Kinetic and Mechanistic Studies of Oxidation of an Antiallergic Drug with Bromamine-T in Acid and Alkaline Media

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Cetrizine dihydrochloride (CTZH) is widely used as an anti-allergic drug. Sodium *N*-bromo-*p*-toluenesulfon-amide or bromamine-T (BAT) is the bromine analogue of chloramine-T (CAT) and is found to be a better oxidizing agent than CAT. In the present research, the kinetics of oxidation of CTZH with BAT in acid and alkaline media was studied at 313 K. The experimental rate laws obtained are: $-d[BAT]/dt = k[BAT][CTZH]^{0.80}[H^+]^{-0.48}$ in acid medium and $-d[BAT]/dt = k[BAT][CTZH]^{0.48}[OH^-]^{0.52}[PTS]^{-0.40}$ in alkaline medium where PTS is *p*-toluenesulfonamide. Activation parameters and reaction constants were evaluated. The solvent isotope effect was studied using D_2O. The dielectric effect is positive. The stoichiometry of the reaction was found to be 1:1 and the oxidation products were identified as 4-chlorobenzophenone and (2-piperazin-1-yl-ethoxy)-acetic acid in both media. The rate of oxidation of CTZH is faster in acid medium. Suitable mechanisms and related rate laws have been worked out.

Key Words : Cetrizine, Oxidation-kinetics, Bromamine-T, Acid and alkaline media

Introduction

Cetrizine dihydrochloride (CTZH) is a piperazine derivative and it is chemically known as [2-[4-[(4-chlorophenyl)-phenylmethyl]-1-piperazinyl]ethoxy]acetic acid. It is a non-sedating antihistamine or histamine (H-1) receptor blocker. The mechanism of action of CTZH is to block the ability of histamine which promotes the allergic reactions in the body. It is mainly used in the treatment of perennial and seasonal allergetic rhinitis and also for chronic hives.[1] An extensive literature survey reveals that several analytical methods have been reported[2,3] for the determination of cetrizine, but no reports are available on the oxidation of this drug by any oxidant from the stand point of its kinetic and mechanistic aspects. In view of the importance of this drug, it is very essential to know its oxidation-kinetic and mechanistic chemistry. The current research knowledge is very beneficial for kineticists who are working on the mechanistic chemistry of this drug in biological systems. The chemistry of organic *N*-haloamines is of great interest due to their diverse chemical behaviour.[4] As a result, they interact with a wide spectrum of functional groups and effect a variety of molecular transformations.[4-6] The prominent member of this group, chloramine-T (CAT), is a well known analytical reagent and the mechanistic aspects of many of its reactions have been clarified kinetically.[4-11] The bromine analogue of CAT is bromamine-T (BAT; *p*-CH₃C₆H₄SO₂NBrNa·3H₂O), which can be prepared easily from the bromination of CAT, has gained importance as an oxidant in acid and alkaline media. Although BAT is a better oxidant than CAT, not much attention has been focussed on its reactions parti-cularly with pharmaceutical compounds.[12-15] Therefore, in the present research, an effort has been made to unfold the

mechanistic picture of oxidation of CTZH by BAT in acid and alkaline media through kinetic studies at 313 K. The other aim of the present study is to know the relative reactivity of this redox system in acid and alkaline solution.

Experimental

Materials. The substrate cetrizine dihydrochloride is of analytical grade of purity, was provided from University of Mysore, Mysore, India, It was used as received and an aqueous solution of the desired strength of the substrate was prepared freshly each time whenever required. The oxidant, BAT, was prepared by standard procedure[16,17] and the authenticity of the product was confirmed by checking the halogen content iodometrically. An aqueous solution of BAT was prepared afresh whenever required, standardized by iodometric method and preserved in amber-coloured bottles to prevent any of its photochemical deterioration. Solvent isotope studies were made with heavy water (D_2O 99.4%) supplied by BARC, Mumbai, India. All the chemicals used were of AnalaR grade of purity. Double distilled water was used throughout the work.

Methodology. The kinetic runs were performed under pseudo first-order conditions with a large excess of substrate over oxidant in both acid and alkaline solutions. Unless specified otherwise, all the kinetic runs were carried out at 313 K. Detailed kinetic procedure followed is similar to that reported earlier.[12] The course of the reaction was studied iodometrically for more than two half-lives. The pseudo first-order rate constants (k' s⁻¹), were calculated from the linear plots of log [BAT] *vs* time. Duplicate kinetic runs showed that the rate constants were reproducible within ± 5%. Regression co-efficient (R^2) calculations were perform-

ed with fx-100W scientific calculator.

Stoichiometry. Reaction mixtures with varying BAT-CTZH compositions in the presence of 6.0×10^{-3} mol dm^{-3} acid/alkali were equilibrated at 313 K for 48 h. The iodometric determination of the residual oxidant showed that one mole of CTZH consumed one mole of BAT, in both the media as shown by the following stoichiometry equation:

$$\text{(1)}$$
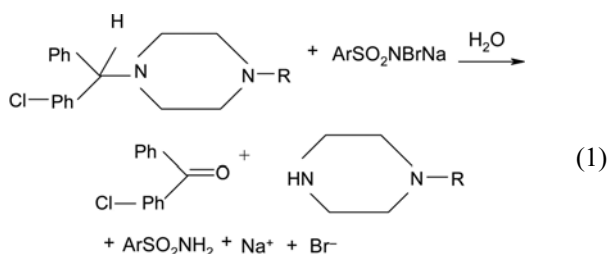
Here Ar = CH$_3$C$_6$H$_4$- ; R = -CH$_2$CH$_2$OCH$_2$COOH.

Product Analysis. The reaction mixtures of CTZH and BAT in acid/alkali solution was stirred for 48 h at 313 K. After completion of the reaction (monitored by TLC), the reaction products were neutralized with NaOH (in acid medium)/and HCl (in alkaline medium). The white crystalline solid which is formed in the reaction mixture was filtered and subjected to chromatographic analysis (TLC technique) which revealed the formation of 4-chlorobenzophenone. Further, the aqueous solution present in the reaction mixture was extracted 2 to 3 times with ethyl acetate and was subjected to chromatographic analysis (TLC technique) which revealed the formation of (2-piperazin-1-yl-ethoxy)acetic acid. The oxidation products were separated by column chromatography on silica gel (60-120 mesh) using hexane and ethyl acetate (3:5 v/v) as the mobile phase. The identity of the product, 4-chlorobenzophenone, was confirmed by LC-MS analysis. The mass spectrum showed a parent molecular ion peak at 216.6 amu (Figure 1) confirm-
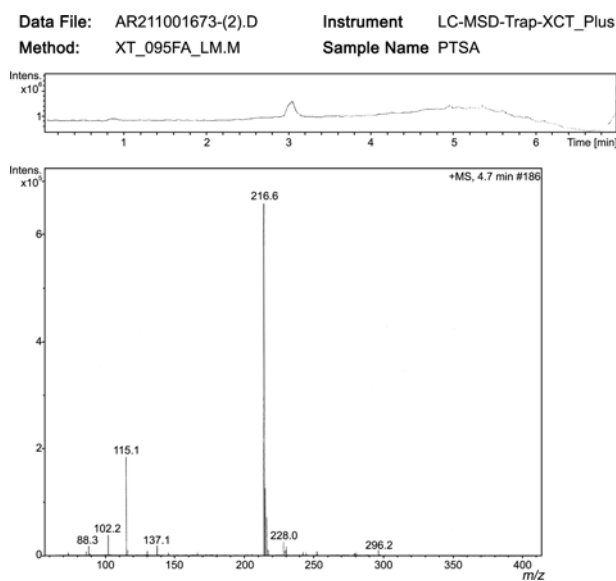

Figure 1. LC-Mass spectrum of 4-chlorobenzophenone with its molecular ion peak at 216.6 amu.
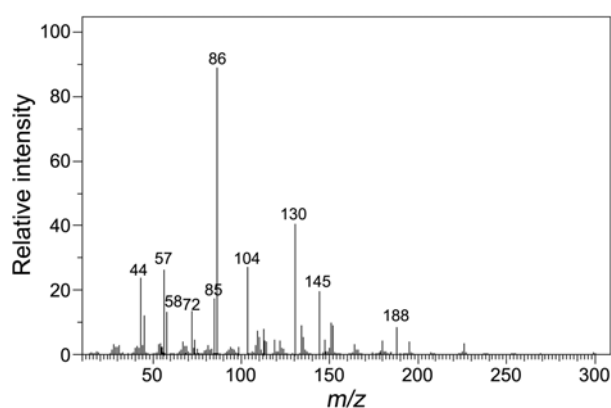

Figure 2. GC-Mass spectrum of (2-piperazin-1-yl-ethoxy)-acetic acid with its molecular ion peak at 188 amu.

ing 4-chlorobenzophenone. LC-MS data was obtained on a LC-MSD-Trap-XCT_plus. Further, (2-piperazin-1-yl-ethoxy)-acetic acid was confirmed by GC-MS data and the mass spectrum showed a molecular ion peak at 188 amu clearly confirming 1-piperazinyl ethoxy acetic acid (Figure 2). GC-MS data were obtained on a 17A Shimadzu gas chromatograph with a QP-5050A Shimadzu mass spectrometer. All other peaks in both LC-MS and GC-MS are interpreted in accordance with the observed structures. The reduction product of BAT, *p*-toluenesulfonamide (PTS or ArSO$_2$NH$_2$), was extracted with ethyl acetate and identified by paper chromatography.[14] Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl solution (in ethanol) as spray reagent ($R_f = 0.905$). One of the oxidation products, 4-chlorobenzophenone is an important organic compound largely used in the organic photochemistry as photoinitiator and also in printing and perfumery industries. It was also observed that there was no further oxidation of these products under the prevailed kinetic conditions.

Results and Discussion

Our preliminary experiments revealed that the oxidation of CTZH with CAT in acid and alkaline media were very slow to be measured kinetically. But the oxidation reactions were become facile with BAT in both the media. Therefore, the kinetics of oxidation of CTZH with BAT was investigated at several initial concentrations of the reactants in acid and alkaline media at 313 K, under similar experimental conditions.

Kinetic Data. Under pseudo first-order conditions ([CTZH]$_o$ >> [BAT]$_o$) at constant [HClO$_4$]/[NaOH] and temperature, plots of log [BAT] *vs* time were linear ($R^2 > 0.9948$), indicating a first-order dependence of the reaction rate on [BAT]$_o$ in both the media. The values of k' calculated from these plots are unaltered with variation of [BAT]$_o$ in both the cases (Table 1). Hence, the rate of disappearance of BAT follows first-order kinetics in both the cases. It is seen that values of k' increases with increase in [CTZH]$_o$ (Table 1) in both the media and plots of log k' *vs* log [CTZH] were linear ($R^2 > 0.9922$) with slopes of 0.80 and 0.48 in HClO$_4$ and

Table 1. Effect of Varying Concentrations of BAT, CTZH, HClO₄ and NaOH on the Rate of Reaction at 313 K

10^4 [CAT]$_o$ mol dm^{-3}	10^3 [CTZH]$_o$ mol dm^{-3}	10^3 [HClO₄]/[NaOH] mol dm^{-3}	10^4 k' (s^{-1})	
			Acid	Alkali
1.0	4.0	6.0	4.62	1.82
2.0	4.0	6.0	4.44	1.74
4.0	4.0	6.0	4.45	1.79
8.0	4.0	6.0	4.52	1.86
10.0	4.0	6.0	4.40	1.75
2.0	1.0	6.0	1.66	0.87
2.0	2.0	6.0	2.26	1.24
2.0	4.0	6.0	4.44	1.74
2.0	8.0	6.0	8.29	2.48
2.0	9.4	6.0	9.12	3.29
2.0	4.0	2.0	7.11	1.09
2.0	4.0	4.0	5.48	1.54
2.0	4.0	6.0	4.44	1.74
2.0	4.0	10.0	3.96	2.90
2.0	4.0	20.0	2.52	3.66

Table 2. Effect of Varying Dielectric Constant (D) of the Medium on the Rate of Reaction at 313 K

% MeOH (v/v)	D	10^4 k' (s^{-1})	
		Acid	Alkaline
0	76.73	4.44	1.74
10.0	72.37	5.28	2.46
20.0	67.48	6.08	3.18
30.0	62.71	6.94	4.24

[BAT]$_o$ = 2.0 × 10^{-4} mol dm^{-3}; [CTZH]$_o$ = 4.0 × 10^{-3} mol dm^{-3}; [HClO₄]/[NaOH] = 6.0 × 10^{-3} mol dm^{-3}

solution. Addition of Cl⁻ or Br⁻ ions in the form of NaCl or NaBr (5.0 × 10^{-3} mol dm^{-3}) had no effect on the rate, signifying no role of halide ions in the reaction in both the cases. Solvent isotope effect was studied using D₂O in both the media. In acid medium, the rate of the reaction was further decreased in D₂O medium with k' = 3.16 × 10^{-4} s^{-1} and in H₂O k' = 4.44 × 10^{-4} s^{-1} leading to a solvent isotope effect k'(H₂O)/k' (D₂O) = 1.41. But in alkaline medium, the reaction rate was further increased in D₂O medium with k' = 3.20 × 10^{-4} s^{-1} and in H₂O k' = 1.74 × 10^{-4} s^{-1} leading to a solvent isotope effect k'(H₂O)/k' (D₂O) = 0.54.

The effect of temperature on the reaction rate was studied by conducting kinetic runs at different temperatures (303 K-318 K), keeping other experimental conditions constant. From the linear Arrhenius plots of log k' *vs* 1/T, (R^2 > 0.9895), values of activation parameters (Ea, ΔH$^{\neq}$, ΔG$^{\neq}$ and ΔS$^{\neq}$ and log A) were evaluated in both the media. All these values are summarized in Table 3. Addition of aqueous solution of acrylamide to the reaction mixture did not initiate polymerization. This suggest the non-involvement of free radical during the oxidation. Appropriate controlled experiments were also run simultaneously.
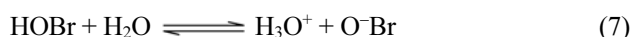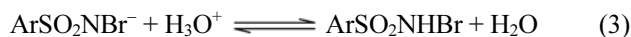
Reactive Species of BAT. Bromamine-T (ArSO₂NBrNa) is known to be a mild oxidant in both acidic and alkaline media.[4] In general, BAT undergoes a two-electron change in its reactions,[19] the products being *p*-toluenesulfonamide and sodium chloride. Because organic haloamines exhibits similar

NaOH media, respectively. This indicates a fractional-order dependence of the rate on [CTZH]$_o$ and shows a complex dependence of rate on [CTZH]$_o$. Further, plots of k' *vs* [CTZH]$_o$ were linear (R^2 > 0.9918) having a Y-intercept confirming the fractional order dependence on [CTZH]$_o$. The rate of the reaction decreases with an increase in [HClO₄] and a log-log plot (R^2 = 0.9878) gives a slope equal to −0.48, indicating a negative fractional-order dependence on [H⁺]. But the reaction rate increases with increase in [NaOH] with a fractional-order dependence of slope equal to 0.52 (R^2 = 0. 9878).

Rate studies were made in H₂O-MeOH mixtures at different compositions (0-30% v/v) in order to study the effect of varying dielectric constant (D) of the solvent medium with all other experimental conditions being held constant. The rate was found to increase with increase in MeOH content (Table 2) in both the media and plots of log k' *vs* 1/D were linear (R^2 > 0.9984) with positive slopes. The values of dielectric constant of MeOH-H₂O mixtures reported in the literature[18] were employed. It was further noticed that no reaction of the dielectric with the oxidant under the experimental conditions used. There is no pronounced effect of the added *p*-toluenesulfonamide (PTS or ArSO₂NH₂) on the rate of the reaction in acid medium but it showed a retardation of the rate in alkaline medium. The reaction rates (10^4 s^{-1}) in alkaline medium at 2.0, 4.0 and 8.0 × 10^3 [PTS] mol dm^{-3} were found to be 1.66, 1.42 and 1.18, respectively. Further, in alkaline medium, a plot of log k' *vs* log [PTS] was linear (R^2 = 0.9875) with a slope of −0.40, confirming a negative fractional-order dependence of rate on [PTS]. It also indicates that PTS is involved in a fast pre-equilibrium to the rate-determining step (rds) in alkaline medium.

No attempt has made to keep the ionic strength constant in both the media since the pseudo first-order rate constant remains unaltered in the presence of 0.20 mol dm^{-3} NaClO₄

Table 3. Effect of Varying Temperature and Values of Activation Parameters for the Oxidation of Cetrizine by BAT in Acid and Alkaline Medium

Temperature (K)	10^4 k' (s^{-1})	
	Acid	Alkaline
303	2.12	0.96
308	3.25	1.40
313	4.44	1.74
318	7.86	2.76
Ea (kJ mol^{-1})	71.8	86.2
ΔH$^{\neq}$ (kJ mol^{-1})	69.2 ±0.01	83.6 ± 0.20
ΔG$^{\neq}$ (kJ mol^{-1})	93.9 ± 0.13	98.6 ± 0.13
ΔS$^{\neq}$ (JK^{-1} mol^{-1})	−79.2 ± 0.15	−40.4 ± 0.52
Log A	8.4 ± 0.01	9.7 ± 0.01

[BAT]$_o$ = 2.0 × 10^{-4} mol dm^{-3}; [CTZH]$_o$= 4.0 × 10^{-3} mol dm^{-3}; [HClO₄]/[NaOH] = 6.0 × 10^{-3} mol dm^{-3}.

chemical properties, it is expected that identical equilibria exist in solutions of these compounds.[19] BAT is analogous to CAT and behaves like a strong electrolyte in aqueous solutions.[19] Pryde and Soper,[20] Morris *et al.*,[21] Bishop and Jennings[19] and Hardy and Johnston[22] have shown the following types of reactive species in solutions of BAT.

$$ArSO_2NBrNa \rightleftharpoons ArSO_2NBr^- + Na^+ \qquad (2)$$

$$ArSO_2NBr^- + H_3O^+ \rightleftharpoons ArSO_2NHBr + H_2O \qquad (3)$$

$$2\,ArSO_2NHBr \rightleftharpoons ArSO_2NH_2 + ArSO_2NBr_2 \qquad (4)$$

$$ArSO_2NHBr + H_2O \rightleftharpoons ArSO_2NH_2 + HOBr \qquad (5)$$

$$ArSO_2NBr_2 + H_2O \rightleftharpoons ArSO_2NHBr + HOBr \qquad (6)$$

$$HOBr + H_2O \rightleftharpoons H_3O^+ + O^-Br \qquad (7)$$

$$HOBr + H^+ \rightleftharpoons H_2O^+Br \qquad (8)$$

The possible oxidizing species in acidified BAT solutions are $ArSO_2NHBr$, $ArSO_2NBr_2$, HOBr and possibly H_2O^+Br. In aqueous alkaline solutions of BAT, $ArSO_2NBr_2$ does not exist, and the expected reactive species are $ArSO_2NBr^-$, $ArSO_2NHBr$, O^-Br and HOBr.

Reaction Scheme and Rate law in Acid Medium. The possible oxidizing species in acidified BAT solutions are $ArSO_2NHBr$, $ArSO_2NBr_2$, HOBr and possibly H_2O^+Br. The involvement of $ArSO_2NBr_2$ in the mechanism leads to a second order rate law according to Eq. (4), which is conflict to the experimental observations. Further, if HOBr is primarily involved, a first-order dependence of rate by the added PTS is expected. Since no such was noticed, HOBr was ruled out as the reacting species. Further, Hardy and Johnston,[22] who have studied the pH-dependant relative concentrations of the species present in acidified bromamine-B solutions of comparable molarities and have shown that its acid form is the predominant species. Extending the same

argument to BAT, it is reasonable to assume that the $ArSO_2NHBr$ is the most probable oxidizing reactive species for the oxidation of CTZH by BAT in acid medium. Additionally, Narayanan and Rao[23] and Shubhashini *et al.*[24] have reported that CAT can get further protonated as $ArSO_2NH_2Cl^+$ in acidic conditions. Because organic halo-amines have similar chemical properties, $ArSO_2NH_2Br^+$ can be expected for BAT also.

In the present investigations, the retardation of rate by H^+ ion indicates that the unprotonated oxidant ($ArSO_2NHBr$) is the active oxidizing species. In view of the preceding discussion and experimental facts, Scheme 1 is proposed to explain the reaction mechanism for the oxidation of CTZH by BAT in $HClO_4$ medium.

In Scheme 1, X is an intermediate-complex species. An initial equilibrium involves a deprotonation of $ArSO_2NH_2Br^+$ forming the active oxidizing species $ArSO_2NHBr$ (step(i)) of Scheme 1. In the next fast pre-equilibrium step, (step(ii)), the lone pair of electrons on nitrogen of CTZH attacks the positive bromine of $ArSO_2NHBr$ forming an intermediate complex (X). This complex in the slow and rds (step(iii)) gives an iminium ion intermediate with the elimination of HBr and $ArSO_2NH_2$ which on further hydrolysis yields the ultimate products 4-chlorobenzophenone and (2-piperazin1-yl-ethoxy)acetic acid.

If $[BAT]_t$ is the total effective concentration of BAT, then
$[BAT]_t = [ArSO_2NH_2Br^+] + [ArSO_2NHBr] + [X]$, from which, solving for [X], we obtain

$$[X] = \frac{K_1K_2[BAT][CTZH]}{[H^+] + K_1 + K_1K_2[CTZH]} \qquad (9)$$

From the slow/rds step (iii) of Scheme 1,

$$\text{rate} = -\frac{d[BAT]_t}{dt} = k_3\,[X] \qquad (10)$$
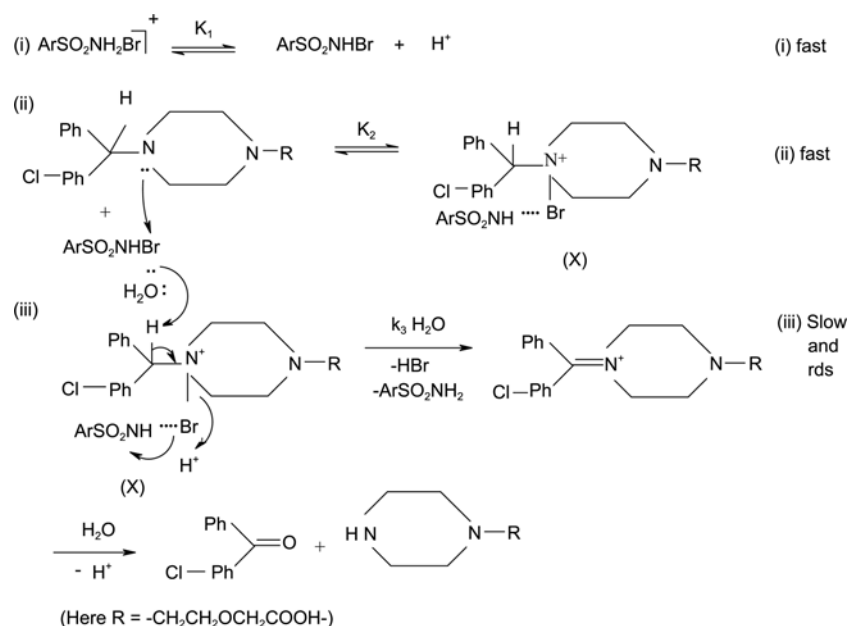
Scheme 1. Detailed mechanistic interpretation for the oxidation of cetrizine by BAT in acid medium.

By substituting for [X] from Eq. (9) into Eq. (10), the following rate law is obtained:

$$\text{rate} = \frac{K_1 K_2 k_3 [BAT]_t [CTZH]}{[H^+] + K_1 + K_1 K_2 [CTZH]} \quad (11)$$

Rate law (11) is in good agreement with the experimental results.

Since rate = k' [BAT]$_t$, Eq. (11) can be transformed as

$$k' = \frac{K_1 K_2 k_3 [CTZH]}{[H^+] + K_1 + K_1 K_2 [CTZH]} \quad (12)$$

$$\frac{1}{k'} = \frac{1}{[CTZH]} \left\{ \frac{[H^+]}{K_1 K_2 k_3} + \frac{1}{K_2 k_3} + \frac{1}{k_3} \right\} \quad (13)$$

$$\frac{1}{k'} = \frac{[H^+]}{K_1 K_2 k_3 [CTZH]} + \frac{1}{K_2 k_3 [CTZH]} + \frac{1}{k_3} \quad (14)$$

Based on Eqs. (13) and (14), plots of 1/k' *vs* 1/[CTZH] and 1/k' *vs* [H$^+$], (values are taken from Table 1) were found to be linear (R^2 > 0.9896; Figure 3). From the slopes and intercepts of such plots, values of deprotonation constant K_1, formation constant K_2 and decomposition constant k_3 were evaluated and found to be 0.07×10^2 mol dm^{-3}, 0.19×10^2 dm^3 mol^{-1} and 1.3×10^{-2} s^{-1}, respectively.

Reaction Scheme and Rate law in Alkaline Medium. In alkaline solutions of BAT, dibromamine does not exist,[25] and the possible oxidizing species are ArSO$_2$N$^-$Br, ArSO$_2$NHBr, O$^-$Br and HOBr. Hardy and Johnston[22] have reported that there could be considerable concentration of ArSO$_2$NHBr even in alkaline bromamine-B solutions. If the toluene derivative is assumed to be similar to the benzene analogue, the same argument holds good for BAT also. In the present
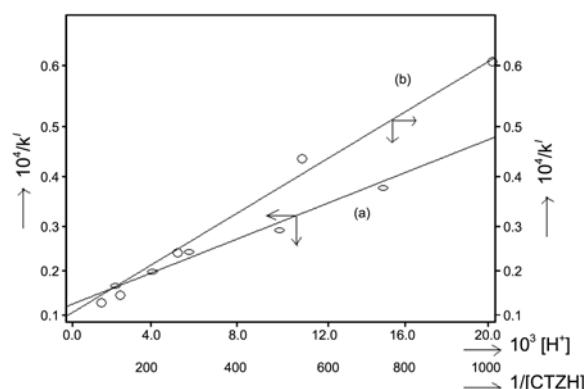

Figure 3. Double reciprocal plots of (a) 1/k' *vs* [H$^+$] and (b) 1/k' *vs* 1/[CTZH] in acid medium. Experimental conditions are as in Table 1.

investigations, a first-order dependence of the rate on [BAT]$_o$, a fractional-order dependence each on [CTZH]$_o$ and [OH$^-$], and the retardation of rate by the added ArSO$_2$NH$_2$ can be rationalized by the mechanism shown in Scheme 2.

In Scheme 2, X' is the complex intermediate species. In a fast pre-equilibrium step (step(i) of Scheme 2), the conjugate acid of BAT, ArSO$_2$NHBr interacts with hydroxyl ion to give an anionic species ArSO$_2$N$^-$Br. In the next fast step (step(ii)), the negatively charged anionic species undergoes hydrolysis to give the bromite ion (O$^-$Br) with the elimination of ArSO$_2$NH$_2$. In the subsequent fast step (step(iii)), the lone pair of electrons on nitrogen atom of CTZH attacks the positive bromine of O$^-$Br forming an intermediate complex (X'). In the next slow/rds (step(iv)) the bromine of the intermediate X' is removed in the form of HBr in the presence of OH$^-$ by the abstraction of a proton from a molecule of H$_2$O to yield the final products.

According to Scheme 2, the total effective concentration
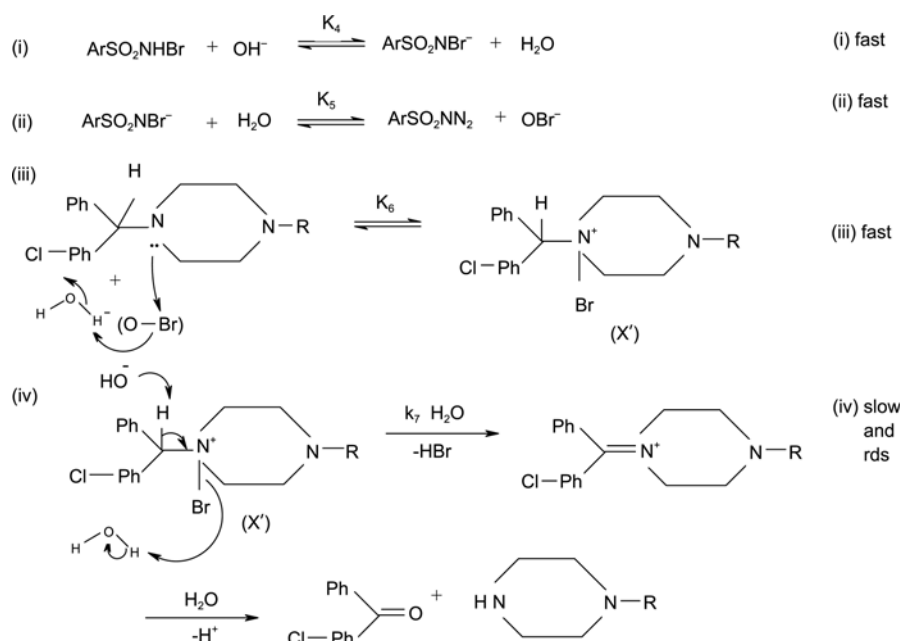
Scheme 2. Detailed mechanistic interpretation for the oxidation of cetrizine by BAT in alkaline medium.

of [BAT] is

$$[BAT]_t = [ArSO_2NHBr] + [ArSO_2N^-Br] + [O^-Br] + [X'] \quad (15)$$

Solving for [X'] from steps (i), (ii) and (iii) of Scheme 2, one obtains

$$[X'] = \frac{K_4K_5K_6[BAT]_t[CTZH][OH^-][H_2O]}{[ArSO_2NH_2]\{[H_2O]+K_4[OH^-]\}+K_4K_5[OH^-][H_2O]+K_4K_5K_6[CTZH][OH^-][H_2O]} \quad (16)$$

From slow/rds (step (iv)) of Scheme 2

$$rate = k_7 [X'] \quad (17)$$

Upon substituting for [X'], from Eq. (16) into Eq. (17), we get

$$rate = \frac{K_4K_5K_6k_7[BAT]_t[CTZH][OH^-][H_2O]}{[ArSO_2NH_2]\{[H_2O]+K_4[OH^-]\}+K_4K_5[OH^-][H_2O]+K_4K_5K_6[CTZH][OH^-][H_2O]} \quad (18)$$

Since rate = k' [BAT]$_t$, Eq. (18) can be transformed as

$$k' = \frac{K_4K_5K_6k_7[CTZH][OH^-][H_2O]}{[ArSO_2NH_2]\{[H_2O]+K_4[OH^-]\}+K_4K_5[OH^-][H_2O]+K_4K_5K_6[CTZH][OH^-][H_2O]} \quad (19)$$

$$\frac{1}{K'} = \frac{[ArSO_2NH_2]}{K_4K_5K_6k_7[CTZH][OH^-]} + \frac{[ArSO_2NH_2]}{K_5K_6k_7[CTZH][H_2O]} + \frac{1}{K_6k_7[CTZH]} + \frac{1}{k_7} \quad (20)$$

$$\frac{1}{K'} = \frac{1}{[CTZH]}\left\{\frac{[ArSO_2NH_2]}{K_4K_5K_6k_7[OH^-]} + \frac{[ArSO_2NH_2]}{K_5K_6k_7[H_2O]} + \frac{1}{K_6k_7}\right\} + \frac{1}{k_7} \quad (21)$$

$$\frac{1}{K'} = [ArSO_2NH_2]\left\{\frac{1}{K_4K_5K_6k_7[CTZH][OH^-]} + \frac{1}{K_5K_6k_7[CTZH][H_2O]}\right\}$$
$$+ \left\{\frac{1}{K_6k_7[CTZH]} + \frac{1}{k_7}\right\} \quad (22)$$

Using Eqs. (20, 21 and 22), plots of $1/k'$ *vs* $1/[OH^-]$ (R^2 = 0.9700), $1/k'$ *vs* $[ArSO_2NH_2]$ (R^2 = 0.9875) and $1/k'$ *vs* $1/[CTZH]$ (R^2 = 0.9811) were found to be linear (Figure 4). From the slopes and intercepts of such plots values of K_4, K_5, K_6 and k_7 were calculated found to be 0.93×10^{-6}, 3.597×10^3, 1.30×10^7 dm^3 mol^{-1} and 2.78×10^{-4} s^{-1} respectively.

Solvent Isotope Effect. As the rate was retarded on [H$^+$] and accelerated on [OH$^-$], solvent isotope studies were made using D$_2$O as the solvent medium. The observed solvent isotope effects support the proposed mechanism and the derived rate expression. For a reaction involving a fast pre-equilibrium H$^+$ or OH$^-$ ion transfer, the rate increases in D$_2$O medium since D$_3$O$^+$ and OD$^-$ are a stronger acid and a stronger base, ($\sim$2 to 3 times greater) respectively, than H$_3$O$^+$ and OH$^-$ ions.[26,27] The reverse holds good for the reactions
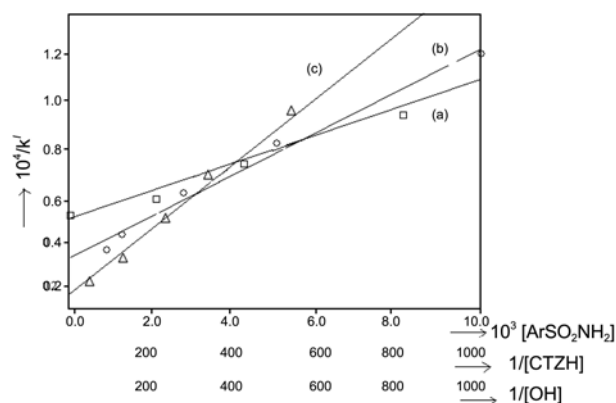

Figure 4. Double reciprocal plots of (a) $1/k'$ *vs* [ArSO$_2$NH$_2$], (b) $1/k'$ *vs* $1/$[CTZH] and (c) $1/k'$ *vs* $1/$[OH$^-$] in alkaline medium. Experimental conditions are as in Table 1.

involving retardation by H$^+$ or OH$^-$ ions. The decrease of rate with D$_2$O in acid medium (k'(H$_2$O)/k'(D$_2$O) = 1.41) and increase of rate with D$_2$O in alkaline medium (k'(H$_2$O)/k'(D$_2$O) = 0.54) conform to the above theory.[26,27] However, the magnitude of retardation and acceleration are small which can be attributed due to the inverse-fractional and fractional-order dependence of rate on [H$^+$] and [OH$^-$], respectively.

Dielectric Constant Effect. Several approaches[28-33] have been made to explain quantitatively the effect of dielectric constant of the medium on the rates of reactions in solutions. A change in the solvent composition by varying the methanol content in methanol-water affects the reaction rate. For the limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis[33] has shown that a plot gives a straight line of log k' *vs*.

1/D gives a straight line, with a negative slope for a reaction between a negative ion and a dipole or between the dipoles, while a positive slope indicates a reaction between a positive ion and a dipole. The positive dielectric effect on the reaction rate observed in both the cases are in agreement with positive ion-dipole nature of rate-determining steps in the proposed Schemes (Schemes 1 and 2) and the reaction pathways has suggested to the kinetic results.

Ionic Strength Effect. The proposed reaction mechanism is also supported by the observed effects of ionic strength on the rate of the reaction in both the media. In the present case, variation of ionic strength of the medium does not alter the rate in both the cases, which signifies that one of the reactant species is a neutral molecule as shown in slow/rds steps of Schemes 1 and 2. Hence, the observed ionic strength effect is in agreement with Bronsted-Bjerrum concept[34] for the proposed mechanisms.

Activation Parameters. The proposed reaction Schemes and derived rate laws are supported by the moderate values of energy of activation and other thermodynamic parameters. The activation energy is highest for the slowest reaction and *vice-versa* (Table 3), indicating that the reaction is enthalpy controlled. The fairly positive values of Gibbs free energy of activation and enthalpy of activation indicates that the transition state is highly solvated. The negative values of

$\Delta S^{\neq}$ suggests the formation of a rigid activated complex with fewer degrees of freedom.

Comparison of Relative Reactivity in Acid and Alkaline Media. In the present research, the detailed kinetic study was carried out on the oxidation of CTZH drug with BAT at pH 2.22 and 11.78 (6.0×10^{-3} mol dm^{-3} in both acidic and alkaline media), the other experimental conditions being held constant (Table 1). The kinetic patterns with respect to oxidant and substrate were identical in both the media. In acid medium, the rate of the reaction was retarded by varying the HClO$_4$ in the concentration range of 2.0×10^{-3} to 20.0×10^{-3} mol dm^{-3} and the order was found to be −0.48. But in case of alkali, the rate of the reaction was accelerated in the same concentration range as of acid and the order was found to be 0.52. The reaction rate was retarded by the addition of the reduction product of BAT, *p*-toluenesulfonamide in alkaline medium and the order was found to be −0.40. Based on kinetic results, ArSO$_2$NHBr and O$^-$Br were considered to be the reactive oxidizing species in acid and alkaline media, respectively. Schemes 1 and 2 explain the detailed mechanistic interpretation in acid and alkaline media, respectively.

Further, Table 3 revealed that the rate of oxidation of CTZH with BAT is about 3 times faster in acid medium in comparison with alkaline medium, under similar experimental conditions. The different reactive oxidizing species of BAT involved in the two media may be responsible for the difference in reactivity. Thus, in the present case, ArSO$_2$NHBr is a better reactive species than O$^-$Br in BAT solutions. The current reactivity trend may also be explained on the basis of the rate-determining steps of Schemes 1 and 2, in which elimination of HBr is crucial in both the cases. In acid medium, elimination of Br$^-$ as HBr is easier whereas in the presence of alkali, the removal of Br$^-$ as HBr by the abstraction of a proton from a molecule of H$_2$O is relatively difficult. Based on these reasonings, it can be concluded that the oxidation reaction of CTZH with BAT is facile in acid medium when compared to alkaline medium.

Summary

The kinetics of oxidation of CTZH with BAT has been studied at 313 K in acid and alkaline media. In these oxidation reactions, the order with respect to oxidant and substrate are same in both the media. But, the rate of the reaction is retarded in presence of H$^+$ ions and accelerated in alkaline medium. The rate of oxidation of CTZH with BAT is about 3 times faster in acid medium in comparison with alkaline medium under similar experimental conditions. 4-chlorobezophenone and (2-piperazin-1-yl-ethoxy)acetic acid were identified as the oxidation products. Activation parameters and reaction constants have been deduced. Based on kinetic data, suitable mechanisms and relevant rate expressions have been worked out.

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