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Spectrophotometric Study of Oxidation Kinetics and Mechanism of Losartan Potassium Using N-chlorosuccinimide

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Authors' contributions

This work resulted from the collaboration between all authors. Author SM performed the literature search, laboratory experiments, data analysis, designed and managed the study, wrote the first draft of the manuscript and communicated it to the journal. Author KR provided the instrumental facilities and valuable discussion. Authors NN and JPS read and approved the final manuscript.

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ABSTRACT

The kinetics of oxidation of Losartan Potassium [LP] by N-Chlorosuccinimide [NCS] in HCl medium is studied spectrophotometrically at 205 nm at 298 K. 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.

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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, by any oxidants in acidic medium, 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.

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 205 nm using Shimadzu UV- 1700 PharmaSp 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 tetramethylsilane (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 205 nm 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 298 K. Reactions were

IR: $\nu_{\max}/\text{cm}^{-1}$
 3399 (OH),
 3061 (C-H stretch),
 2958 (N-H stretch),
 1745 (C=O stretch),
 1464 (imidazole),
 1415 (C=N stretch),
 1006 (C-O stretch),
 759 (O-H bend)

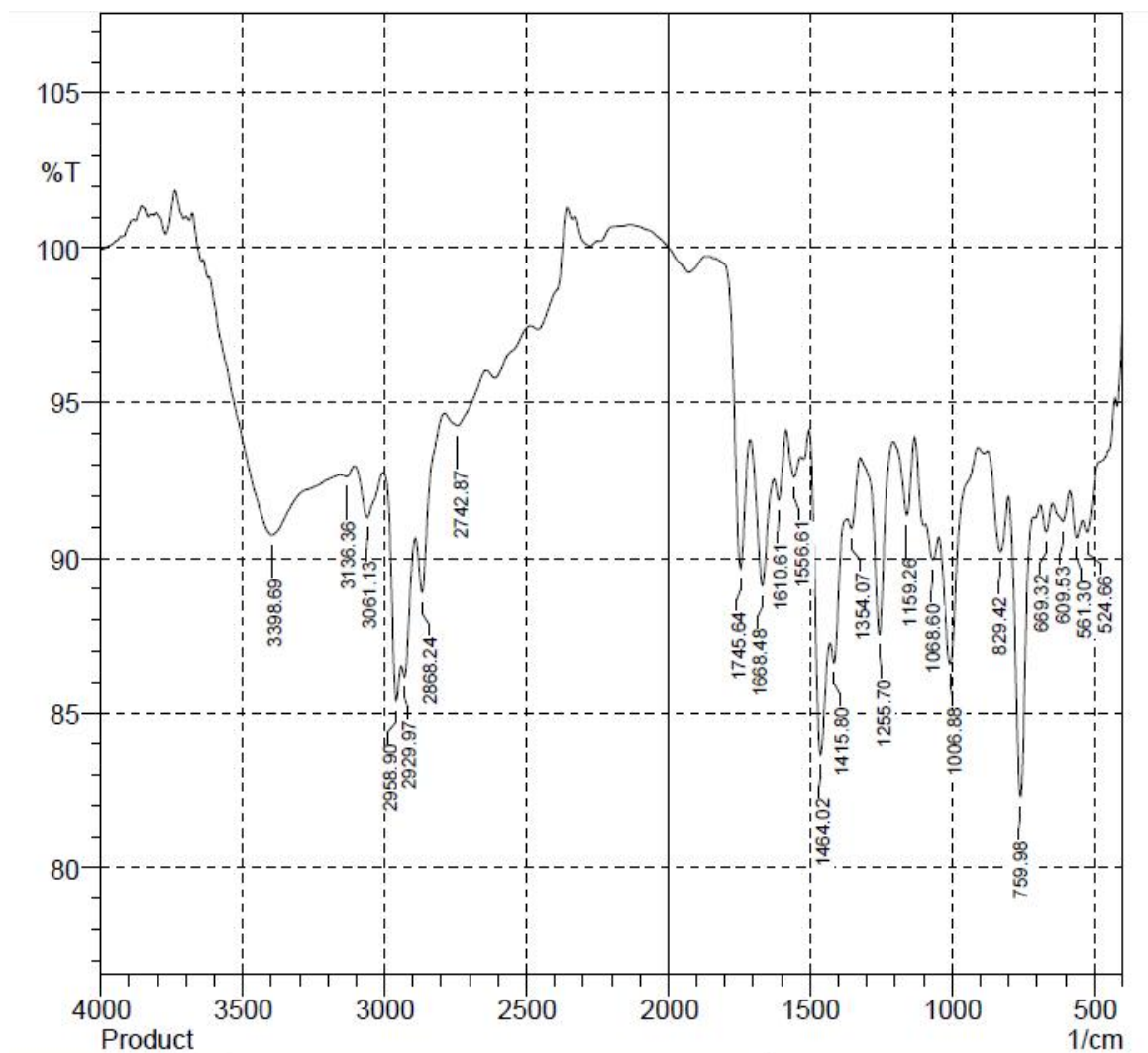
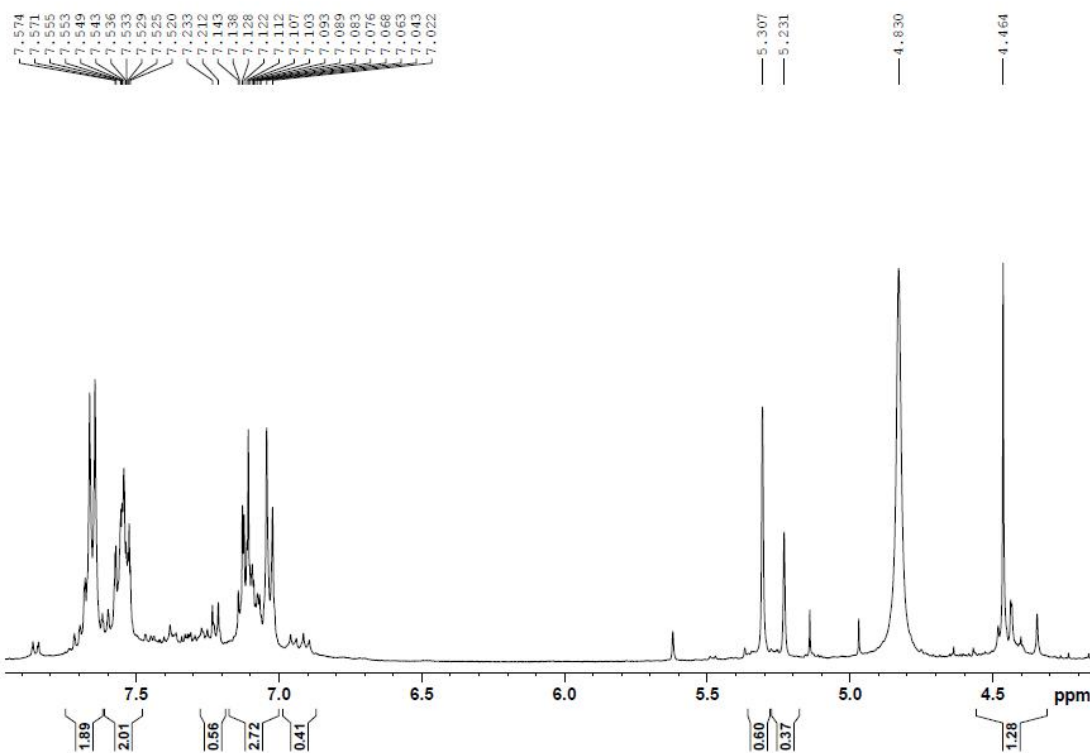
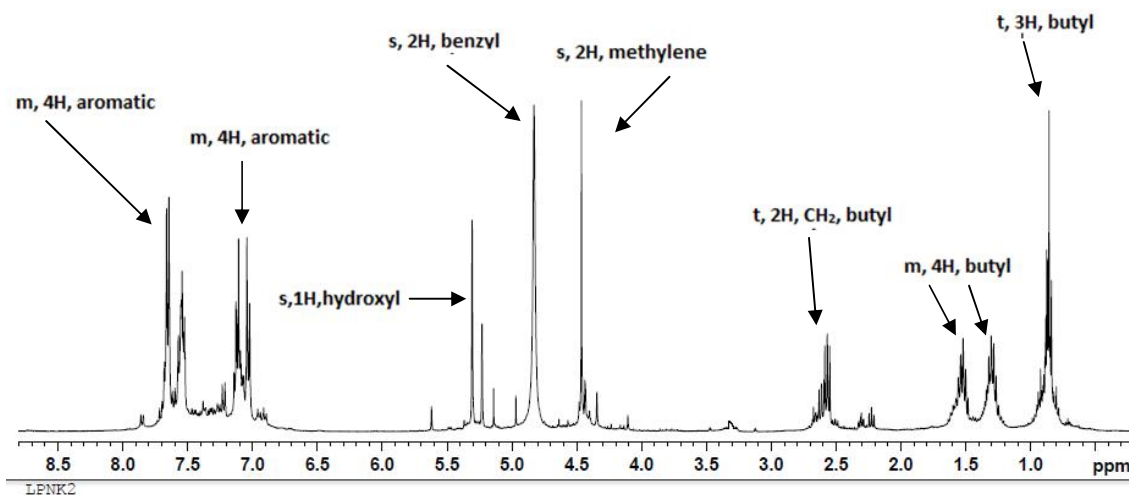


Fig. 1. IR spectrum of oxidized product

$^1\text{H NMR}$: δ/ppm (600 MHz, deuteriated methanol, TMS)

0.89	(t, 3H, CH_3 , $J=2.88$ Hz),
1.3-1.55	(m, 4H, $\text{CH}_2\text{-CH}_2$, $J=1.70$ and 1.71)
2.59	(t, 2H, CH_2 , $J = 1.00$)
4.46	(s, 2H, CH_2 , $J = 1.28$)
4.83	(s, 2H, CH_2 , 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)



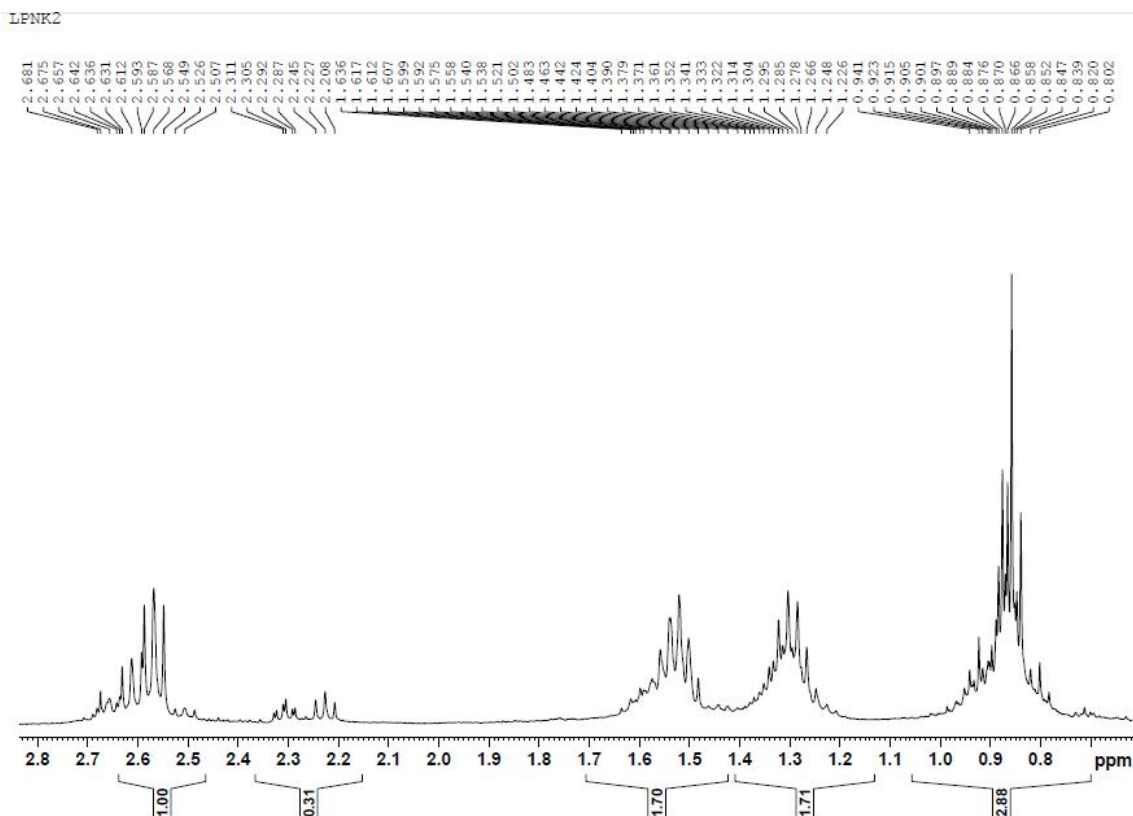


Fig. 2. ^1H NMR spectrum of the oxidized product

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).

3. RESULTS AND DISCUSSION

The kinetics of oxidation of LP by NCS was investigated at 298 K 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 298 K 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 dependence of rate on 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 dependence of rate on [LP]. However this is a negligible contribution towards the rate of the reaction.

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 dependence of rate on [HCl].

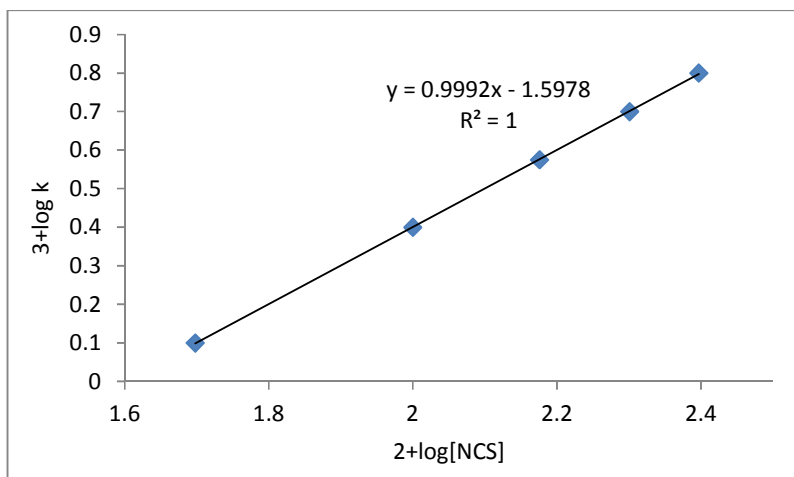


Fig. 3. Plot of log k Vs log [NCS]

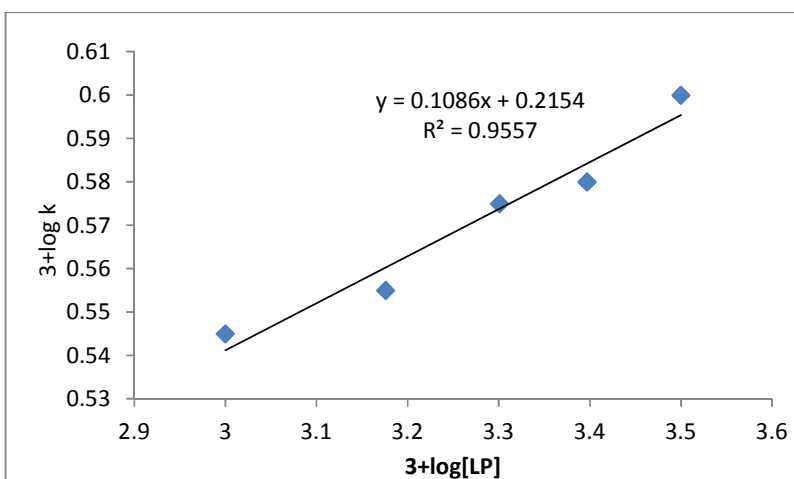


Fig. 4. Plot of log k Vs log [LP]

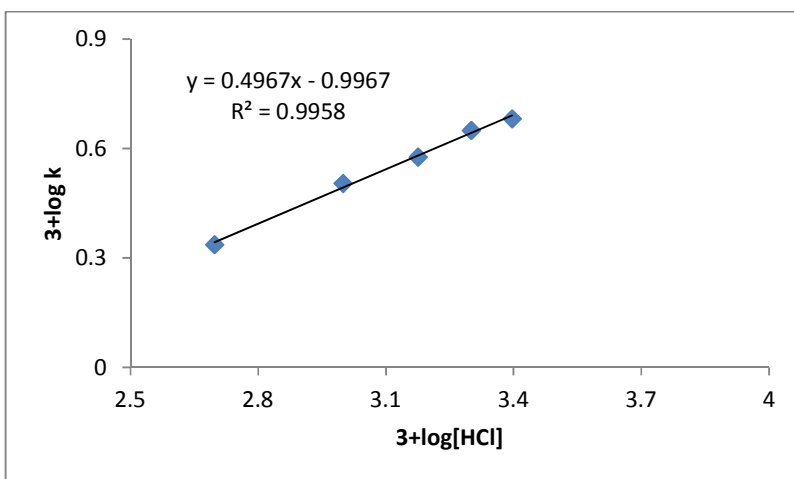


Fig. 5. Plot of log k Vs log [HCl]

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 298 K

[LP] = 1.5 x 10⁻³ M [NCS] = 1.5 x 10⁻² M

10 ⁻³ [HCl] M	10 ⁻³ [NaCl] M	k x 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

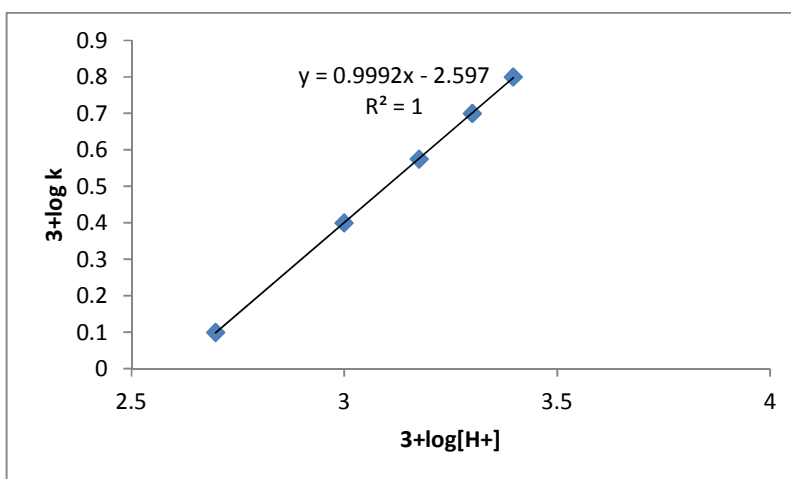


Fig. 6. Plot of log k Vs log [H⁺]

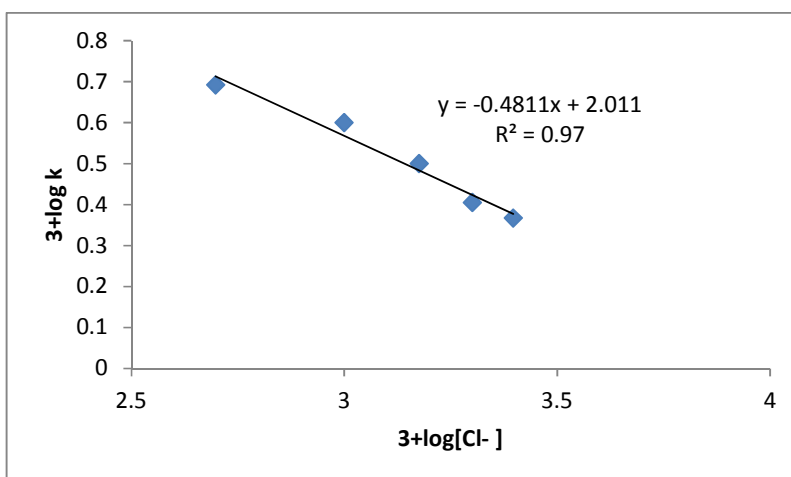


Fig. 7. Plot of log k Vs log [Cl⁻]

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).

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

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

3.6 Effect of Varying Ionic Strength on the Rate

The reaction was conducted at different ionic strength using NaClO₄ 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 [NaClO₄] 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 10⁻³ M for all kinetic runs.

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

[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

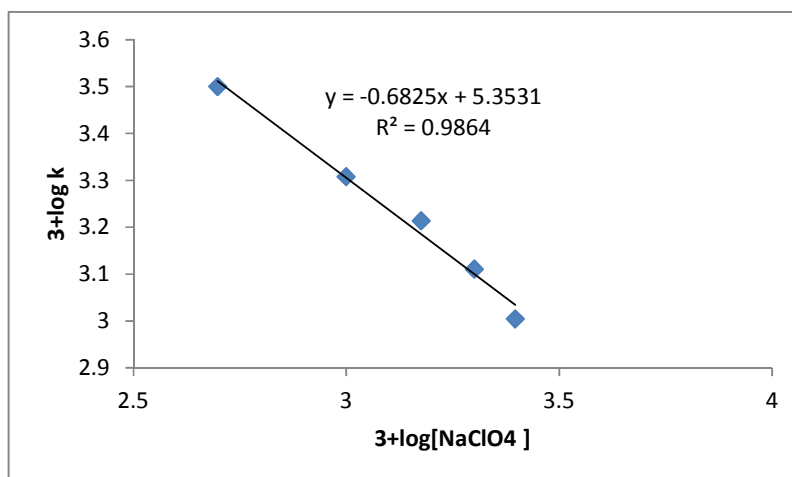


Fig. 8. Plot of log k Vs log [NaClO₄]

3.7 Effect of Varying Solvent Polarity and Dielectric Medium

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 [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 (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].

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

3.8 Effect of Temperature

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[‡]), entropy of activation (ΔS[‡]), and Gibbs free energy of activation (ΔG[‡]) along with Arrhenius factor (A) were obtained (Table 6).

Recently, oxidation by NBS [21] analogous to the present discussed scheme was reported.

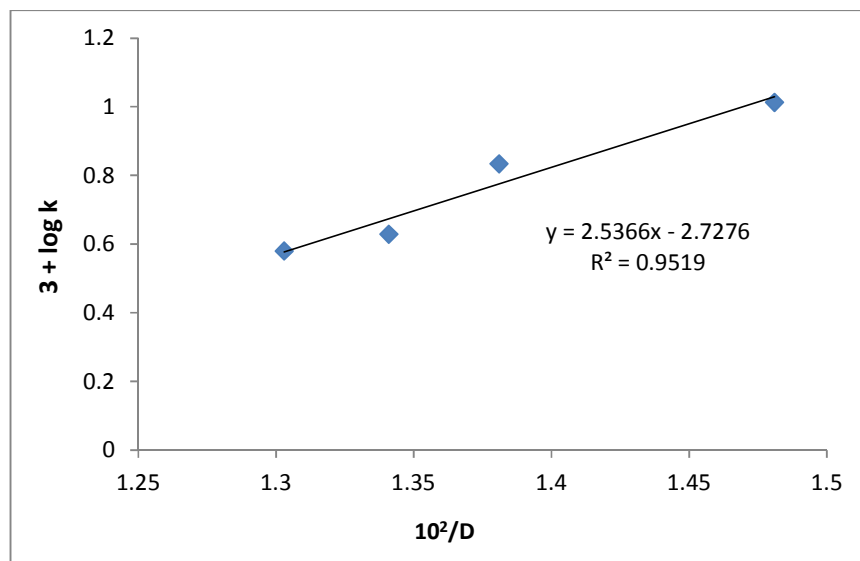


Fig. 9. Plot of log k Vs 1/D

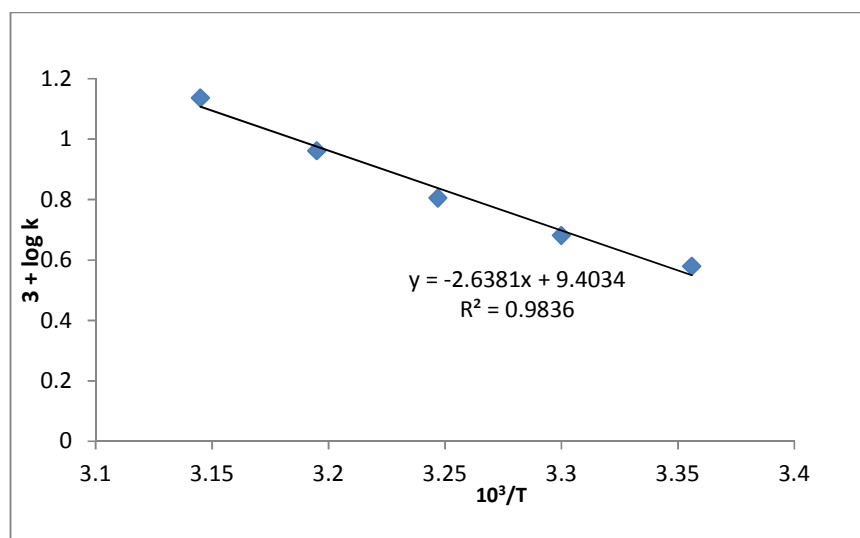


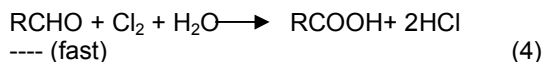
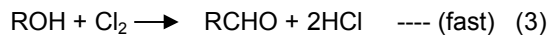
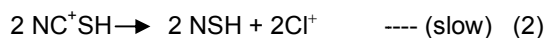
Fig. 10. Plot of log k Vs 1/T

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	ΔH^\ddagger ($kJ mol^{-1}$) = 47.8
308	0.806	ΔG^\ddagger ($kJ mol^{-1}$) = 92.5
313	0.962	ΔS^\ddagger ($J.K^{-1} mol^{-1}$) = -147
318	1.137	$\log A = 7.78$

However, there are certain differences owing to the 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^+ , $NCSH^+$ or NCS . The oxidation of Alcohols by N-Chlorosuccinimide has been reported [22] to take place through the intermediate $NCSH^+$. As 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 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

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, dissociates 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.

The negligible effect of reduction product Succinimide on the reaction rate indicates its non

The rate law would probably be

$$\text{The total effective concentration } [\text{NCS}]_{\text{total}} = [\text{NC}^+\text{SH}] + [\text{Cl}^-] + [\text{NCS}] \text{ (5)}$$

$$\text{From scheme 1, } k_1 = \frac{[\text{NC}^+\text{SH}][\text{Cl}^-]}{[\text{NCS}][\text{HCl}]}$$

$$[\text{NCS}] = \frac{[\text{NC}^+\text{SH}][\text{Cl}^-]}{k_1[\text{HCl}]} \text{ (6)}$$

Putting (vi) in (v)

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

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

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

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

$$[\text{NC}^+\text{SH}] = \frac{k_1[\text{HCl}]([\text{NCS}]_{\text{total}} - [\text{Cl}^-])}{k_1[\text{HCl}] + [\text{Cl}^-]} \text{ (7)}$$

From the slow step of (scheme 1),

$$\text{Rate} = k_2 [\text{NC}^+\text{SH}][\text{Cl}^-] \text{ (8)}$$

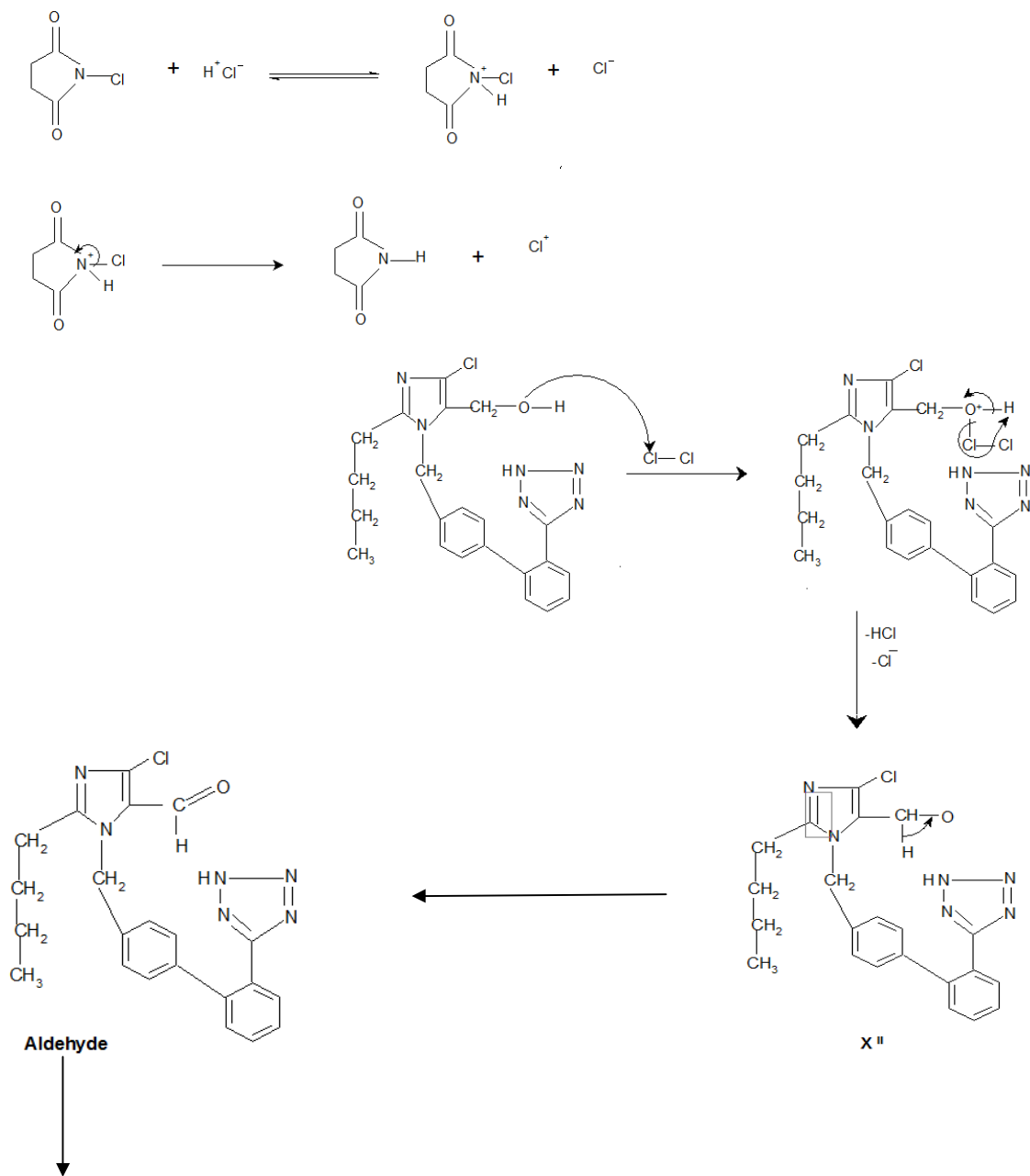
Substitutions for $[\text{NC}^+\text{SH}]$ in eq (viii) from eq (vii) leads to

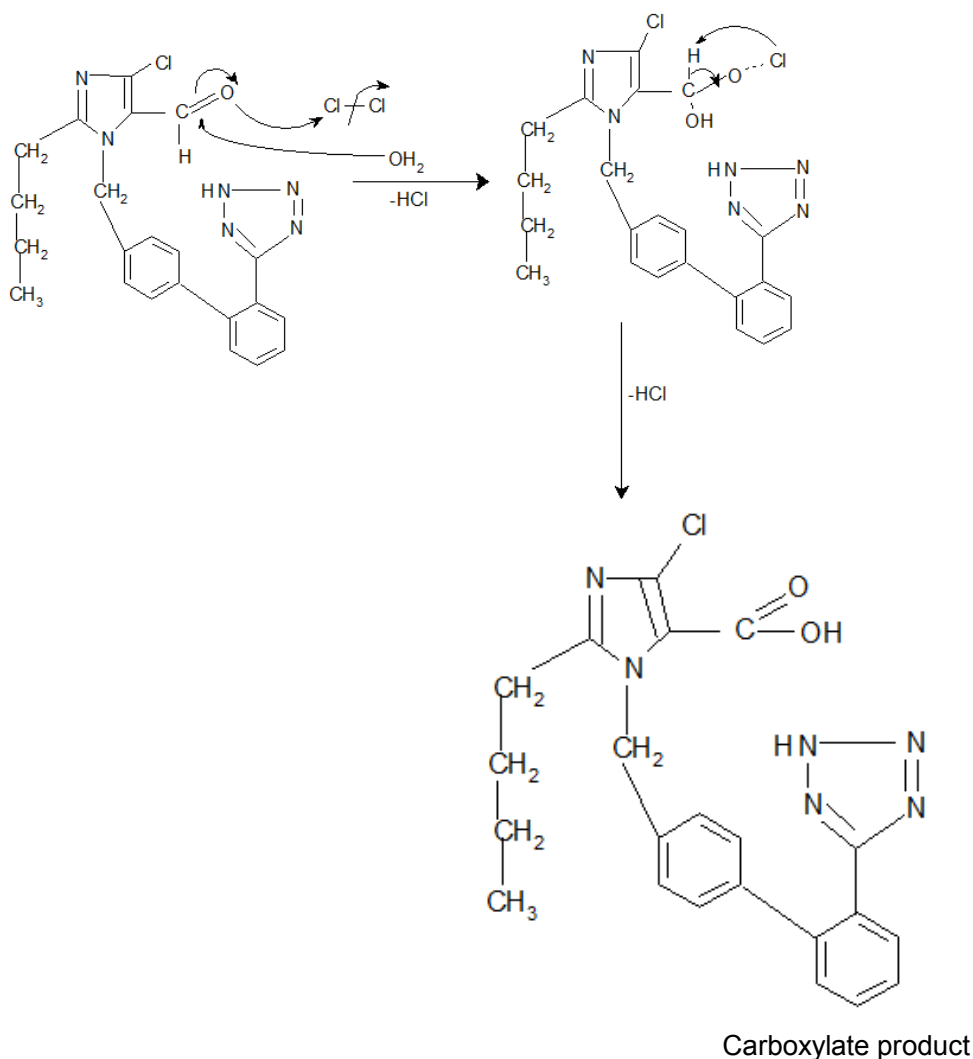
$$\text{Rate} = \frac{k_2 k_1 [\text{HCl}]([\text{NCS}] - [\text{Cl}^-])}{k_1[\text{HCl}] + [\text{Cl}^-]}$$

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 fractional order on $[\text{Cl}^-]$ and a negligible effect of the substrate.

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

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.





Scheme 2. Detailed mechanism of oxidation of LP by NCS in acid medium

The increased rate with increase in $[H^+]$ could be traced to increased protonation of NCS while decrease in rate with increasing $[Cl^-]$ 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 [23], 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

$$\text{Log}k = \text{log } k_0 + 1.02 Z_A Z_B I^{1/2} \quad (9)$$

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:

$$\ln k = \ln k_0 + 3/8kT(2/D-1)[\mu^2A/r^3A + \mu^2B/r^3B - \mu^2/r^3\#] \quad (10)$$

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 $r^3\# = r^3A + r^3B$ representing that the extent of charge scattering in the transition state is different. On the other hand, $r^3\# \approx r^3A + r^3B$ implies the absence of a 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 and charge of the transition state and the reactants.

The dielectric permittivity of the medium was varied by adding different proportions of Methanol to the reaction mixture. Increase in content of Methanol in the reaction mixture leads to increase in the rate of the reaction. The plot of $\log k$ versus $1/D$ was linear, having positive slope. The dependence of the rate constant on the dielectric constant of the medium is given [24] by the following equation:

$$\ln k = \frac{\ln k_0 - NZ_A Z_B e^2}{DRTr\#} \quad (11)$$

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 radius of the activated complex, R, T and N have their usual meanings.

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

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 negative entropy of activation suggests the formation of compact and ordered transition state with fewer degrees of freedom.

4. CONCLUSION

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 products of LP was analysed by the spectral data and the Activation parameters were calculated. The present study is easy, cost effective attempt 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 action and rate law which establishes a relationship between the various factors affecting the rate of the reaction. The study helps in a better understanding of the metabolism pathway in biological systems and also throws light on the bioavailability and the dosage for effective oral administration of the studied drug.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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