Mechanistic Chemistry of Oxidation of Butacaine Sulfate

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Articles

Kinetics and Mechanistic Chemistry of Oxidation of Butacaine Sulfate by Chloramine-B in Acid Medium

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Butacaine sulfate is an ester of *p*-aminobenzoic acid which has been widely used as a local anaesthetic and it is a long standing agent particularly for spinal anaesthesia. For this reason, a kinetic study of oxidation of butacaine sulfate by sodium *N*-chlorobenzenesulfonamide (chloramine-B or CAB) has been carried out in $HClO_4$ medium at 303 K in order to explore this redox system mechanistic chemistry. The rate shows a first-order dependence on both $[CAB]_o$, and $[substrate]_o$, and a fractional-order dependence on acid concentration. Decrease of dielectric constant of the medium, by adding methanol, increases the rate of the reaction. Variation of ionic strength and addition of benzenesulfonamide or NaCl have no significant effect on the rate. The reaction was studied at different temperatures and the activation parameters have been evaluated. The stoichiometry of the reaction has been found to be 1:2 and the oxidation products have been identified by spectral analysis. The observed results have been explained by plausible mechanism and the related rate law has been deduced.

Key Words : Butacaine sulfate, Local anaesthetics, Oxidation-kinetics, Chloramine-B, Acid medium

Introduction

The diverse nature of chemistry of *N*-metallo-*N*-haloaryl-sulfonamides, generally known as *N*-haloamines is due to their ability to act as sources of halonium cations, hypo-halites, and *N*-anions which act as bases, nucleophiles and nutrenoids.[1-5] They behave as mild oxidants and are suitable for the limited oxidation of several functional groups. Consequently, these reagents react with a variety of functional groups affecting an array of molecular transformations. Generally monohaloamines undergo a two-electron change while dihaloamines are four-electron oxidants.[1] The reduction products are the respective sulfonamides and NaCl or HCl. The prominent members of this class of compounds are chloramine–T (CAT) and chloramine–B (sodium *N*-chlorobenzenesulfonamide or CAB). The N-Cl bond in CAT and CAB is highly polar, hence these two compounds are fairly strong electrophiles, since chlorine leaves as Cl^+ in these reactions. CAT has been used for the oxidation of a variety of organic and inorganic substrates and the oxidation mechanisms have been kinetically well investigated.[6-10] CAB is a stable compound, with slightly higher active chlorine content than CAT. CAB is gaining importance as a mild oxidant and hence has considerable scope for the extension of work with CAB to get a better insight of the speciation of CAB in reaction models and for understanding its redox chemistry in solution.

Local anesthetics are compounds which reversibly prevent the generation and propagation of active potentials in all excitable membranes including nerve fibers by stabilizing the membrane. Butacaine sulfate [3-dibutylamino propyl-*p*-aminobenzoate sulfate, $C_{18}H_{30}N_2O_2 \cdot 1/2 \cdot H_2SO_4$, BS] is one of the least toxic and most commonly used local anesthetics. It finds use as a surface anaesthetic having effects similar to those of cocaine.[11-13] Hence butacaine sulfate forms one of the important drugs in pharmaceutical industry. After reviewing the literature, we found that there was no information available on the oxidation kinetics of BS with any oxidant. There was a need for understanding the oxidation mechanism of this drug in acid medium, so that the study could throw some light on the fate of the drug in the biological systems. Hence the present kinetic study gives an impetus, as the substrate BS is a potent drug.
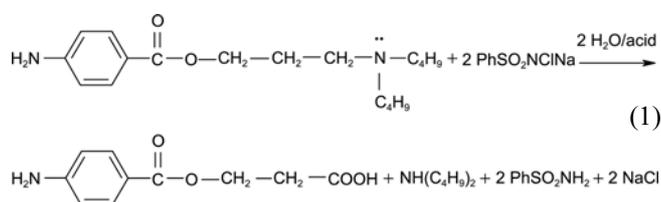
Experimental

An aqueous solution of CAB (Aldrich Chemical Co.) was prepared and stored in brown bottles to prevent its photo-chemical deterioration. BS (Alfa Chem) was used as received and an aqueous solution of BS was freshly prepared whenever required. Solvent isotope studies were made with D_2O (99.4%) supplied by BARC, Mumbai, India. Analytical grade chemicals and double distilled water were used throughout. Regression coefficient (r) was calculated using

fx-350 TL scientific calculator.

Kinetic runs were carried out under pseudo first-order conditions of ([substrate]$_o$ >> [oxidant]$_o$) at constant temperature 303 K in glass stoppered pyrex boiling tubes coated black from outside to eliminate photochemical deterioration. Raaga digital proportional temperature controller (Raaga, CH-16, Madras) was used to maintain the desired temperature with an accuracy of ± 0.1 °C. Requisite amounts of solutions of substrate and HClO$_4$ and water (for constant total volume) for all kinetic runs were equilibriated at 303 K for about 30 min. A measured amount of the CAB solution also equilibriated at the same temperature was rapidly added to the reaction mixture which was periodically shaken for uniform concentration. The progress of the reaction was monitored by withdrawing measured aliquots (5 mL each) from the reaction mixture at regular time intervals and determining the unreacted CAB iodometrically. The course of the reaction was studied for more than two half-lives. The pseudo first-order rate constants (k' s^{-1}) calculated from the linear plots of log [CAB] *versus* time were reproducible within 3-4%.

Varying mole ratios of CAB to BS were equilibriated at 303 K for 24 h in the presence of 0.2 mol dm^{-3} HClO$_4$. The unreacted oxidant was determined by iodometry and the analysis showed that one mole of BS consumed 2 moles of CAB as shown in Eq. (1).

$$\text{H}_2\text{N}-\bigcirc-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\overset{\cdot\cdot}{\underset{\underset{\text{C}_4\text{H}_9}{|}}{\text{N}}}-\text{C}_4\text{H}_9 + 2\,\text{PhSO}_2\text{NClNa} \xrightarrow{2\,\text{H}_2\text{O/acid}}$$

$$\text{H}_2\text{N}-\bigcirc-\overset{\overset{\text{O}}{\|}}{\text{C}}-\text{O}-\text{CH}_2-\text{CH}_2-\text{COOH} + \text{NH}(\text{C}_4\text{H}_9)_2 + 2\,\text{PhSO}_2\text{NH}_2 + 2\,\text{NaCl} \tag{1}$$

The BS-CAB reaction mixture in the stoichiometric ratio in the presence of HClO$_4$ under stirred conditions was allowed to progress for 24 h at 303 K. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized with NaOH and the products were extracted with ether. The organic products subjected to spot tests revealed the formation of corresponding acid with dibutyl amine. These oxidation products separated by column chromatography were confirmed by GCMS analysis. The GC-MS data were obtained from 17A Shimadzu gas chromatograph with QP-5050 Shimadzu mass spectrometer. It was also noticed that there was no further oxidation of these products under current kinetic conditions.

The reduction product of CAB, benzenesulfonamide (PhSO$_2$NH$_2$) was detected by thin layer chromatography, using light petroleum – chloroform – 1-butanol (2:2:1 v/v/v) as the solvent and iodine as the detecting agent (R_f = 0.88). All other peaks observed in GC-MS can be interpreted in accordance with the observed structure.

Results and Discussion

The kinetics of oxidation of butacaine sulphate by CAB

Table 1. Effect of varying oxidant, substrate and HClO$_4$ concentrations on the reaction rate at 303 K

10^3 [CAB]$_o$ (mol dm^{-3})	10^2 [substrate] (mol dm^{-3})	10 [HClO$_4$] (mol dm^{-3})	10^4 k' (s^{-1})
0.5	2.0	2.0	4.71
1.0	2.0	2.0	4.86
2.0	2.0	2.0	4.90
4.0	2.0	2.0	4.92
6.0	2.0	2.0	4.75
2.0	0.5	2.0	1.26
2.0	1.0	2.0	2.62
2.0	2.0	2.0	4.90
2.0	3.0	2.0	7.31
2.0	4.0	2.0	10.2
2.0	2.0	0.5	2.72
2.0	2.0	1.0	3.95
2.0	2.0	2.0	4.90
2.0	2.0	3.0	6.32
2.0	2.0	4.0	7.57

was investigated at several initial concentrations of the reactants at 303 K. Under pseudo first-order conditions of [substrate]$_o$ >> [oxidant]$_o$ at constant [HClO$_4$] and temperature, plots of log [CAB] *versus* time were linear (r > 0.9925) indicating a first-order dependence of rate on [CAB]$_o$. The pseudo-first-order rate constants (k') calculated from these plots are given in Table 1. Further, the values of k' calculated are unaltered with the variation of [CAB]$_o$, confirming the first-order dependence on [CAB]$_o$. The rate increased with increase in [BS]$_o$ (Table 1). A plot of log k' *versus* log [BS] was linear (r = 0.9982) with a unit slope indicating a first-order dependence of the rate on [BS]$_o$. Values of k' increased with increase in [HClO$_4$]. A plot of log k' *versus* log [HClO$_4$] was linear (r = 0.9975) with fraction (0.65) slope indicating a fractional-order dependence of rate on [H$^+$] (Table 1).

Addition of the reaction product, benzenesulfonamide (2.0 × 10^{-4} - 6.0 × 10^{-4} mol dm^{-3}) or variation of ionic strength of the medium (0.1-2.0 mol dm^{-3}) had no significant effect on the rate. Hence no attempt was made to keep the ionic
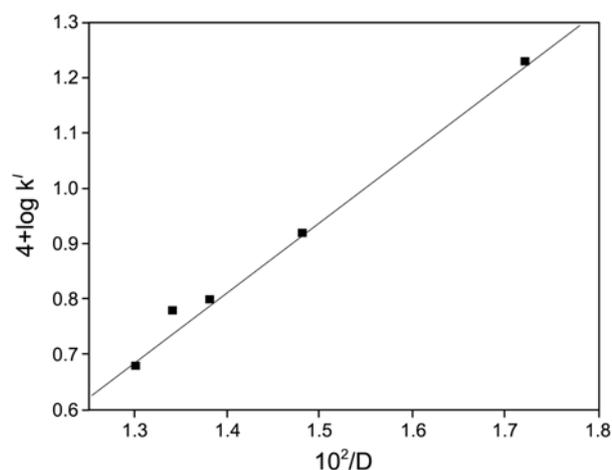

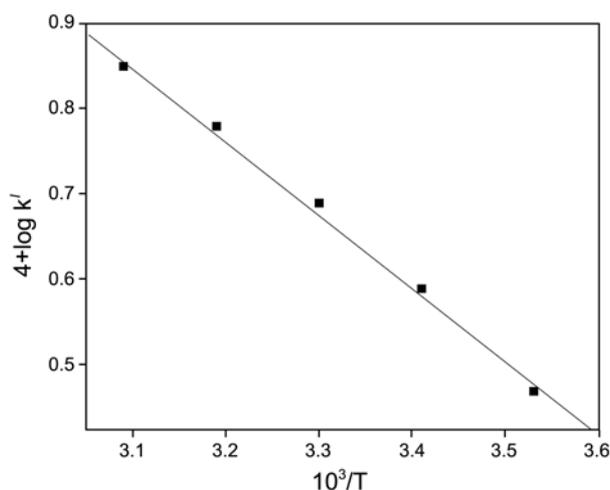**Figure 1.** Plot of 10^2/D *versus* 4+log k'.

Figure 2. Plot of $10^3/T$ *versus* $4+\log k'$.

strength constant for kinetic runs. Addition of Cl^- ions (4.0×10^{-2} - 8.0×10^{-2} mol dm^{-3}) in the form of NaCl had no effect on the rate.

The effect of dielectric constant (D) on the reaction rate was studied by adding various proportions of methanol (0-40% v/v) to the reaction system.[7,8] It was observed that an increase in methanol content in the reaction system increased the reaction rate and a plot of log k' *versus* 1/D (Fig. 1) was linear with a positive slope. The values of D for methanol–water mixtures reported in the literature were employed.[14] Blank experiments run with methanol indicated negligible oxidation under the experimental conditions employed.
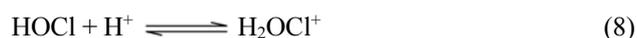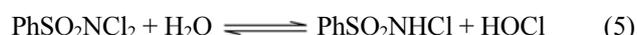
The solvent isotope effect[9,10] was studied in D$_2$O, where k' = 4.93×10^{-4} s^{-1} in D$_2$O medium and 4.90×10^{-4} s^{-1} in water leading to a solvent isotope effect, k'(H$_2$O)/k'(D$_2$O) = 0.994. The reaction was studied at different temperatures (283-323 K), keeping other experimental conditions constant. From linear Arrhenius plot of log k' *versus* 1/T (Figure 2; r = 0.9921), values of activation parameters (E_a, $\Delta H^{\neq}$, $\Delta G^{\neq}$, and $\Delta S^{\neq}$) for the overall reaction were computed. These results are compiled in Table 2. Absence of free radicals during the course of oxidation was confirmed when no polymerization

Table 2. Effect of varying temperature on the reaction rate and activation parameters. [CAB] = 2.0×10^{-3} mol dm^{-3}, [BS] = 2.0×10^{-3} mol dm^{-3}, [HClO$_4$] = 0.2 mol dm^{-3}.

Temperature (K)	$10^4 k'$ (s^{-1})
283	3.01
293	3.95
303	4.90
313	6.00
323	7.06
E_a/kJ mol^{-1}	15.6
$\Delta H^{\neq}$/kJ mol^{-1}	13.3
$\Delta G^{\neq}$/kJ mol^{-1}	93.5
$\Delta S^{\neq}$/JK^{-1} mol^{-1}	-264

was initiated with the addition of acrylonitrile solution to the reaction mixture.

CAB is analogous to CAT and exhibits similar equilibria in aqueous acidic and basic solutions.[15-17] In general CAB undergoes a two-electron change in its reactions forming the reduction products, benzenesulfonamide (BSA; PhSO$_2$NH$_2$) and NaCl. The oxidation potential of CAB-BSA redox couple varies[15] with pH of the medium (values are 1.14 V at pH 0.65 and 0.50 V at pH 12). In aqueous solutions CAB behaves as a strong electrolyte and depending on the pH CAB furnishes different types of reactive species as follows:

$$PhSO_2NClNa \rightleftharpoons PhSO_2NCl^- + Na^+ \qquad (2)$$

$$PhSO_2NCl^- + H^+ \rightleftharpoons PhSO_2NHCl \qquad (3)$$

$$2\,PhSO_2NHCl \rightleftharpoons PhSO_2NH_2 + PhSO_2NCl_2 \qquad (4)$$

$$PhSO_2NCl_2 + H_2O \rightleftharpoons PhSO_2NHCl + HOCl \qquad (5)$$

$$PhSO_2NHCl + H_2O \rightleftharpoons PhSO_2NH_2 + HOCl \qquad (6)$$

$$HOCl \rightleftharpoons H^+ + OCl^- \qquad (7)$$

$$HOCl + H^+ \rightleftharpoons H_2OCl^+ \qquad (8)$$

Therefore, the possible oxidizing species in acid solutions of CAB are PhSO$_2$NHCl, PhSO$_2$NCl$_2$, HOCl and possibly H$_2$OCl$^+$ and in alkaline CAB solutions they are PhSO$_2$NHCl, PhSO$_2$NCl$^-$, HOBr and OBr$^-$.

The first-order dependence of rate on [CAB]$_o$ and the addition of benzenesulfonamide (PhSO$_2$NH$_2$) having no effect on the reaction rate, both indicate that PhSO$_2$NCl$_2$ and HOCl may not be the reactive species [Eqs. (4) and (6)]. These species are present in very low concentrations at the experimental conditions employed.[16,17] Furthermore, variation of [H$^+$], ionic strength of the medium and addition of the reaction product, benzenesulfonamide, have virtually no effect on the rate. Based on the experimental results, the possible active oxidizing species is the protonated conjugate acid (PhSO$_2$NH$_2$Cl$^+$) and Scheme 1 has been proposed to explain the oxidation of BS by CAB in acid medium.

In Scheme 1, an initial equilibrium acid accelerating step (step (i)), the protonated acid further protonates to form diprotonated species. In the slow and rate determining step (step (ii)) the diprotonated species reacts with substrate to form a complex (X). This complex X consumes another mole of the oxidant yields the products followed by several steps. Two moles of the oxidant are consumed to yield the ultimate products.

Based on Scheme 1 the rate law below has been derived.

$$\text{rate} = \frac{K_1 k_2 [\text{CAB}]_t [\text{BS}][\text{H}^+]}{1 + K_1[\text{H}^+]} \qquad (9)$$

Rate law (9) is in good agreement with the observed experimental results.

Reactions in aqueous medium that are susceptible to acid-base catalysis have been studied in heavy water (D$_2$O) after equilibrium. Since most oxidation reactions of organic
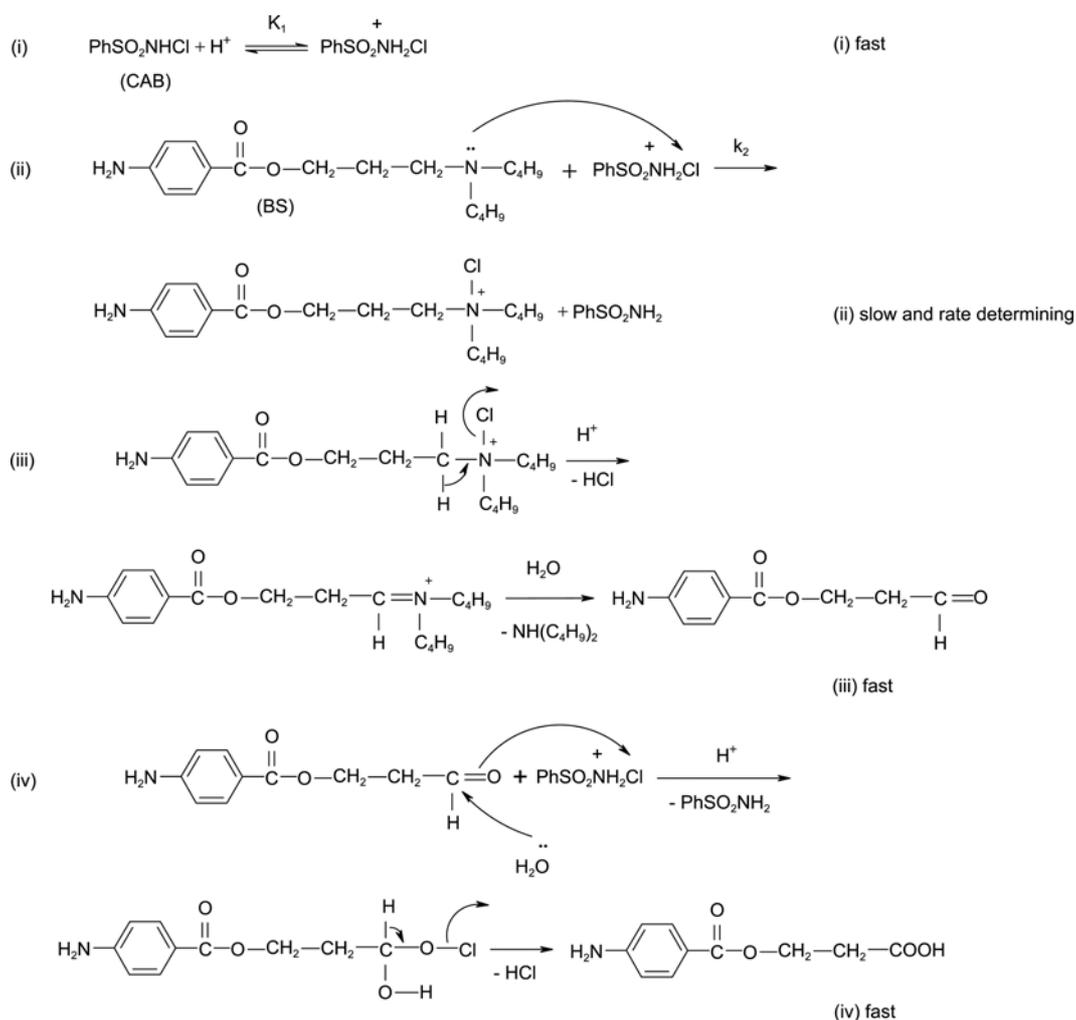
Scheme 1. Detailed mechanistic interpretation for the oxidation of butacaine sulfate by CAB in acid medium.

compounds involve the cleavage of C-H bond, deuterium isotope effect on such reactions gives information regarding the nature of the rate-determining step. In the present investigations, solvent isotope studies have shown that the rate of reaction is higher in D_2O medium. For a reaction involving a fast equilibrium with H^+ or OH^- ion transfer, the rate increases in D_2O medium since D_3O^+ and OD^- are a stronger acid and a stronger base respectively, than H_3O^+ and OH^- ions.[18-20] The observed solvent isotope effect of k' $(H_2O)/k'$ $(D_2O) < 1$ is due to the greater acidity of D_3O^+ as compared to H_3O^+. However, the magnitude of increase in rate in D_2O is very small as compared to the expected value which is 2-3 times greater. This may be due to the fractional order dependence of the rate on $[H^+]$. Hence, this observation supports the proposed mechanism.

The effect of varying solvent composition on the reaction kinetics has been described in detail in the well-known monographs.[21-25] For a limiting case of zero angle of approach between two dipoles or an ion-dipole system, 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 a negative ion and a dipole or between two dipoles, while a positive slope results for a positive ion-dipole interaction. The latter

concept agrees with the present observations, where a positive ion and a dipole are involved in the rate determining step of Scheme 1. Also, as the transition state is less polar than the ground state, the decreased polarity increases the rate by stabilizing the transition state.

Addition of halide ions, Cl^- or Br^-, in the form of their sodium salts (1.0×10^{-3} - 8.0×10^{-3} mol dm^{-3}) showed no pronounced effect on the rate. This indicates that the halide ions play no role in the reaction. The ionic strength of the reaction medium was varied from 0.1 to 0.3 mol dm^{-3} with $NaClO_4$ solution keeping other experimental conditions constant. It was found that addition of $NaClO_4$ showed negligible effect on the reaction rate, indicating the involvement of nonionic species in the rate-determining step. Hence no attempts were made to keep the ionic strength of the medium constant for kinetic runs.

The reaction product, benzenesulfonamide ($PhSO_2NH_2$) does not influence the rate showing that it is not involved in a pre-equilibrium. All these observations also confirm the proposed mechanism.

The proposed mechanism is also supported by the moderate values of energy of activation and other activation parameters. The fairly high positive value of free energy of

activation indicates that the transition state is highly solvated, while the large negative $\Delta S^{\neq}$ suggests the formation of a compact activated complex with a reduction in the degrees of freedom of molecules.

Conclusion

The kinetics of oxidation of butacaine sulfate by CAB has been studied at 303 K. The reaction follows the rate law rate = k [CAB]$_o$ [BS] [H$^+$]$^{0.47}$. On the basis of experimental results a suitable mechanism has been proposed that leads to a derived rate law which is in agreement with the kinetic results.

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