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Research Article

OXIDATION OF SALBUTAMOL BY CHLORAMINE-B IN HClO4 MEDIUM: A KINETIC AND MECHANISTIC APPROACH

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ABSTRACT
Oxidation of Salbutamol (SBL) by sodium – N- chloro benzenesulphonamide(Chloramine-B or CAB) in HClO4 medium has been studied at 303K by kinetic method. Oxidation reaction follows first order kinetics with [CAB], positive fractional order dependence on [SBL] and negative fractional order dependence on [HClO4]. Effect of halide ions, added benzenesulphonamide had no effect on the rate of reaction. Variation in ionic strength had no effect on the rate of the reaction indicating that non-ionic species are involved in the rate limiting step. Dielectric effect of the medium showed negative effect. Kinetic parameters were evaluated by studying the reaction at different temperatures. Addition of reaction mixture to aqueous acrylamide did not initiate polymerization showing the absence of free radical species. Oxidation products were identified. TsNHCl of CAB, the reactive oxidant combines with the substrate to give the product. Based on kinetic results, reaction stoichiometry and oxidation products, a suitable mechanism have been proposed.
KEY WORDS: Salbutamol, Oxidation, Chloramine – B, Kinetics, Mechanistic, HClO4

INTRODUCTION

Salbutamol (SBL) [(RS)-4-[2-(tert-butylamino)-1-hydroxy ethyl]-2-(hydroxyl methyl) phenol] is a drug used in the treatment of asthma, a chronic lung disease caused by inflammation of the lower airways[1,2]. Asthma causes airways to become sensitive, swollen and inflamed, even when there are no visible symptoms and hence causes hyper responsiveness of tissues lining the bronchi to certain triggers. The most serious symptom is the constriction of the smooth muscle lining the bronchi of the lungs. Salbutamol can be taken orally or more commonly used inhaler device. Inhaled Salbutamol is the most commonly used quick relief medication.
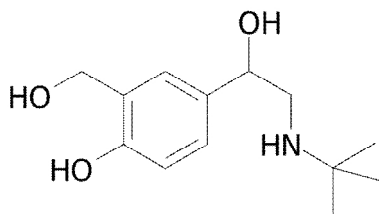
Aromatic N- halosulphonamides behave as mild oxidants, halogenating agents containing strong polarized N- linked halogen which is in +1 state. They are employed as analytical reagents in the determination of variety of industrially and biologically important organic and inorganic substances in the solution. As a result these compounds react with wide range of functional groups and affect a variety of molecular changes. The oxidation potential of the haloamine-sulphonamide system is pH dependent and decreases with the pH of the medium. Depending on the pH of the medium these haloamines generate different types of reactive species in the solution. In general these haloamines undergo a two-electron change in its reaction.

Chloramine -B (sodium – N- chloro benzenesulphonamide or CAB; $C_6H_5 SO_2NCl\cdot Na$) can be easily prepared by chlorination of benzenesulphonamide. Literature survey reveals that several work have been carried out using other oxidants[3-9] but little information is available on CAB as oxidant[10-12].
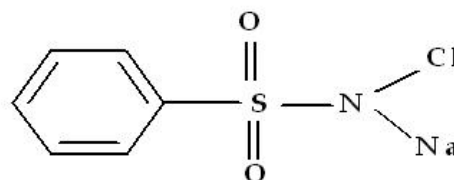
Chloramine-B (CAB)

Kinetics of oxidation of Salbutamol in alkaline medium has been carried out[13] by Ramachandrappa et al. There was a need to understand the kinetic aspects of Salbutamol in acid medium, therefore we have studied kinetics of oxidation of Salbutamol(SBL)[(RS)-4-[2-(tert-butylamino)-1-hydroxyeth yl]-2-(hydroxymethyl)phenol] by CAB in HClO4 medium at 303K and also we found that the reaction is faster with respect to CAT and BAT.
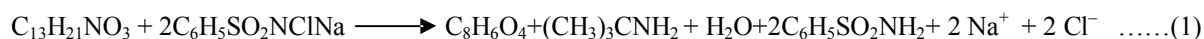
MATERIAL AND METHODS

Chloramine- B the sodium salt of N-chlorobenzene sulphonamide was first proposed by Alfanas' ev as a substitute for Chloramine- T for volumetric work[14]. It is prepared by the action of chlorine on benzene sulphonamide in the presence of NaOH. Benzene sulphonamide was added gradually to 4-5N NaOH solution at 25°C with stirring. The homogenous solution was heated at 65-70°C and chlorine was bubbled slowly for a period of 1 hour. The mass was stirred for one hour at the same temperature then subsequently heated to 85°C and was then filtered through a schotts funnel. A 99% yield was produced. If chlorine is passed more rapidly dichloramine- B is formed with CAB as only an intermediate product. Chloramine- B is soluble in water and alcohol. The active chlorine content in CAB has been estimated by iodometric method and found to be 28-29.5%.It has been observed that CAB does not liberate chlorine in acid solution. On acidifying an aqueous solution of CAB with either HCl or H2SO4, a white precipitate of Dichloramine- B (DCB) is formed. The prepared Chloramine- B was preserved in glass stoppered coloured bottles at room temperature to prevent further reaction.

Salbutamol (Biocon, India) and Benzenesulphonamide (E.Merck) was used without further purification and aqueous solution of desired strength was prepared freshly each time.

All other chemicals used were of analytical grade. Permittivity of the reaction medium was altered by addition of methanol in varying proportions (v/v) and values of permittivity of methanol – water mixtures reported in literature were employed[15]. Double distilled water was used in preparing all aqueous solutions throughout the studies.

Kinetic Procedure

All reactions were carried out under pseudo – first order conditions ($[SBL]_o \gg [CAB]_o$) at constant temperature 303K, in a glass – stoppered pyrex boiling tubes coated black on outside to eliminate photochemical effects. Oxidant and the requisite amounts of substrate, $HClO_4$ solution and water (for constant total volume) taken in separate boiling tubes were thermally equilibrated at 303K. Reaction was initiated by rapid addition of measured amount of CAB to the mixture and was shaken intermittently. Progress of the reaction was monitored by iodometric determination of unconsumed CAB in known aliquots (5ml each) of the reaction mixture at regular intervals of time. Reaction was studied for more than two half- lives. The pseudo – first order rate constants ($k^/$) calculated from the linear plots of log $[CAB]_o$ versus time were reproducible within ± 3-4 %.

Stoichiometry

Various ratios of SBL and CAB were equilibrated in presence of 5×10^{-3} mol dm^{-3} $HClO_4$ at 303K under the condition [CAB]>>[SBL]. Determination of unreacted oxidant in the reaction mixture showed that one mole of the Salbutamol consumed two moles of oxidant confirming the following stoichiometry.

$$C_{13}H_{21}NO_3 + 2C_6H_5SO_2NClNa \longrightarrow C_8H_6O_4 + (CH_3)_3CNH_2 + H_2O + 2C_6H_5SO_2NH_2 + 2\ Na^+ + 2\ Cl^- \quad \ldots\ldots(1)$$

Product Analysis

The reduction product of the oxidant, benzene sulfonamide was detected[16] by thin layer chromatography using light petroleum- chloroform - butan-1-ol (2:2:1v/v/v) as the solvent and the iodine as the reducing agent ($R_f=0.88$).The reported R_f value is consistent with the given literature[17]. Further it was confirmed by its melting point 150-151°C (Melting point: 149-152°C). One of the product tertiary butyl amine was detected by the spot tests[18] and the major product (4- hydroxy 3- hydroxy methyl benzoic acid) was detected by IR spectra and the spot tests. Strong peaks were observed at 1750cm^{-1} and 3000cm^{-1}.

RESULTS

Effect of the reactants

From the experiments conducted under pseudo-order conditions, [SBL]>> [CAB] at constant [SBL], [$HClO_4$]and temperature, plots of log [CAB] vs time were made and found to be linear, (plots not shown).The rate constant was unaffected with the change in $[CAB]_o$ confirming the first order dependence on the reaction rate of $[CAB]_o$(Table 1). Under identical experimental conditions, an increase in the [SBL] lead to increase in $k^/$ values (Table 1), showing a positive fractional order dependence of the rate of [SBL]. Plot of log $k^/$ vs log[SBL] was linear with unit slopes showing a first order dependence on the rate of the [SBL](Fig. 1). When [$HClO_4$] was increased, keeping [SBL], [CAB] and temperature constant resulted in retardation of rate (Table 1). Plots of log $k^/$ vs [$HClO_4$] was linear (Fig.2) with negative fractional slopes of 0.245 indicating a negative fractional order in [$HClO_4$].

TABLE 1 – EFFECT OF REACTANT CONCENTRATIONS ON THE REACTION RATE

$10^4[CAB]_o$ mol dm^{-3}	$10^3[SBL]$ mol dm^{-3}	$10^3[HClO_4]$ mol dm^{-3}	$10^4k^/$ s^{-1}
5.0	10.0	5.0	2.10
10.0	10.0	5.0	2.20
15.0	10.0	5.0	2.02
20.0	10.0	5.0	2.32
10.0	1.0	5.0	0.52
10.0	2.0	5.0	0.90
10.0	5.0	5.0	1.52
10.0	10.0	5.0	2.20
10.0	20.0	5.0	3.27
10.0	50.0	5.0	5.98
10.0	10.0	1.0	3.77
10.0	10.0	5.0	2.20
10.0	10.0	10.0	1.88
10.0	10.0	20.0	1.56
10.0	10.0	50.0	1.20

Effect of halide ions and benzene sulphonamide[BSA]

Addition of NaCl, NaBr did not affect the rate of the reaction(Table 2). Hence it reflected that rate of the reaction depends only on [H^+].

Reaction rate was unaffected by addition of benzenesulfonamide and indicated its non involvement in a pre-equilibrium with the oxidant.

TABLE 2: EFFECT OF [NaCl], [NaBr], [NaClO$_4$] AND [BSA] ON THE REACTION RATE.

10^{-4}[Conc.] mol dm^{-3}	[NaCl] $10^4k^/(s^{-1})$	[NaBr] $10^4k^/(s^{-1})$	[NaClO$_4$] $10^4k^/(s^{-1})$	[BSA] $10^4k^/(s^{-1})$
1.00	2.31	2.32	2.72	2.09
5.00	2.48	2.41	2.68	2.98
10.00	2.50	2.12	2.74	2.89
20.00	2.42	2.03	2.69	2.02

Effect of ionic strength and dielectric constant of medium

Variation in ionic strength using NaClO$_4$ solution did not affect the rate of the reaction (Table 2) indicating that non-ionic species are involved in the rate limiting step.

Dielectric constant (D) of the medium was varied by adding methanol to the reaction mixture. An increase in the addition of the methanol resulted in decrease in rate of the reaction (Table 3). Plot of (10^2/D) vs log$k^/$ was found to be linear (Fig 3) with the negative slope of 3.4. Values of dielectric constant (D) of water-methanol system of different compositions are reported in the literature[15]. Blank experiments showed that MeOH was oxidized slightly (~3%) by the oxidants under experimental conditions. This was corrected for the calculation of net reaction rate constant of oxidation of SBL.

TABLE 3 – EFFECT OF DIELECTRIC CONSTANT OF THE MEDIUM ON THE REACTION RATE

MeOH (% v/v)	D	10^2/D	10^4 $k^/(s^{-1})$
0	76.93	1.30	2.22
10	72.37	1.38	1.16
20	67.38	1.48	0.53
30	62.71	1.60	0.21

Effect of temperature

The reaction was studied over a range of the temperatures 293K to 313K, by varying the concentration of salbutamol and keeping the other experimental conditions constant(Table 4). It was found that the rate of the reaction increased with increase in temperature(Fig. 4). From the linear Arrhenius plots (Fig. 5) of log$k^/$ vs 1/T, values of energy of activation(E_a) , enthalpy of activation($\Delta H^{\#}$), entropy of activation($\Delta S^{\#}$) and free energy of activation($\Delta G^{\#}$), were computed(Table 5)

TABLE 4 – EFFECT OF [SBL] ON THE REACTION RATE AT DIFFERENT TEMPERATURES

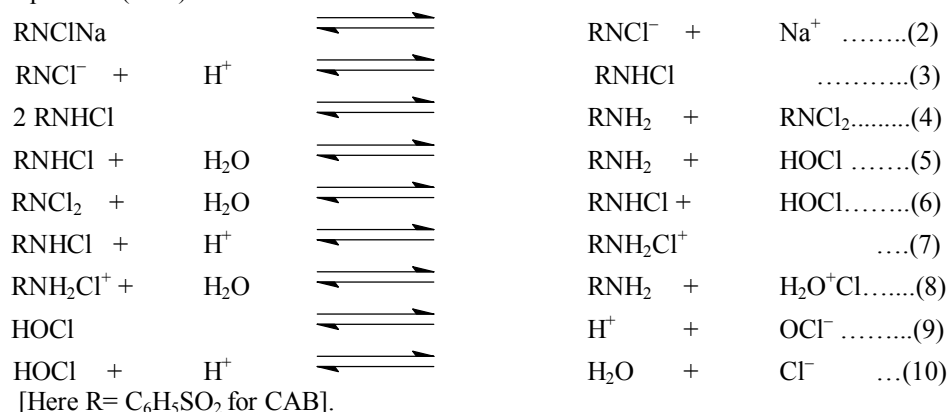| 10^3 [SBL] mol dm^3	$10^4 k^/(s^{-1})$		
	293K	303K	313K
1.0	0.21	0.40	0.78
5.0	0.65	1.26	2.50
10.0	1.19	2.20	4.20
20.0	1.96	3.80	6.50

TABLE 5: EFFECT OF TEMPERATURE ON THE REACTION RATE AND VALUES OF ACTIVATION PARAMETERS

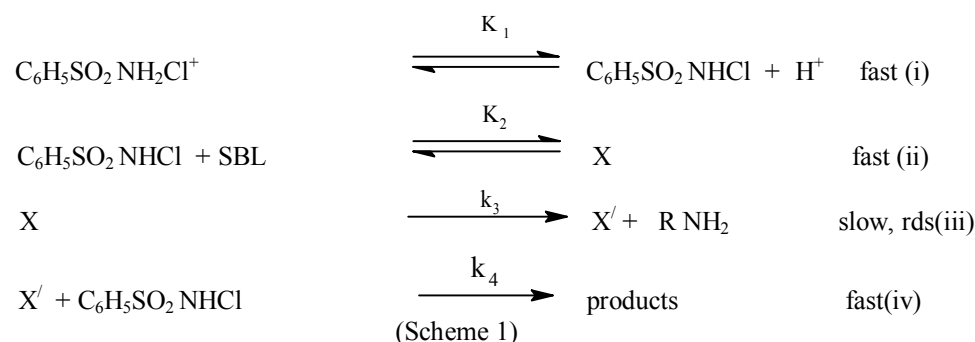| Temperature (K)	$10^4 k^/(s^{-1})$	Activation parameters	
		Parameter	Value
293	1.25	Ea(kJ mol^{-1})	51.448
303	2.20	$\Delta H^{\neq}$(kJ mol^{-1})	48.928
313	4.20	$\Delta G^{\neq}$ (kJ mol^{-1})	74.920
323	7.80	$\Delta S^{\neq}$ (JK^{-1} mol^{-1})	-84.392
		logA	5.225

DISCUSSION

Bishop and Jennings[19], Pyrde and Soper[20] and Morris et.al.[21] have shown the existence of the similar equilibria in acid and the alkaline medium. Haloamines behave as an electrolyte in aqueous solution forming different species as shown in equations (2-10)

$$RNClNa \rightleftharpoons RNCl^- + Na^+ \quad ....(2)$$

$$RNCl^- + H^+ \rightleftharpoons RNHCl \quad ....(3)$$

$$2\ RNHCl \rightleftharpoons RNH_2 + RNCl_2 ....(4)$$

$$RNHCl + H_2O \rightleftharpoons RNH_2 + HOCl ....(5)$$

$$RNCl_2 + H_2O \rightleftharpoons RNHCl + HOCl........(6)$$

$$RNHCl + H^+ \rightleftharpoons RNH_2Cl^+ \quad ....(7)$$

$$RNH_2Cl^+ + H_2O \rightleftharpoons RNH_2 + H_2O^+Cl.......(8)$$

$$HOCl \rightleftharpoons H^+ + OCl^- ....(9)$$

$$HOCl + H^+ \rightleftharpoons H_2O + Cl^- ...(10)$$

[Here R= C$_6$H$_5$SO$_2$ for CAB].

Test for free radicals

Addition of reaction mixture to aqueous acrylamide solution did not initiate polymerization, showing the absence of free radicals species during the reaction sequences.

Possible oxidizing species in acid medium are RNHCl, RNCl$_2$, HOCl and probably H$_2$O$^+$Cl and in the alkaline solutions RNHCl, HOCl, RNCl$^-$ and OCl$^-$. In present case of CAB, if RNCl$_2$ were to be the reactive species, the rate law predicts a second order dependence of rate on [CAB] and a negative effect of C$_6$H$_5$SO$_2$NH$_2$ is expected according to the equation(4,5) which are contrary to the experimental observations. If HOCl is primarily involved, a first order of rate by added benzene sulfonamide is expected. Since no such effect is noticed, HOCl can be ruled out as oxidizing species. Hardy and Johnston[22]who have studied the pH dependent relative concentrations of the species present in acidified haloamine solutions of comparable molarities have shown that RNHBr is likely oxidizing species in the acid medium. Narayanan Rao[23] and Subhashini et.al.[24] have reported that monohaloamines can be further protonated at pH 2.

$$C_6H_5SO_2NHCl + H^+ \rightleftharpoons C_6H_5SO_2NH_2Cl^+$$
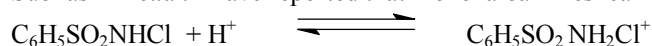
In the present investigations, the retardation of rate by H$^+$ ion indicates that unprotonated oxidant (RNHCl) is the active oxidizing species. This is being suggested by the similar kinetic parameters observed in the oxidation of Aspirin by Ramachandrappa et.al.[25] using these oxidants BAT, NBS and NBP in acid medium. Hence a general mechanism (Scheme 1) is proposed from observed kinetic results.

$$C_6H_5SO_2\ NH_2Cl^+ \underset{}{\overset{K_1}{\rightleftharpoons}} C_6H_5SO_2\ NHCl + H^+ \quad fast\ (i)$$

$$C_6H_5SO_2\ NHCl + SBL \underset{}{\overset{K_2}{\rightleftharpoons}} X \quad fast\ (ii)$$

$$X \overset{k_3}{\longrightarrow} X^/ + R\ NH_2 \quad slow,\ rds(iii)$$

$$X^/ + C_6H_5SO_2\ NHCl \overset{k_4}{\longrightarrow} products \quad fast(iv)$$

(Scheme 1)

X and X$^/$ represents complex intermediate species, whose structures are shown in Scheme 2 in which a detailed mechanistic interpretation of SBL oxidation by CAB in acid medium is proposed. In this, the oxidant species TsNHCl formed from dissociation of TsNH$_2$Cl$^+$ reacts with the substrate in a fast equilibrium step to form substrate – BAT complex (X). This gives another intermediate complex (X$^/$) in a rate limiting step. X$^/$ will give the final products on rearrangement.

$$RNHCl + H_2O \rightleftharpoons RNH_2 + HOCl \qquad \text{...(i)}$$

$$HOCl \rightleftharpoons H^+ + OCl^- \qquad \text{...(ii)}$$
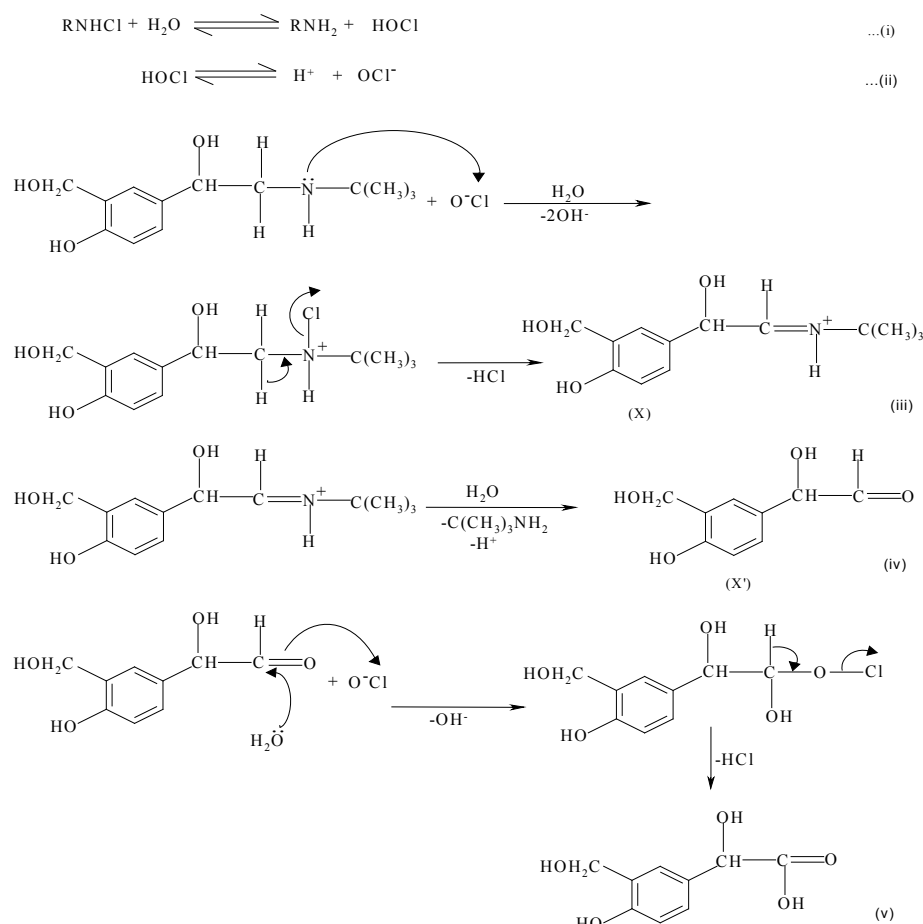
Scheme 2

The actual concentration [CAB] is given by

$$[CAB]_t = [RNH_2Br] + [RNHBr] + [X] \qquad \text{.....(11)}$$

The above scheme leads to the rate law

$$\text{Rate} = \frac{-d(CAB)}{dt} = \frac{K_1 K_2 k_3 [SBL][CAB]}{[H^+] + K_1(1 + K_2[SBL])} \qquad \text{............(12)}$$

Since rate = $k_3[X]$, rate law (12) can be transformed as

$$\frac{1}{k^{/}} = \frac{1}{K_2 k_3 [SBL]}\left(\frac{[H^+]}{K_1} + 1\right) + \frac{1}{k_3} \qquad \text{............(13)}$$

Plots of $1/k^{/}$ vs $1/[SBL]$ and $1/k^{/}$ vs $[H^+]$ (Figures not shown) at constant temperatures and other reaction conditions were linear. From the slopes and the intercepts of these plots, values of formation constants K_1, K_2 and decomposition constants k_3 were found to be 8×10^{-4}, 0.4×10^4 and 2.25×10^{-2}. Since the rate was fractional in [SBL], Michaelis Menten type of kinetics was adopted.

Reduction product of oxidant ($C_6H_5SO_2 NO_2$) does not interfere in the reaction sequence showing its non involvement in the pre-equilibrium step. Change in ionic strength of the medium does not alter the rate indicating that non-ionic species are involved in the rate determining step. Effect of varying solvent composition on the rate of reaction has been described in several publications for the limiting case of zero angle of approach between dipoles or an anion – dipole system. Amis[26] has shown that a plot of log$k^{/}$ vs $1/D$ gives a straight line with a negative slope for reaction between a negative ion and a dipole or between two dipoles, while a positive slope indicates a reaction between a positive ion and a dipole. Negative dielectric effect observed in present case, supports the interaction of dipoles in the rate determining step. Moderate E_a values support the proposed mechanism while the values of $\Delta S^{\#}$ indicate the formation of rigid associative transition.

CONCLUSION

Kinetics and oxidation of Salbutamol by sodium – N- chloro benzenesulphonamide(Chloramine-B or CAB) in HClO$_4$ medium has been studied at 303K. Activation parameters were computed. Major oxidation product (4- hydroxy 3- hydroxy methyl benzoic acid) was detected by IR spectra and the spot tests. TsNHCl is the reactive species which reacted with the substrate to give corresponding product. Based on

kinetic results and reaction stoichiometry, a suitable mechanism and rate law has been proposed.

ACKNOWLEDGEMENT

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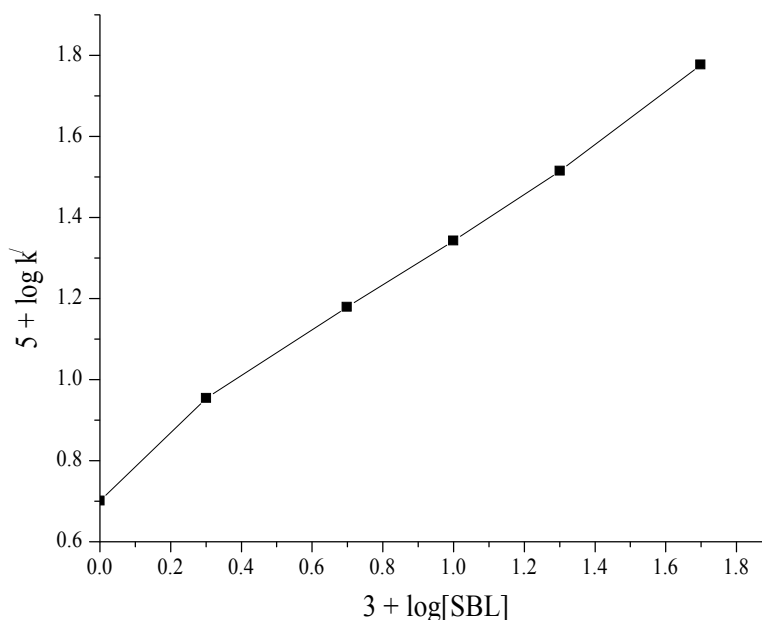**Fig. 1 Effect of [SBL] on the reaction rate**

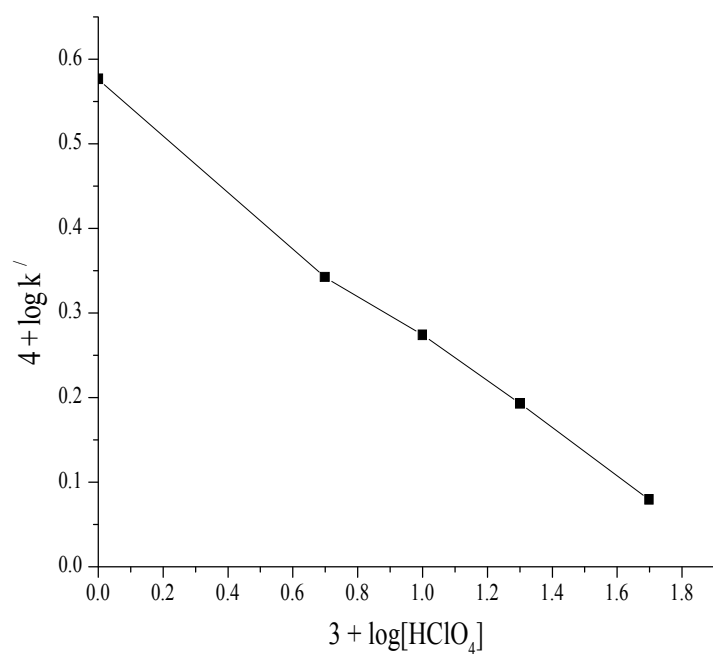**Fig 2: Effect of [HClO₄] on the reaction rate**

Fig 3: Effect of dielectric constant of the medium on reaction rate

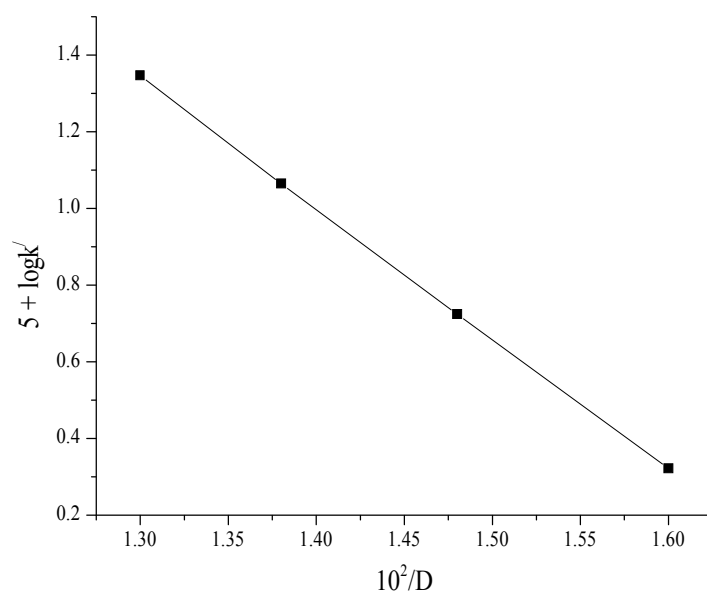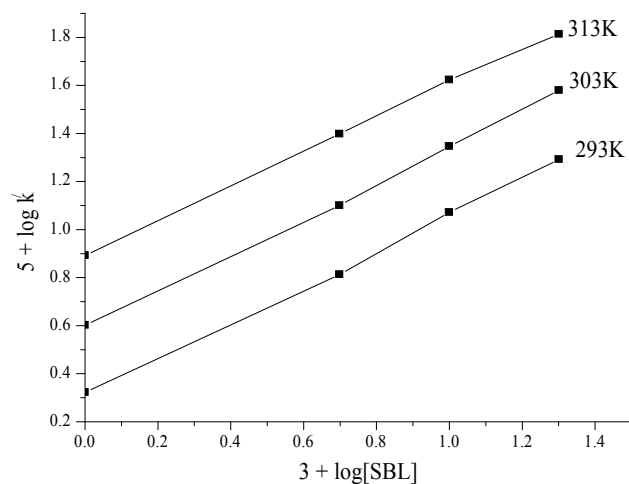**Fig 4: Effect of [SBL] at different temperatures on reaction rate**

Fig 5: Effect of temperature on the rate of the reaction