

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

J.P. Shubha^{1*}, M. Dinamani², P.C. Paramesh³, Puttaswamy⁴

¹Department of Chemistry, Don Bosco Institute of Technology, Mysore Road, Bangalore, India

¹Department of Chemistry, Dayananda Sagar College of Engineering, Kumarasawmy Layout, Bangalore, India

³Department of Chemistry, Stracey Memorial PU College, St. Marks Road, Bangalore, India

⁴Department of Chemistry, Bangalore University, Central College, Bangalore, India

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 hydrochloride by sodium N-chlorobenzenesulfonamide (chloramine-B or CAB) has been carried out in HClO₄ medium at 298 K in order to explore this redox system mechanistic chemistry. The rate shows a first-order dependence on both [CAB]₀ and [substrate]₀, 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-haloarylsulfonamides, generally known as N-haloamines is due to their ability to act as sources of halonium cations, hypohalites, and N-anions which act as bases, nucleophiles and nutrenoids¹⁻⁵. 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 oxidants¹. 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⁺ 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 investigated⁶⁻¹⁰. 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 cocaine¹¹⁻¹³. 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 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

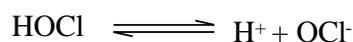
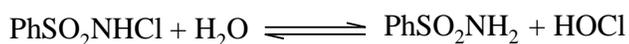
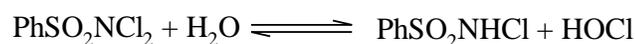
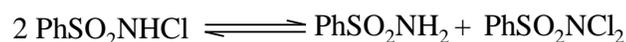
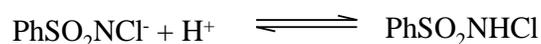
An aqueous solution of CAB (Aldrich) was prepared and stored in brown bottles to prevent its photochemical deterioration. AML (Alfa Chem) was used as received and an aqueous solution of AML was freshly prepared whenever required. Solvent isotope studies were made with D₂O, 99.4 % supplied by BARC, Mumbai, 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]₀ >> [oxidant]₀) at constant

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 (Figure 1; $r = 0.9922$) with a positive slope. The values of permittivity (dielectric constant) for MeOH–water mixtures reported in the literature were employed¹⁴. Blank experiments run with methanol indicated negligible oxidation under the experimental conditions employed.

The solvent isotope effect⁹⁻¹⁰ was studied in D_2O , where $k' = 4.93 \times 10^{-4} \text{ s}^{-1}$ in D_2O medium and $4.90 \times 10^{-4} \text{ s}^{-1}$ in water leading to a solvent isotope effect, $k' (H_2O) / k' (D_2O) = 1.01$. 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.

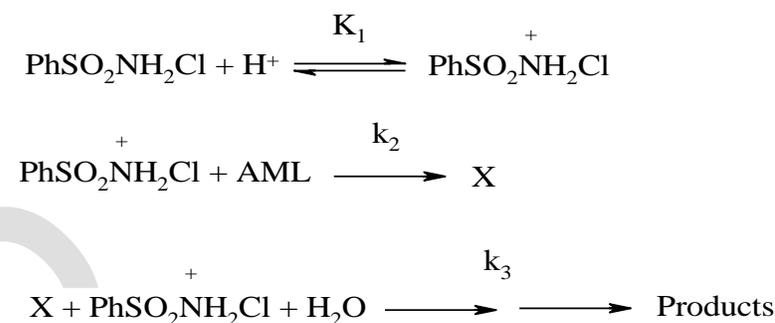
CAB is analogous to CAT and exhibits similar equilibria in aqueous acidic and basic solutions¹⁵⁻¹⁷. In general CAB undergoes a two electron change in its reactions forming the reduction products, benzenesulfonamide (BSA; $PhSO_2NH_2$) and NaCl. The oxidation potential of CAB-BSA redox couple varies¹⁵ 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:



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^- .

The first-order dependence of rate on $[CAB]_0$ 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 employed¹⁶⁻¹⁷. 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 ($PhSO_2NH_2Cl^+$) 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.



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 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 following rate law has been proposed, which is in good agreement with the experimental results. ... (5)

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

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

Reactions in aqueous medium that are susceptible to acid-base 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 D₂O medium. For a reaction involving a fast equilibrium with H⁺ or OH⁻ ion transfer, the rate increases in D₂O medium since D₃O⁺ and OD⁻ are a stronger acid and a stronger base respectively, than H₃O⁺ and OH⁻ ions¹⁸⁻²⁰. The observed solvent isotope effect of $k'(H_2O) / k'(D_2O) < 1$ is due to the greater acidity of D₃O⁺ compared to H₃O⁺. However, the magnitude of increase in rate in D₂O 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⁺]. 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 monographs²¹⁻²⁵. For a limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis²⁴ 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 (PhSO₂NH₂) 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 ΔS^\ddagger 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]₀ [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 HClO₄ concentrations on reaction rate at 298 K

10^4 [CAB] ₀ (mol dm ⁻³)	10^3 [AML] (mol dm ⁻³)	10^2 [HClO ₄] (mol dm ⁻³)	10^4 <i>k</i> ' (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. $[CAB] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$, $[BS] = 2.0 \times 10^{-3} \text{ mol dm}^{-3}$, $[HClO_4] = 0.2 \text{ mol dm}^{-3}$.

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

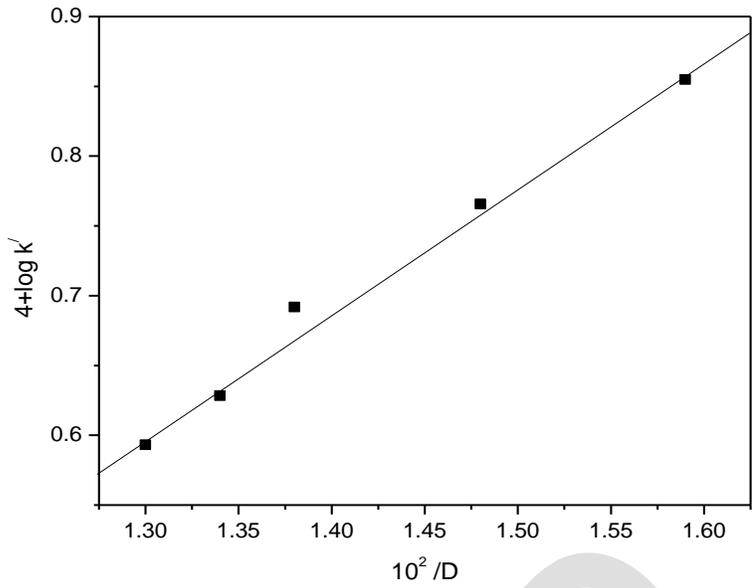


Fig. 1- Plot of $10^2/D$ versus $4+\log k'$

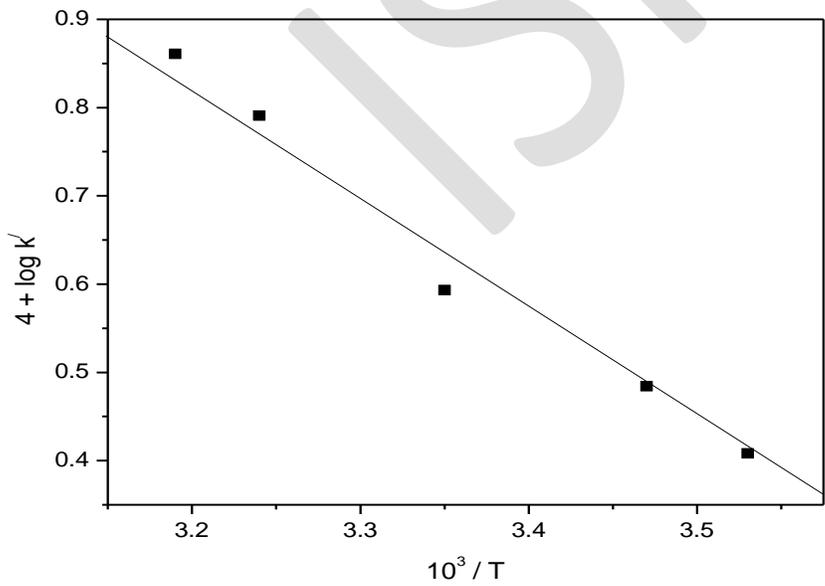
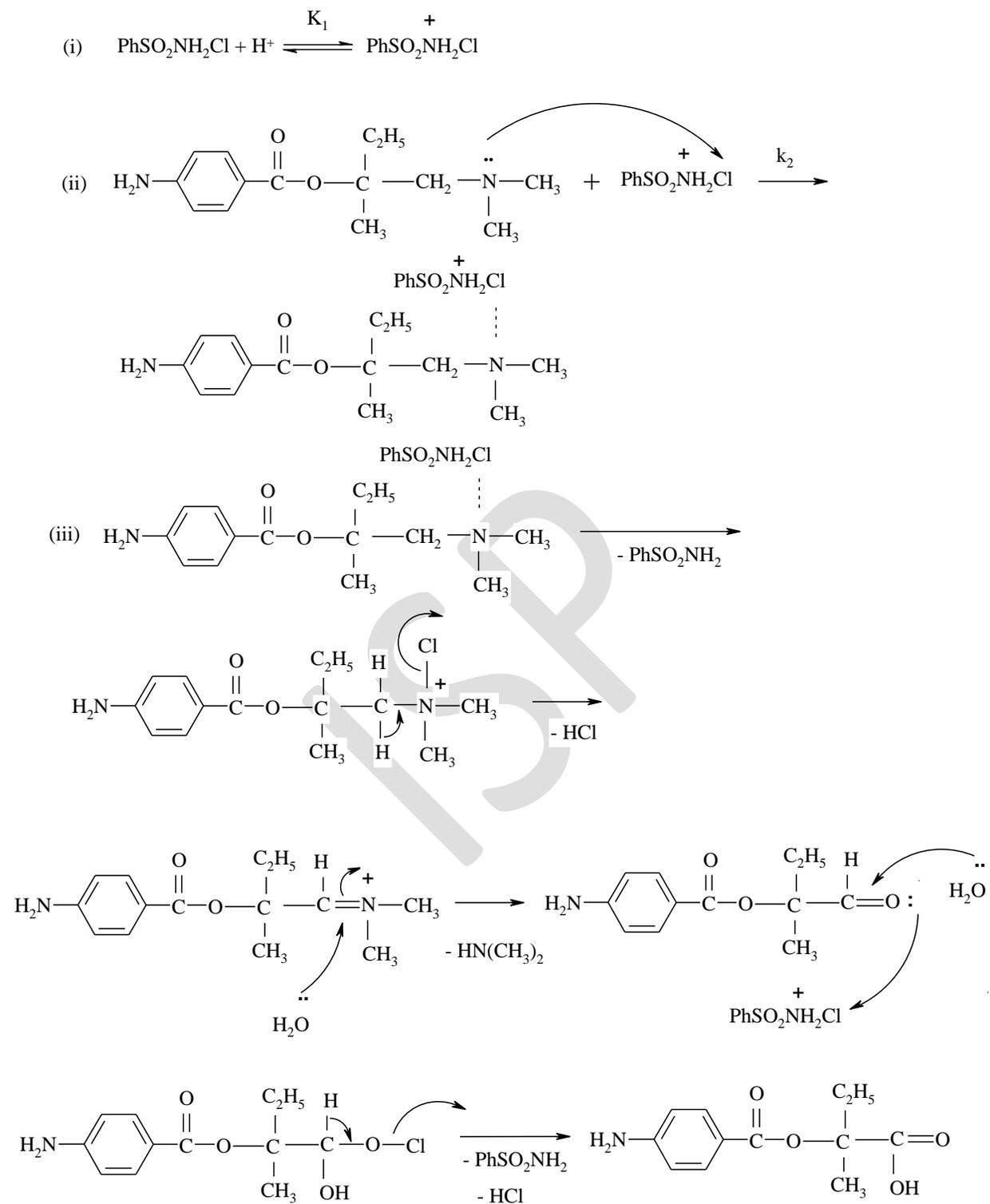


Fig. 2 Plot of $10^3/T$ versus $4+\log k'$



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