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Kinetics and Mechanistic Investigation on Oxidation of Cetirizine Dihydrochloride (CTZ) by Bromamine-T (BAT) in HCl Medium.

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ABSTRACT

The kinetics of oxidation of cetirizine di hydrochloride [2-(2-{4-[(4-chlorophenyl)(phenyl)methyl]-1-piperazino}ethoxy)acetic acid dihydrochloride**,** CTZ] with sodium N-bromo p-toluene sulphonamide (BAT) in hydrochloric acid solution has been studied at 303 K. The reaction rate shows a first order dependence on [BAT], [CTZ] and negative fractional dependence on [HCl]. The dielectric constant of the solvent shows negative effect on the rate of reaction. The addition of reduction product of BAT has no significant effect on the rate. The rate unchanged with the variation in the ionic strength ($NaClO_4$) of the medium. Addition of reaction mixture to aqueous acryl amide solution did not initiate polymerization, indicating the absence of free radical species. Thermodynamic parameters have been computed by Arrhenius plot. The stoichiometry of the reaction was found to be 1:1 and oxidation product of CTZ is identified. The Michaelis-Menten type of kinetics has been proposed. The $CH_3C_6H_5SO_2NHBr$ has been assumed to be the reactive oxidizing species. Thermodynamic parameters were computed by studying reactions at different temperatures. A mechanism consistent with observed kinetics is proposed.

Key wards: Oxidation Kinetics, Cetirizine hydrochloride, Bromamine-T, Hydrochloric acid medium

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INTRODUCTION

Aromatic N-halosulphinamides behave as mild oxidants and good halogenating agents, containing a strong polarized N-linked halogen. The oxidizing agent BAT can be easily prepared by the bromination of Chloramine-T (CAT) and is found to be better oxidizing agent than CAT. Literature survey reveals that several work have been carried out using BAT as an oxidant in kinetic studies [1-9]. The drug CTZ is a medication used for the prevention and treatment of high fever, itchy eyes, itchy nose, sneezing, stuffy nose, water eyes and other symptoms of allergies in upper respiratory tract. It can also be used for the prevention and treatment of chronic type of hives. The CTZ is actually an antihistamine and its main purpose is to block the action of histamine in the human body and to reduce the symptoms of certain allergic reaction. Literature survey revealed no information in the kinetics and mechanism of oxidation of this drug by oxidants. The Kinetics and mechanism of oxidation of CTZ by BAT in HCl medium have been studied at 303 K.

MATERIALS AND METHODS

EXPERIMENTAL

BAT was obtained [6] by partial-debromination of dibromamine-T (DBT) in 4M NaOH. The purity of BAT obtained was checked iodometrically and through its mass spectrometer, UV, IR and ^{1}H and ^{13}C NMR data. An aqueous solution of BAT was prepared, standardized by the iodometric method, and preserved in brown bottles.

CTZ, supplied by Embiotic Laboratories, Bangalore was used without further purification. A solution of the compound was prepared in double distilled water. All solutions ware prepared using AR chemicals and double distilled water. A constant ionic strength of the medium was maintained using a concentrated solution of sodium perchlorate.

Kinetic Measurement

The reaction was carried out in glass – stoppered pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effects. Requisite amount of the solutions of CTZ, HCl and Water (to keep the total volume constant for all runs) were taken in the boiling tube and thermostated at 303 K for thermal equilibrium. A measured amount of the oxidant solution, also thermostated at the same temperature, has rapidly added to the CTZ and HCl mixture with stirring. The progress of the reaction was monitored by iodometric determination of the unreacted oxidant in measured aliquots of the reaction mixture withdrawn at different intervals of time. The pseudo-first-order rate constants ($k^/$) calculated were reproducible ($\pm$ 3%)

Stoichiometry

Reaction mixtures containing varying ratios of BAT to CTZ in the presence of HCl were equilibrated at 303 K for 48 h. Estimation of unreacted BAT showed that one mole of CTZ consumed one mole of oxidant, confirming the following stochiometry.

$$C_{21}H_{25}ClN_2O_3 + RNBrNa + H_2O \longrightarrow C_{21}H_{25}ClN_2O_4 + RNH_2 + Br^- + Na^+ \qquad ...(1)$$

Where, R = $CH_3C_6H_5SO_2$.

Product Analysis

The oxidation product, cetirizine N-oxide was identified by the spot tests [12]. Further the product wasconfirmed by IR and ^1H NMR spectral analysis. The p-toluene sulphonamide ($CH_3C_6H_5SO_2NH_2$), the reduction product of BAT was extracted with ethyl acetate and identified by TLC using petroleum ether-chloroform-1-butanol (2:2:1 v/v) as the solvent system [11] and iodine as spray reagent (R_f = 0.84).

RESULTS AND DISCUSSION

Effect of Reactants concentration

With substrate in excess, at constant $[CTZ]_0$, [HCl] and temperature, the plots of log $[BAT]_0$ vs. Time were drawn and found to be linear, (plots are not shown) confirming the first order dependence on the reaction rate of $[BAT]_0$. (Table1). Under identical experimental conditions, an increase in the [CTZ] leads to an increase in the $k^/$ values at constant [BAT], [HCl] and temperature showing a first order (+0.9375) dependence of the rate on [CTZ]. Plots of log $k^/$ vs. log [CTZ] were linear (Fig.1) with unit slopes showing I order dependence of the rate on the [CTZ]. When [HCl] was increased, at constant [CTZ], [BAT] and temperature resulted in decrease of the rate. Plots of log $k^/$ vs [HCl] were linear (Fig.2) with negative fractional slopes (0.63) indicating a negative fractional order in [HCl].

Effect of Halide ions and p-Toluene sulfonamide (PTS)

At constant $[H^+] = 2 \times 10^{-1}$ mol dm^{-3} of HCl, addition of NaCl (1×10^{-2} mol dm^{-3} to 10×10^{-2} mol dm$^{-3)}$ does not affect the rate of reaction (Table 1).

Under suitable experimental conditions, the addition of reduction product of oxidant p-Toluene sulfonamide (5×10^{-4} mol dm^{-3} to 20×10^{-4} mol dm$^{-3)}$ to the reaction mixture not affected the rate of the reaction (Table 2) which indicates that its non-involvement in a pre-equilibrium with the oxidant.

Table 1: Effect of [BAT], [CTZ], [NaCl], [NaBr] and [HCl] on the reaction rate

10^4[BAT]/M	10^3[CTZ]/M	10^2[HCl]/M	10^2[NaCl]/M	10^2[NaBr]/M	10^4 $k^/$/S
5	10	20	_	_	3.41
10	10	20	_	_	3.52
20	10	20	_	_	3.48
30	10	20	_	_	3.46
10	5	20	_	_	1.8
10	10	20	_	_	3.52
10	20	20	_	_	6.47
10	30	20	_	_	9.16
10	10	5	_	_	8.14
10	10	10	_	_	5.77
10	10	20	_	_	3.52
10	10	30	_	_	2.6
10	10	50	_	_	1.8
10	10	20	1	_	3.42
10	10	20	5	_	3.41
10	10	20	10	_	3.41
10	10	20	_	1	3.49
10	10	20	_	5	3.25
10	10	20	_	10	3.55

I = 5 x10^{-3} mol dm^{-3}; T = 303 K\

Table 2: Effect of $NaClO_4$ and PTS concentration on the reaction rate.

10^3 [$NaClO_4$]/M	10^4 $k^/$ s^{-1}	10^4 [PTS]/M	10^4 $k^/$ s^{-1}
5	3.11	5	2.33
10	3.04	10	2.5
20	2.96	20	2.68

[BAT]= 1x10^{-3}mol dm^{-3} ; [CTZ] = 10x10^{-3}mol dm^{-3}; I=5x10^{-3}mol dm^{-3};[HCl]=20x10^{-2}mol dm^{-3}; T=303K

Effect of ionic strength (I) effect of dielectric constant (D) of medium

The variation of ionic strength using the solution of $NaClO_4$ (5 x 10^{-3} mol dm^{-3} to 20 x 10^{-3} mol dm^{-3}) not affected the rate of reaction (Table 2), indicating that non-ionic species were involved in the rate limiting step.

The dielectric constant (D) of the medium was varied by adding methanol (MeOH) to the reaction mixture. An increase in the addition of the methanol resulted in a decrease of the rate of the reaction. Plots of dielectric constant [D] vs. log $k^/$ were made (Table 3) and slopes were found to be linear (Fig. 3) with the negative order (0.7636). The values of the dielectric constant [D] of H_2O and MeOH system of different compositions are reported in the literature [10]. Blank experiments showed that MeOH was oxidized slowly (~3%) by the oxidants under the experimental conditions. This was corrected for the calculations in the net reaction for the rate constant for the oxidation of CTZ.

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

[MeOH] (%v/v)	D	10^2/D	10^4 k$^/$ s^{-1}
0	76.73	1.3032	3.52
10	72.37	1.3817	3.1
20	67.48	1.4819	2.45
30	62.71	1.5946	2.08

[BAT]= $1x10^{-3}$mol dm^{-3} ; [CTZ] = $10x10^{-3}$mol dm^{-3} ;
I=$5x10^{-3}$mol dm^{-3} ;[HCl]=$20x10^{-2}$ mol dm^{-3} ; T=303K

Effect of temperature

The reaction was studied over a range of temperature 298 K to 313 K, by varying the concentration of (CTZ) and keeping other experimental conditions constant (Table 4). It was found that rate of the reaction increased with increase in the temperature (fig 4). From the linear Arrhenius plot in (Fig 4), log k$^/$ vs.1/T gave energy of activation (E_a) from which other activation parameters, enthalpy of activation ($\Delta H^\#$), entropy of activation ($\Delta S^\#$) and free energy of activation ($\Delta G^\#$) were computed. The data is given in the Table 5.

Table: 4 Effect of varying [CTZ] on the reaction rate at different temperatures

10^3 [CTZ]/M	10^4 k$^/$ s^{-1}		
	293K	**303K**	**313K**
5	1.282	1.8	2.5
10	2.68	3.52	5.11
20	4.53	6.47	8.5

[BAT]= $1x10^{-3}$mol dm^{-3} ; I=$5x10^{-3}$mol dm^{-3} ;[HCl]= 20 x 10^{-2} mol dm^{-3}

Table: 5 Effect of temperature and the activation parameters for the oxidation of CTZ by BAT

Temperature (K)	104 k$^/$ s^{-1}	Activation parameter
293	2.68	Ea = 24.33 kJmol^{-1}
303	3.52	$\Delta H^\#$ = 21.79 kJmol^{-1}
313	5.11	$\Delta S^\#$ = -240.07 JK^{-1}mol^{-1}
		$\Delta G^\#$ = 94.54 kJmol^{-1}
		log A = 0.7428

Test for free radicals

The addition of the reaction mixture to the aqueous acryl amide solution did not initiate polymerization, showing the absence of the free radical species during the reaction sequences.
N-halo amines are mild oxidants generally undergo two electron change per mole in its reactions. Depending on the p^H of the medium these halo amines generate different types of species in solution. Bishop and Jennings [15] Pryde and Soper [13], Morris et al [14] and Hardy and John ston [16] have shown the existence of similar equilibrium in acid and alkaline solutions

of N-halo amines. Bromamine-T and Bromamine-B like Chloramine –T and Chloramine –B behaves as strong electrolyte in aqueous solutions forming different species of the following types:

$$TsNBrNa \rightleftharpoons TsNBr^- + Na^+ \quad ...(2)$$

[Here Ts = p-$CH_3C_6H_4SO_2$-]

$$TsNBr^- + H^+ \rightleftharpoons TsNHBr \quad ...(3)$$

$$2\ TsNHBr \rightleftharpoons TsNH_2 + TsNBr_2 \quad ...(4)$$

$$TsNHBr + H_2O \rightleftharpoons TsNH_2 + HOBr \quad ...(5)$$

$$TsNHBr + H^+ \rightleftharpoons TsN^+H_2Br \quad ... (6)$$

$$TsN^+H_2Br + H_2O \rightleftharpoons TsNH_2 + H_2O^+ Br \quad ...(7)$$

(Here Ts = p-CH_3 $C_6H_4SO_2$ for BAT)

Therefore, the possible oxidizing species in acid medium are TsNHBr, $TsNBr_2$, HOBr and probably H_2O^+Br and in alkaline solution RNHBr, HOBr, RNBr $^-$ and OBr $^-$. In the present case of BAT, if $TsSO_2NBr_2$ were to be reactive species, the rate law predicts a second order dependence of rate on [BAT] and a negative effect of p-CH_3 $C_6H_4SO_2NH_2$ is expected according to the equation (4), but both are contrary to the experimental observations. If HOBr is primarily involved, a first order retardation of rate by the added PTS is expected.

Hardy and John ston [16], who have studied the p^H dependent relative concentrations of the species present in acidified halo amine solutions of comparable molarities, have shown that CH_3 Ph SO_2 NHBr is likely oxidizing species in acid medium. Narayanan and Rao [17] and Subhashini et al [18] have reported that mono haloamines can be further protonated at p^H 2, as shown in equations (8) for Chloramine-T.

$$p^-CH_3C_6H_4SO_2NHCl + H^+ \leftrightarrow (p^-CH_3C_6H_4SO_2NH_2Cl)^+ \quad ...(8)$$

The results of oxidation of CTZ with Bromamine-T in HCl medium indicated the first order dependence each on the concentration of BAT, CTZ. The decrease in the rate by increasing concentration of H^+ assumes that the de protonated species of BAT and the reaction indicates that the rate remains same with increase in Cl^- ion in the presence of sodium chloride salt. Therefore in the present investigation it was proposed that

Ts NH_2Br^+ is the reactive species.

$$TsNH_2Br^+ \underset{}{\overset{K_1}{\rightleftharpoons}} TsNHBr + H^+$$

$$TsNHBr + S \xrightarrow{k_2} Products$$

Rate = k_2 [TsNHBr] [S] -------------- (1)

From step (1)

$$K_1 = \frac{[TsNHBr][H^+]}{[TsNH_2Br^+]}$$

Or $[TsNH_2Br^+] = \frac{[TsNHBr][H^+]}{K_1}$

Total effective concentration of BAT is

$$[BAT]_t = [TsNH_2Br^+] + [TsNHBr]$$

$$= \frac{[TsNHBr][H^+]}{K_1} + [TsNHBr]$$

$$[BAT]_t = \frac{[TsNHBr][H^+] + K_1[TsNHBr]}{K_1}$$

$$= \frac{[TsNHBr]\{[H^+] + K_1\}}{K_1} \qquad [TsNHBr] = \frac{K_1[BAT]_t}{[H^+] + K_1} ------(2)$$

Substitute Eqn. (2) in eqn. (1)

Rate = $\frac{k_2[S].\,K_1[BAT]_t}{[H^+] + K_1}$

Rate = $\frac{K_1k_2[BAT]_t[S]}{[H^+] + K_1}$

Since, Rate = $k^/$ $[BAT]_t$

$k^/$ = $\frac{K_1k_2[S]}{[H^+] + K_1}$

Or $\frac{1}{k^/} = \frac{[H^+]}{K_1k_2[S]} + \frac{1}{k_2[S]}$

Plot of $\frac{1}{k^/} >< [H^+]$

In t = $\frac{1}{k_2[S]} \rightarrow k_2[S^{-1}]$ can be calculate

Slope = $\frac{1}{K_1k_2[S]}$ $mol\,dm^{-3}.\,K_1$ can be calculated.

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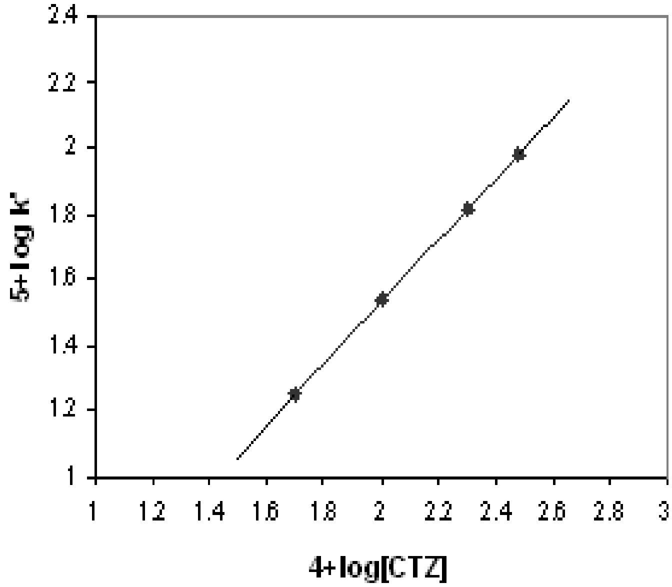

Fig.1: Effect of of [CTZ] on the reaction rate.

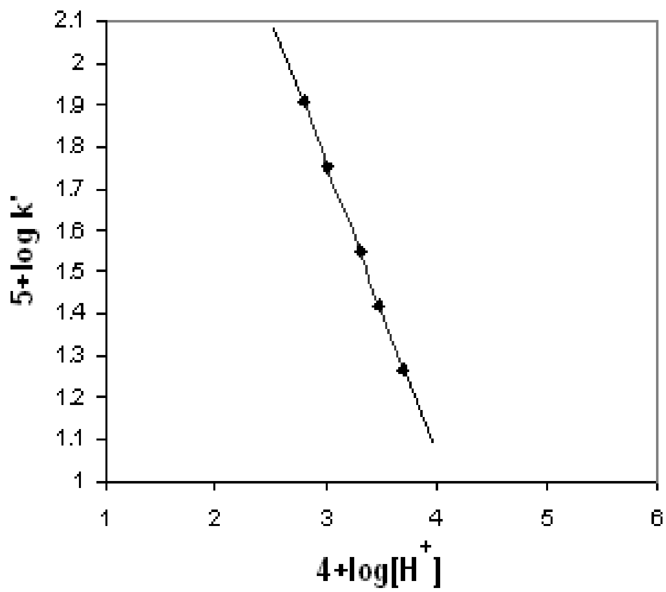

Fig.2: Effect of [HCl] on the reaction rate.

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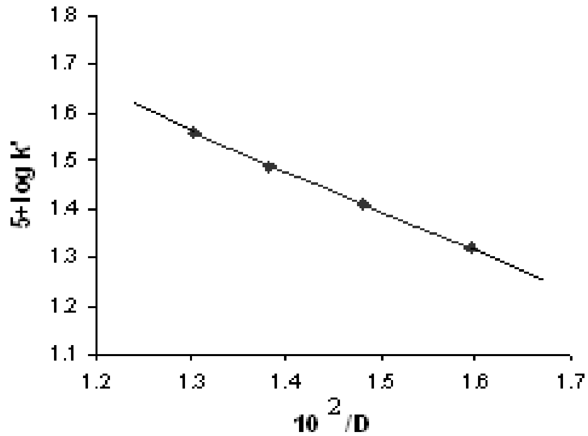

Fig.3: Effect Methanol (D) on the reaction rate.

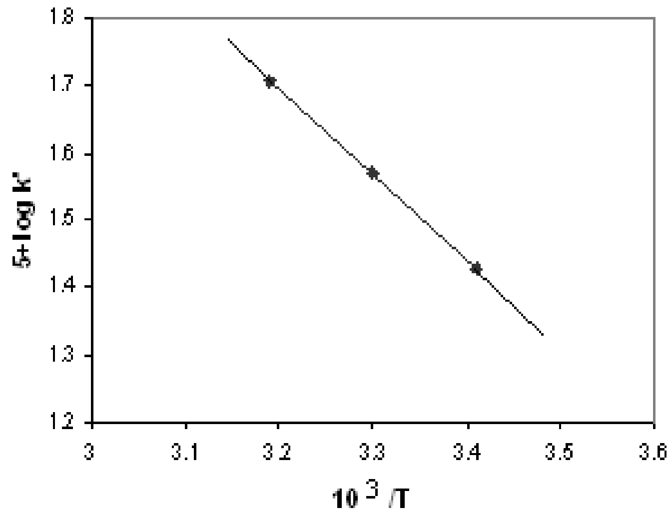

Fig.4: Effect of [CTZ] on the reaction rate at different temperatures.

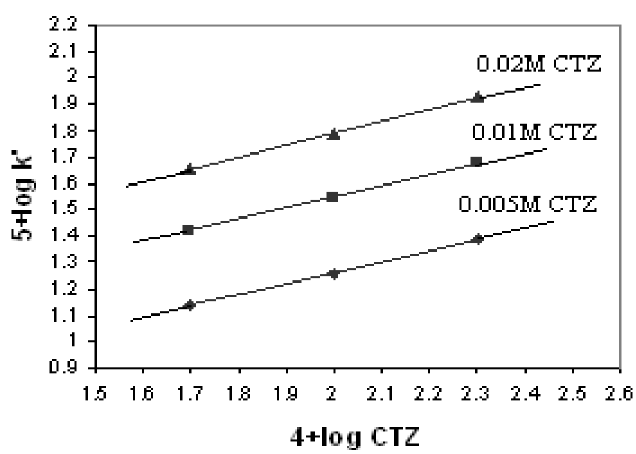

Fig.5: Effect of substrate on the reaction rate at different temperatures

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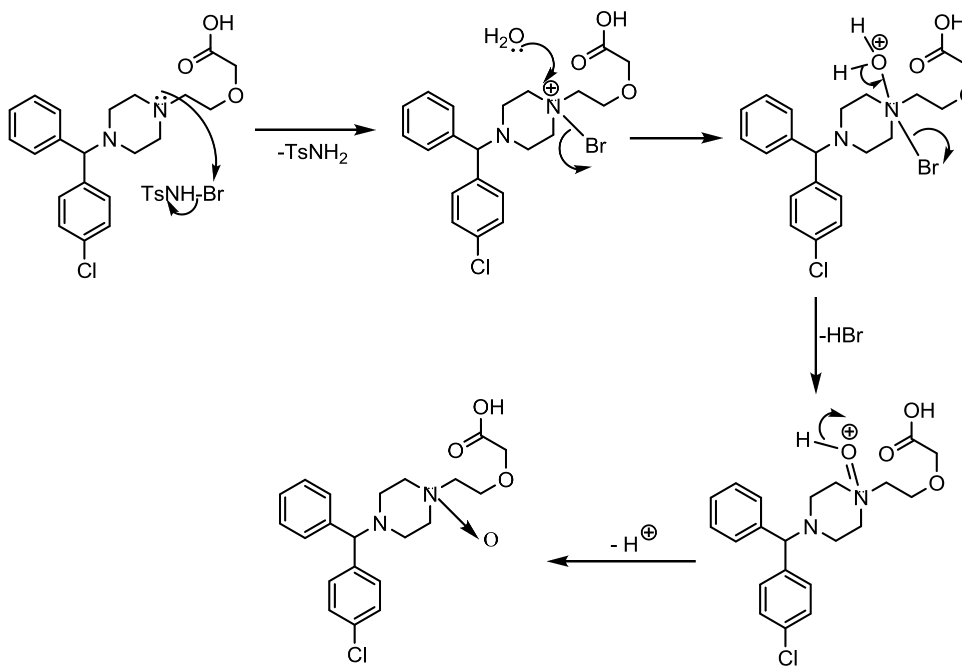
Scheme 2: Mechanism of oxidation of [CTZ] with [BAT] in HCl medium



CONCLUSION

Oxidation of CTZ by BAT in HCl medium has been studied. The stochiometry of oxidation of CTZ with BAT in acid medium is found to be 1:1. The oxidation product is identified as cetirizine-N-oxide. The active oxidizing species involved in the acid medium is $CH_3C_6H_5SO_2NHBr$. Activation parameters are computed from the Arrhenius plot. The observed results are explained with plausible mechanism and the related rate laws are deduced.

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