

SPECTROPHOTOMETRIC STUDY OF OXIDATION KINETICS AND MECHANISM OF
LOSARTAN POTASSIUM USING N-CHLOROSUCCINIMIDE

ABSTRACT

The kinetics of oxidation of Losartan Potassium [LP] by N-Chlorosuccinimide [NCS] in HCl medium is studied spectrophotometrically at 205nm at 298K. The reaction rate shows fractional order dependence on [LP], [HCl] and first order dependence on [NCS]. The reaction rate also shows an inverse fractional order in [Cl⁻]. Addition of reduction product did not have any significant effect on reaction rate. However, an increase in ionic strength decreases and increase in solvent polarity increases the reaction rate. The activation parameters for the reaction are evaluated. The proposed general mechanism and derived rate law are consistent with observations.

Keywords : Kinetics, Oxidation, N-Chlorosuccinimide, spectrophotometric, Losartan Potassium

1. INTRODUCTION

N-halogeno compounds are exploited as oxidants in the study of kinetics of variety of organic compounds since times. Recently these reagents are combined with analytical techniques and are spectrophotometrically used to oxidize various classes of organic compounds like anaesthetics [1-4] and dyes[5-8]. In the literature, an important N-halogenated imide, namely N-Chlorosuccinimide[NCS] is reported to have quantitatively oxidized selenides [9] and chalcones [10] very effectively.

Losartan Potassium [LP] is an angiotensin II receptor type AT1 antagonist chemically described as 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol monopotassium salt. It works by relaxing blood vessels, lowers the blood pressure and hence used in treating cardiac arrest, stroke and kidney problems. From the literature, it is evident that extensive studies have been made on analytical methods of estimation of LP for single dosage form [11]and simultaneous quantitative estimations, as the drug is often co-administered with calcium channel blockers [12], ACE inhibitors[13] and diuretics [14,15]. Also, invitro evaluation of drug release is reported from mucoadhesive buccal tablets [16], matrix tablets[17], microspheres [18] and interaction of drug with antidiabetic agents [19].

It is known that the drug undergoes substantial first pass metabolism by CYP-450 2C9 and 3A4 enzymes and 14% of an oral dose is converted to an active-5-carboxylic acid metabolite by the oxidation of C5-hydroxy methyl group. However, no report exists in the literature on invitro kinetics of oxidation of LP, which may give some information on the mechanism of metabolism in biological systems. Hence the present study deals with the kinetic behaviour and mechanistic information and a plausible rate law governing the oxidation of C₅ hydroxymethyl group in the imidazole ring of Losartan Potassium to carboxylic acid metabolite. The literature survey reveals that there is no report on kinetics of oxidation of LP by any oxidants in acidic medium. Hence the present study deals with the kinetic behaviour and mechanistic information and a plausible rate law governing the oxidation of C₅ hydroxymethyl group in the imidazole ring of Losartan Potassium to carboxylic acid metabolite.

2. EXPERIMENTAL

2.1 Materials

N-Chlorosuccinimide was obtained by Merck, India. The compound purity was checked iodometrically and by IR spectrum. An aqueous solution of NCS 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. LP obtained from Apotex, India was used without further purification. All other reagents namely double distilled water, hydrochloric acid, NaClO₄, 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 an 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.

¹H 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.

Elemental analysis was done on a Perkin Elmer CHN 2400 analyser.

2.3 Kinetic measurements

Kinetic measurements were performed on Shimadzu UV 2401 PC UV-Vis Spectrophotometer. LP exhibited an absorption maximum at 205 nm. The progress of the reaction was followed spectrophotometrically at 205nm by monitoring the decrease in absorbance of LP.

All kinetic measurements were performed under pseudo-first order condition where [oxidant] >> [substrate] in the presence of HCl at constant concentration of NaClO₄ (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 thermostated 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 are D₀ and D_t. Plots of log D₀/D_t Vs time resulted in pseudo-first order rate constants k(Table 1).

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

10^2 [NCS] (M)	10^3 [HCl] (M)	10^3 [LP] (M)	10^3 k (s ⁻¹)
1.50	1.50	0.50	3.507
1.50	1.50	0.10	3.589
1.50	1.50	1.50	3.758
1.50	1.50	2.00	3.801
1.50	1.50	2.50	3.900
0.50	1.50	1.50	1.258
0.10	1.50	1.50	2.511
1.50	1.50	1.50	3.776
2.00	1.50	1.50	4.466
2.50	1.50	1.50	4.808
1.50	0.50	1.50	2.172
1.50	0.10	1.50	3.548
1.50	1.50	1.50	3.775
1.50	2.00	1.50	4.466
1.50	2.50	1.50	4.808

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60 2.4 Reaction Stoichiometry

61 Job's method of continuous variation [20] was employed where a plot of mole ratio between the drug and oxidant Vs absorbance was drawn.
62 The results suggested that one mole of LP reacted with two moles of NCS.



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66 LP 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanol

67 Oxidised product 2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]imidazole-5-methanoic acid

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69 2.5 Product Analysis

70 Keeping the concentration of NCS in excess over LP, the two solutions were mixed in presence of HCl and the reaction was allowed to progress
71 for 24 hours under stirred conditions in the presence of acid.

72 After completion of the reaction, water insoluble and water soluble products were observed.

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74 Water insoluble product was filtered using Whatman filter paper 40, dried and the purity was checked using TLC technique with 1:1 Benzene
75 and Ethanol as eluting solvent. The product was soluble in dilute NaHCO₃ with brisk effervescence indicating the presence of carboxylate group.
76 Elemental Analysis resulted in carbon 62.57%, Hydrogen 4.98%, and Nitrogen 19.95% for C₂₂H₂₁ClN₆O₂ confirming the structure of oxidized
77 product.

78 The product was identified by the following analytical data.

79 IR: ν_{max} /cm⁻¹

80 3399 (OH),

81 3061 (C-H stretch),

82 2958 (N-H stretch),

83 1745 (C=O stretch),

84 1464 (imidazole),

85 1415 (C=N stretch),

86 1006 (C-O stretch),

87 759 (O-H bend)

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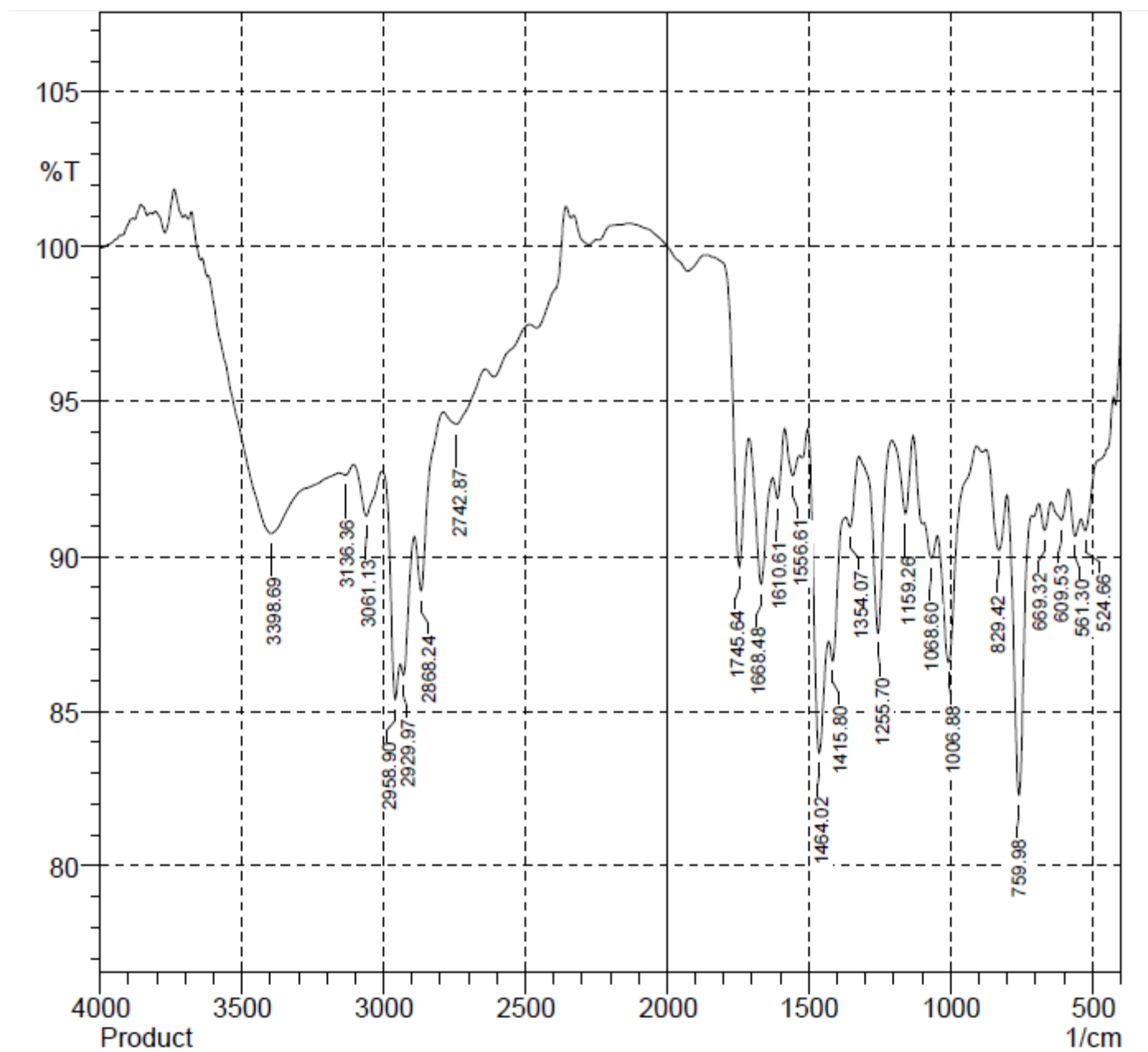


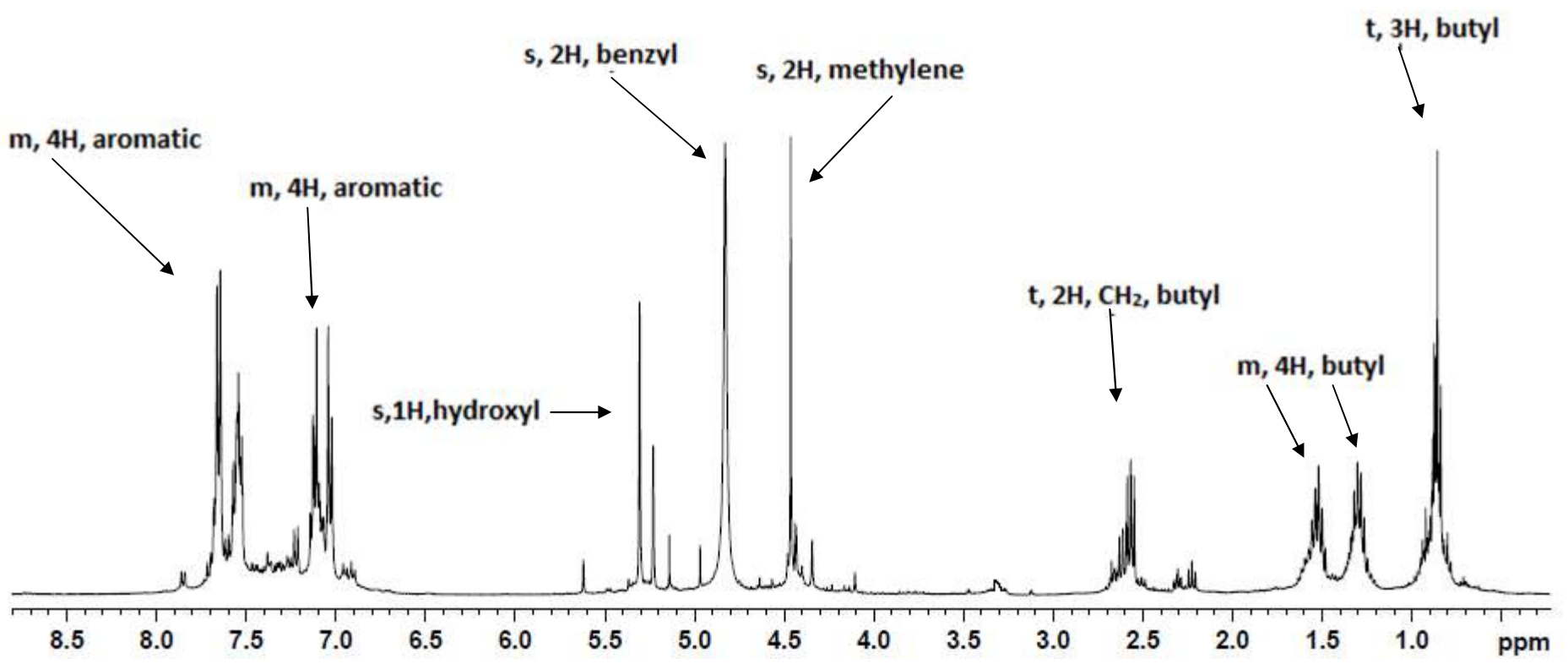
Fig 1: IR spectrum of oxidized product

¹H NMR : δ /ppm (600 MHz, deuteriated methanol, TMS)

- 0.89 (t, 3H, CH₃, J=2.88 Hz),
- 1.3-1.55 (m, 4H, CH₂-CH₂, J=1.70 and 1.71)
- 2.59 (t, 2H, CH₂, J = 1.00)
- 4.46 (s, 2H, CH₂, J = 1.28)
- 4.83 (s, 2H, CH₂, benzyl)
- 5.30 (s, 1H, OH, J = 0.6)
- 7.12 (m, 4H, aromatic, J = 2.72)
- 7.53 (m, 4H, aromatic, J = 2.01)

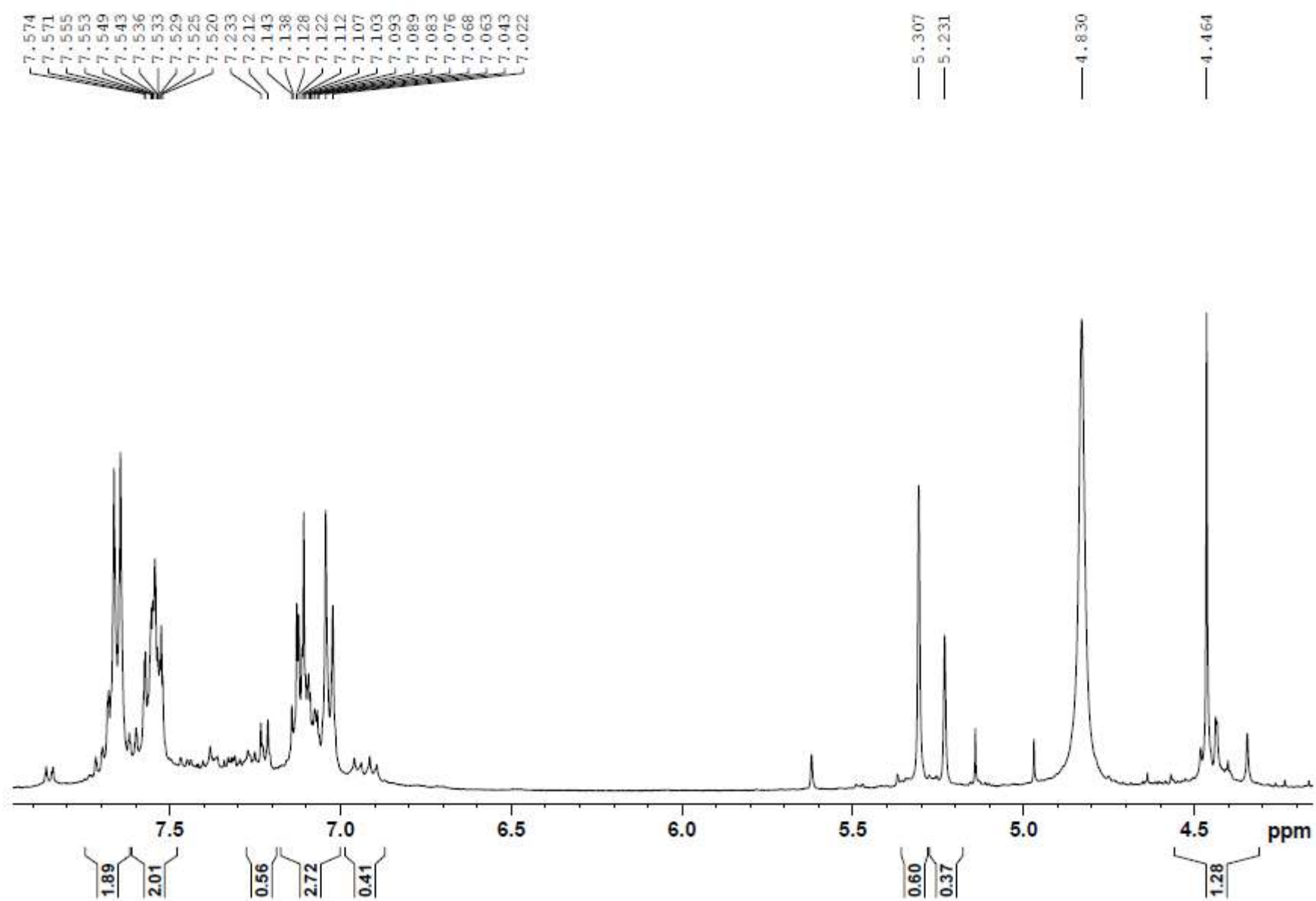
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0.847
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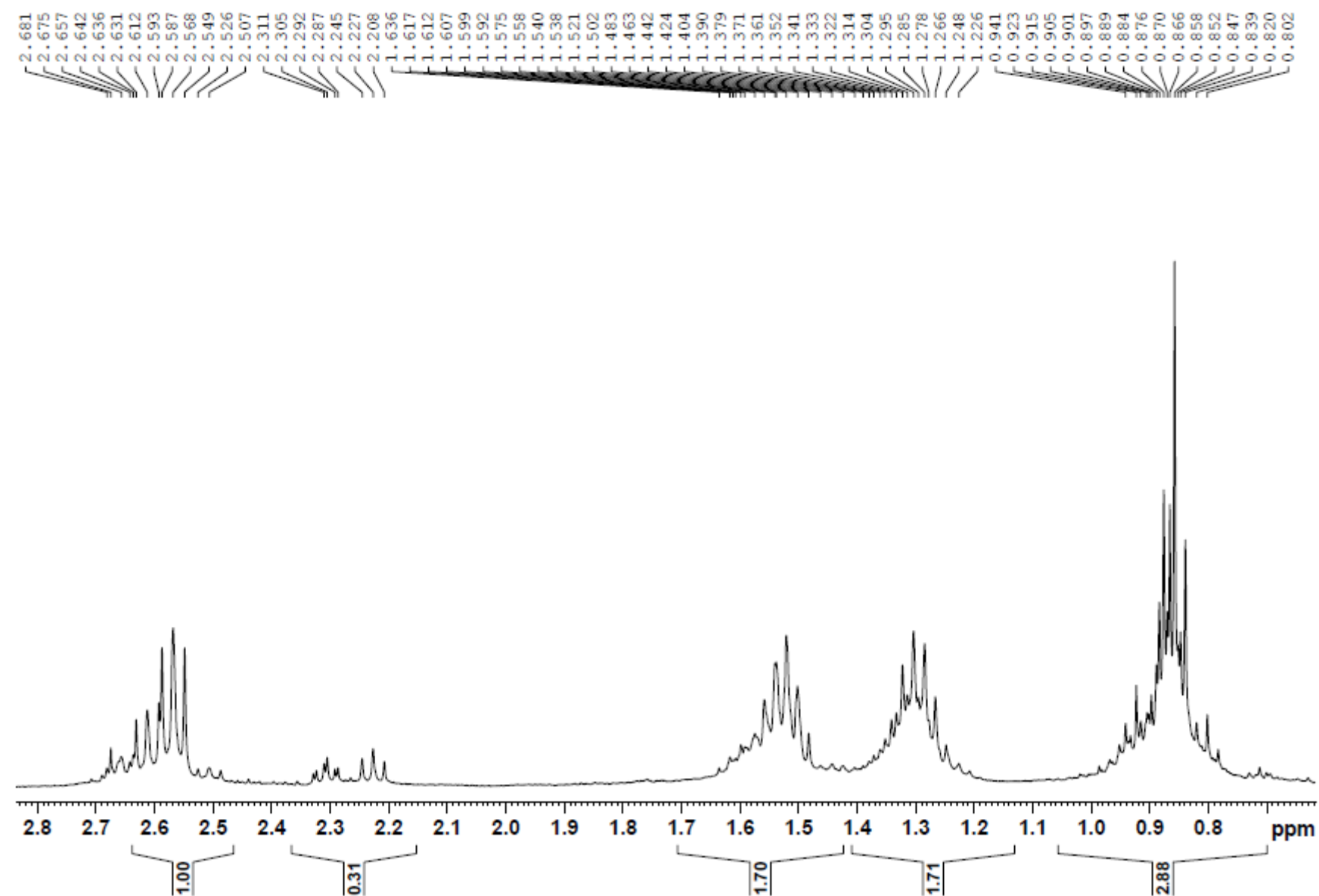
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Fig 2: ^1H NMR spectrum of the oxidized product

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The water soluble product, was isolated from the reaction mixture by evaporating the water in vacuo and crystallizing the solid residue from Benzene and was identified as Succinimide with melting point 125°C . The purity was checked by TLC using Petroleum Ether-Chloroform-n-Butyl alcohol (2:2:1 v/v/v) as the mobile phase, and Iodine as the detecting agent. Succinimide was also confirmed by IR: $\nu_{\text{max}}/\text{cm}^{-1}$ 3450 br (NH) and 1698 (CO).

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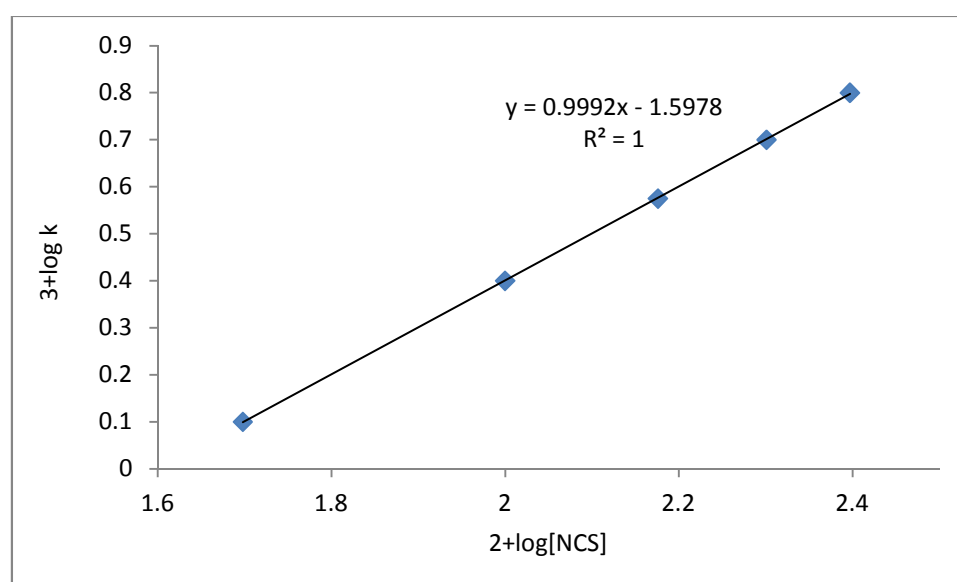
3. RESULTS AND DISCUSSION

131 The kinetics of oxidation of LP by NCS was investigated at 298K in presence of known concentration of HCl. The reaction orders, rate law and
132 other experimental data was obtained.

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3.1 Effect of varying oxidising agent on the rate

135 Kinetics of oxidation of LP by NCS was studied at various initial concentrations $[0.5 - 2.5 \times 10^{-2}]$ of NCS at 298K keeping the concentration of
136 LP $[1.5 \times 10^{-3}]$ and HCl $[1.5 \times 10^{-3}]$ as constant. Plot of $\log [\text{NCS}]$ Vs $\log k$ were linear with unit slope (Fig.3) indicating a first order
137 dependance of rate on NCS.

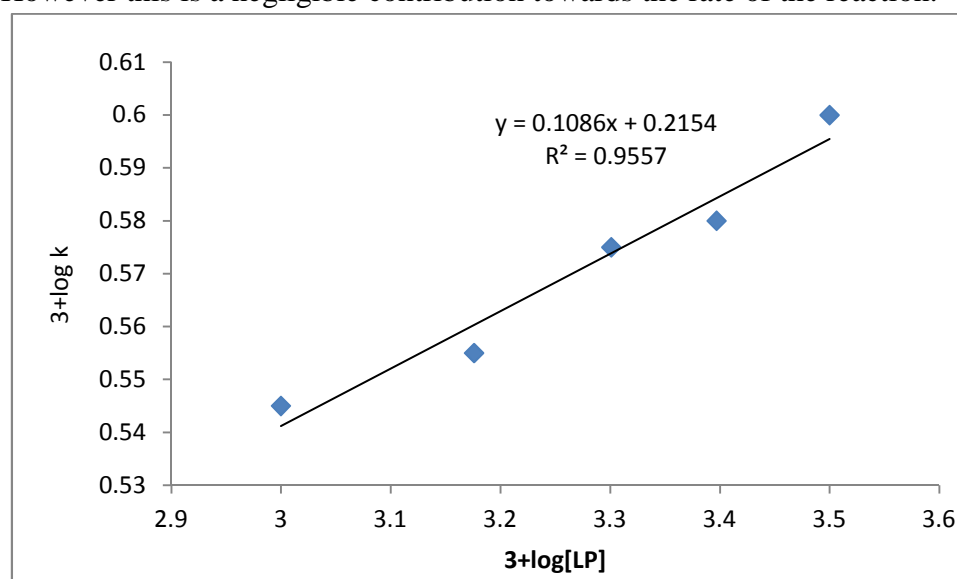


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Fig 3: Plot of $\log k$ Vs $\log [\text{NCS}]$

3.2 Effect of varying LP on the rate

142 The oxidation was carried out with various initial concentrations of LP $[0.5 - 2.5 \times 10^{-3}]$ by using $[1.5 \times 10^{-2}]$ of NCS and $[1.5 \times 10^{-3}]$ of HCl.
143 The rate of the reaction increased with increasing [LP]. Plot of $\log [\text{LP}]$ Vs $\log k$ were linear with slope of 0.2 (Fig.4) indicating a fractional
144 order dependance of rate on [LP]. However this is a negligible contribution towards the rate of the reaction.
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Fig 4: Plot of $\log k$ Vs $\log [\text{LP}]$

3.3 Effect of varying HCl on the rate

151 The reaction was also carried out with $[1.5 \times 10^{-2}]$ of NCS and $[1.5 \times 10^{-3}]$ of LP, by varying
152 HCl $[0.5 - 2.5 \times 10^{-3}]$. The rate increased with increase in [HCl] (table 1). A Plot of $\log k$ versus $\log [\text{HCl}]$ was linear with unit slope (Fig.5)
153 indicating a first order dependance of rate on [HCl].
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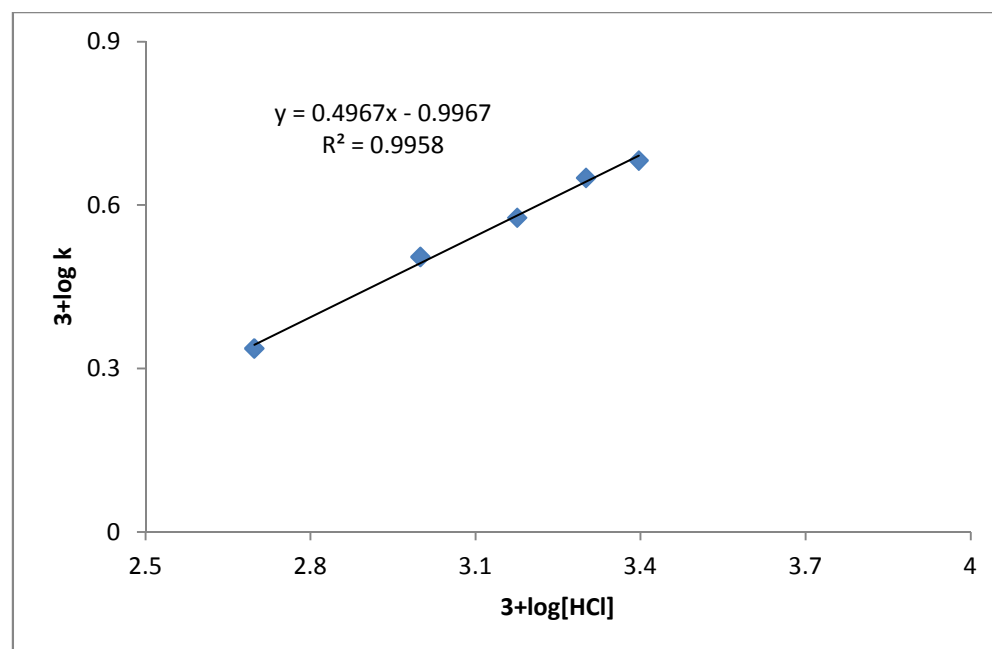


Fig 5: Plot of log k Vs log [HCl]

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3.4 Effect of varying $[H^+]$ and $[Cl^-]$ on the rate

In order to determine the order of the reaction with respect to $[H^+]$ and $[Cl^-]$ separately, the reaction was also studied by varying the concentration of one ion while keeping the concentration of the other constant. The effect of $[H^+]$ on the rate was studied by adding HCl at constant high $[Cl^-]$ maintained with NaCl and the effect of $[Cl^-]$ on the rate was studied by varying $[NaCl]$ at constant $[H^+]$. The plot of log k Vs log $[H^+]$ was linear with unit slope (Fig.6) showing a first-order dependence of the rate on $[H^+]$ and the plot of log k Vs log $[Cl^-]$ indicated a negative fractional order(Fig.7) dependence with a slope of -0.5 (Table 2)

Table 2: Effect of varying $[H^+]$ and $[Cl^-]$ on the reaction rate at 298K

$[LP] = 1.5 \times 10^{-3} M$ $[NCS] = 1.5 \times 10^{-2} M$

$10^{-3}[HCl] M$	$10^{-3}[NaCl] M$	$k \times 10^{-3}$
0.5	1.5	1.922
1.0	1.5	2.089
1.5	1.5	2.570
2.0	1.5	2.951
2.5	1.5	3.235
1.5	0.5	3.975
1.5	1.0	3.235
1.5	1.5	2.571
1.5	2.0	2.089
1.5	2.5	1.742

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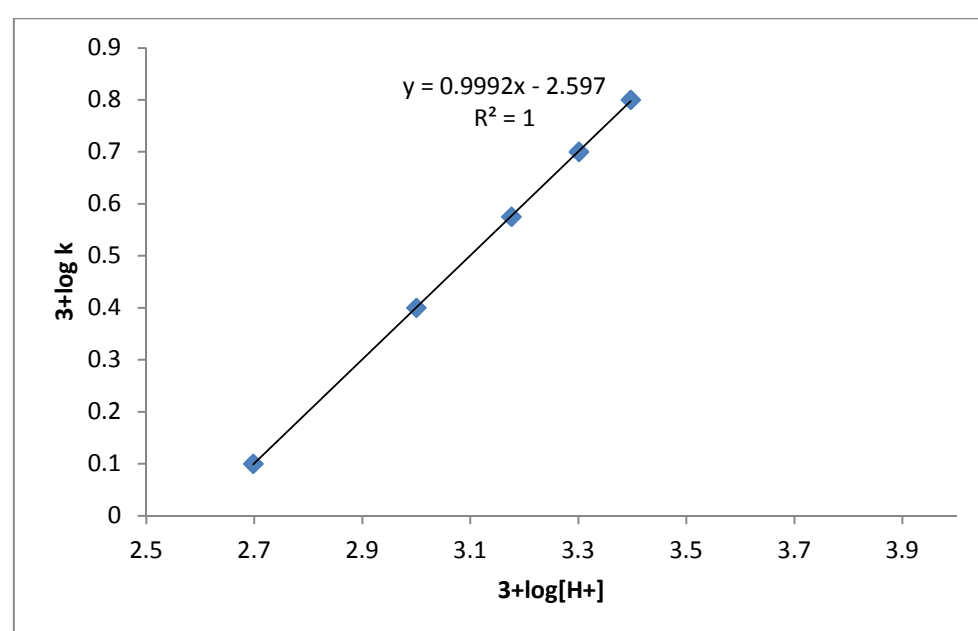


Fig 6: Plot of log k Vs log $[H^+]$

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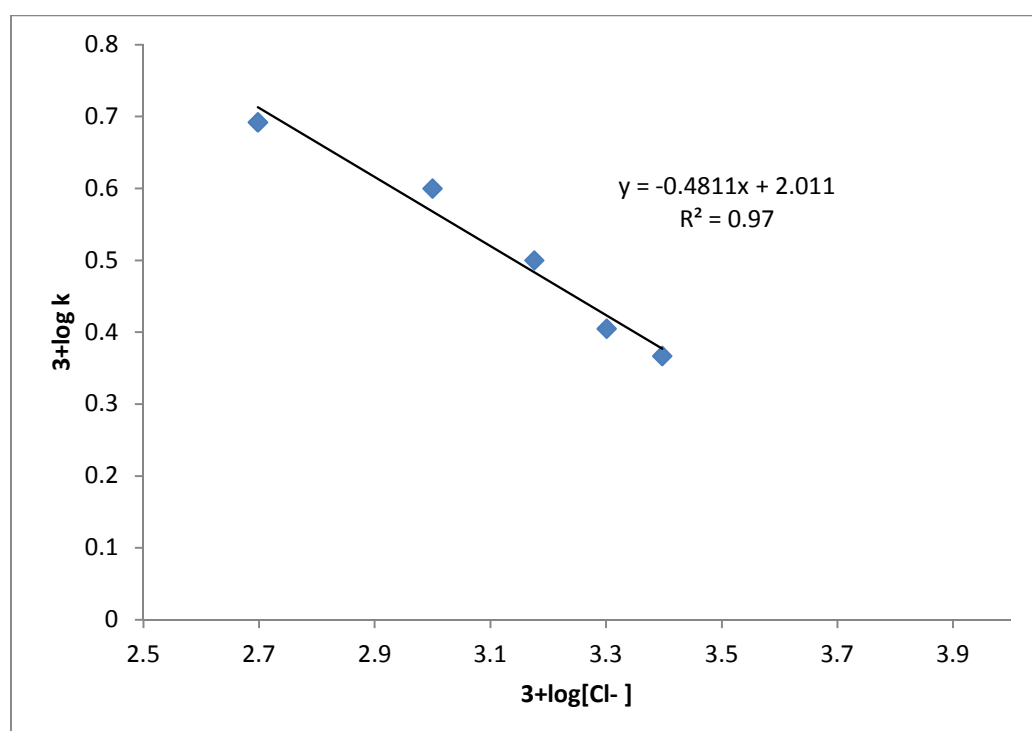


Fig 7: Plot of log k Vs log [Cl⁻]

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3.5 Effect of added Succinimide on the rate

178 Addition of Succinimide, the reduction product of the oxidant had no significant effect on rate of the reaction (Table 3).

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Table 3: Effect of varying concentration of succinimide on the reaction rate at 298K

[succinimide] x 10 ⁻³	k x 10 ⁻³
0.50	2.191
0.10	2.181
1.50	2.170
2.00	2.100

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3.6 Effect of varying ionic strength on the rate

182 The reaction was conducted at different ionic strength using NaClO₄ solution, keeping the other experimental conditions constant. Increase in
183 ionic strength of the medium decreases the rate (Table 4). A plot of log k Vs log [NaClO₄] is linear with negative slope of -0.6 (Fig.8). Hence,
184 the ionic strength of the medium was maintained at a concentration of 1.5 x 10⁻³ M for all kinetic runs.

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Table 4: Effect of varying concentration of NaClO₄ on the reaction rate at 298K

[NaClO ₄] x 10 ⁻³	k x 10 ⁻³
0.5	2.621
1.0	2.311
1.5	2.070
2.0	1.699

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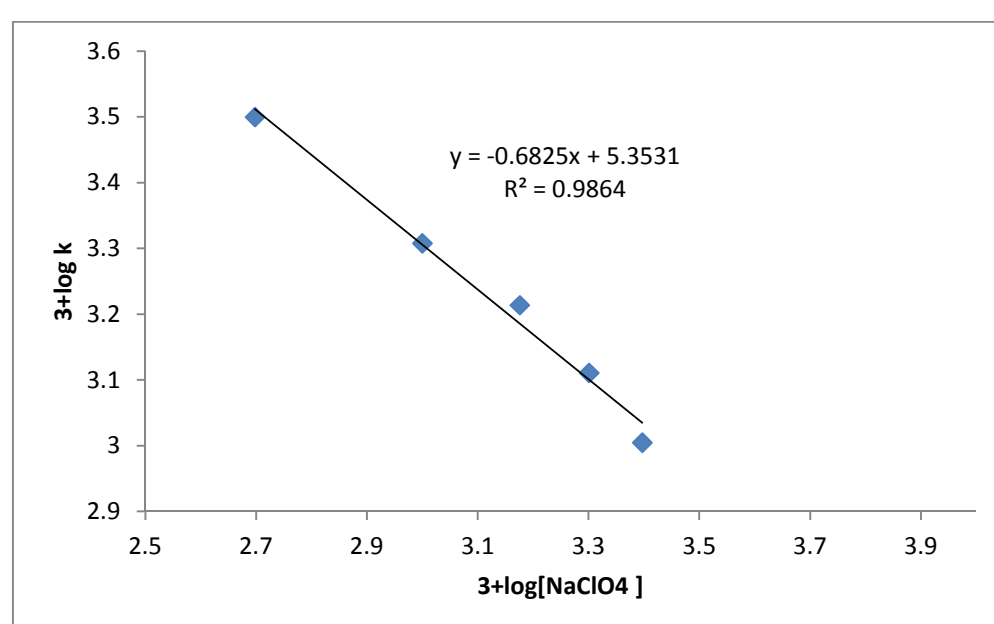


Fig 8: Plot of log k Vs log [NaClO₄]

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3.7 Effect of varying solvent polarity and Dielectric medium

193 The reaction of LP [1.5 x 10⁻³] with NCS [1.5 x 10⁻²] was carried out in methanol-water mixtures of various compositions (% v/v) containing HCl
194 [1.5 x 10⁻³] at 298 K. The reaction rate increased with increase in methanol content (i.e. decrease in dielectric constant D) in the solvent medium
195 (Table 5). The plots of log k Versus 1/D (fig.9) were linear having positive slopes. The D values were obtained from the literature [19].

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Table 5. Effect of solvent composition on the reaction rate

MeOH (%)	D	$10^3 k (s^{-1})$
0	76.73	1.437
5	74.55	1.854
10	72.37	2.849
20	67.48	6.218

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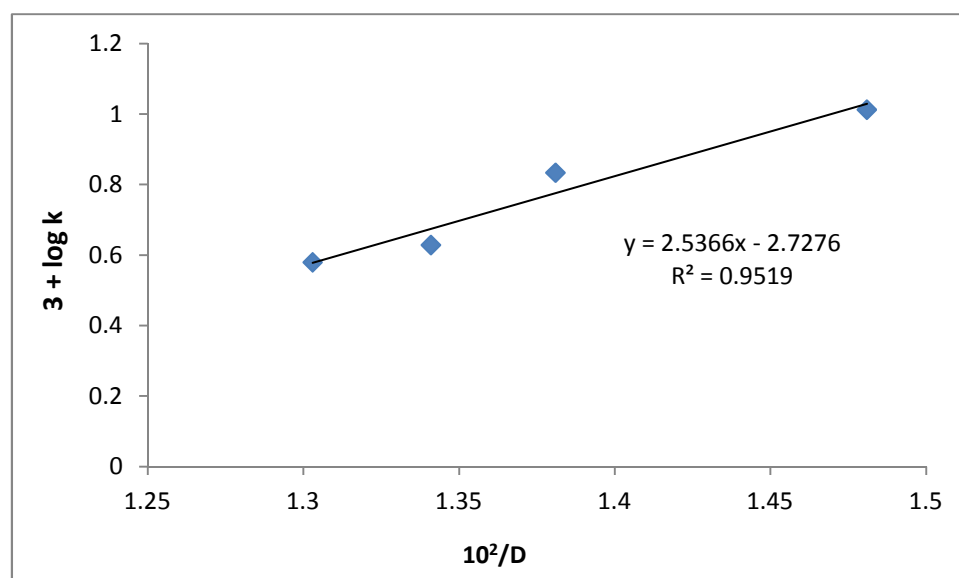


Fig 9: Plot of log k Vs 1/D

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3.8 Effect of Temperature

208 The rate constants (k) of the reaction were determined at different temperatures (298-305K). From the linear Arrhenius plot of $\log k$ Vs $1/T$ (Fig.10) the activation parameters, namely, energy of activation (E_a), enthalpy of activation (ΔH^\ddagger), entropy of activation (ΔS^\ddagger), and Gibbs free energy of activation (ΔG^\ddagger) along with Arrhenius factor (A) were obtained (Table 6).

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Table 6. Rate constants at varying temperatures and activation parameters

Temperature (K)	$10^3 k (s^{-1})$	Activation parameter
298	0.580	$E_a(kJ mol^{-1}) = 50.2$
303	0.682	$\Delta H^\ddagger (kJ mol^{-1}) = 47.8$
308	0.806	$\Delta G^\ddagger (kJ mol^{-1}) = 92.5$
313	0.962	$\Delta S^\ddagger (J.K^{-1} mol^{-1}) = -147$
318	1.137	$\log A = 7.78$

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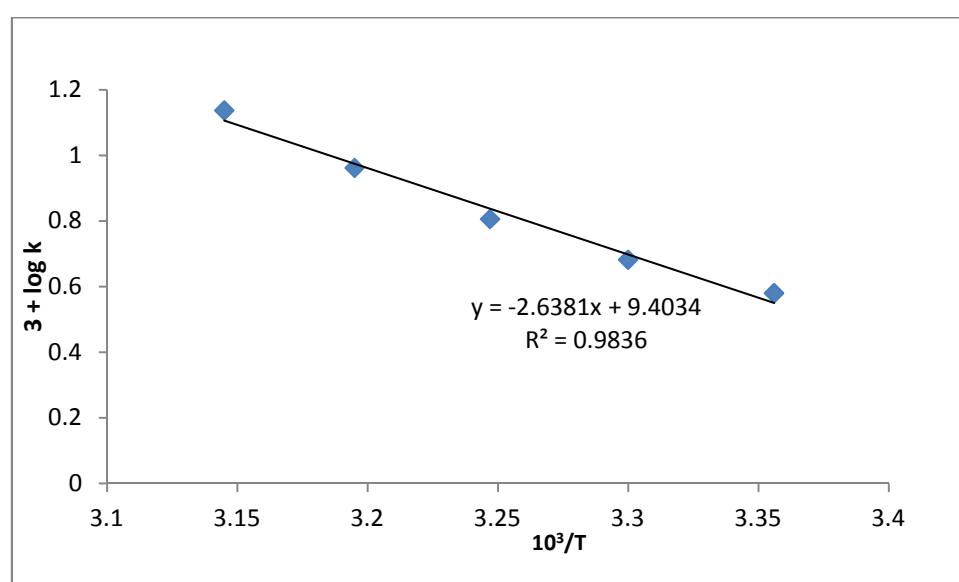


Fig 10: Plot of log k Vs 1/T

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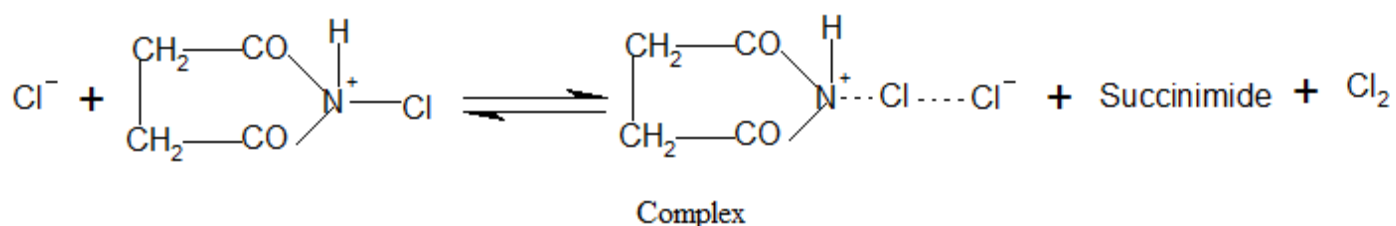
220 Recently, oxidation by NBS [21] analogous to the present discussed scheme was reported. However, there are certain differences owing to the
221 fact that NBS has a more positive halogen than NCS. In aqueous acidic media, the probable reactive species of NCS are Cl_2 , $HOCl$, H_2OCl^+ ,
222 $NCSH^+$ or NCS . The oxidation of Alcohols by N-Chlorosuccinimide has been reported [22] to take place through the intermediate $NCSH^+$. As
223 the rate increases with increase in $[HCl]$, it is assumed that $NCSH^+$ is the oxidizing species which reacts with chloride ions and produces a steady
224 small concentration of molecular Chlorine acting as an effective oxidant. Based on the preceding facts, the proposed LP oxidation mechanism is
225 presented in scheme below
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234
235 **Scheme 1: Mechanism of oxidation of LP by NCS in acid medium**

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237 The negligible effect of reduction product Succinimide on the reaction rate indicates its non involvement in the pre-equilibrium step prior to the
238 rate determining step. An initial equilibrium step (i) involves the formation of protonated NCS. In the next step, the protonated NCS, reacts
239 with the chloride ions and chlorine is released slowly in small concentrations. Low polarity of N-Cl, makes the rupture of N-Cl difficult and
240 consequently, step (ii) becomes a slow and rate determining step. The liberated Chlorine interacts with substrate to form an Aldehyde which
241 further is oxidized to the corresponding carboxylic acid derivative in the subsequent fast steps.

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244 Assuming the slow rate determining step to go via the formation of a complex, the eq (ii) may be expressed as



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246 The rate law would probably be
247 The total effective concentration $[\text{NCS}]_{\text{total}} = [\text{NC}^+\text{SH}] + [\text{Cl}^-] + [\text{NCS}]$ (v)

248 From scheme 1, $k_1 = \frac{[\text{NC}^+\text{SH}][\text{Cl}^-]}{[\text{NCS}][\text{HCl}]}$
249
250 $[\text{NCS}] = \frac{[\text{NC}^+\text{SH}][\text{Cl}^-]}{k_1[\text{HCl}]}$ (vi)

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253 Putting (vi) in (v)
254 $[\text{NCS}]_{\text{total}} = [\text{NC}^+\text{SH}] + [\text{Cl}^-] + \frac{[\text{NC}^+\text{SH}][\text{Cl}^-]}{k_1[\text{HCl}]}$

255
256 $[\text{NCS}]_{\text{total}} = \frac{k_1[\text{HCl}][\text{NC}^+\text{SH}] + k_1[\text{HCl}][\text{Cl}^-] + [\text{NC}^+\text{SH}][\text{Cl}^-]}{k_1[\text{HCl}]}$

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259 $[\text{NCS}]_{\text{total}} = \frac{[\text{NC}^+\text{SH}](k_1[\text{HCl}] + [\text{Cl}^-]) + k_1[\text{HCl}][\text{Cl}^-]}{k_1[\text{HCl}]}$

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262 $[\text{NC}^+\text{SH}] = \frac{[\text{NCS}]_{\text{total}} k_1[\text{HCl}] - k_1[\text{HCl}][\text{Cl}^-]}{k_1[\text{HCl}] + [\text{Cl}^-]}$

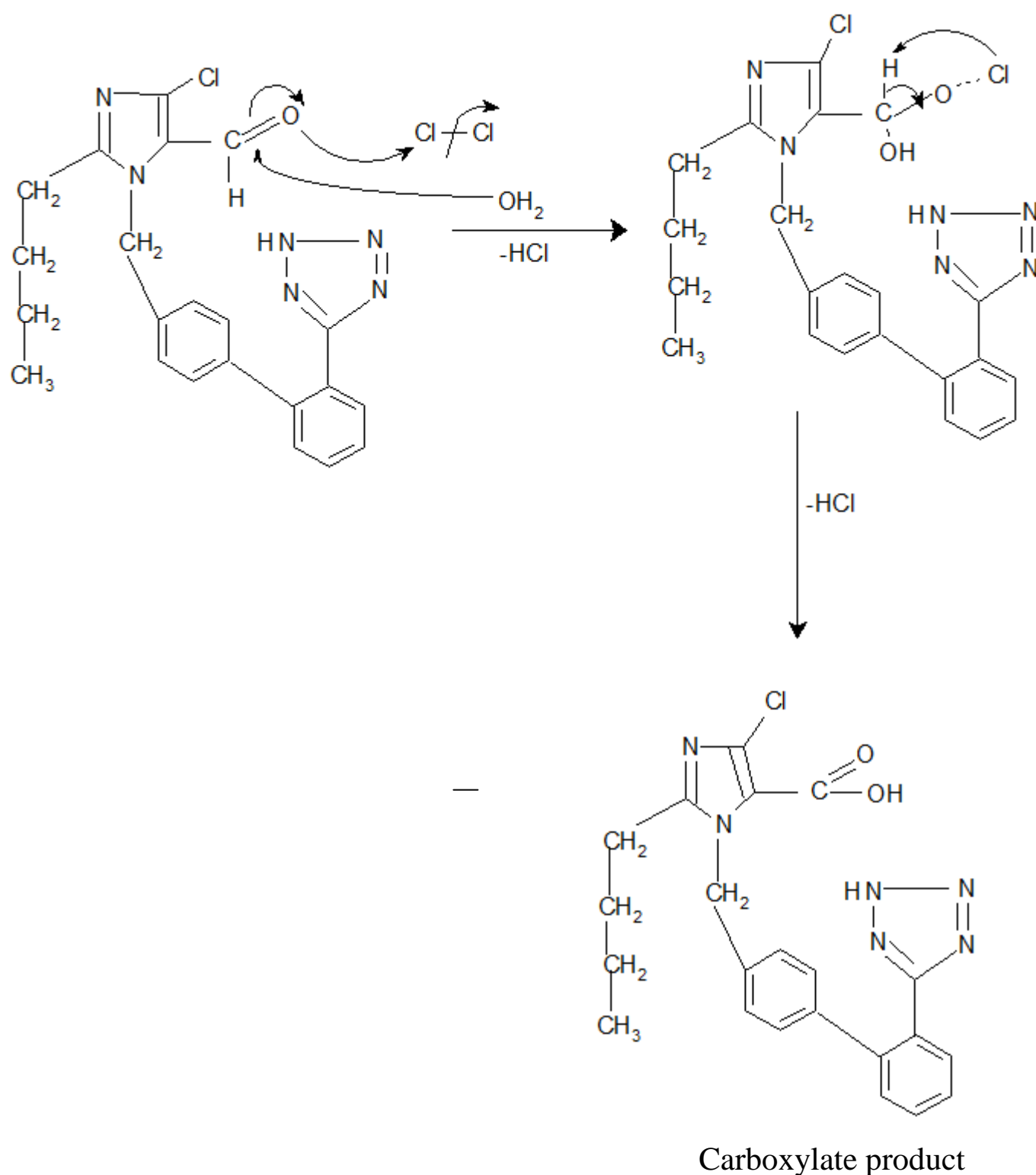
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265 $[\text{NC}^+\text{SH}] = \frac{k_1[\text{HCl}]([\text{NCS}]_{\text{total}} - [\text{Cl}^-])}{k_1[\text{HCl}] + [\text{Cl}^-]}$ (vii)

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269 From the slow step of (scheme 1),
270 $\text{Rate} = k_2 [\text{NC}^+\text{SH}][\text{Cl}^-]$ (viii)

271 Substitutions for $[\text{NC}^+\text{SH}]$ in eq (viii) from eq (vii) leads to
272 $\text{Rate} = \frac{k_2 k_1 [\text{HCl}]([\text{NCS}] - [\text{Cl}^-])}{k_1[\text{HCl}] + [\text{Cl}^-]}$

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275 The rate law clearly supports the experimental results such as first order dependence of the rate on $[\text{NCS}]$, a fractional order on $[\text{HCl}]$, negative
276 fractional order on $[\text{Cl}^-]$ and a negligible effect of the substrate.

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278 A detailed mode of oxidation of LP by NCS in acid solutions is presented in scheme 2
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Scheme 2: Detailed Mechanism of oxidation of LP by NCS in acid medium

The negligible effect of added Succinimide on the reaction rate, excludes the possibility of its involvement in the pre-equilibrium prior to the rate determining step. A very slight observed retardation in rate by added Succinimide is probably due to the reaction between Cl_2 and Succinimide which significantly hinders the breakdown of protonated NCS.

The increased rate with increase in $[\text{H}^+]$ could be traced to increased protonation of NCS while decrease in rate with increasing $[\text{Cl}^-]$ points that chloride ions are formed in the reaction.

The ionic strength (I) effect on the reaction rates has been described according to the theory of Bronsted and Bjerrum [26], which postulates the reaction through the formation of an activated complex. According to this theory, the effect of ionic strength on the rate for a reaction involving two ions is given by the relationship

$$\log k = \log k_0 + 1.02 Z_A Z_B I^{1/2} \quad (\text{ix})$$

Here Z_A and Z_B are the valency of the ions A and B, and k and k_0 are the rate constants in the presence and absence of the added electrolyte, respectively. A plot of $\log k$ against $I^{1/2}$ should be linear with the slope of $1.02 Z_A Z_B$. If Z_A and Z_B have similar signs, the quantity $Z_A Z_B$ is positive and the rate increases with the ionic strength, having a positive slope, while if the ions have dissimilar charges, the quantity $Z_A Z_B$ is negative and the rate would decrease with the increase in ionic strength, having a negative slope.

In the present case, the decrease in rate with increasing ionic strength shows that the reaction is between two oppositely charged ions in the rate determining step.

The effect of varying solvent composition and dielectric constant on the rate of reaction has been described in several studies. For limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis has shown that a plot of $\log k$ versus $1/D$, gives a straight line with a negative slope for a reaction between a negative ion and a dipole or between two dipoles, where a positive slope results for a positive ion-dipole interaction. The total absence of the effect of varying dielectric constant on the rate cannot be explained by the Amis theory. Applying the Born equation, Laidler has anticipated the following equation for a dipole-dipole interaction:

$$\ln k = \ln k_0 + \frac{3}{8kT} \left(\frac{2}{D} - 1 \right) \left[\frac{\mu_{2A}}{r_{3A}} + \frac{\mu_{2B}}{r_{3B}} - \frac{\mu_{2\ddagger}}{r_{3\ddagger}} \right] \quad (\text{x})$$

where k_0 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. It can be seen that the rates should be greater in a medium of lower dielectric constant when $r_{3\ddagger} = r_{3A} + r_{3B}$ representing that the extent of charge scattering in the transition state is different. On the other hand, $r_{3\ddagger} \approx r_{3A} + r_{3B}$ implies the absence of a

325 dielectric effect of the solvent on the rate, signifying that the transition state is not very much different from the reactants with respect to the size
326 and charge of the transition state and the reactants.

327 The dielectric permittivity of the medium was varied by adding different proportions of Methanol to the reaction mixture. Increase in
328 content of Methanol in the reaction mixture leads to increase in the rate of the reaction. The plot of $\log k$ versus $1/D$ were linear, having positive
329 slope. The dependence of the rate constant on the dielectric constant of the medium is given [27] by the following equation:

$$\ln k = \frac{\ln k_0 - NZ_A Z_B e^2}{DR_{\ddagger}} \quad (\text{xi})$$

330 In this equation, k_0 is the rate constant in a medium of infinite dielectric constant, $Z_A e$ and $Z_B e$ the total charges on the ions A and B, r_{\ddagger} the
331 radius of the activated complex, R, T and N have their usual meanings.

332 This equation predicts a linear plot of $\log k$ against $1/D$ with a negative slope if the charges on the ions are of the same sign and a positive slope
333 if they are of opposite sign. The positive dielectric effect observed in the present studies (Table 5) clearly supports the involvement of dissimilar
334 charges in the rate limiting step in the mechanism proposed (scheme 2).

335 The fairly high positive of ΔG^{\ddagger} and ΔH^{\ddagger} indicate that the transition state formed during liberation of Chlorine is highly solvated while the
336 negative entropy of activation suggests the formation of compact and ordered transition state with fewer degrees of freedom.
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339 4. CONCLUSION:

340 The kinetics of oxidation of LP by NCS in acid medium is investigated. The Stoichiometry of the reaction was found to be 1:2 and the oxidation
341 products of LP was analysed by the spectral data and the Activation parameters were calculated. The present study is easy, cost effective attempt
342 to study the rate or extent of conversion of Losartan Potassium to its active metabolite. This can serve as a tool in predicting the mechanism of
343 action and rate law which establishes a relationship between the various factors affecting the rate of the reaction. The study helps in a better
344 understanding of the metabolism pathway in biological systems and also throws light on the bioavailability and the dosage for effective oral
345 administration of the studied drug.
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