$$PhSO_2NClNa \rightleftharpoons PhSO_2NCl^- + Na^+ \ldots 2$$

$$PhSO_2NCl^- + H^+ \rightleftharpoons PhSO_2NHCl \ldots 3$$

$$2PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + PhSO_2NCl_2 \ldots. 4$$

$$PhSO_2NCl_2 + H_2O \rightleftharpoons PhSO_2NHCl + HOCl \ldots. 5$$

$$PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + HOCl \ldots.6$$

$$HOCl^+ \rightleftharpoons H^+ + OCl^- \ldots7$$

$$HOCl + H^+ \rightleftharpoons H_2OCl^+ \ldots\ldots 8$$

$PhSO_2NHCl$, $PhSO_2NCl_2$, HOCl, and maybe H_2OCl+ are the likely oxidizing species in acidic CAB solutions, whereas $PhSO_2NHCl$, $PhSO_2NCl$-HOCl, and OCl^- are the likely oxidizing species in alkaline CAB solutions [18].

4. Discussion

The absence of a reaction speed increase when benzene sulfonamide ($PhSO_2NH_2$) is added shows that $PhSO_2NCl_2$ and HOCl are not reactive species in equations (4), (5) and (6). These species are found in extremely small numbers under the experimental circumstances.

Changes in $[H^+]$, the ionic strength of the medium, or the addition of the reduction product, benzene sulfonamide, have no effect on the reaction rate. Based on the experimental findings, the protonated conjugate acid ($PhSO_2NH_2Cl^+$) has been proposed as a suitable oxidizing species, and Figure-7 has been proposed to explain the oxidation of LVT by CAB in an acid media.

Based on the foregoing rationale and experimental data, the following general reaction pathway involving the oxidizing species of CAB ($PhSO_2NHCl$) interacting with substrate is proposed. The rate of reaction is first order dependent on $[substrate]_0$, shows prior equilibrium followed by a rate-determining step.

$PhSO_2NHCl + LVT \rightleftharpoons X$ fast

$X \longrightarrow X'$ Slow and rate determining step

$X' + 2PhSO_2NHCl \longrightarrow$ Products fast

Based on reaction mechanism (Figure-7) the below rate law has been derived.

$$Rate = \frac{K_1K_2[CAB]_t[LVT][H^+]}{1+K_1[H^+]} \quad \text{,……..(9)}$$

The obtained experimental results match well with the rate law (9). The discovered activation parameters support the detailed manner of LVT oxidation via CAB described in figure 7. Furthermore, strong positive values of Gibbs activation free energy and activation enthalpy imply highly solvated transition states, whereas a high negative value of entropy implies the formation of a compact transition state with numerous degrees of freedom lost [19].

Mechanism:

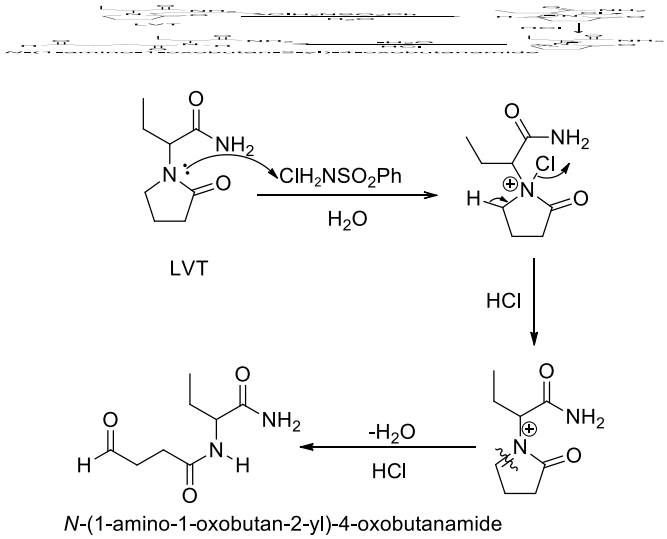

Figure- 7 Detailed mechanism for LVT oxidation with chloramine-B in acid media

5. Conclusion

The kinetics of Levetiracetam oxidation by Chloramine-B in an acid medium were studied at 308 K. The stoichiometry of the reaction was discovered to be 1:2. An Arrhenius plot of oxidation products was used to compute thermodynamic parameters. The observed results have been backed up by plausible mechanism. However, related rate law has been deduced.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors do not have any conflict of interest.

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