

**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<sup>-</sup>]. 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**

The kinetic studies of various hypertension drugs have received attention in recent years owing to their therapeutic importance. 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 is highly specific and works by relaxing blood vessels, lowering high blood pressure thereby preventing cardiac arrest, stroke and kidney problems[1-3].

While undergoing metabolism, 14% of an oral dose is converted to an active 5-carboxylic acid metabolite which has higher potency and longer half life than Losartan and hence responsible for antihypertensive effect.

In vitro experiments are conducted to determine the rate of oxidation in human liver microsomes[4] and the pathway for three trace level degradates are identified to the aldehyde and dimeric derivatives by using HPLC-MS[5].

A comparative study of microsomes prepared from different human liver samples responsible for oxidation [6] is also found in the literature. Various analytical methods are developed for quantitative determination of LP in tablet dosage forms [7, 8] and biological samples [9]. A kinetic spectrophotometric method of estimation [10] and a comparative study of analytical methods [11] for evaluation of LP in capsules is also reported.

N-halogenated imides in general is used to spectrophotometrically oxidize various classes of organic compounds like anaesthetics [ 12- 15 ] and dyes [16-19]. N-Chlorosuccinimide (NCS) in particular is known to quantitatively oxidise organic compounds like alcohols [20], Carbazides [21], Selenides [22], Chalcones [23] and various functional groups. These oxidants serve as a source of positive halogen in polar media [24] and hence have been widely used as a halogenating reagents also.

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 C<sub>5</sub> 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, NaClO<sub>4</sub>, 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.

<sup>1</sup>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. 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.

54 All kinetic measurements were performed under pseudo-first order condition where [oxidant] $\gg$ [substrate] in the presence of HCl at constant  
 55 concentration of NaClO<sub>4</sub> (to maintain a constant ionic strength) at 298K. Reactions were carried out in glass stoppered pyrex boiling tubes  
 56 whose outer surfaces were coated black to prevent photochemical effects.  
 57 The solutions were thermostated and the reaction was initiated by rapid addition of a measured amount of oxidant to the stirred reaction mixture.  
 58 Immediately, 4mL of the solution was pipetted in to a cuvette placed in the spectrophotometer. Absorbance measurements were made for two  
 59 half lives.  
 60 The absorbance readings at t=0 and t=t are D<sub>0</sub> and D<sub>t</sub>. Plots of log D<sub>0</sub>/D<sub>t</sub> Vs time resulted in pseudo-first order rate constants k(Table 1).  
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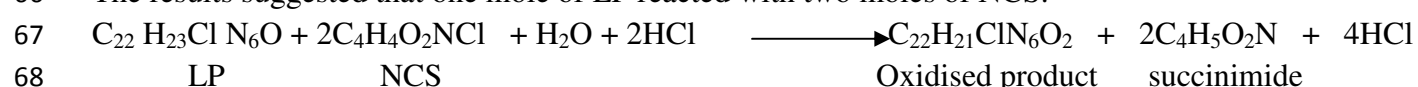
**Table 1. Effect of varying concentrations of reactants on the reaction rate at 298 K**

10 <sup>2</sup> [NCS] (M)	10 <sup>3</sup> [HCl] (M)	10 <sup>3</sup> [LP] (M)	10 <sup>3</sup> k (s <sup>-1</sup> )
1.00	1.00	0.50	3.507
1.00	1.00	0.10	3.589
1.00	1.00	1.50	3.758
1.00	1.00	2.00	3.801
1.00	1.00	2.50	3.900
0.50	1.00	1.00	1.258
0.10	1.00	1.00	2.511
1.50	1.00	1.00	3.776
2.00	1.00	1.00	4.466
2.50	1.00	1.00	4.808
1.00	0.50	1.00	2.172
1.00	0.10	1.00	3.548
1.00	1.50	1.00	3.775
1.00	2.00	1.00	4.466
1.00	2.50	1.00	4.808

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#### 64 2.4 Reaction Stoichiometry

65 Job's method of continuous variation [25] was employed where a plot of mole ratio between the drug and oxidant Vs absorbance was drawn.  
 66 The results suggested that one mole of LP reacted with two moles of NCS.



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70 LP                      2-butyl-4-chloro-1-[p-(o-1H-tetrazol-5-yl)phenyl]benzyl]imidazole-5-methanol

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

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#### 73 2.5 Product Analysis

74 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  
 75 for 24 hours under stirred conditions in the presence of acid.

76 After completion of the reaction, water insoluble and water soluble products were observed.  
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78 Water insoluble product was filtered using whattman filter paper 40, dried and the purity was checked using TLC technique with 1:1 Benzene  
 79 and ethanol as eluting solvent. The product was soluble in dil NaHCO<sub>3</sub> with brisk effervescence indicating the presence of carboxylate group.

80 The product was identified by the following analytical data.

81 IR:  $\nu_{\text{max}}$ /cm<sup>-1</sup>

82 3399 (OH),

83 3061 (C-H stretch),

84 2958 (N-H stretch),

85 1745 (C=O stretch),

86 1464 (imidazole),

87 1415 (C=N stretch),

88 1006 (C-O stretch),

89 759 (O-H bend)

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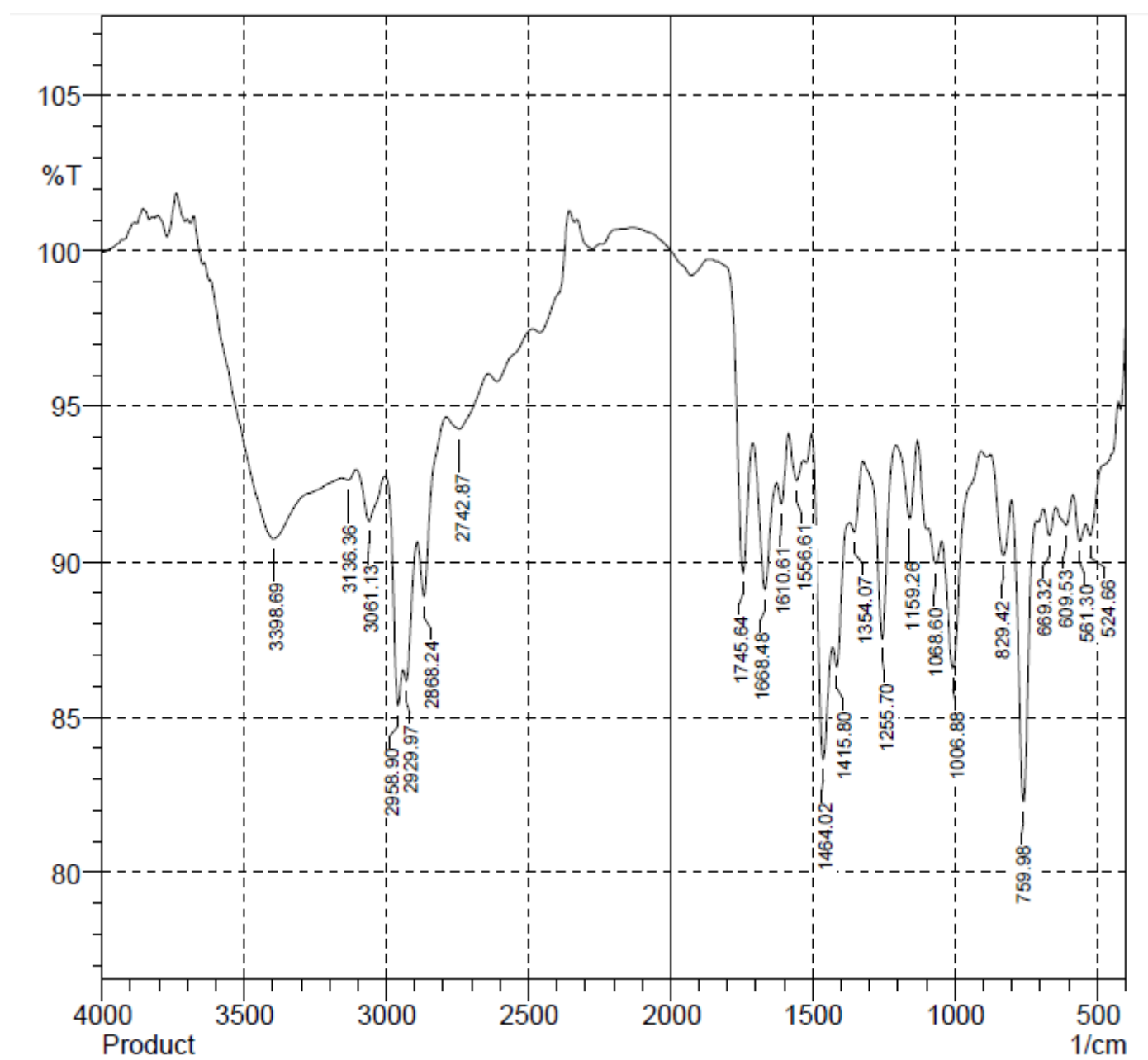
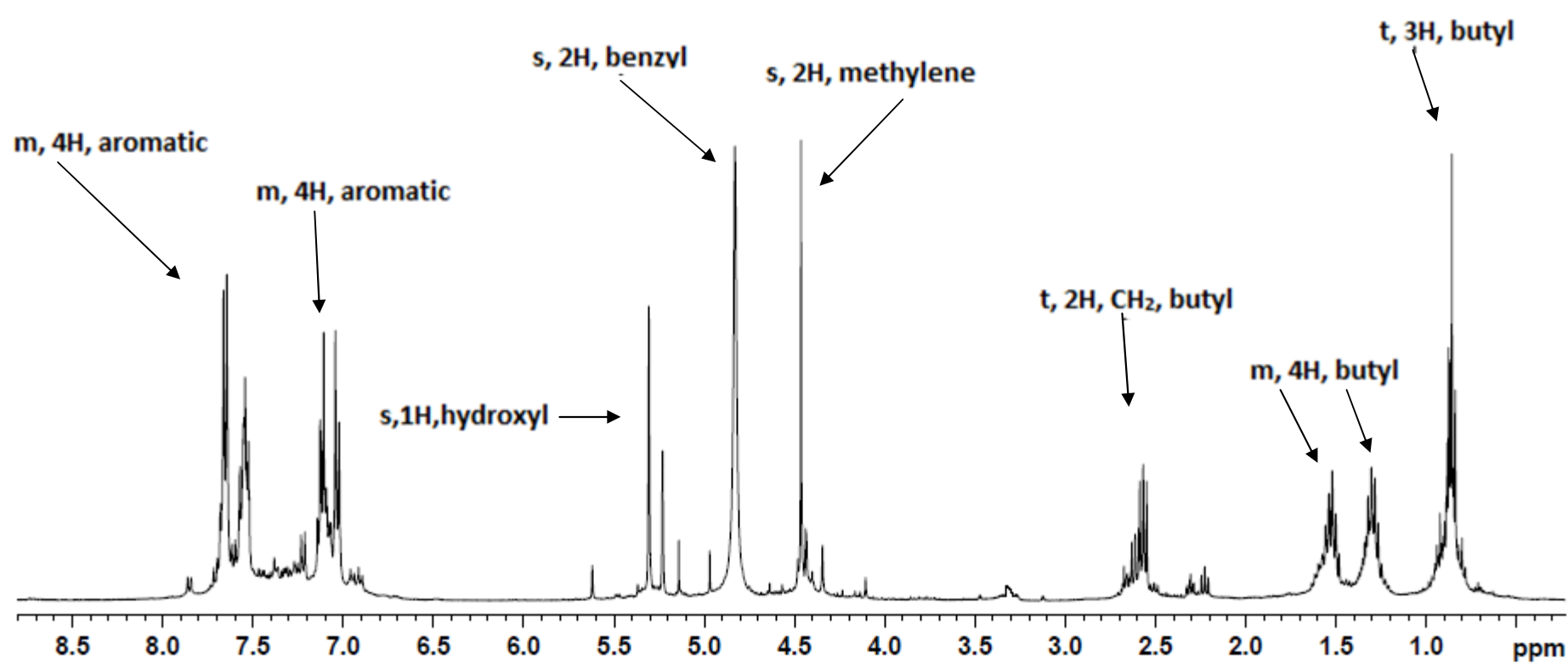
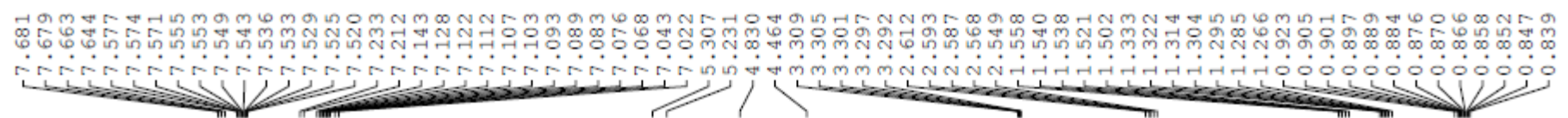


Fig 1: IR spectrum of oxidized product

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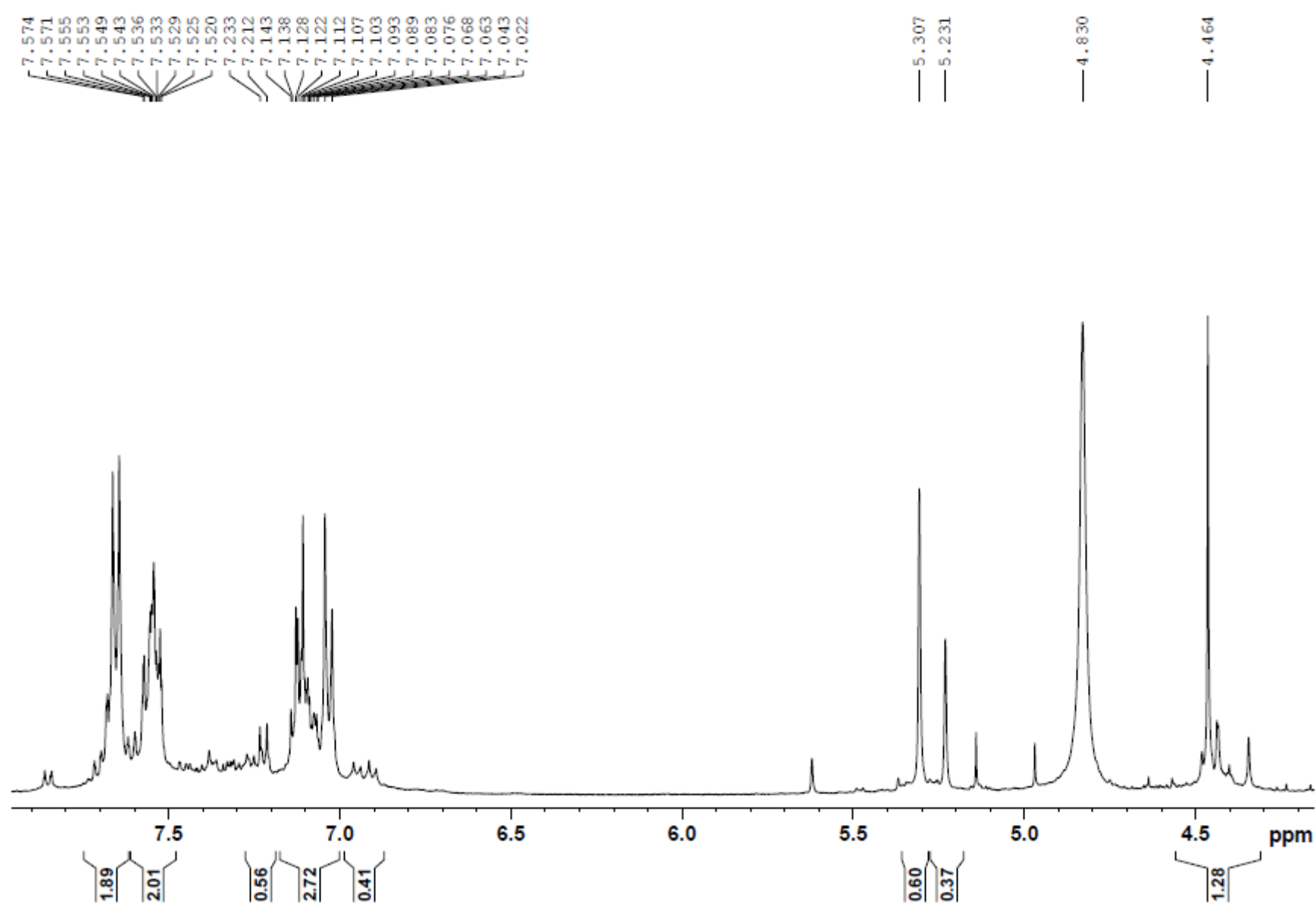
<sup>1</sup>H NMR : δ/ppm (600 MHz, deuteriated methanol, TMS)

- 0.89 (t, 3H, CH<sub>3</sub>, J=2.88 Hz),
- 1.3-1.55 (m, 4H, CH<sub>2</sub>-CH<sub>2</sub>, J=1.70 and 1.71)
- 2.59 (t, 2H, CH<sub>2</sub>, J = 1.00)
- 4.46 (s, 2H, CH<sub>2</sub>, J = 1.28)
- 4.83 (s, 2H, CH<sub>2</sub>, 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)



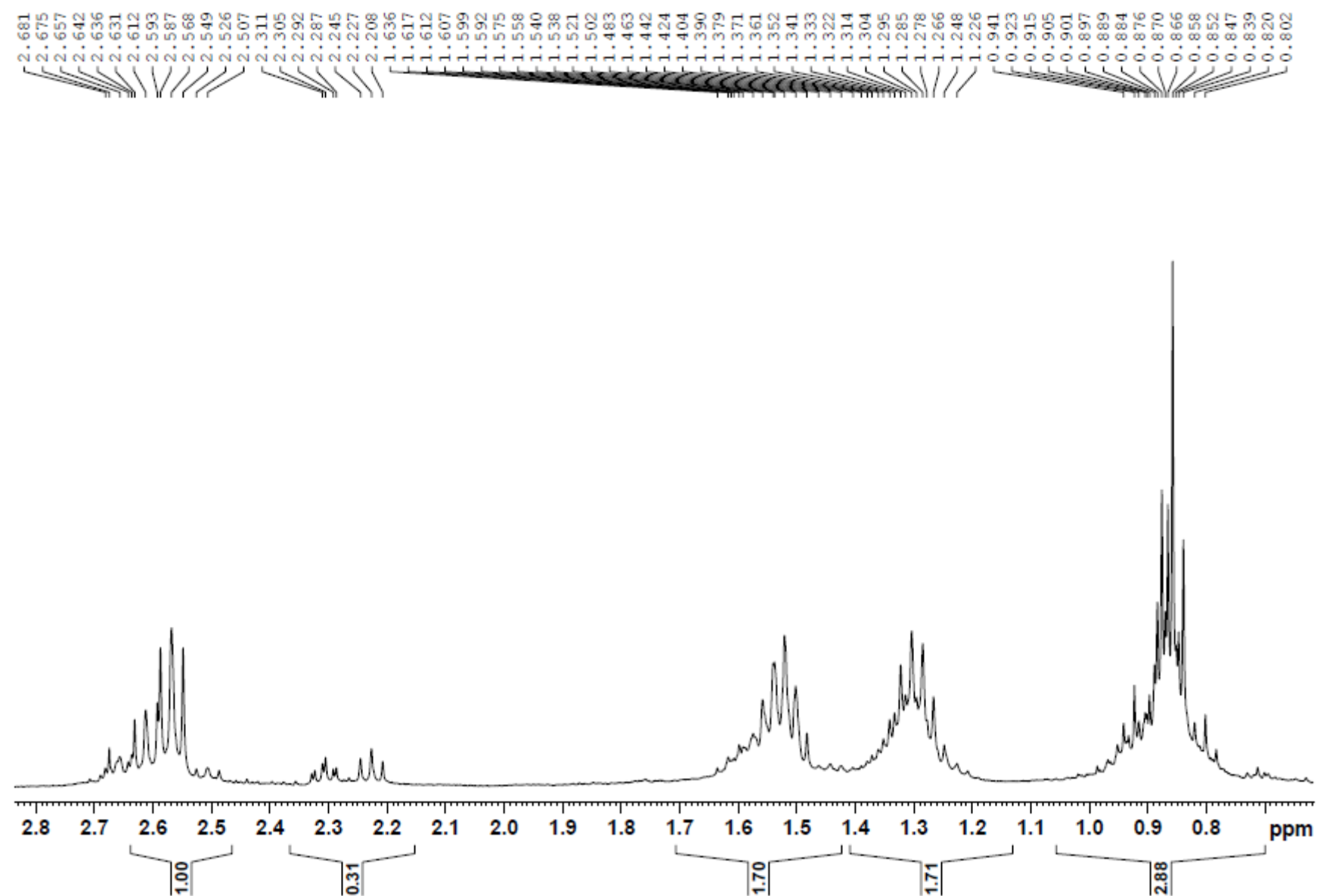
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Fig 2: <sup>1</sup>H NMR spectrum of the oxidized product

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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:  $\nu_{\max}/\text{cm}^{-1}$  3450 br (NH) and 1698 (CO).

### 3. RESULTS

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 other experimental data was obtained.

#### 3.1 Effect of varying oxidising agent on the rate

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 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 dependance of rate on NCS.

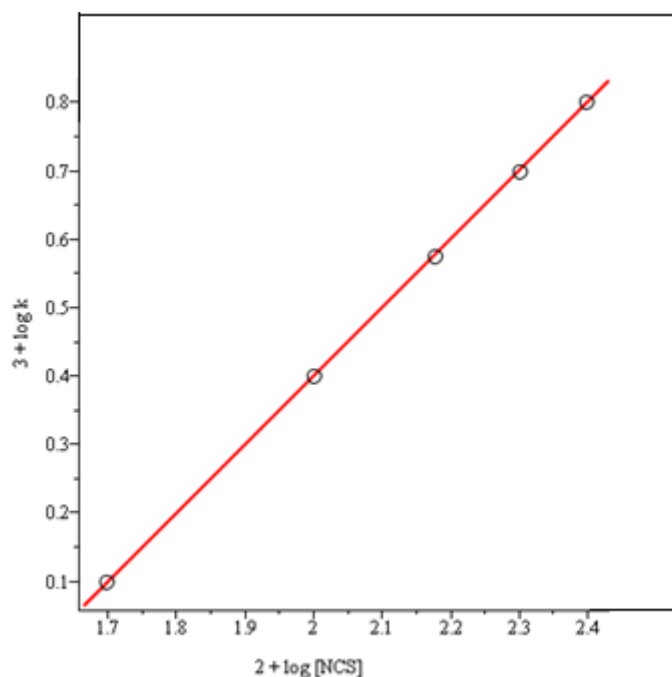


Fig 3: Plot of  $\log k$  Vs  $\log [\text{NCS}]$

#### 3.2 Effect of varying LP on the rate

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. 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 order dependance of rate on [LP]. However this is a negligible contribution towards the rate of the reaction.

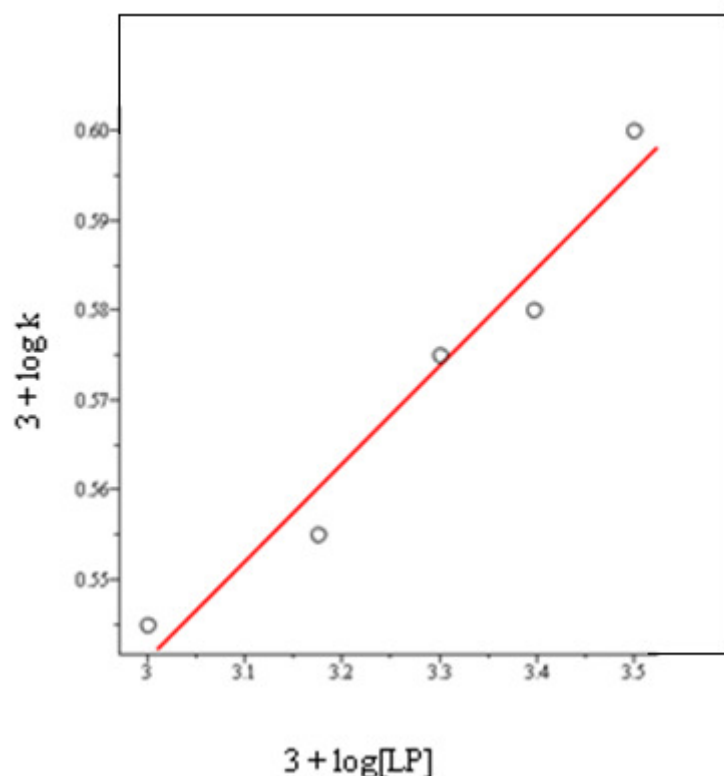


Fig 4: Plot of  $\log k$  Vs  $\log [\text{LP}]$

#### 3.3 Effect of varying HCl on the rate

The reaction was also carried out with  $[1.5 \times 10^{-2}]$  of NCS and  $[1.5 \times 10^{-3}]$  of LP, by varying 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) indicating a first order dependance of rate on [HCl].

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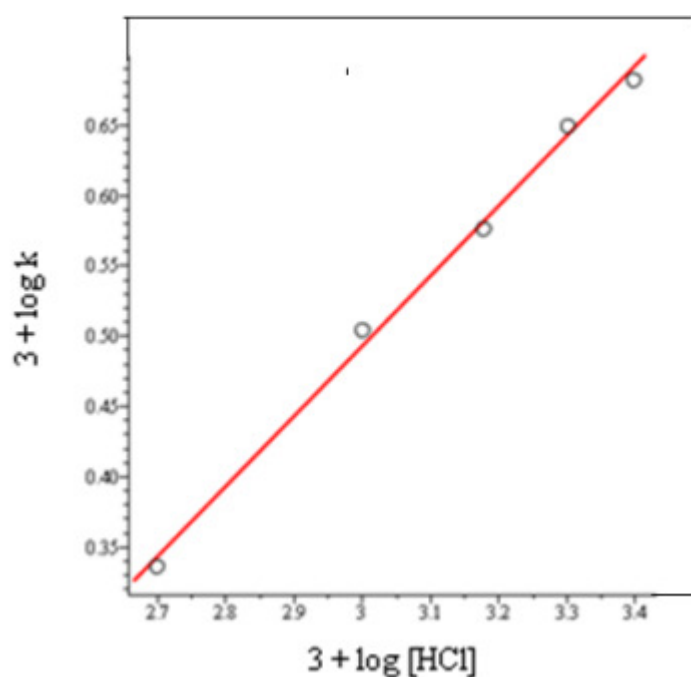


Fig 5: Plot of log k Vs log [HCl]

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155 **3.4 Effect of varying  $[H^+]$  and  $[Cl^-]$  on the rate**

156 In order to determine the order of the reaction with respect to  $[H^+]$  and  $[Cl^-]$  separately, the reaction was also studied by varying the  
157 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  
158 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  
159 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  
160 negative fractional order(Fig.7) dependence with a slope of -0.5 (Table 2)

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**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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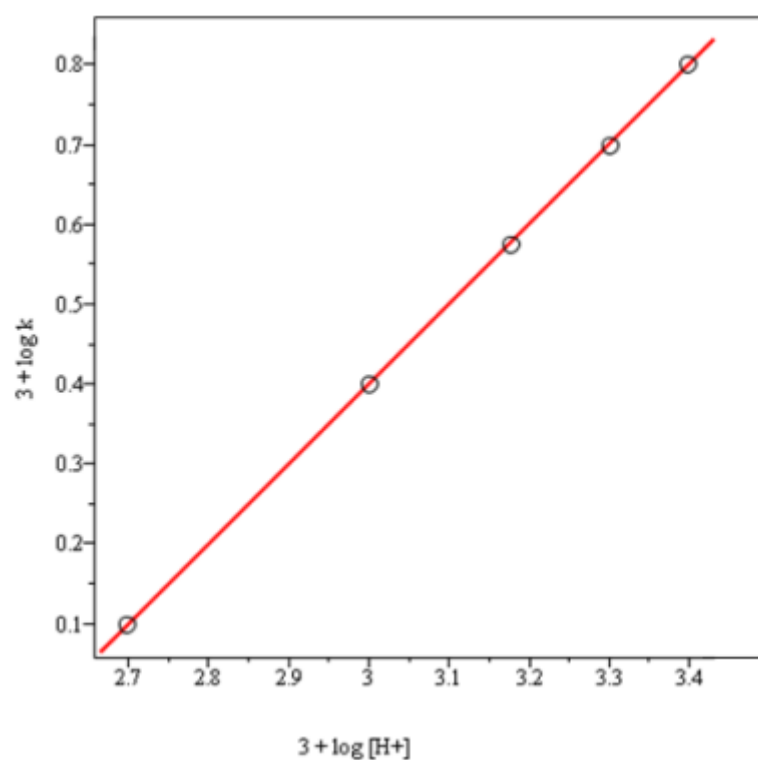


Fig 6: Plot of log k Vs log  $[H^+]$

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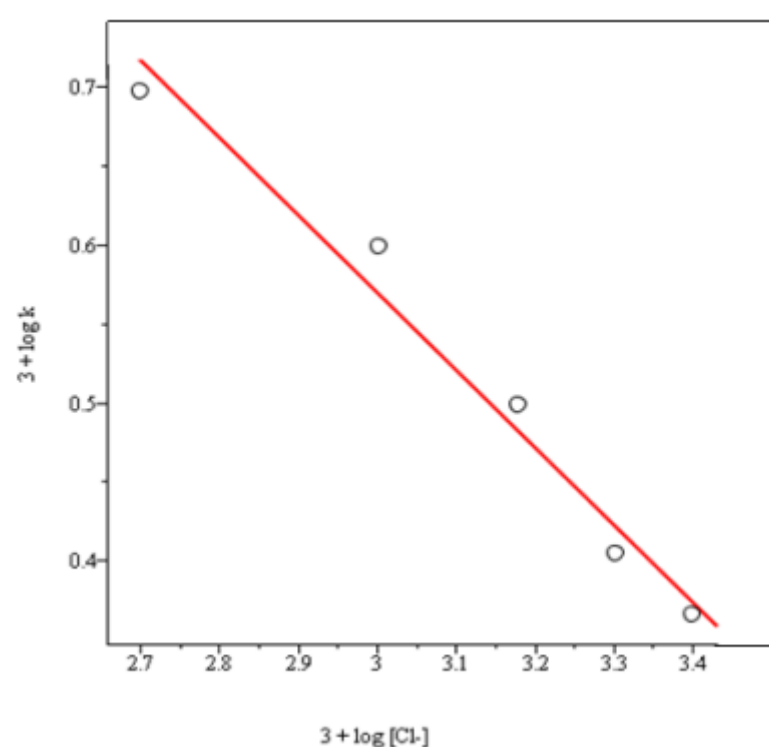


Fig 7: Plot of log k Vs log [Cl<sup>-</sup>]

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3.5 Effect of added succinimide on the rate

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 <sup>-3</sup>	k x 10 <sup>-3</sup>
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

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

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**Table 4: Effect of varying concentration of NaClO<sub>4</sub> on the reaction rate at 298K**

[NaClO <sub>4</sub> ] x 10 <sup>-3</sup>	k x 10 <sup>-3</sup>
0.5	2.621
1.0	2.311
1.5	2.070
2.0	1.699

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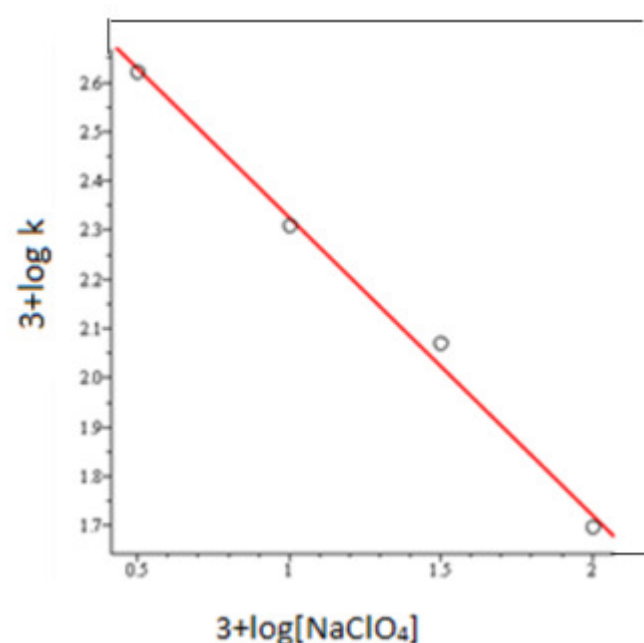


Fig 8: Plot of log k Vs log [NaClO<sub>4</sub>]

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194 3.7 Effect of varying solvent polarity and Dielectric medium

195 The reaction of LP [ $1.5 \times 10^{-3}$ ] with NCS [ $1.5 \times 10^{-2}$ ] was carried out in methanol-water mixtures of various compositions (%v/v) containing HCl  
 196 [ $1.5 \times 10^{-3}$ ] at 298 K. The reaction rate increased with increase in methanol content (ie decrease in dielectric constant D) in the solvent medium  
 197 (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].

198 **Table 5.** Effect of solvent composition on the reaction rate

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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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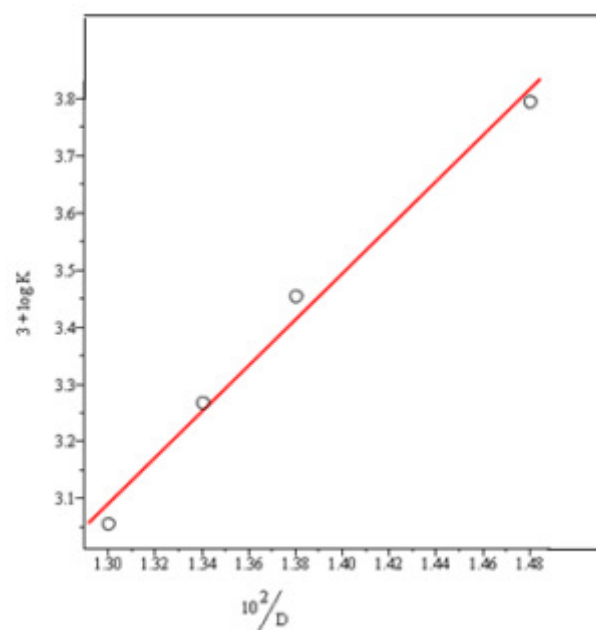


Fig 9: Plot of log k Vs 1/D

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205 3.8 Effect of Temperature

206 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  
 207 (Fig.10) the activation parameters, namely, energy of activation ( $E_a$ ), enthalpy of activation ( $\Delta H^\ddagger$ ), entropy of activation ( $\Delta S^\ddagger$ ), and Gibbs free  
 208 energy of activation ( $\Delta G^\ddagger$ ) along with Arrhenius factor (A) were obtained (Table 6).

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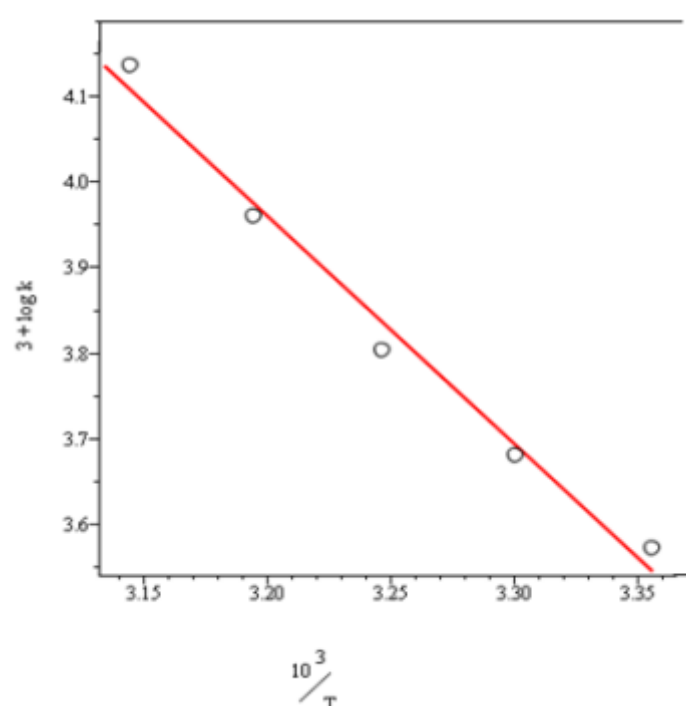
210 **Table 6.** Rate constants at varying temperatures and activation parameters

Temperature (K)	$10^3 k (s^{-1})$	Activation parameter
298	3.75	$E_a (kJ mol^{-1}) = 50.2$
303	4.81	$\Delta H^\ddagger (kJ mol^{-1}) = 47.8$
308	6.39	$\Delta G^\ddagger (kJ mol^{-1}) = 92.5$
313	9.17	$\Delta S^\ddagger (J.K^{-1} mol^{-1}) = -147$
318	13.71	$\log A = 7.78$

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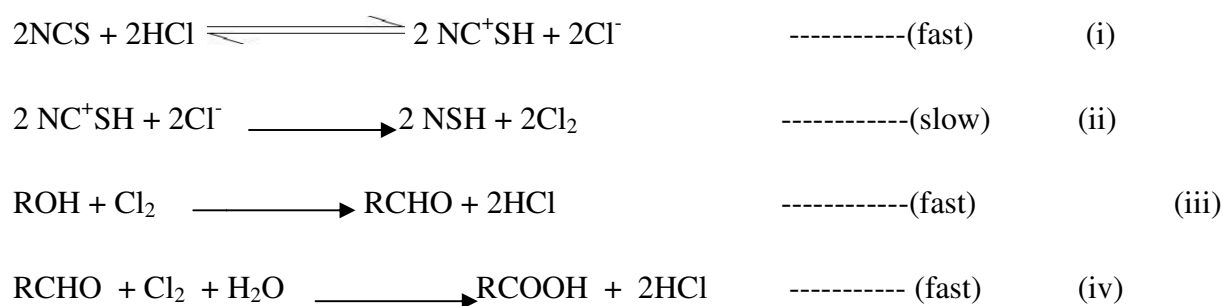
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Fig 10: Plot of log k Vs 1/T

4. DISCUSSION

In aqueous acidic media, the probable reactive species of NCS are Cl<sub>2</sub>, HOCl, H<sub>2</sub>OCl<sup>+</sup>, NCSH<sup>+</sup> or NCS.

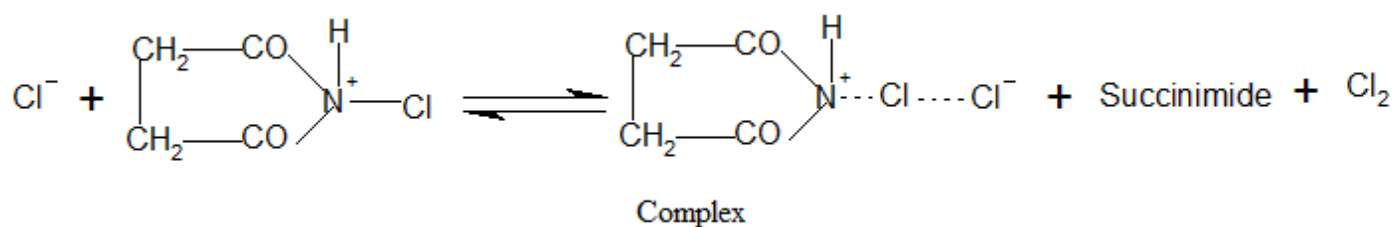
The oxidation of alcohols by N-Chlorosuccinimide has been reported [12] to take place through the intermediate NCSH<sup>+</sup>. As the rate increases with increase in [HCl], it is assumed that NCSH<sup>+</sup> is the oxidizing species which reacts with chloride ions and produces a steady small concentration of molecular chlorine acting as an effective oxidant. Based on the preceding facts, the proposed LP oxidation mechanism is presented in scheme below



Scheme 1: Mechanism of oxidation of LP by NCS in acid medium

The negligible effect of reduction product succinimide on the reaction rate indicates its non involvement in the pre-equilibrium step prior to the rate determining step. An initial equilibrium step (i) involves the formation of protonated NCS. In the next step, the protonated NCS, reacts 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 consequently, step (ii) becomes a slow and rate determining step. The liberated chlorine interacts with substrate to form an aldehyde which further is oxidized to the corresponding carboxylic acid derivative in the subsequent fast steps.

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



The rate law would probably be

From the slow step of (scheme 1),

$$\text{Rate} = k_2 [\text{NC}^+\text{SH}][\text{Cl}^-] \quad \text{(v)}$$

$$\text{The total effective concentration } [\text{NCS}]_{\text{total}} = [\text{NC}^+\text{SH}] + [\text{Cl}^-] + [\text{NCS}] \quad \text{(vi)}$$

Substitutions for [NCS] in equation (vi) from the fast equilibria (step 1 in scheme 1) lead to

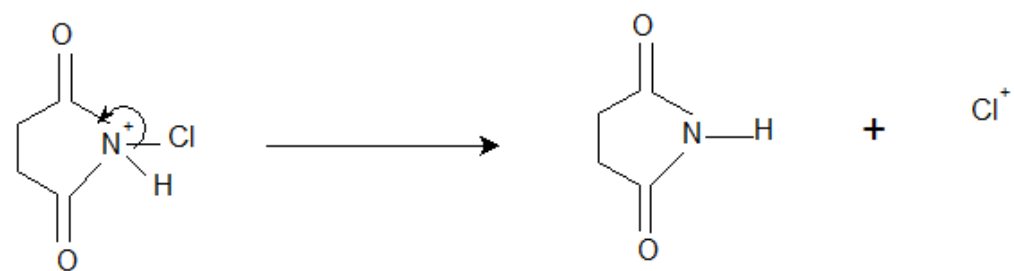
$$[\text{NCS}]_{\text{total}} = [\text{NC}^+\text{SH}] + [\text{Cl}^-] + [\text{NC}^+\text{SH}] [\text{Cl}^-] / k_1[\text{HCl}] \quad \text{(vii)}$$

Solving (vii) leads to the rate law

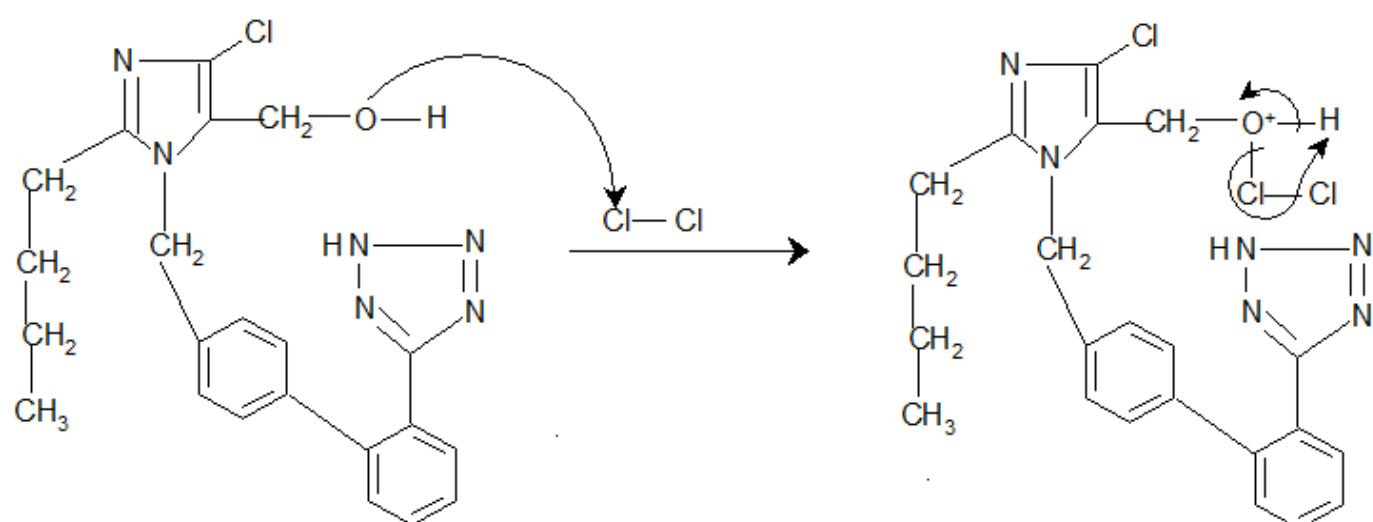
$$\text{Rate} = \frac{k_2 k_1 [\text{HCl}] ([\text{NCS}] - [\text{Cl}^-])}{k_1[\text{HCl}] + [\text{Cl}^-]} \quad \text{(viii)}$$

The rate law clearly supports the experimental results such as first order dependence of the rate on [NCS], a fractional order on [HCl], negative fractional order on [Cl<sup>-</sup>] and a negligible effect of the substrate.

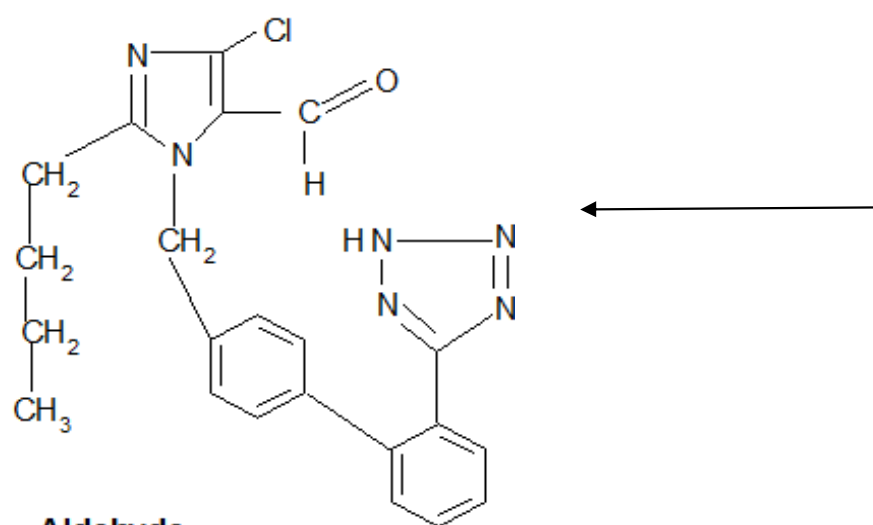
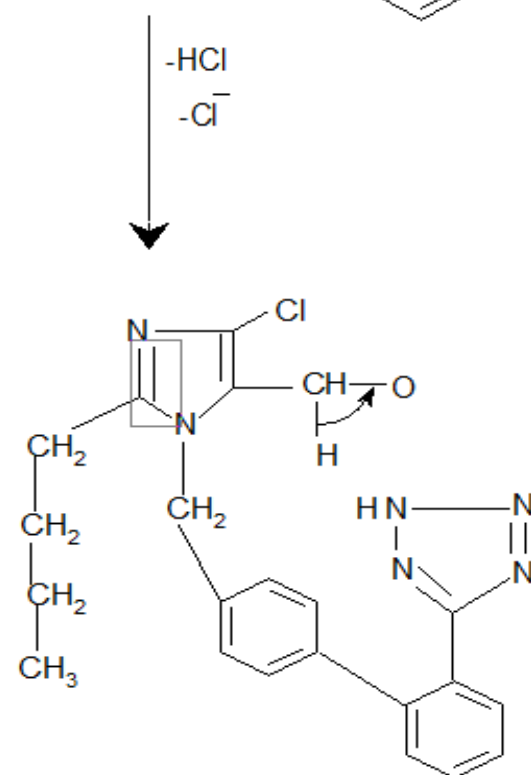
A detailed mode of oxidation of LP by NCS in acid solutions is presented in scheme 2



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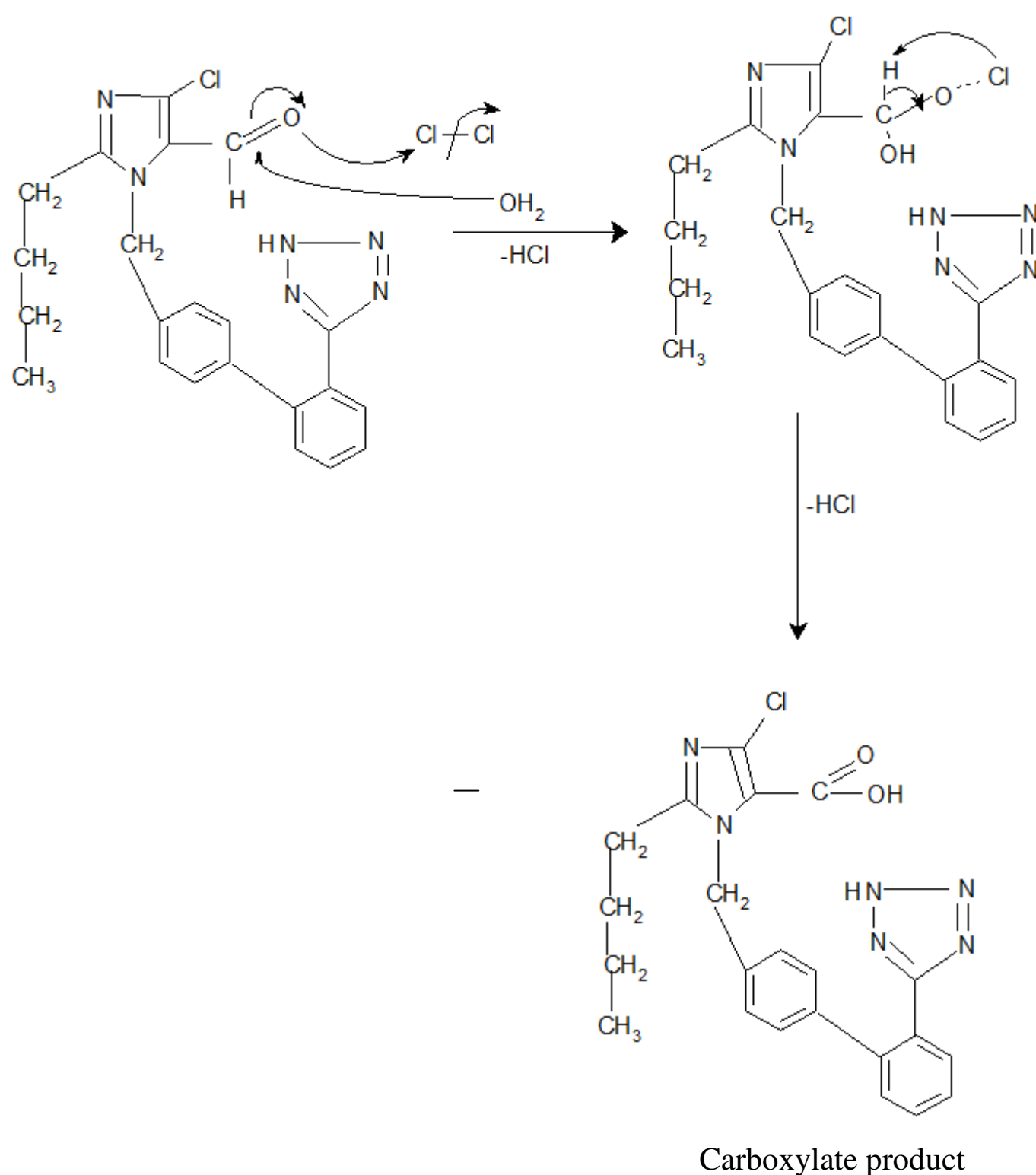
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**Aldehyde**

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**Scheme 2: Detailed Mechanism of oxidation of LP by NCS in acid medium**

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283 The negligible effect of added succinimide on the reaction rate, excludes the possibility of its involvement in the pre-equilibrium prior to  
284 the rate determining step. A very slight observed retardation in rate by added succinimide is probably due to the reaction between Cl<sub>2</sub> and  
285 succinimide which significantly hinders the breakdown of protonated NCS.

286 The increased rate with increase in [H<sup>+</sup>] could be traced to increased protonation of NCS while decrease in rate with increasing [Cl<sup>-</sup>]  
287 points that chloride ions are formed in the reaction.

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

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

292 Here Z<sub>A</sub> and Z<sub>B</sub> are the valency of the ions A and B, and k and k<sub>0</sub> are the rate constants in the presence and absence of the added electrolyte,  
293 respectively. A plot of log k against I<sup>1/2</sup> should be linear with the slope of 1.02 Z<sub>A</sub> Z<sub>B</sub>. If Z<sub>A</sub> and Z<sub>B</sub> have similar signs, the quantity Z<sub>A</sub> Z<sub>B</sub> is  
294 positive and the rate increases with the ionic strength, having a positive slope, while if the ions have dissimilar charges, the quantity Z<sub>A</sub> Z<sub>B</sub> is  
295 negative and the rate would decrease with the increase in ionic strength, having a negative slope.

296 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  
297 determining step.

298 The effect of varying solvent composition and dielectric constant on the rate of reaction has been described in several studies. For limiting case  
299 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  
300 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-  
301 dipole interaction. The total absence of the effect of varying dielectric constant on the rate cannot be explained by the Amis theory. Applying the  
302 Born equation, Laidler has anticipated the following equation for a dipole-dipole interaction:

$$\ln k/ = \ln k_0 + 3 / 8kT (2/D - 1) [\mu_2A / r_3A + \mu_2B / r_3B - \mu_2\neq / r_3\neq] \quad (\text{x})$$

304 where k<sub>0</sub> 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  
305 and activated complex. It can be seen that the rates should be greater in a medium of lower dielectric constant when r<sub>3\neq</sub> = r<sub>3A</sub> + r<sub>3B</sub>  
306 representing that the extent of charge scattering in the transition state is different. On the other hand, r<sub>3\neq</sub> ≈ r<sub>3A</sub> + r<sub>3B</sub> implies the absence of a

307 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  
308 and charge of the transition state and the reactants.

309 The dielectric permittivity of the medium was varied by adding different proportions of methanol to the reaction mixture. Increase in  
310 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  
311 slope. The dependence of the rate constant on the dielectric constant of the medium is given [27] by the following equation:

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

312 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,  $r_{\#}$  the  
313 radius of the activated complex, R, T and N have their usual meanings.

314 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  
315 if they are of opposite sign. The positive dielectric effect observed in the present studies (Table 5) clearly supports the involvement of dissimilar  
316 charges in the rate limiting step in the mechanism proposed (scheme 2).

317 The fairly high positive of  $\Delta G^\ddagger$  and  $\Delta H^\ddagger$  indicate that the transition state formed during liberation of chlorine is highly solvated while the  
318 negative entropy of activation suggests the formation of compact and ordered transition state with fewer degrees of freedom.  
319

### 321 CONCLUSION:

322 The kinetics of oxidation of LP by NCS in acid medium is investigated. The present study is easy, cost effective attempt to study the rate or  
323 extent of conversion of Losartan Potassium to its active metabolite. This has served as a tool in predicting the mechanism of action and rate law  
324 which establishes a relationship between the various factors affecting the rate of the reaction. The study also throws light on the bioavailability  
325 and the dosage for effective oral administration of the studied drug.  
326

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