KINETICS OF OXIDATION OF SALBUTAMOL BY CHLORAMINE-B IN NaOH MEDIUM: A MECHANISTIC APPROACH

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ABSTRACT
The kinetics of oxidation of salbutamol (SBL) by N-chlorobenzenesulphonamide (CAB) in NaOH medium   has been investigated at 303K. The reaction rate shows a first order dependence on $[CAB]_0$, fractional order with respect to $[SBL]_0$ and a negative fractional order with respect to $[OH^-]$. The addition of the reduction product, benzenesulphonamide , retards the reaction rate. The effect of dielectric constant of the medium by varying [MeOH] shows an inverse effect. The addition of chloride ions and variation of ionic strength of the medium have no significant effect on the rate of the reaction. The reaction fails to initiate polymerization of acrylamide. The oxidation products were identified. The Michaelis – Menten type of kinetics has been proposed. The reaction was studied at different temperatures and the values of thermodynamic parameters were computed. A mechanism consistent with the observed kinetics is proposed.
Keywords: Kinetics, Oxidation, Chloramine-B, Salbutamol

INTRODUCTION

 N-haloamines are mild oxidants and generally undergo a two electron change per mole in its reactions. They act as sources of halonium cations, hypohalite species and N-anions, which act both as bases and nucleophiles.[1]There are many reports on N-halocompounds behaving as oxidizing agents.[2-5] However, a review of literature shows that there are sparse reports on chloramines-B (CAB)[6,7] as an oxidizing agent.
 Salbutamol [1-(4-hydroxy-3-hydroxymethyl phenyl)-2-(t-butylamino) ethanol] , is a drug used in the treatment of asthma,[8] a chronic lung disease caused by inflammation of the lower airways. This medicine is also used to prevent wheezing caused by exercise. It acts quickly on the nerves that control the airway muscles and causes them to relax. It also relieves swelling of the airways that can be caused by the allergic response and helps to clear mucous that may contribute to asthmatic symptoms. This drug is used as a nasal decongestant. Literature survey shows that there is no information available on the kinetics and oxidation of salbutamol by CAB from the mechanistic view point. There was a need for understanding the mechanism of oxidation of this drug, so that this study may throw some light on the metabolic conversions in the biological system. Therefore, in the present communication, we report the kinetics and mechanism of oxidation of salbutamol by chloramime-B in NaOH medium 303K .
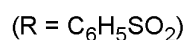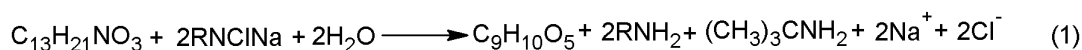
MATERIALS AND METHODS

An aqueous solution of CAB was prepared[9] standardized iodometrically and stored in brown bottles to prevent any photochemical deterioration. The substrate salbutamol (Biocon Ltd) was used as received. The aqueous solution of the substrate was prepared freshly each time. All the other chemicals used were of analytical grade. Doubly distilled water was used for all the measurements.

Experimental
The reactions were carried out under pseudo- first order conditions by keeping an excess of salbutamol over BAT. Solutions containing appropriate amounts of SBL, NaOH and water (to keep the total volume constant for all runs) were taken in a glass-stoppered Pyrex boiling tube, and thermostated at 303K. A measured amount of CAB solution, also thermostated at the same temperature, was rapidly added to the mixture. The progress of the reaction was monitored by iodometric estimation of unreacted CAB in a measured aliquot (5ml) of the mixture at different time intervals. The course of the reaction was studied up to 75 to 80% completion. The pseudo- first order rate constants (k') evaluated from the plots of log[CAB] versus   time were reproducible within $\pm$ 4%.

Stoichiometry and Product Analysis
Reaction mixtures containing varying proportions of CAB and salbutamol in the presence of 5×10^{-3} mol dm^{-3} NaOH were equilibrated at 303K for 24h. Estimation of unreacted CAB showed that one mole of salbutamol consumed two moles of oxidant   .

$$C_{13}H_{21}NO_3 + 2RNClNa + 2H_2O \longrightarrow C_9H_{10}O_5 + 2RNH_2 + (CH_3)_3CNH_2 + 2Na^+ + 2Cl^- \quad (1)$$

$$(R = C_6H_5SO_2)$$

The reduction product of oxidant, benzenesulphonamide (BSA) was detected[10] by thin layer chromatography using petroleum ether, chloroform and 1- butanol(2:2:1v/v/v) as the solvent and iodine as the detecting agent ($R_{f} = 0.88$). It was further confirmed by its melting point 150-151°C (reported m.p.= 149-152°C). One of the product tertiary butylamine was detected by spot tests [11] and the major product 4-hydoxy-3-hydroxymethyl(phenyl -2-hydroxy acetic acid) was detected by spot tests and IR spectroscopy which shows a strong peak at 1750 cm^{-1}and 3000cm^{-1}.

RESULTS

Effect of varying reactant concentrations on the reaction rate

The oxidation of salbutamol (SBL) by CAB was kinetically investigated at different initial concentrations of reactants in NaOH medium at 303K. Under pseudo-first order conditions, with the substrate in excess, at constant [SBL], [NaOH] and temperature, plots of log $[CAB]_0$ versus time were linear, indicating a first order dependence of the reaction rate on $[CAB]_0$. Under identical experimental conditions, an increase in $[SBL]_0$ leads to an increase in the k' values (Table 1). A plot of log k' versus log $[SBL]_0$ was linear with a slope of 0.80 (Fig.1) showing a fractional order dependence of the rate on $[SBL]_0$.

Effect of varying [OH⁻] and [Cl⁻] on the reaction rate

The rate of the reaction decreased with increase in [NaOH]. A plot of log k' versus [NaOH] was linear with negative slope (Table 1, Fig.1) indicating a negative fractional order dependence on [OH⁻]. At constant [OH⁻], addition of Cl⁻ in the form of NaCl had no significant effect on the rate of the reaction (Table 2).

Effect of added benzenesulphonamide on the reaction rate

The addition of reduction product of CAB, benzenesulphonamide (BSA or RNH_2) had a retardation effect on the rate of the reaction (Table 2). A plot of log k' versus [BSA] was linear with negative fractional slope (Fig.2) indicating a negative fractional order dependence on [BSA] and thus suggesting that RNH_2 is involved in a pre-equilibrium to the rate determining step.

Effect of dielectric permittivity of the medium and varying ionic strength on the reaction rate

The dielectric permittivity of the medium was varied by adding different proportions of methanol to the reaction mixture. The rate of the reaction decreased with increase in methanol content (0- 40% v/v). A plot of log k' versus 1/D, where D is the dielectric permittivity of the medium (D values taken from the literature)[12] gave a straight line with a negative slope (Table 3, Fig.3). Blank experiments with methanol however showed that there was slight decomposition of the solvent under the given experimental conditions. Variation of ionic strength of the medium had a negligible effect on the rate of the reaction.
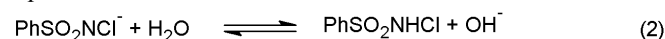
Effect of varying temperature on the reaction rate

The reaction was studied at different temperatures (Table 4) and from the linear Arrhenius plot of log k' versus 1/T, (Fig.4) values of activation parameters have been computed.
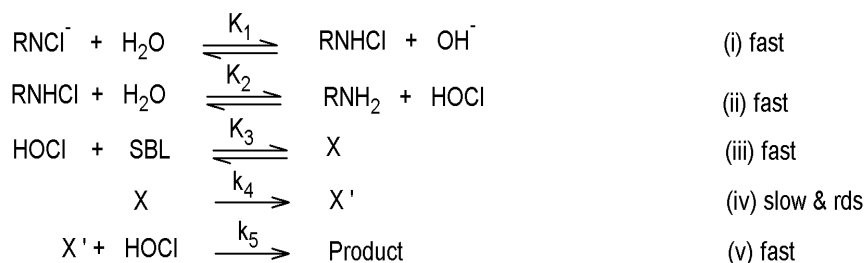
Test for free radicals

Addition of the reaction mixtures to acrylamide did not initiate polymerization which indicates the absence of free radicals species.

DISCUSSION

Chloramine-B is similar to chloramine-T and behaves as a strong electrolyte in aqueous solutions.[13,14] The following equilibrium exists in alkaline solution of CAB.[15]

$$PhSO_2NCl^- + H_2O \rightleftharpoons PhSO_2NHCl + OH^- \quad (2)$$

$$PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + HOCl \quad (3)$$

The possible oxidizing species in alkaline CAB solutions are $RNHCl$, $RNCl_2$ and HOCl. If $RNCl_2$ were to be the oxidizing species, the rate law should predict a second order dependence of the rate on $[CAB]_0$, which is contrary to the experimental observations. The observed retardation effect of rate by both OH⁻ ion and addition of reduction product (RNH_2) can be best explained by Scheme 1.

$$RNCl^- + H_2O \overset{K_1}{\rightleftharpoons} RNHCl + OH^- \qquad \text{(i) fast}$$

$$RNHCl + H_2O \overset{K_2}{\rightleftharpoons} RNH_2 + HOCl \qquad \text{(ii) fast}$$

$$HOCl + SBL \overset{K_3}{\rightleftharpoons} X \qquad \text{(iii) fast}$$

$$X \overset{k_4}{\longrightarrow} X' \qquad \text{(iv) slow \& rds}$$

$$X' + HOCl \overset{k_5}{\longrightarrow} Product \qquad \text{(v) fast}$$

Scheme 1

In Scheme 1, step (iii), SBL represents the substrate. In this step, the reactive oxidizing species HOCl attacks the substrate to form complex (X). The complex (X) slowly decomposes to give complex intermediate species (X') with the elimination of tertiary butylamine. This complex reacts with one more molecule of HOCl to form the final product. The structures of complex intermediate species X and X' are illustrated in Scheme 2 where a detailed mechanistic interpretation of SBL-CAB reaction in alkaline medium is presented.

$$RNCl^- + H_2O \rightleftharpoons RNHCl + OH^- \qquad\qquad -(i)$$

$$RNHCl + H_2O \rightleftharpoons RNH_2 + HOCl \qquad\qquad -(ii)$$
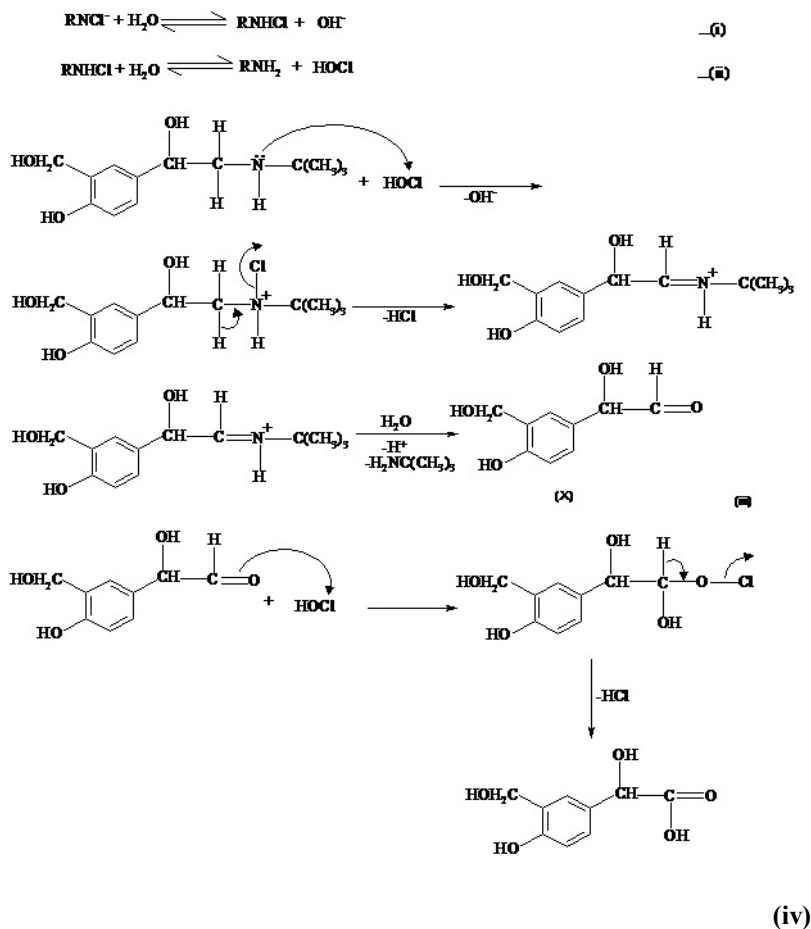
Scheme 2

If $[CAB]_t$ represents the total effective concentration of CAB , from Scheme 1

$$[CAB]_t \;=\; [RNCl^-] \;+\; [RNHCl] \;+\; [HOCl] \;+\; [X] \qquad (4)$$

From steps (i), (ii) & (iii) of Scheme 1, the value of [X] obtained is,

$$[X] \;=\; \frac{K_1 K_2 K_3\,[CAB]_t\,[SBL]\,[H_2O]^2}{[OH^-][RNH_2] + K_1[RNH_2][H_2O] + K_1K_2[H_2O]^2 + K_1K_2K_3[SBL][H_2O]^2} \qquad (5)$$

From slow step (step (iv)) of Scheme 1,

$$Rate \;=\; k_4\,[X] \qquad (6)$$

By substituting the value of [X] from equation (5) into equation (6), we get

$$[Rate] \;=\; \frac{K_1 K_2 K_3 k_4[CAB]_t[SBL][H_2O]^2}{[OH^-][RNH_2] + K_1[RNH_2][H_2O] + K_1K_2[H_2O]^2 + K_1K_2K_3[SBL][H_2O]^2} \qquad (7)$$

Above rate law (equation 7) is in good agreement with the experimental results wherein a first order dependence of rate on $[CAB]_0$, fractional order on $[SBL]_0$ and inverse fractional order on both $[OH^-]$ and $[RNH_2]$ was observed.

Since, rate = $k^/ [CAB]_t$, rate law (equation 7) can be transformed into equations (8)- (9)

$$k' \;=\; \frac{K_1K_2K_3 k_4\,[SBL]\,[H_2O]^2}{[OH^-][RNH_2] + K_1[RNH_2][H_2O] + K_1K_2[H_2O]^2 + K_1K_2K_3[SBL][H_2O]^2} \qquad (8)$$

$$1/k' \;=\; \frac{1}{K_3 k_4[SBL]} + \left\{ \frac{[OH^-][RNH_2]}{K_1K_2[H_2O]^2} + \frac{[RNH_2]}{K_2[H_2O]} + 1 \right\} + \frac{1}{k_4} \qquad (9)$$

From the slopes and intercepts of plots of $1/k^/$ versus $1/[SBL]_0$ and $1/k^/$ versus $[OH^-]$, the values of formation constant K_3 and decomposition constants k_4 were calculated. The decomposition constant was found to be $5.0 \times 10^{-4}s^{-1}$. Since the rate was fractional order in $[SBL]_0$, Michaelis-Menten type of kinetics[16] was adopted. The effect of [SBL] on the rate at different temperatures was studied and by plotting $1/k^/$ versus $1/[SBL]_0$ values of decomposition constants k_4 were calculated. Activation parameters for the rate determining step were evaluated using the Arrhenius plot of log k_4 versus 1/T. These data are presented in Table 4.

A change in the solvent composition by varying the methanol content in methanol-water affects the reaction rate. The plot of log k$^/$ versus 1/D is linear with a negative slope, thus supporting the participation of two dipole species in the rate limiting step. The addition of halide ions had no effect on the rate indicating that no interhalogen or free chlorine was formed. Variation of the ionic strength of the medium does not alter the rate indicating that non-ionic species are involved in the rate determining step.

The proposed mechanism is also supported by the moderate values of energy of activation. The fairly high positive values of $\Delta H^\#$ and $\Delta G^\#$ indicate that the transition state is highly solvated, while the high negative value of $\Delta S^\#$, suggests that the transition state is fairly rigid with less degree of freedom.

ACKNOWLEDGEMENT

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TABLE 1: EFFECT OF VARYING CONCENTRATIONS OF THE REACTANTS

10^4[CAB] (mol dm^{-3})	10^3 [SBL] (mol dm^{-3})	10^3[NaOH] (mol dm^{-3})	10^4 k$^/$ (s^{-1})
10.0	1.0	5.0	0.32
10.0	2.0	5.0	1.16
10.0	5.0	5.0	1.54
10.0	10.0	5.0	2.09
10.0	20.0	5.0	3.42
10.0	50.0	5.0	7.90
5.0	10.0	5.0	2.10
10.0	10.0	5.0	2.09
15.0	10.0	5.0	2.20
20.0	10.0	5.0	2.00
10.0	10.0	1.0	3.10
10.0	10.0	2.0	2.50
10.0	10.0	5.0	2.09
10.0	10.0	10.0	1.75
10.0	10.0	20.0	1.50
10.0	10.0	50.0	1.19

I= 5.0 x10^{-3}mol dm^{-3} ; T = 303K

TABLE 2 : EFFECT OF CHLORIDE IONS, NaClO$_4$ AND BENZENESULPHONAMIDE

10^3[Conc.] (mol dm^{-3})	[NaCl] 10^4 k$^/$ (s^{-1})	[NaClO$_4$] 10^4 k$^/$ (s^{-1})	[BSA] 10^4 k$^/$ (s^{-1})
1.0	2.01	2.00	1.36
5.0	2.05	1.98	1.15
10.0	2.03	2.12	1.05
20.0	2.09	2.06	0.95

[CAB] = 1.0 x10^{-3}mol dm^{-3} ; [SBL] = 10.0 x10^{-3}mol dm^{-3} ; I= 5.0 x10^{-3}mol dm^{-3} ; [NaOH] =5.0 x10^{-3} mol dm^{-3} ; T= 303K

TABLE 3 : EFFECT OF VARYING DIELECTRIC CONSTANT OF THE MEDIUM

[MeOH] (%v/v)	10^2 /D	10^4 k$^/$ (s^{-1})
0.0	1.30	2.09
10.0	1.38	1.26
20.0	1.48	0.67
30.0	1.60	0.30

[CAB] = 1.0 x10^{-3}mol dm^{-3} ; [SBL] = 10.0 x10^{-3}mol dm^{-3} ; I= 5.0 x10^{-3}mol dm^{-3} ; [NaOH] = 5.0x10^{-3}mol dm^{-3} ; T = 303K

TABLE 4 : EFFECT OF VARYING TEMPERATURE AND ACTIVATION PARAMETERS

Temperature (K)	$10^4 k'$ (s^{-1})	Activation Parameters	
		Parameter	Value
293	1.22 (1.10)	E_a (kJ mol^{-1})	42.50 (34.80)
303	2.09 (5.00)	$\Delta H^{\#}$ (kJmol^{-1})	39.97 (32.31)
313	3.73 (9.09)	$\Delta S^{\#}$ (Jk^{-1} mol^{-1})	-69.60 (-44.26)
323	6.20 (12.32)	$\Delta G^{\#}$ (kJ mol^{-1})	61.05 (45.70)

Values in parenthesis are the decomposition constants and activation parameters for the rate determining step.
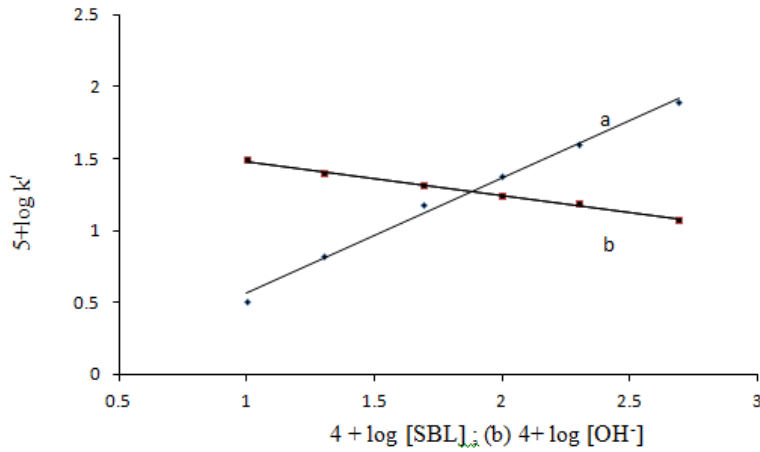
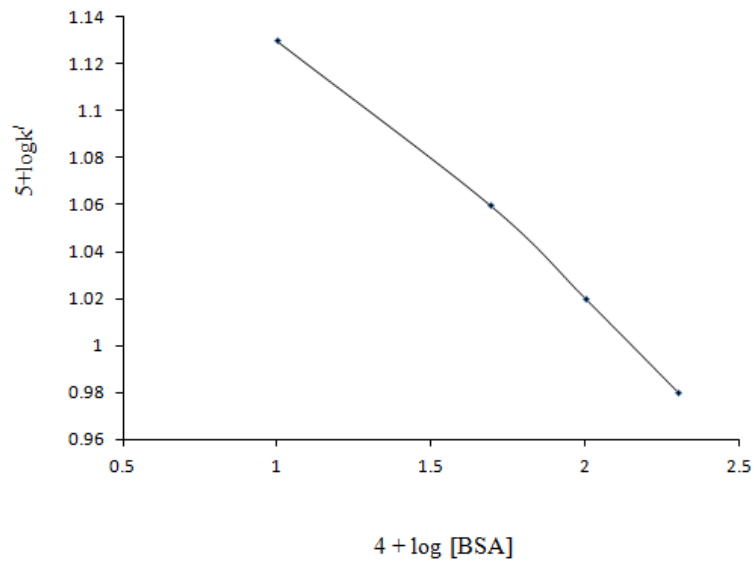**Fig 1 : Effect of varying concentrations of salbutamol and NaOH**

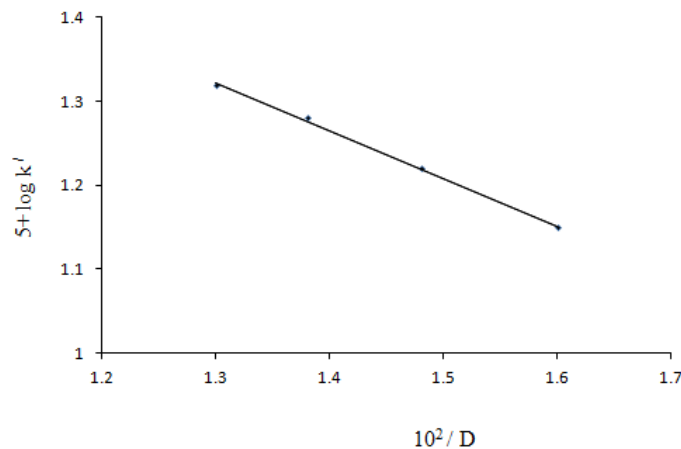**Fig 2 : Effect of varying concentrations of benzenesulphonamide**

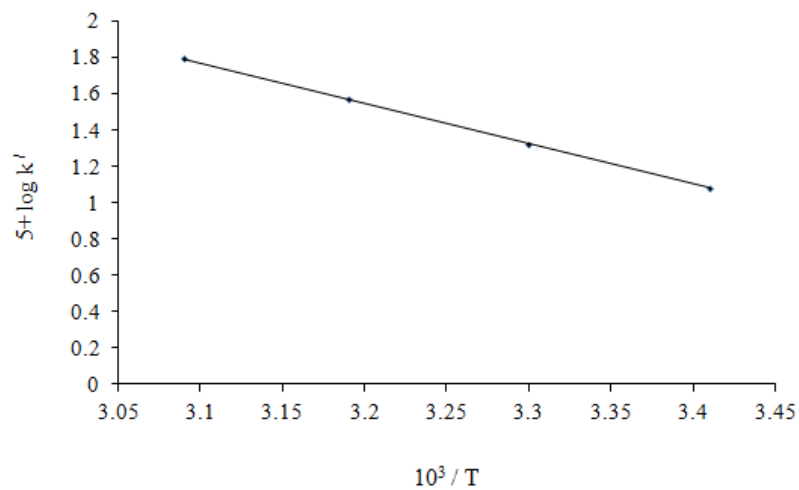**Fig 3 : Effect of varying dielectric constant of the medium**

Fig 4 : Effect of temperature on the rate of the reaction