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STUDY OF THE KINETICS AND MECHANISM OF OXIDATION REACTION OF AMBROXOL HYDROCHLORIDE DRUG WITH CHLORAMINE-T IN NAOH MEDIUM

Fathyah Omar Abdulsalam and Dr. Asha Iyengar*

Department of Chemistry, Yuvaraja's College, Autonomous, University of Mysore, Mysuru, Karnataka, India.

Corresponding Author: Dr. Asha Iyengar
Department of Chemistry, Yuvaraja's College, Autonomous, University of Mysore, Mysuru, Karnataka, India.

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ABSTRACT

Kinetics of oxidation of Ambroxol Hydrochloride (ABL) drug by Chloramine-T (CAT) in NaOH at 308 K has been investigated by iodometry. The reaction showed first-order dependence of rate on [CAT] and $[ABL]_o$ and inverse fractional-order dependence on $[OH^-]$ and [PTS]. The stoichiometry of the reaction was found to be 1:1 with respect to the substrate and oxidant respectively. The oxidation products were identified by spectral and FTIR analysis. Variation of ionic strength had no effect on the rate. Addition of p-toluenesulfonamide (PTS) retarded the rate of reaction. Activation parameters have been computed. Probable mechanism and the derived rate law have been proposed to explain the observed kinetic results.

KEYWORDS: Ambroxol Hydrochloride, CAT, Oxidation, Kinetics, Alkaline medium.

INTRODUCTION

Ambroxol hydrochloride (ABL), with molecular formula $C_{13}H_{19}Br_2ClN_2O$ and IUPAC name trans-4-[(2-Amino-3, 5-dibromo benzyl) amino] cyclo hexanol hydrochloride is an active N-desmethyl metabolite of the mucolytic bromhexine.[1] and is used to treat respiratory diseases associated with viscid or excessive mucus. It promotes mucus clearance, facilitates expectoration and eases cough to ensure deep breathing. Ambroxol hydrochloride drug is used as pain killer in acute sore throat caused by viral infection. It is also anti-inflammatory which reduces redness of a sore throat.[2-4] The chemical structure of Ambroxol given in Fig.1:

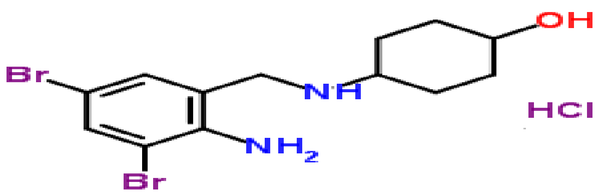


Fig. 1: Chemical structure of Ambroxol HCl molecule.

The review of literature reveals that methods like spectrophotometry and chromatography have been employed for the determination of ambroxol hydrochloride.[5-8] whereas the kinetics and mechanism of the oxidation reaction of the drug have not been explored much. Chloramine-T (CAT, p-$CH_3C_6H_4SO_2NClNa.3H_2O$) is known as a strong oxidant in both acidic and alkaline media . As inferred from above, no information is available in the literature on the treatment of ambroxol HCl with chloramine-T (CAT) as an oxidant and its kinetic mechanism. Hence, the systematic study of kinetics of oxidation of ambroxol hydrochloride by CAT in presence of alkaline medium was followed to understand the mechanistic aspects of this redox system. The main objective of this research was to elucidate the mechanism of oxidation of ambroxol HCl drug by iodometry and to obtain the rate law compatible with the experimental results.

MATERIAL AND METHODS

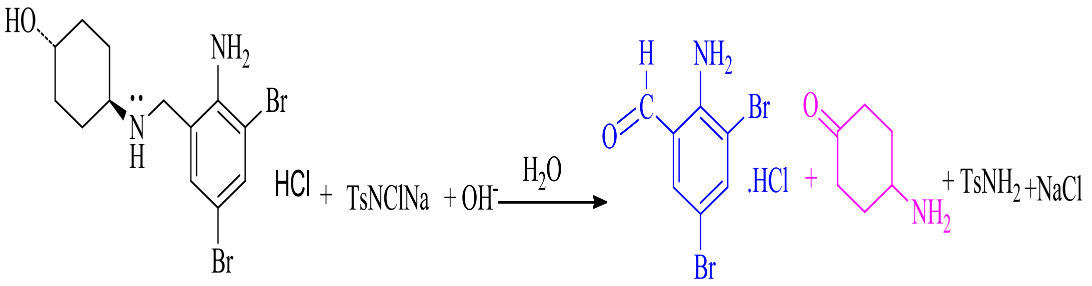
The stock solution of chloramine-T (SDF CHEM LIMITED) was prepared in double distilled water and standardized iodometrically. Amroxol hydrochloride (ABL) drug (LOBA CHEMIE) was used without further purification. Aqueous solutions of desired strengths were freshly prepared prior to use. Other reagents were of analytical grade.

Kinetic measurement

The kinetic runs were performed under pseudo first-order conditions with a known excess of $[ABL]_0$ over $[CAT]_0$ in NaOH medium at 308 K by iodometry, A constant temperature was maintained. Reactions were performed in glass stoppered pyrex boiling tubes, the outer surface of which were coated black to avoid the light effects. The calculated amounts of ABL, NaOH solution and water (for constant volume in all runs) were placed in a boiling tube and kept in digital thermostat at the desired temperature for 30 min. An excess amount of the oxidant solution was also thermostated at same temperature and then calculated amount of the oxidant was quickly added to the reaction mixture in the tube. The progress of the reaction was monitored by withdrawing known aliquots from the reaction mixture at regular intervals of time and iodometrically determining the amount of the unreacted oxidant. The iodometric titration was carried out by pipetting out 5 mL aliquot of the reaction mixture into a conical flask containing 50 mL of distilled water, 10% KI, 2N H_2SO_4 and a few drops of freshly prepared starch solution (added near the end point) as indicator and titrated against standard solution of sodium thiosulphate which was added drop by drop near the end point indicated by disappearance of blue colour. The course of the reaction was studied for more than two half-lives. The titre value at t=0 gives the value of ‘a’ (initial concentration) and the titre value at any instant “t” denotes remaining concentration of the unreacted oxidant (a-x). Plots of log V_t (titer volume of $Na_2S_2O_3$ at time t) versus time were made and values of pseudo first- order rate constant ($k's^{-1}$) were calculated from these plots.

Reaction Stoichiometry

Reaction mixtures containing different ratios of CAT and ABL in 0.1 $moldm^{-3}$ NaOH were maintained to react at 308 K for 24 h. The determination of unreacted CAT in the reaction mixture showed that one mole of the drug consumed one mole of CAT leading to products 2-amino-3, 5-dibromobenzaldehyde hydrochloride and 4-aminocyclohexanone. The molecular reaction is given in Eq.1.



(1)

Product Analysis

The reaction mixture in the stoichiometric ratio in the presence of NaOH medium was allowed to progress for 24 h at 308 K under stirred condition. After completion of the reaction, the reaction products were extracted with ethylacetate. The products of oxidation were found to be 2-amino-3, 5-dibromobenzaldehye hydrochloride and 4-aminocyclohexanone which were confirmed by LC-MS analysis. The mass spectrum showed molecular ion peaks at m/z 316 (M^++1) and 114 (M^++1) amu (Fig.2) indicating the presence of 2-amino-3,5-dibromobenzaldehyde hydrochloride and 4-aminocyclohexanone respectively. A reduction product of the oxidant (PTS) was identified by paper chromatography using butanol-acetic acid-water mixture (4:1:1 v/v/v) as solvent and iodine as spray reagent (R_f= 0.922). This was further confirmed by LC-MS spectrum (Fig.3) which showed a peak at m/z 172 (M^++1). The oxidation products were further characterized by FT-IR analysis (Fig.4).

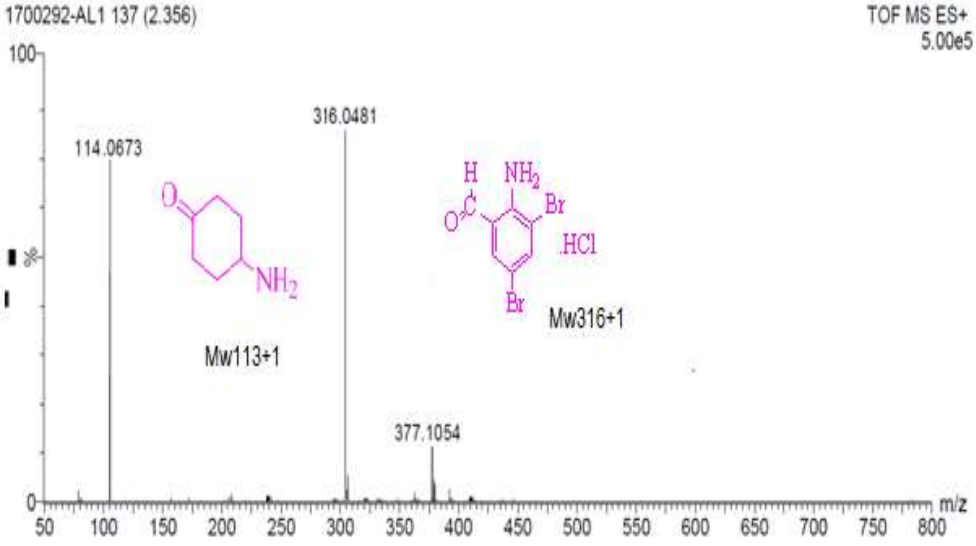


Fig. 2: The LC-MS spectra of the oxidized products (peaks at m/z 316 and 114 amu).

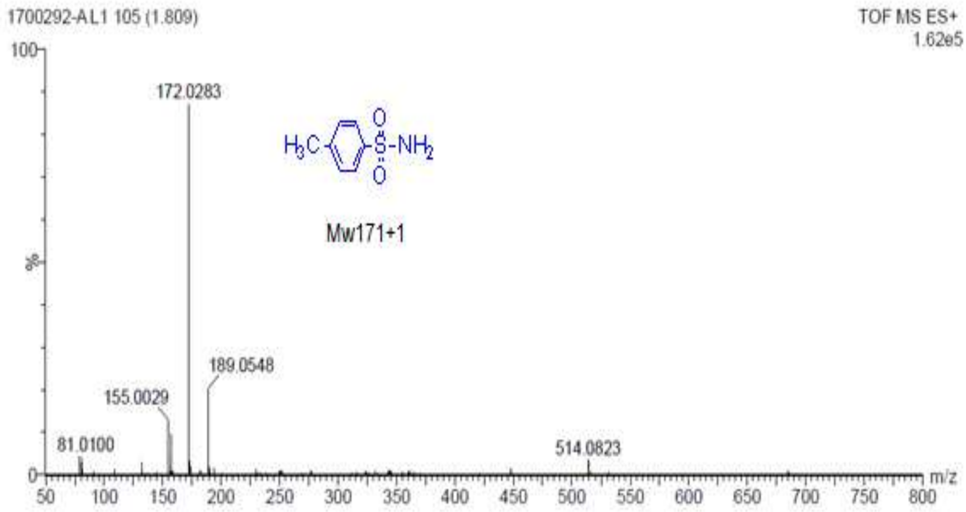


Fig. 3: The LC-MS spectra of the reduction products (PTS) peaks at m/z 172amu).

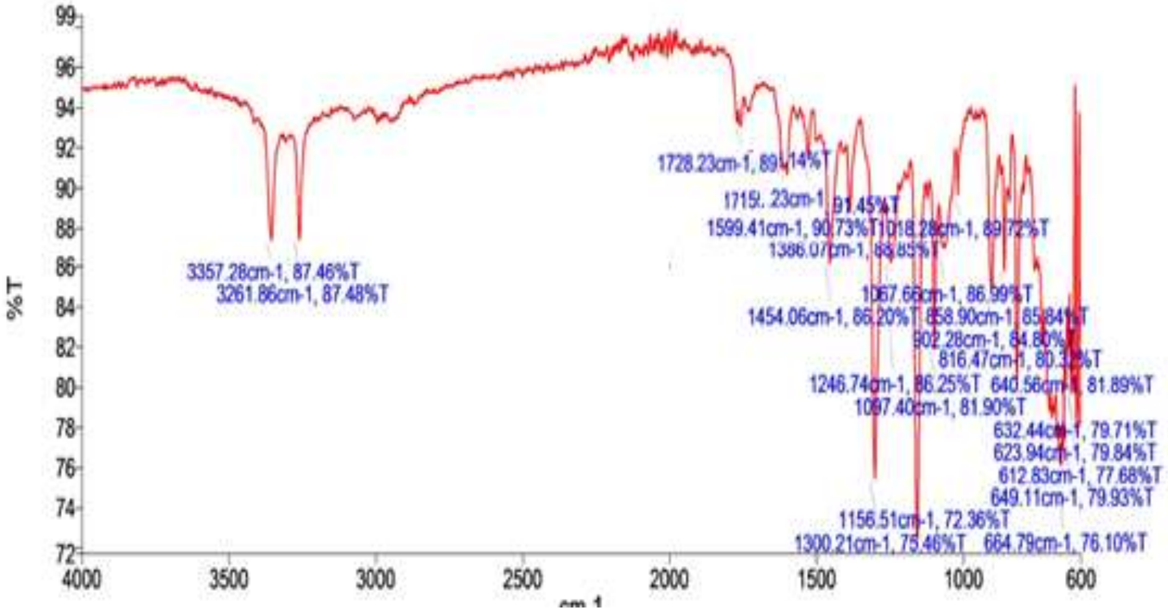


Fig. 4: FT-IR spectrum of oxidation product of ABL.

KINETIC RESULTS

With the drug concentration in excess over [CAT], the standard oxidation reaction run was carried out in presence of NaOH at 308 K. A plot of logV_t **(**titer volume of $Na_2S_2O_3$) versus time was found to be linear (Table 1, Fig.4, R^2 = 0.999) with unit slope. Also, rate constant values were unchanged when [CAT] was increased while keeping the concentration of other reactants the same indicating first-order kinetics in CAT. Under the same experimental conditions, with constant [CAT], an increase in [ABL] increased the value of k' (Table 1). A plot of log k' vs log [ABL] was linear (Fig.4, R^2 = 0.991) with a slope of 0.91 indicating a first-order dependence of rate on [ABL]. The effect of NaOH on the rate of the reaction was studied by varying [NaOH] in the range 1×10^{-3}- 5×10^{-3} mol dm^{-3}. A plot of log k' vs log [NaOH] was linear (Table.1, Fig.5, R^2 = 0.992) with a slope of -0.74 which indicated an inverse fractional-order dependence of rate on [NaOH]. The effect of ionic-strength (I) of the medium on the reaction rate was studied and was found to have no significant effect. This indicated the involvement of atleast one non-ionic species in the rate determining step. Hence, no attempt was made to keep the ionic strength of the medium constant during kinetic runs. The addition of halide ions, Cl^- and Br^- (1.0×10^{-3}- 10× 10^{-3}mol dm^{-3}) to the reaction mixture had negligible effect on the reaction rate of ambroxol HCl oxidation. Addition of the reaction product (PTS) retarded the rate of the reaction giving a slope of -0.78 in the plot of log k versus [PTS] which indicated an inverse fractional-order rate dependence on [PTS]. This predicts the involvement of PTS in the fast pre-equilibrium to the rate determining step. The effect of dielectric constant (D) of the medium on the reaction rate has been studied by adding methanol (0% - 30%) to the reaction mixture. The rate of the reaction decreased with the increase in the methanol content of the reaction medium. The values of D for various MeOH-H_2O mixtures reported in the literature,[9] were employed for calculation. The oxidation reaction was performed at different temperatures (298-318 K) keeping other experimental conditions constant. The rate constant values at different temperatures are given in Table 2. The Arrhenius plot of log k' vs 1/T (Fig. 6, $R^2 = 0.996$) was linear. The activation parameters were evaluated which are tabled in Table 2. Addition of the reaction mixture to aqueous acrylamide monomer solutions did not initiate polymerization, indicating the absence of in-situ formation of free radical species in the reaction sequence.

DISCUSSION

Reactive Species of CAT

Chloramine-T acts as an oxidizing agent in both acidic and alkaline media. It undergoes a two electron change per mole to give PTS and NaCl. The redox potential of CAT-PTS.[10] is pH dependent and it decreases with the increase in the pH of the medium. Hence, the nature of the reactive oxidizing species taking part in the reaction can be predicted based upon the pH of the medium and the experimentally obtained kinetic data. Chloramine-T behaves as a strong oxidizing species in aqueous solutions.[11] Depending upon the pH of the medium, CAT furnishes.[11-15] the following types of reactive species in solutions:

$$TsNClNa \rightleftharpoons Ts\bar{N}Cl + Na^+ \qquad (2)$$

$$Ts\bar{N}Cl + H^+ \rightleftharpoons TsNHCl \qquad (3)$$

$$2\,TsNHCl \rightleftharpoons TsNH_2 + TsNCl_2 \qquad (4)$$

$$TsNHCl + H_2O \rightleftharpoons TsNH_2 + HOCl \qquad (5)$$

$$TsNCl_2 + H_2O \rightleftharpoons TsNHCl + HOCl \qquad (6)$$

$$HOCl \rightleftharpoons H^+ + \bar{O}Cl \qquad (7)$$

$$HOCl + H^+ \rightleftharpoons H_2\overset{+}{O}Cl \qquad (8)$$

In alkaline solutions of CAT, $TsNCl_2$ does not exist and the possible oxidizing species are TsNHCl, $TsNCl^-$, HOCl and OCl^-. Amongst these, one species is predicted as the reactive oxidizing species from the observed kinetic data. In the present case, HOCl is predicted to be the reactive species involved in the reaction. Since the rate showed an inverse fractional order dependence on $[OH^-]$, it clearly indicates the hydrolysis of $TsNCl^-$ which results in the formation of conjugate acid, TsNHCl (Eq.3). Also, the rate showed an inverse fractional order dependence on [PTS], hence, TsNHCl formed above once again undergoes hydrolysis to give the reduction product of CAT (PTS) along with the formation of HOCl as shown in Eq.5. therefore, From the observed kinetic data it was concluded that HOCl was the reactive species of CAT taking part in the oxidation reaction of ABL by CAT.

Reaction Scheme

$$Ts\bar{N}Cl + H_2O \underset{fast}{\overset{K_1}{\rightleftharpoons}} TsNHCl + \bar{O}H \qquad (i)$$

$$TsNHCl + H_2O \underset{fast}{\overset{K_2}{\rightleftharpoons}} TsNH_2 + HOCl \qquad (ii)$$

$$HOCl + ABL \xrightarrow[r.d.s]{k_3} X \qquad (iii)$$

$$X \longrightarrow Products$$

Scheme 1: A general reaction scheme for the oxidation of ABL by CAT in alkaline medium.

The anion $TsNCl^-$ undergoes hydrolysis to give the free acid monochloramine-T as shown in step i. The free acid on further hydrolysis gives HOCl which interacts with the substrate in the slow step to give the complex (X). The complex (X) finally gives the oxidation products.
From steps (i) and (ii):

$$K_1 = \frac{[TsNHCl]\,[\bar{O}H]}{[Ts\bar{N}Cl]\,[H_2O]} \qquad (9)$$

$$K_2 = \frac{[TsNH_2]\,[HOCl]}{[TsNHCl][H_2O]} \qquad (10)$$

Rearranging Eqs.9 and 10:

$$[Ts\bar{N}Cl] = \frac{[TsNHCl]\,[\bar{O}H]}{K_1[H_2O]} \qquad (11)$$

$$[TsNHCl] = \frac{[TsNH_2]\,[HOCl]}{K_2[H_2O]} \qquad (12)$$

Substituting Eq.12 into Eq.11:

$$[Ts\bar{N}Cl] = \frac{[TsNH_2][\bar{O}H][HOCl]}{K_1K_2[H_2O]^2} \qquad (13)$$

If $[CAT]_t$ is the total effective concentration of CAT, then

$[CAT]_t = [TsNCl^-] + [TsNHCl] + [HOCl]$

(14)

Substituting for [TsNHCl] Eq.12 and $[TsNCl^-]$ Eq.13 into Eq.14, and solving for [HOCl]

$$[HOCl] = \frac{K_1K_2[CAT]_t[H_2O]^2}{K_1[TsNH_2][O\bar{H}] + K_1[TsNH_2][H_2O] + K_1K_2[H_2O]^2} \qquad (15)$$

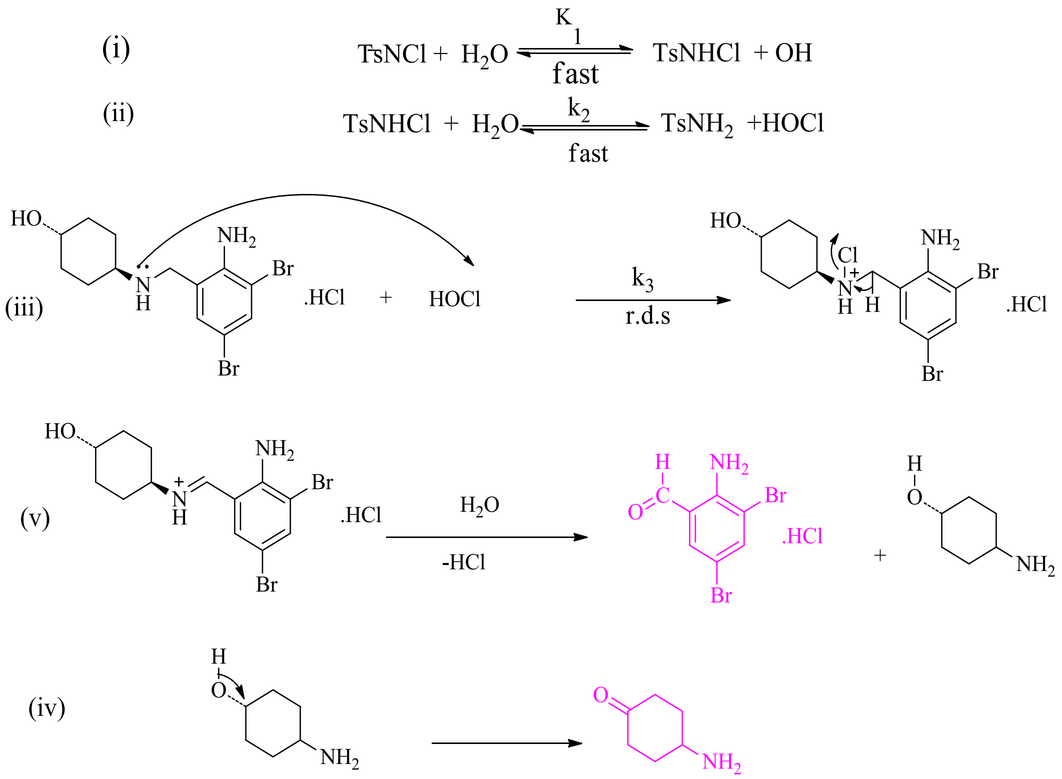
Also, from step (iv) , the rate determining step:

$$Rate = k_3\,[HOCl]\,[ABL] \qquad (16)$$

Substituting Eq.15 into Eq.16, the following rate law is obtained:

$$Rate = \frac{K_1K_2k_3[CAT]_t[ABL][H_2O]^2}{K_1[TsNH_2][\bar{O}H] + K_1[TsNH_2][H_2O] + K_1K_2[H_2O]^2} \qquad (17)$$

The above rate law (17) agrees well with the observed kinetic data showing a first order dependence of rate on [ABL] and [CAT] and inverse fractional orders on $[OH^-]$ and [PTS]. The detailed reaction scheme is proposed in Scheme 2.



Scheme 2: A detailed reaction scheme of oxidation of ABL by CAT in NaOH medium.

The observed mechanism and the derived rate law are supported by the solvent effects which indicated the dipole-dipole interaction in the r.d.s (the slow step of the reaction). Amis [18] has reported that a plot of log k′ vs 1/D should give a straight line with a negative slope for dipole-dipole interaction as observed in this case. Also, the rate of the ionic reactions is influenced by the charges carried by the ions and the ionic strength of the medium. The ionic-strength remains constant for dipole-dipole interaction. In the present study, the rate constant remained constant with the increase in the ionic-strength of the medium which clearly signifies the involvement of neutral molecules in the rate determining step. The unaffected rate constant with addition of chloride and bromide ions indicating that no free halgen is formed during the reaction further lends support to the proposed mechanism. The moderate values of activation parameters like energy of activation and other thermodynamic parameters also support the proposed mechanism. The negative value of ΔS indicates a rigid transition state.

Table 1: Effect of variation of reactants on the oxidation reaction rate.
[ABL] = 8.0 ×10^{-3}moldm^{-3}, $[CAT]_o$= 5.0 × 10^{-4} mol dm^{-3}, $[NaOH]_o$= 3.0 × 10^{-3} mol dm^{-3},T=308 K

[ABL] x10^3 moldm^{-3}	[CAT]x10^4 moldm^{-3}	[NaOH]x10^3 moldm^{-3}	kx10^4 s^{-1}
2.0	5.0	3.0	1.16
4.0	5.0	3.0	2.12
8.0	5.0	3.0	**3.83**
10.0	5.0	3.0	4.87
12.0	5.0	3.0	6.15
8.0	3.0	3.0	3.64
8.0	4.0	3.0	3.72
8.0	5.0	3.0	**3.83**
8.0	6.0	3.0	3.82
8.0	8.0	3.0	3.66
8.0	5.0	1.0	7.88
8.0	5.0	2.0	4.75
8.0	5.0	3.0	**3.83**
8.0	5.0	4.0	2.84

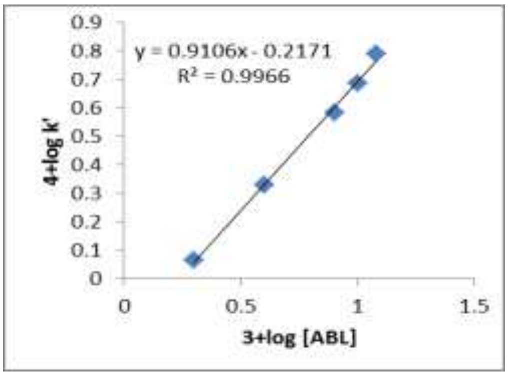


Fig. 5: A Plot of log k′ versus log [ABL].

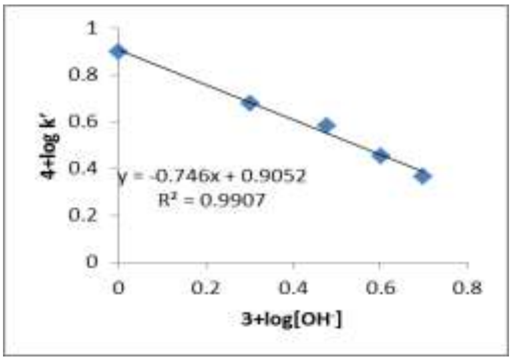


Fig. 6: A Plot of log k′ versus log [OH$^-$].

Table 2: Effect of variation of temperature and Activation parameters on the oxidation reaction rate.
$[ABL]_o$ = 8.0 × 10^{-3}mol dm^{-3}, $[CAT]_o$ = 5.0 × 10^{-4} mol dm^{-3},$[NaOH]_o$= 3.0 × 10^{-4} mol dm^{-3},

Temperature (K)	10^3(1/T) (K^{-1})	10^4 k$'$ (s^{-1})	4+logk'
298	3.35	1.45	0.161
303	3.30	2.38	0.376
308	3.24	3.83	0.583
313	3.19	7.18	0.856
318	3.14	11.23	1.051

Ea (kJ mol^{-1})	ΔH$^{\neq}$ (kJ mol^{-1})	ΔG$^{\neq}$ (kJ mol^{-1})	ΔS$^{\neq}$ (JK^{-1} mol^{-1})	log A
52.59	49.72	96.36	-121.80	7.72

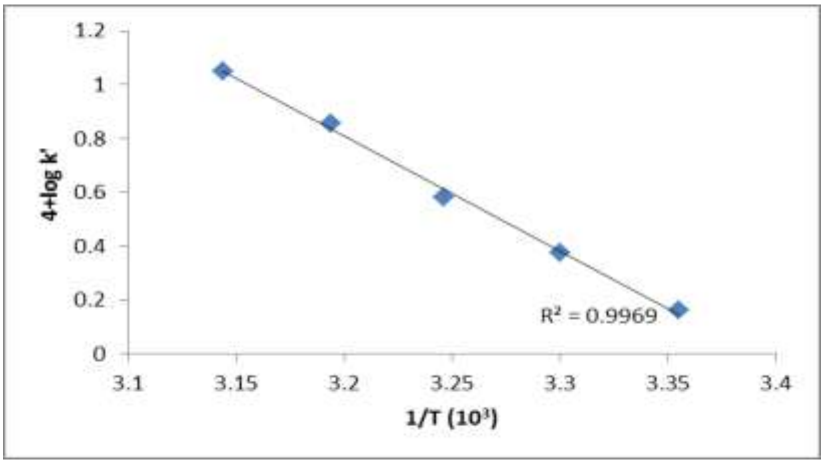


Fig.7: Arrhenius plot of log k′ versus 1/T

CONCLUSION

- The kinetics of oxidation of ABL drug were carried out with the CAT as an oxidizing agent in alkaline medium at 308 K by iodometry.
- The rate law derived was $-d\,[CAT]/dt = k\,[ABL]^{0.91}\,[CAT]^{1}[OH^{-}]^{-0.74}[PTS]^{-0.78}$, in accordance with the experimental data.
- Based on the results obtained, a possible reaction mechanism is proposed.

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