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KINETICS OF BUTACAINE SULFATE OXIDATION BY SODIUM N-CHLOROBENZENESULFONAMIDE IN ACIDIC MEDIUM : A MECHANISTIC APPROACH

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ABSTRACT

A kinetic study of oxidation of butacaine sulfate (one of the potent local anesthetics) by sodium N-chlorobenzenesulfonamide (Chloramine-B or CAB) in the presence of $HClO_4$ at 303 K has been investigated. The reaction exhibits first order kinetics with respect to [CAB] and fractional order dependence with substrate, but it is independent of the $[HClO_4]$. The stoichiometry of the reaction was found to be 1 : 3 and oxidation products were identified. The experimental rate laws obtained are $-d[CAB]/dt = k[CAB]_0[S]^x[H^+]^y$, where x is less than unity and y is zero. The reaction was subjected to changes in (a) concentration of benzene sulfonamide, (b) concentration of added neutral salts, (c) ionic strength, and (d) dielectric permittivity of the medium. The oxidation reactions were studied at different temperatures and overall activation parameters have been evaluated. The oxidation reaction fails to induce the polymerization of added acrylonitrile. Formation and decomposition constants have been determined. The proposed mechanism and derived rate law are consistent with the observed kinetic data. The observed results have been explained by plausible mechanisms and the relative rate laws have been deduced.

Key words: Chloramine- B, Butacaine sulfate, Oxidation kinetics, Perchloric acid medium

INTRODUCTION

Butacaine sulfate (BTC) is one of the topical anesthetic[1]. It is an all purpose local anesthetic drug used frequently in surface infiltration, block, and spinal anesthesia. It exhibits more rapid onset of action followed by a prolonged action. Its solution finds usage as a topical local anesthesia in dentistry. It has also been employed in several ear and nose drops for the relief of pain along with other drugs. No information is available on the oxidation kinetics of butacaine sulfate with any oxidant. This prompted us to undertake the present investigations. The chemistry of N-halogeno compounds containing the halogen in

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the +1 oxidation state has received considerable attention. Chloramine – T is the prominent member of this group. It is well known as an analytical reagent for determining diverse substrates, and the mechanistic aspects of these reactions have been reported[2,3].

The benzene analogue chloramine-B ($C_6H_5SO_2NClNa.1.5\ H_2O$ or CAB) is being important and received considerable attention as an oxidimetric reagent[4-6]. Conductometric studies of the interaction of CAB with some metal ion solutions[7] and photolysis of aqueous solution of CAB have been reported[8]. A review of the literature reveals the absence of investigations on the oxidation kinetics of BTC with any oxidant. This promoted us to undertake the present investigations and report herein the results of kinetics of oxidation of BTC with CAB in $HClO_4$ medium. In the light of the available information, the present paper reports for the first time a detailed kinetics of oxidation of butacaine with CAB in perchloric acid medium in order to (i) elucidate the reaction mechanism (ii) put forward appropriate rate law (iii) ascertain the reactive species of CAB and (iv) identify the products of the reaction.

EXPERIMENTAL

Materials

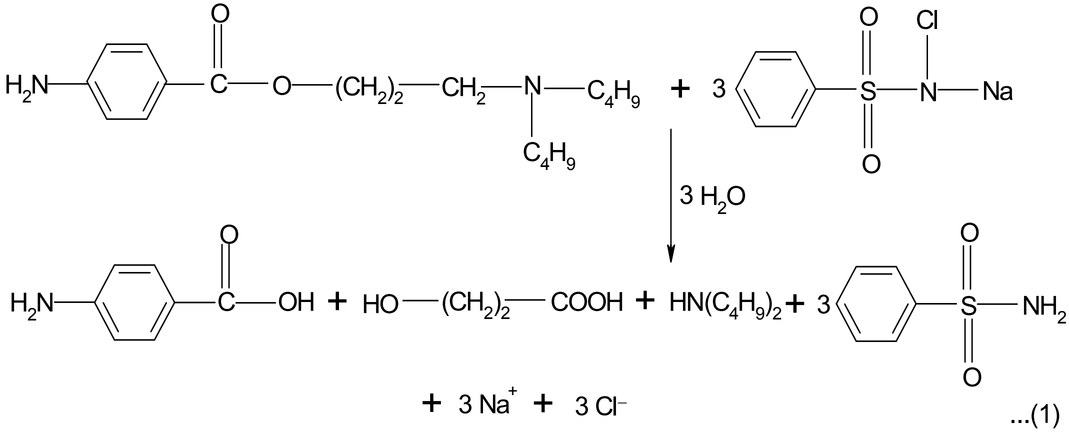
An aqueous solution of chloramine –B (Fluka, Switzerland) was standardized iodometrically and stored in brown bottles to prevent photochemical deterioration. Butacaine sulfate (Merck) was used as received. Aqueous solution of the compound was prepared freshly each time. All other chemicals were of analytical grade. Doubly distilled water was used throughout. A constant ionic strength of the medium was maintained ($\mu = 0.5\ mol\ dm^{-3}$) by a concentrated solution of $NaClO_4$.

Kinetic measurements

The kinetic experiments were carried out under pseudo-first-order conditions ([BTC] >> [CAB]) at 303 K. The reaction was carried out in glass stoppered Pyrex boiling tubes coated black from outside to eliminate photochemical effects. For each run, requisite amount of solutions of BTC, $HClO_4$, $NaClO_4$ and water (to keep the total volume constant for all runs) were taken in the tube and thermally equilibrated at 303 ± 0.1 K. A measured amount of CAB solution also pre-equilibrated at the same temperature was rapidly added to the mixture and stirred well. The progress of the reaction was monitored by the iodometric determination of unreacted CAB in 5 mL aliquots of the reaction mixture withdrawn at different time intervals. The course of the reaction was studied up to 75 to 80% of the reaction to complete. The pseudo-first-order rate constants (k') calculated from the linear plots of log [CAB] versus time were reproducible within ± 4%. Regression analysis of the experimental data to obtain regression coefficient, r, was calculated using an fx-570MS scientific calculator.

Stoichiometry and product analysis

Reaction mixture containing varying ratios of $[CAB]_0$ to $[Substrate]_0$ in the presence of 2.0×10^{-3} mol dm^{-3} $HClO_4$ were equilibrated at 303 K for 48 hr. Estimation of unreacted CAB in the reaction mixture showed that 1 mole of butacaine sulfate consumed 3 moles of oxidant, confirming the following stoichiometry,



...(1)

After completion of the reaction, the reaction products were neutralized with alkali and extracted with ether. The organic products were subjected to spot tests[9] and chromatographic analysis using TLC. Further, these products were confirmed by IR and GC-MS analysis, which revealed the formation of oxidation products as p- aminobenzoic acid, 3-hydroxypropanoic acid and dibutaylamine. IR spectral bands of p-aminobenzoic acid were observed at 1693 cm^{-1} (-C=O), 3468 cm^{-1} (-OH), 3366 cm^{-1} and 3234 cm^{-1} ($-NH_2$); 3-hydroxypropanoic acid at 1740 cm^{-1}(-C=O) and a broad peak at 3475 cm^{-1} (-OH) and dibutylamine at 3445 cm^{-1}(-NH-). GC-MS was obtained on a 17A Shimadzu gas chromatograph with a QP-5050A Shimadzu mass spectrometer. The mass spectrum was obtained using the electron impact ionization technique. The mass spectrum showed a molecular ion peaks at 137, 90 and 129 amu, clearly confirming p-aminobenzoic acid, 3-hydroxypropanoic acid and dibutylamine respectively.

The reduction product of CAB, benzenesulfanamide (RNH_2) was extracted with ethylacetate and detected[10] by TLC using petroleum ether : $CHCl_3$: 1-butanol (2 : 2 : 1, v/v) as the solvent system and iodine as spraying agent (R_f = 0.88). Further, it was confirmed by IR and GC-MS spectral analysis. IR spectral analysis (N-H stretch: 3365, 3275; Ar.C=C: 1556, 1448; SO_2 asymmetric stretch: 1334 SO_2 symmetric stretch: 1160; S-N stretch: 997 cm^{-1}). Molecular ion peak of 157 amu clearly confirms benzene sulfonamide. All other peaks observed in MS can be interpreted in accordance with the observed structure. It was also observed that there was no further oxidation of these products under present kinetic conditions.

RESULTS AND DISCUSSION

The oxidation of BTC with CAB has been kinetically investigated at different initial concentrations of the reactants in the presence of $HClO_4$ at 303 K.

Table 1. Effect of varying concentrations of reactants and $HClO_4$ on the reaction rate at 303 K

10^4 [CAB] (mol dm^{-3})	10^3 [BTC] (mol dm^{-3})	10^3 [$HClO_4$] (mol dm^{-3})	$k_{obs} \times 10^4$ (s^{-1})
1.0	2.0	2.0	4.92
2.5	2.0	2.0	4.89
5.0	2.0	2.0	4.75
2.0	2.0	2.0	4.98
2.0	0.5	2.0	2.72
2.0	1.0	2.0	3.95
2.0	2.0	2.0	4.89
2.0	3.0	2.0	6.32
2.0	4.0	2.0	7.57
2.0	2.0	0.5	4.92
2.0	2.0	1.0	4.91
2.0	2.0	2.0	4.89
2.0	2.0	3.0	4.75
2.0	2.0	4.0	4.93

Cont…

10^4 [CAB] (mol dm^{-3})	**10^3 [BTC] (mol dm^{-3})**	**10^3 [$HClO_4$] (mol dm^{-3})**	**$k_{obs} \times 10^4$ (s^{-1})**
[a]2.0	2.0	2.0	4.80
[b]2.0	2.0	2.0	4.85
[c]2.0	2.0	2.0	4.95

$\mu = 0.5$ mol dm^{-3}, a - in presence of benzenesulfonamide, b - at ionic strength of 1.0 mol dm^{-3} and c - in presence of NaCl.

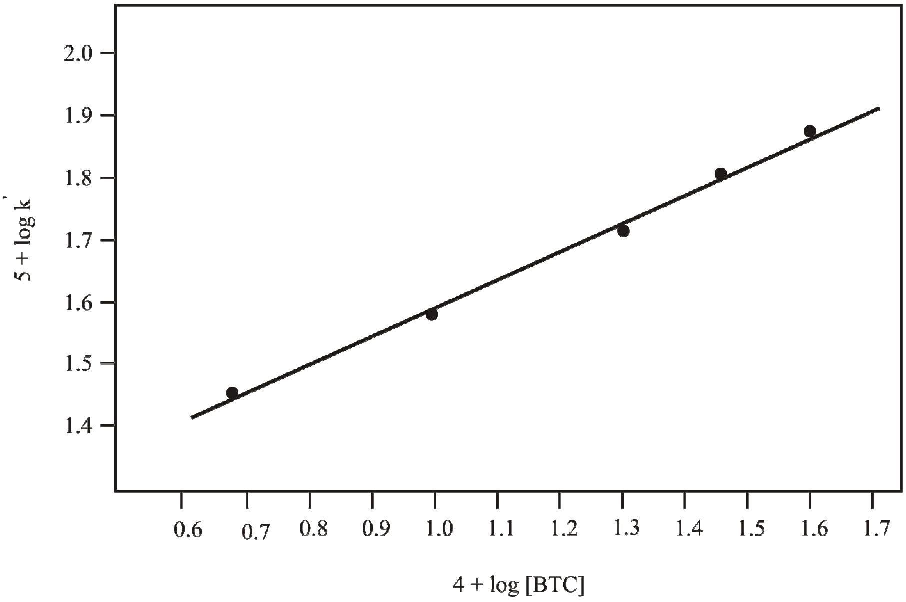


Fig. 1: Plot of log[BTC] verses log k'

Effect of varying reactant concentrations on the reaction

The oxidation of butacaine sulfate has been kinetically investigated at different initial concentrations of the reactants in the presence of $HClO_4$ at 303 K. Under pseudo-first-order conditions of $[BTC]_0 >> [CAB]_0$ at constant [$HClO_4$] and temperature, plots of log $[CAB]_0$ versus time were linear (r = 0.9978) indicating a first order dependence of rate on $[CAB]_0$. The pseudo-first-order rate constants (k') calculated from these plots are given in Table 1. Further, the values of k' calculated from these plots are unaltered with variation of $[CAB]_0$, confirming the first-order dependence of the rate on [CAB]. Under similar experimental conditions, the rate increased with increase in $[BTC]_0$ (Table 1). A plot of log k' versus log [BTC] was linear (Fig. 1, r = 0.9978) with a slope of 0.48 indicating a fractional order dependence of the rate on $[BTC]_0$ in acidic medium (Table 1).

Effect of varying $[H^+]$ and $[Cl^-]$ on the rate

The $[H^+]$ was varied using $HClO_4$. The rate of the reaction is not affected with a change in $HClO_4$ (Table 1). At constant $[H^+]$, addition of Cl^- in the form of NaCl had no significant effect on the rate of reaction (Table 1).

Effect of added benzene sulfonamide on the rate

The addition of reduced product, benzene sulfonamide (1×10^{-3} to 5×10^{-3} mol dm^{-3}) had no effect on the rate, indicating that it is not involved in pre-equilibrium step before the rate-determining step.

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

The reaction rate remained unaffected by varying ionic strength of the medium through addition of $NaClO_4$ (0.5 – 1.0 mol dm^{-3}). The effect of dielectric constant (D) on the reaction rate was studied by adding various proportions of methanol (0-30% v/v) to the reacting system.

Table2. Effect of solvent composition and temperature on the reaction rate

Temperature (K)	CH_3OH (%, v/v)	10^4 k' (s^{-1})
303	0	4.92
303	10	6.70
303	20	8.42
303	30	12.8
283	-	2.99
293	-	3.95
303	-	4.89
313	-	5.99
323		7.10

The reaction rates increases with decrease in dielectric permittivity of the reaction mixture (Table 2). Plot of log k' versus 1/D were found to be linear (r > 0.9540) with a positive slope, where D is the dielectric permittivity of the medium (D values are taken from the literature[11-13]. Blank experiments showed that methanol was not oxidized by CAB under the experimental conditions employed.

Effect of varying temperature on the rate

The reaction was studied at different temperature (283-323 K) keeping other experimental conditions constant (Table 2). From the linear Arrhenius plot of log k' versus 1/T (Fig. 2; r = 0.9978), activation energy and other thermodynamic parameters for composite reaction were found to be; E_a = 15.963 kJ mol^{-1}, ΔH = 13.44 kJ mol^{-1}, ΔS = -264.35 JK^{-1} mol^{-1}; ΔG = 93.55 kJ mol^{-1}.

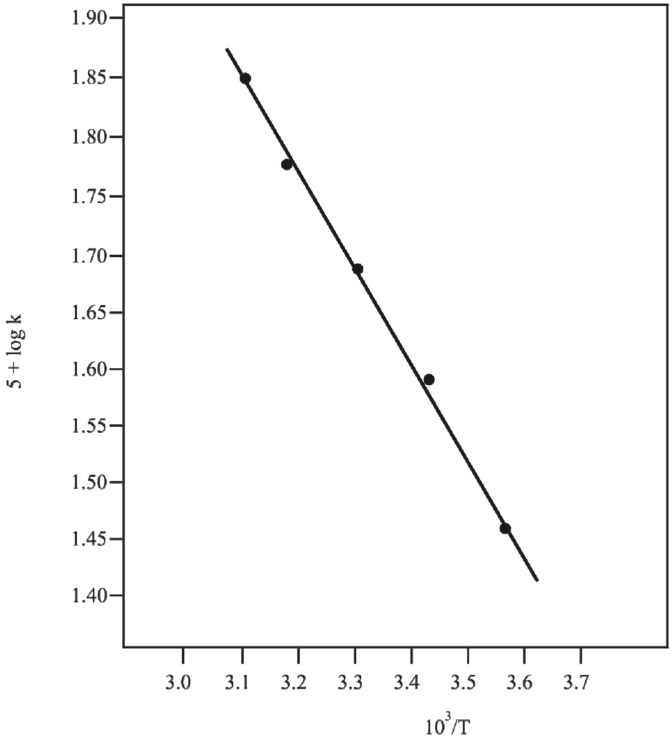


Fig. 2: Plot of 10^3/T versus log k'

Test for free radicals

The addition of aqueous acrylamide monomer solution to the reaction mixture in an inert atmosphere did not initiate polymerization indicating the absence of free radicals species in reaction sequence.

Chloramine-B is analogous to chloramine-T and exhibits similar equilibria in aqueous acidic and basic solutions[14-17]. In conductometric and pH titrations between aqueous solutions of CAB and HCl were performed and it was observed that the behavior of CAB is identical with that of CAT[18-20]. The possible equilibria in acidified CAB solutions are:

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

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

$$\text{RNHCl} + \text{H}_2\text{O} \rightleftharpoons \text{RNH}_2 + \text{HOCl} \quad ...(4)$$

$$2\,\text{RNHCl} \rightleftharpoons \text{RNH}_2 + \text{RNCl}_2 \quad ...(5)$$

$$\text{HOCl} + \text{H}^+ \rightleftharpoons \text{H}_2\text{OCl}^+ \quad ...(6)$$

Where $R = C_6H_5SO_2$-

Therefore, the possible oxidizing species in acidic solutions of CAB are the free acid RNHCl, $RNCl_2$, HOCl and possibly H_2OCl^+.

The involvement of $RNCl_2$ in the mechanism leads to a second order rate law and negative effect of RNH_2 according to equation (5), which is contrary to the experimental observations. If HOCl were the primary oxidizing species, a first-order retardation of the rate by the added RNH_2 would be expected. However, no such effect was noticed.

The oxidation potential of haloaminesulfonamide system is pH dependent and decreases with increase in pH of the medium. Bishop and Jennings[15], as a first approximation, have calculated the concentrations of different species in 0.05 mol dm^{-3} CAT solutions at different pH. The acid form of CAT (RNHCl) is found to be predominant species under acidic conditions. Hardy and Johnston[16] have pointed out that bromamine-B solution consist of [RNHBr] $\approx 4.1 \times 10^{-5}$ M at pH 7 and [HOBr] $\approx 6.0 \text{X}\ 10^{-6}$ M and [OBr] $\approx 10^{-8}$ M in alkaline medium. Since chloramine-B is chlorine analogue of bromamine –B, it behaves identical to BAB chemically. Thus, the results of Hardy and Johnston[16] can be extrapolated to CAB also. This supports the assumption that RNHCl is the oxidizing species in acid solutions. It is therefore probable that RNHCl is the reactive species. Further protonation of RNHCl at pH < 2, according to equation (7) has been reported[21].

$$RNHCl + H^+ \rightleftharpoons RNH_2^+Cl \qquad ...(7)$$

Where R = p-$CH_3C_6H_4SO_2$-, K = 1.02 x 10^2 at 25^0C, when R = $C_6H_5SO_2$-, K = 61 ± 5 mol^{-1} at 25^0C.

Further, variation of $[H^+]$, ionic strength of the medium has no significant effect on the rate. A fractional order dependence on $[BTC]_0$ indicates a pre-equilibrium followed by the rate limiting step. Based on the preceding discussion, Scheme 1 for BTC-CAB reaction in acid medium has been proposed to substantiate the observed kinetics.

$$RNHCl + BTC \underset{}{\overset{K_1}{\rightleftharpoons}} X \qquad \text{fast} \qquad ...(8)$$

$$X \xrightarrow{k_2} X' \qquad \text{slow and r.d.s} \qquad ...(9)$$

$$X' + 2\,RNHCl \xrightarrow{k_3} \text{products} \qquad \text{fast} \qquad ...(10)$$

Scheme 1

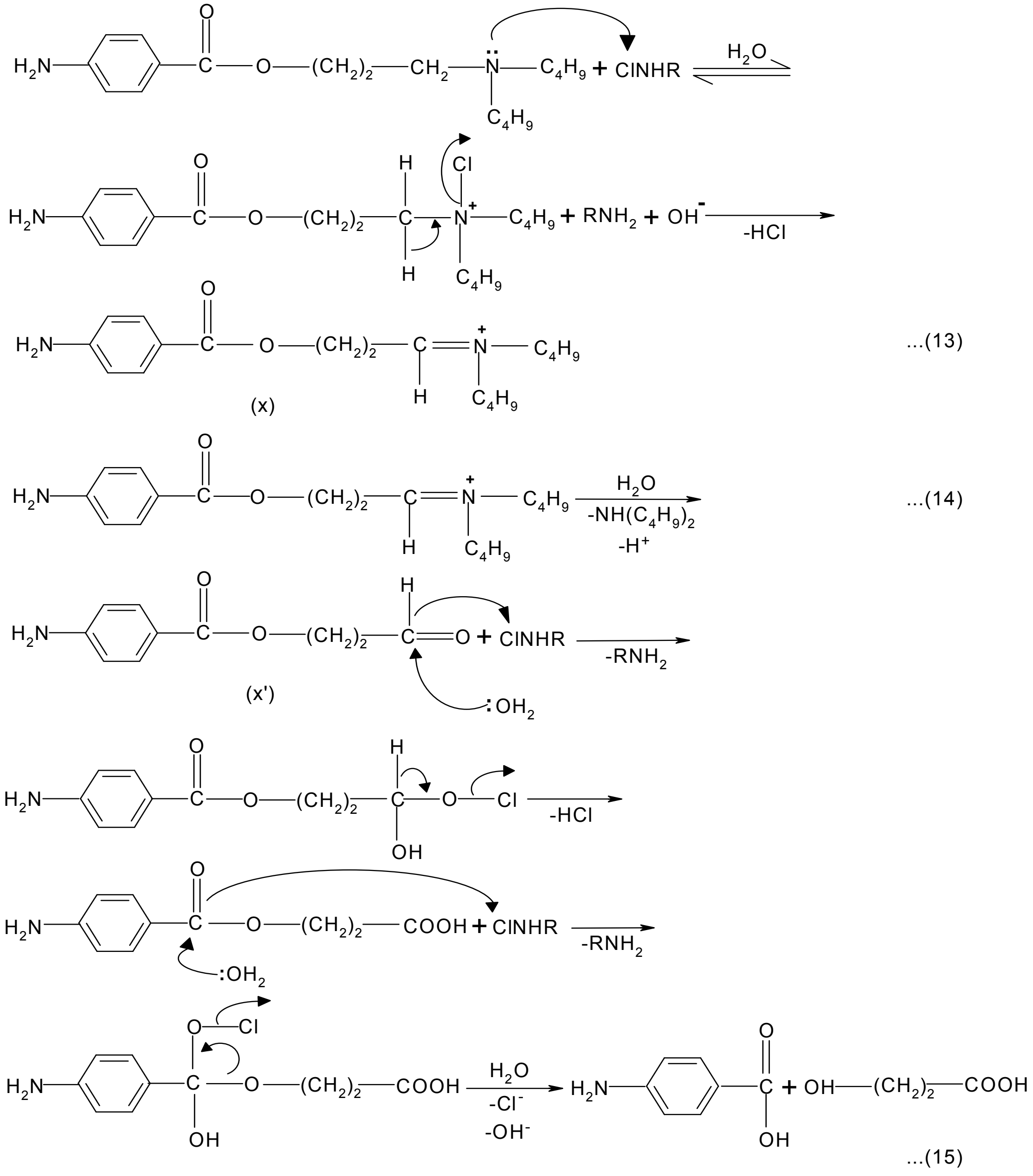
In this Scheme, BTC represents the substrate, X and X ' represent the complex intermediate species, whose structures are shown in Scheme 2, where a detailed mechanistic interpretation of butacaine sulfate oxidation by CAB in acid medium has been proposed.

From the slow step of Scheme 1,

$$rate = \frac{-d[CAB]}{dt} = k_2[X] \qquad ...(11)$$

If $[CAB]_t$ represents the total effective concentration of CAB in solution , then

$$[CAB]_t = [RNHCl] + [X] \qquad ...(12)$$



Scheme 2

By substituting for [RNHCl] from equilibrium step (8) in equation (11) and solving for [X] one obtains,

$$[X] = \frac{[CAB]_t K_1[BTC]}{1+K_1[BTC]} \quad \text{...(16)}$$

Substituting [X] from equation (16) into equation (11), the following rate equation (17) is obtained:

$$\text{rate} = \frac{K_1 k_2 [CAB]_t [BTC]}{1+K_1[BTC]} \quad \text{...(17)}$$

The rate law is in good agreement with the experimental results observed.

Since rate = k ' $[CAB]_t$, rate law (17) can be transformed into equations (18) and (19);

$$k' = \frac{K_1 k_2 [BTC]}{1+K_1[BTC]} \quad \text{...(18)}$$

$$\frac{1}{k'} = \frac{1}{K_1 k_2 [BTC]} + \frac{1}{k_2} \quad \text{...(19)}$$

Based on rate law (18), a plot of 1/k' versus 1[BTC] at constant $[CAB]_0$, $[H^+]$ and temperature, was found to be linear (Fig. 3, r = 0.9976). From the slope and intercept of this plot, the formation constant K_1 and the decomposition constant k_2 of the substrate-oxidant species were found to be 9.79×10^2 M^{-1} and 8.3×10^{-4} s^{-1}, respectively.

The effect of varying dielectric permittivity (D) of the medium on the rate has been described in detail in the well known monographs[22,23]. For a limiting case of zero angle of approach between two dipoles or ion–dipole system supports the proposed mechanism. An increase in the rate with decreasing dielectric permittivity of the medium supports the proposed mechanism. Amis[24] has shown that a plot of log k' versus 1/D gives a straight line with a negative slope for a reaction between an anion and a dipole or between two dipoles and a positive slope for a reaction between a cation and dipole.

In the present study, plot of log k' versus 1/D is linear with a positive slope supports the suggested mechanism. The reduction product of the oxidant *p*-toluene sulfonamide did not influence the rate showing that it is not involved in any pre equilibrium step.

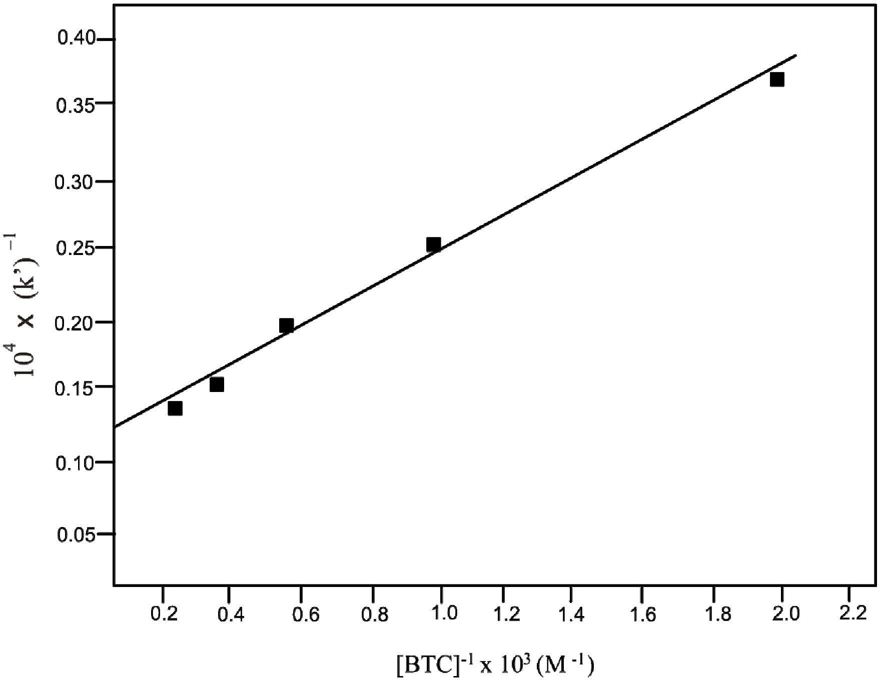


Fig. 3: Plot of $[BTC]^{-1}$ versus $(k')^{-1}$

The suggested mechanism is also supported by the values of energy of activation (E_a = 15.963 kJ mol^{-1}) and other activation parameters. The moderate values of Gibbs free energy of activation ($\Delta G^{\#}$ = 93.55 kJ mol^{-1}) and enthalpy of activation ($\Delta H^{\#}$ = 13.44 kJ mol^{-1}) indicate that the transition state is highly solvated, while high negative value of entropy of activation ($\Delta S^{\#}$ = -264.35 JK^{-1} mol^{-1}) accounts for the formation of compact and a more ordered transition state.

CONCLUSION

In conclusion, the stoichiometry of oxidation of butacaine sulphate with chloramine-B in acidic medium is 1 : 3. The oxidation products were identified as p-amino benzoic acid, 3-hydroxy propanoic acid and dibutylamine. The products are confirmed by IR and GC-MS spectral analysis. The different oxidizing species involved in the acidic medium are interpreted.

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