# Oxidation of Amylocaine Hydrochloride by Chloramine-B in Acid Medium: Kinetic and Mechanistic Approach

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Abstract-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 amylocaine hvdrochloride bv sodium N-chlorobenzenesulfonamide (chloramine-B or CAB) has been carried out in HClO<sub>4</sub> medium at 298 K in order to explore this redox system mechanistic chemistry. The rate shows a first-order dependence on both [CAB], and [substrate], 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 was found to be 1:2 and the oxidation products were identified by spectral analysis. The observed results have been explained by plausible mechanism and the related rate law has been deduced.

*Keywords:* Amylocaine hydrochloride, oxidation, kinetics, chloramine-B, acid medium

# I.INTRODUCTION

The diverse nature of chemistry of N-metallo-N-L haloarylsulfonamides, generally known as Nhaloamines is due to their ability to act as sources of halonium cations, hypohalites, and N-anions which act as bases, nucleophiles and nutrenoids<sup>1-5</sup>. They behave as mild oxidants and are suitable for the limited oxidation of several groups. Consequently, these reagents react with a variety of functional groups affecting an array of molecular transformations. Generally monohaloamines undergo two electron change while dihaloamines are four electron oxidants<sup>1</sup>. The reduction products are the respective sulfonamide 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<sup>+</sup> 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<sup>6-10</sup>. CAB is a stable compound, with slightly higher active chlorine content than its analogue CAT. CAB gaining importance as a mild oxidant and hence there is a considerable scope for the extension of work with CAB to get better insight of the speciation of CAB species reaction models and understanding its redox chemistry in solution.

Local anesthetics are drugs which reversibly prevent the generation and propagation of active potentials in all excitable membranes including nerve fibers by stabilizing the membrane. Amylocaine hydrochloride, chemically it is the hydrochloride of the benzoyl ester of 1-(dimethylaminomethyl)-1-methyl propanol 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<sup>11-13</sup>. 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 AML 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 AML is a potent drug.

# Materials and methods

An aqueous solution of CAB (Aldrich) was prepared and stored in brown bottles to prevent its photochemical deterioration. AML (Alfa Chem) was used as received and an aqueous solution of AML 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 procedure:** Reactions were carried out under pseudo first-order conditions were maintained for the kinetic runs ([substrate]<sub>o</sub> >> [oxidant]<sub>o</sub>) at constant

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temperature 298 K in glass stoppered pyrex boiling tubes coated black from outside to eliminate photochemical deterioration. Raaga digital proportional temperature controller (CH-16) was used to maintain the desired temperature with an accuracy of  $\pm$  0.1 <sup>o</sup>C. The requisite amounts of solutions of substrate and HClO<sub>4</sub> solutions and water (for constant total volume) for all kinetic runs were equilibriated at 303 K for about 30 min. A measured amount of CAB 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 determined the unreacted CAB iodometrically. The course of the reaction was studied more than two half-lives. The pseudo first-order rate constants (k s<sup>-1</sup>) calculated from the linear plots of log [CAB] versus time were reproducible within  $\pm$  3-4%.

## Stoichiometry and product analysis

Varying ratios of CAB to AML were equilibriated at 298 K for 24 h in presence of 0.2 mol dm<sup>-3</sup> HClO<sub>4</sub>. The unreacted oxidant was determined by iodometry and the analysis showed that one mole of AML consumed 2 moles of CAB as shown in Eq. 1.



The AML-CAB reaction mixture in the stoichiometric ratio in presence of  $HClO_4$  under stirred condition was allowed to progress for 24 h at 298 K. after completion of the reaction (monitored by TLC), the reaction products were neutralized with NaOH and extracted with ether. The organic products were subjected to spot tests revealed the formation of corresponding acid with dimethyl amine. These oxidation products were separated by column chromatography and 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 precuts under current kinetic conditions.

The reaction product of CAB, benzenesulfonamide (PhSO<sub>2</sub>NH<sub>2</sub>) was detected by thin layer chromatography, using light petroleum – chloroform – butan – 1 – ol (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.

## II. RESULTS AND DISCUSSION

The kinetics of oxidation of AML by CAB was investigated at several initial concentrations of the reactants at 298 K. Under pseudo first-order conditions of  $[AML]_o >> [CAB]_o$ 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 from these plots are unaltered with variation of  $[CAB]_o$ , confirming the firstorder dependence on  $[CAB]_o$ . The rate increased with increase in  $[AML]_o$  (Table 1). A plot of log k' versus log [AML] was linear (r = 0.9982) with a unit slope indicating a first-order dependence of the rate on  $[AML]_o$ . Values of k'are increased with increase in [AML], indicating a fractional-order dependence of rate on  $[H^+]$  (Table 1).

Addition of the reaction product, benzenesulfonamide (2.0 x  $10^{-4} - 6.0 \times 10^{-4} \mod \text{dm}^{-3}$ ) or variation of ionic strength of the medium (0.1 – 2.0 mol dm<sup>-3</sup>) had no significant effect on the rate. Hence no attempt was made to keep ionic strength constant for kinetic runs. Addition of Cl<sup>-</sup> ion (4.0 x  $10^{-2} - 8.0 \times 10^{-2} \mod \text{dm}^{-3})$  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 (0-30 % v/v) to the reacting system<sup>7-8</sup>. It was observed that an

increase in methanol composition in the reaction system increased the reaction rate (Table 2) and a plot of log k' versus 1/D was linear (Figure1; r = 0.9922) with a positive slope. The values of permittivity (dielectric constant) for MeOH–water mixtures reported in the literature were employed<sup>14</sup>. Blank experiments run with methanol indicated negligible oxidation under the experimental conditions employed.

The solvent isotope effect<sup>9-10</sup> was studied in D<sub>2</sub>O, where  $k' = 4.93 \times 10^{-4} \text{ s}^{-1}$  in D<sub>2</sub>O medium and 4.90 x  $10^{-4} \text{ s}^{-1}$  in water leading to a solvent isotope effect, k' (H<sub>2</sub>O) / k' (D<sub>2</sub>O) = 1.01. The reaction was studied at different temperatures (283 - 303 K), keeping other experimental conditions constant. From the linear Arrhenius plot of log k' versus 1/T (Figure 2; r = 0.9921), values of activation parameters for the overall reaction were computed. These results are compiled in Table 3. Absence of free radicals during the course of oxidation was confirmed when no polymerization 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<sup>15-17</sup>. In general CAB undergoes a two electron change in its reactions forming the reduction products, benzenesulfonamide (BSA; PhSO<sub>2</sub>NH<sub>2</sub>) and NaCl. The oxidation potential of CAB-BSA redox couple varies<sup>15</sup> with pH of the medium (values are 1.14 V at pH 0.65 and 0.50 V at pH 12). Aqueous solution of CAB behaves as a strong electrolyte and depending on the pH CAB furnishes different types of reactive species:

 $PhSO_2NCINa \implies PhSO_2NCI^{-} + Na^{+}$   $PhSO_2NCI^{-} + H^{+} \implies PhSO_2NHCl$   $2 PhSO_2NHCl \implies PhSO_2NH_2 + PhSO_2NCl_2$   $PhSO_2NCl_2 + H_2O \implies PhSO_2NHCl + HOCl$   $PhSO_2NHCl + H_2O \implies PhSO_2NH_2 + HOCl$   $HOCl \implies H^{+} + OCl^{-}$ 

$$HOCl + H^+ = H_2OCl^+$$

Therefore, the possible oxidizing species in acid solution of CAB are  $PhSO_2NHCl$ ,  $PhSO_2NCl_2$ , HOCl and possibly  $H_2OCl^+$  and in alkaline CAB solutions they are  $PhSO_2NHCl$ ,  $PhSO_2NCl^-$ , HOBr and OBr<sup>-</sup>.

The first-order dependence of rate on  $[CAB]_{\rm o}$  and the addition of benzenesulfonamide  $(PhSO_2NH_2)$  having no

effect on the reaction rate, both indicate that  $PhSO_2NCl_2$  and HOCl may not be the reactive species [Eqs (4) and (6)]. Further, these species are present in very low concentrations at the experimental conditions employed <sup>16-17</sup>. Furthermore, variation of [H<sup>+</sup>], 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<sub>2</sub>NH<sub>2</sub>Cl<sup>+</sup>) and Scheme 1 has been proposed to explain the oxidation of AML by CAB in acid medium. A detailed mode of oxidation of AML by CAB in acid medium and the structures of intermediates are depicted in Scheme 2.

$$PhSO_2NH_2Cl + H^+ \xrightarrow{K_1} PhSO_2NH_2Cl$$

$$\stackrel{+}{\longrightarrow} PhSO_2NH_2Cl + AML \xrightarrow{k_2} X$$

$$\stackrel{+}{\longrightarrow} X$$

$$X + PhSO_2NH_2Cl + H_2O \xrightarrow{k_3} Product$$

**Scheme 1.** A general reaction scheme for the oxidation of amylocaine hydrochloride by CAB in acid medium.

In scheme 2, 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( $\mathfrak{D}$ )th 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 following rate law has been proposed, which is in good agreement with the experimental results.  $\dots(5)$ 

Rate = 
$$\frac{K_1 k_2 [CAB]_t [AML] [H^+]}{1 + K_1 [H^+]}$$
...(7)

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

Reactions in aqueous medium that are susceptible to acidbase catalysis have been studied in heavy water ( $D_2O$ ) after equilibrium. Since most oxidation reactions of organic 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<sub>2</sub>O medium. For a reaction involving a fast equilibrium with H<sup>+</sup> or OH<sup>-</sup> ion transfer, the rate increases in D<sub>2</sub>O medium since D<sub>3</sub>O<sup>+</sup> and OD<sup>-</sup> are a stronger acid and a stronger base respectively, than H<sub>3</sub>O<sup>+</sup> and OH<sup>-</sup> ions<sup>18-20</sup>. The observed solvent isotope effect of k' (H<sub>2</sub>O) / k' (D<sub>2</sub>O) < 1 is due to the greater acidity of D<sub>3</sub>O<sup>+</sup> compared to H<sub>3</sub>O<sup>+</sup>. However, the magnitude of increase in rate in D<sub>2</sub>O is 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<sup>+</sup>]. 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<sup>21-25</sup>. For a limiting case of zero angle of approach between two dipoles or an ion–dipole system, Amis<sup>24</sup> 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 2.

The reaction product, benzenesulfonamide  $(PhSO_2NH_2)$ does not influence the rate showing that it is not involved in a pre-equilibrium. Addition of chloride ions had no effect on the rate indicating that no interhalogen or free chlorine is formed. 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 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.

#### CONCLUSIONS

The kinetics of oxidation of AML by CAB has been studied at 298 K. The reaction follows the rate law rate = k [CAB]<sub>o</sub> [AML]  $[H^+]^{0.47}$ . On the basis of experimental results a suitable mechanism and appropriate rate law have been derived.

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Table 1- Effect of varying oxidant, substrate and HClO<sub>4</sub> concentrations on reaction rate at 298 K

10 <sup>4</sup> [CAB] <sub>o</sub>	10 <sup>3</sup> [AML]	10 <sup>2</sup> [HClO <sub>4</sub> ]	$10^4  k$	
$(\text{mol dm}^{-3})$	$(\text{mol dm}^{-3})$	$(\text{mol dm}^{-3})$	$(s^{-1})$	
0.5	2.0	2.0	3.76	
1.0	2.0	2.0	3.88	
2.0	2.0	2.0	3.92	
4.0	2.0	2.0	3.93	
6.0	2.0	2.0	3.80	
2.0	0.5	2.0	1.26	
2.0	1.0	2.0	2.01	
2.0	2.0	2.0	3.92	
2.0	3.0	2.0	5.84	
2.0	4.0	2.0	8.16	
2.0	2.0	0.5	2.17	
2.0	2.0	1.0	3.16	
2.0	2.0	2.0	3.92	
2.0	2.0	3.0	5.05	
2.0	2.0	4.0	6.04	

Table 2 - Effect of varying dielectric constant on the reaction rate.

% MeOH (v/v)	$10^4 k^{(s^{-1})}$		
0	3 92		
5	4.85		
10	6.02		
20	7.25		
30	8.13		

Table 3 - Effect of varying temperature on the reaction rate and activation parameters.  $[CAB] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$ ,  $[BS] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$ ,  $[BS] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$ ,  $[BC] = 0.2 \text{ mol dm}^{-3}$ .

Temperature (K)	$10^4 k' (s^{-1})$	
283	2.56	
288	3.05	
298	3.92	
308	6.18	
313	7.26	
$E_a / kJ mol^{-1}$	25.5	
$\Delta H^{\neq} / \text{kJ mol}^{-1}$	23.0	
$\Delta G^{\neq} / \text{kJ mol}^{-1}$	92.5	
$\Delta S^{\neq}/ \mathrm{JK}^{-1} \mathrm{mol}^{-1}$	- 233	
Log A	6.72	

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



Scheme 2. Detailed mechanistic interpretation for the oxidation of amylocaine hydrochloride by CAB in acid medium.