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Research Article

Oxidation of Tetracaine Hydrochloride by Chloramine-B in Acid Medium: Kinetic Modeling

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Tetracaine hydrochloride (TCH) is one of the potent local anaesthetics. A kinetic study of oxidation of tetracaine hydrochloride by sodium N-chlorobenzenesulfonamide (chloramine-B or CAB) has been carried in $HClO_4$ medium at 303 K. The rate shows first-order dependence on $[CAB]_o$, shows fractional–order dependence on $[substrate]_o$, and is self-governing on acid concentration. Decrease of dielectric constant of the medium, by adding methanol, increased the rate. 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 : 5 and the oxidation products were identified by spectral analysis. The conjugate free acid $C_6H_5SO_2NHCl$ of CAB is postulated as the reactive oxidizing species. The observed results have been explained by plausible mechanism and the related rate law has been deduced.

1. Introduction

Local anesthetics are drugs which produce reversible blockade of nerve impulse conduction. They act directly on specific receptors on sodium channels inhibiting sodium ion influx. Local anesthetics are valued for the ability to avoid membrane depolarization [1]. Tetracaine hydrochloride [2-dimethylaminoethy-4-n-butylaminobenzoate hydrochloride, TCH], an ester of p-aminobenzoic acid, has been widely used as local anaesthetic and is long-standing agent for spinal anaesthesia. In biomedical research, TCH is used to modify the function of calcium release channels (ryanodine receptors) that control the release of calcium from intracellular stores. TCH is an allosteric blocker of channel function. At low concentrations, TCH causes an initial inhibition of spontaneous calcium release events, while at high concentrations, TCH blocks release completely [2, 3]. Hence tetracaine hydrochloride 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 TCH with any oxidant. Therefore the title investigation was undertaken.

The miscellaneous nature of chemistry of N-haloamines is a significance of their aptitude to act as sources of species, such as halonium cations, hypohalites, and N-anions which act as bases, nucleophiles, and nutrenoids [3–7]. They behave as mild oxidants and are suitable for the partial oxidation of several groups. As a result, these reagents react with a selection of functional groups distressing an array of molecular transformations. In general, monohaloamines undergo two electron changes while dihaloamines are four-electron oxidants [3]. The reduction products are the respective sulfonamide and NaCl or HCl. The outstanding member of this class of compounds is chloramine-T (CAT) and the other member is chloramine-B (sodium N-chlorobenzenesulfonamide or CAB). The N–Cl bond in CAT and CAB is highly polar and 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 [5, 6]. But there is meager information available in literature [7, 8] on the use of CAB. CAB is a stable compound with slightly higher active chlorine content than its analogue CAT. CAB is 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 reaction models and deliberate its redox chemistry in solution.

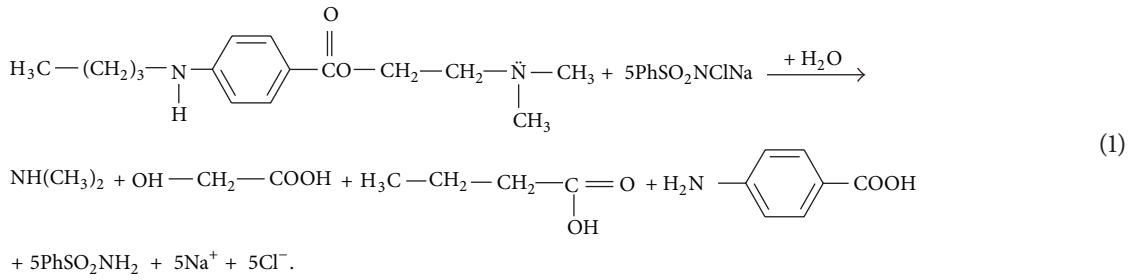
In the glow of the available information and in continuationof work on oxidation studies with organic chloramines in general and medicinal compounds in particular, the present investigations were undertaken. The main objectives of the present study are to (i) explicate plausible mechanisms, (ii) deduce suitable rate laws, and (iii) determine the various reactive species.

2. Experimental

2.1. Materials. An aqueous solution of CAB (Merck) was prepared and stored in brown bottles to prevent its photochemical deterioration [9]. TCH (Alfa Chem) was used as received and an aqueous solution of TCH 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.

2.2. Kinetic Procedure. Reactions were carried out under pseudo-first-order conditions were maintained for the kinetic runs ($[\text{substrate}]_o \gg [\text{oxidant}]_o$) at constant temperature 303 K in glass stoppered Pyrex boiling tubes coated black fromoutside to eliminate photochemical deterioration. A Raaga digital proportional temperature controller (CH-16) was used to maintain the desired temperature with an accuracy of ±0.1°C. The requisite amounts of solutions of substrate and $HClO_4$ solutions and water (for constant total volume) for all kinetic runs were equilibrated at 303 K for about 30 min. A measured amount of CAB also equilibrated at the same temperature was rapidly added to the reaction mixture which was periodically shaken for uniform concentration. The improvement 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^{-1}) calculated from the linear plots of log [CAB] versus time were reproducible within ± 3-4%.

2.3. Stoichiometry. Varying ratios of CAB to TCH were equilibriated at 303 K for 24 h in the presence of mol dm^{-3} $HClO_4$. The residual oxidant was determined by iodometry and the analysis showed that one mole of TCH consumed 5 moles of CAB as



(1)

2.4. Product Analysis. The TCH-CAB reaction mixture in the stoichiometric ratio in the presence of $HClO_4$ under stirred condition was allowed to progress for 24 h at 303 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 and chromatographic analysis (TLC technique) which revealed the formation of p-aminobenzoic acid (Figure 1), dimethylamine, and glycolic acid. These oxidation products were separated by column chromatography and were confirmed by GCMS analysis (molecular ion peak at 45, 76, 88, and 137 amu (Figure 1). It was also noticed that there was no further oxidation of these products under current kinetic conditions.

The reaction product of CAB, benzenesulfonamide, ($PhSO_2NH_2$) was detected [7] 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) and also confirmed by GCMS analysis (157 amu).

3. Results and Discussion

The kinetics of oxidation of TCH by CAB was investigated at several initial concentrations of the reactants at 303 K. Under pseudo-first-order conditions of $[\text{substrate}]_o \gg [\text{oxidant}]_o$ 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 from these plots are unaltered with variation of $[CAB]_o$, confirming the first-order dependence on $[CAB]_o$. The rate increased with the increase in $[\text{substrate}]_o$ (Table 1). A plot of $\log k'$ versus log [TCH] was linear (r = 0.9892, Figure 3) with a slope

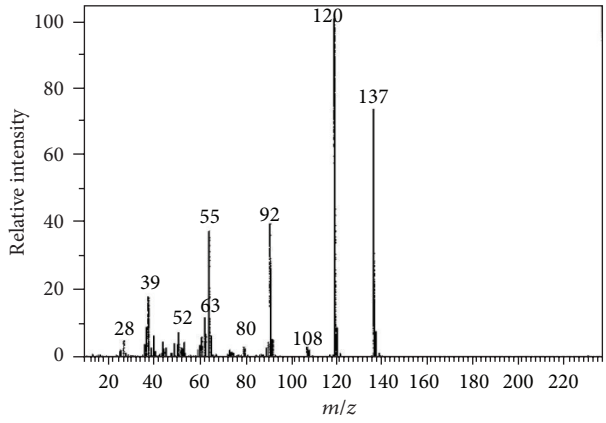


Figure 1: GC-mass spectrum of p-aminobenzoic acid with its molecular ion peak at 137 amu.

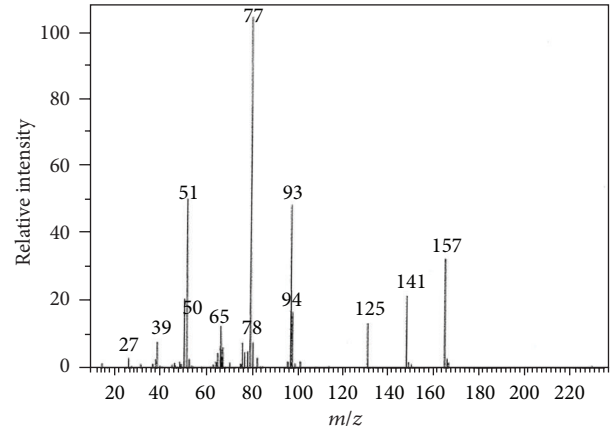


Figure 2: GC-Mass spectrum of benzenesulfonamide with its molecular ion peak at 157 amu.

Table 1: Effect of varying CAB, TCH, and $HClO_4$ concentrations on reaction at 303 K.

10^3 [CAB]$_o$ (mol dm^{-3})	10^2 [TCH] (mol dm^{-3})	10 [$HClO_4$] (mol dm^{-3})	$10^4 k'$ (s^{-1})
0.5	2.0	2.0	7.65
1.0	2.0	2.0	7.55
2.0	2.0	2.0	7.95
4.0	2.0	2.0	7.80
6.0	2.0	2.0	7.87
2.0	0.5	2.0	4.66
2.0	1.0	2.0	6.46
2.0	2.0	2.0	7.95
2.0	3.0	2.0	10.1
2.0	4.0	2.0	12.3
2.0	2.0	0.5	8.25
2.0	2.0	1.0	7.93
2.0	2.0	2.0	7.95
2.0	2.0	3.0	8.13
2.0	2.0	4.0	7.88

of 0.46 indicating a fractional-order dependence of the rate on $[TCH]_o$. Furthermore, a plot of k' versus $[TCH]_o$ is linear (r = 0.9864, Figure 4) with y-intercept, confirming fractional-order dependence on $[substrate]_o$. Values of k' are unaffected with the increase in $[HClO_4]$, indicating a zero-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}) and addition of Cl^- ion (4.0×10^{-2}–8.0×10^{-2} mol dm^{-3}) in the form of NaCl had no significant effect on the rate. The effect of ionic strength of the medium was studied by varying the sodium perchlorate concentration in a range of 0.10–0.30 mol dm^{-3} by keeping the other experimental conditions constant. It was found that ionic strength has a negligible effect on the reaction rate. Hence no attempt was made to keep ionic strength constant for kinetic runs.

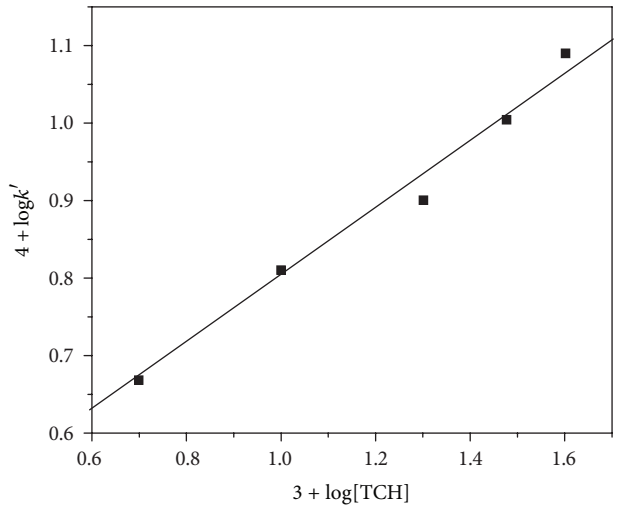


Figure 3: Plot of log k' versus log [TCH].

Table 2: Effect of varying dielectric constant of medium on the reaction rate at $[CAB]_o = 2.0 \times 10^{-3}$ mol dm^{-3}; $[TCH]_o = 2.0 \times 10^{-2}$ mol dm^{-3}; and $[HClO_4] = 0.2$ mol dm^{-3}; temp = 303 K.

% MeOH (v/v)	D	$10^4 k'$ (s^{-1})
0	76.73	7.95
5	74.50	8.42
10	72.37	9.75
20	67.48	11.4
30	62.71	12.7
40	58.06	15.9

The effect of dielectric constant (D) on the reaction rate was studied by adding various proportions of methanol (0–40% v/v) to the reacting system. It was observed that an increase in methanol composition in the reaction system

Table 3: Effect of varying temperature on the reaction rate and activation parameters for the oxidation of tetracaine hydrochloride in acid medium at $[CAB]_o = 2.0 \times 10^{-3}$ mol dm^{-3} ; $[substrate]_o = 2.0 \times 10^{-2}$ mol dm^{-3}; and $[HClO_4] = 0.2$ mol dm^{-3}.

Temperature (K)	$10^4 k'$ (s^{-1})
283	4.56
293	6.31
303	7.95
313	10.3
323	13.6
E_a/kJ mol^{-1}	46.0
$\Delta H^{\neq}$ /kJ mol^{-1}	43.7
$\Delta G^{\neq}$ /kJ mol^{-1}	93.2
$\Delta S^{\neq}$ /JK^{-1} mol^{-1}	−159

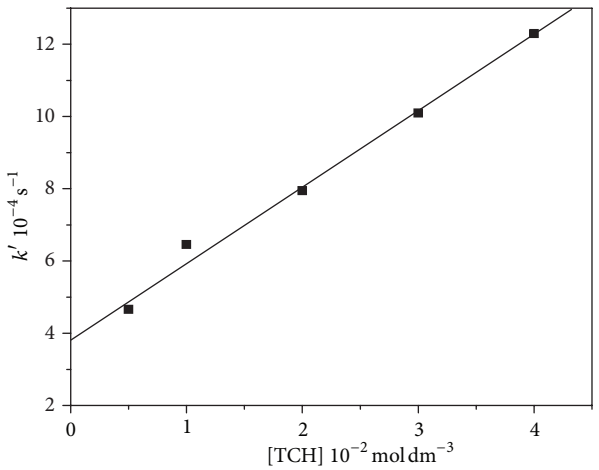


Figure 4: Plot of k' versus [TCH].

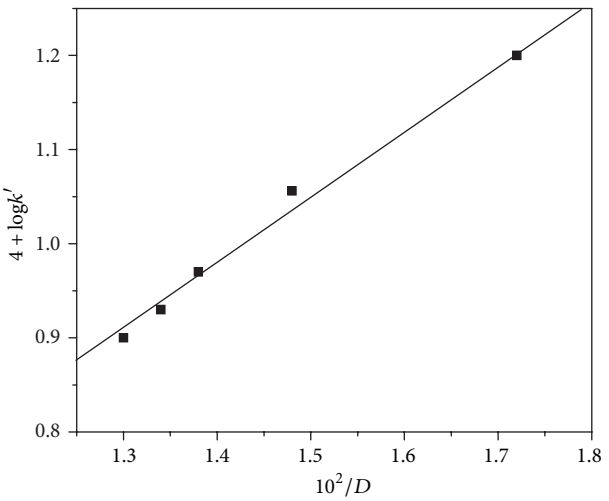


Figure 5: Plot of $\log k'$ versus $1/D$.

increased the reaction rate (Table 2) and a plot of $\log k'$ versus $1/D$ was linear (Figure 5; $r = 0.9926$) with a positive slope. The values of permittivity (dielectric constant) for MeOH-water mixtures reported in the literature were employed [9]. Blank experiments run with methanol indicated negligible oxidation under the experimental conditions employed. The solvent isotope effect was studied in D_2O, where $k' = 7.95 \times 10^{-4}$ s^{-1} in D_2O medium and 7.95×10^{-4} s^{-1} in water leading to a solvent isotope effect, k' (H_2O)/k' (D_2O) = 1.07.

The reaction was studied at different temperatures (283–323 K), keeping other experimental conditions constant. From the linear Arrhenius plot of $\log k'$ versus $1/T$ ($r = 0.9921$, Figure 6), values of activation parameters (E_a, $\Delta H^{\neq}$, $\Delta S^{\neq}$, and $\Delta G^{\neq}$) 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 [5, 8, 10, 11]. 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 varies [12] 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

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

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

$$2PhSO_2NHCl \rightleftharpoons PhSO_2NH_2 + PhSO_2NCl_2 \quad (4)$$

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

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

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

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

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 $[CAB]_o$ 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 (4) and (6). Further, these species are present in very low concentrations at the experimental conditions employed. 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 above discussion and experimental observation, the following general scheme involving the direct interaction of the substrate with $PhSO_2NHCl$ (Scheme 1) is proposed. A fractional order dependence on $[substrate]_o$ indicates a prior equilibrium followed by the rate determining step.

In Scheme 1, X is a CAB-TCH complex species and X′ is another intermediate complex species whose structures

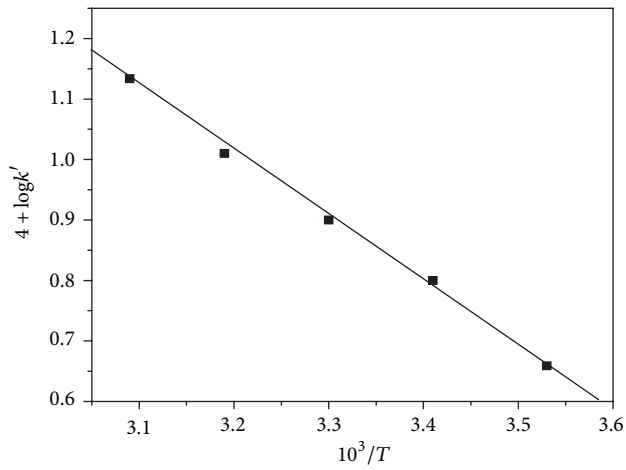


FIGURE 6: Plot of $\log k'$ versus $1/T$.

$$\mathrm{PhSO_2NHCl + TCH} \rightleftharpoons \mathrm{X} \quad \text{(i) Fast}$$

$$\mathrm{X} \longrightarrow \mathrm{X'} \quad \text{(ii) Slow and rate determining}$$

$$\mathrm{X' + 2\ PhSO_2NHCl} \longrightarrow \mathrm{Products} \quad \text{(iii) Fast}$$

SCHEME 1: A general mechanistic scheme for the oxidation of tetracaine hydrochloride by CAB in acid medium.

are shown in Scheme 2, where a detailed mechanistic interpretation of procaine hydrochloride oxidation by CAB in acid medium is proposed. In this, the conjugate-free acid ($PhSO_2NHCl$) directly reacts with the substrate in a fast equilibrium step to form the substrate-oxidant complex (X). This decomposes in a rate-determining step to the products. Five moles of the oxidant is consumed to yield the ultimate products.

Step (ii) of Scheme 1 determines the overall rate,

$$\text{rate} = \frac{-d\,[\mathrm{CAB}]}{dt} = k_2\,[\mathrm{X}]\,. \tag{9}$$

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

$$[\mathrm{CAB}]_t = \left[\mathrm{PhSO_2NHCl}\right] + [\mathrm{X}]\,, \tag{10}$$

from which solving for [X] and substituting its value in (9), rate law (11) can be derived

$$\text{rate} = \frac{K_1 k_2 [\mathrm{CAB}]_t\,[\mathrm{TCH}]}{1 + K_1\,[\mathrm{TCH}]}. \tag{11}$$

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

Since rate $= k'[\mathrm{CAB}]_t$, rate law (11) can be transformed into (12) and (13) as follows:

$$k' = \frac{K_1 k_2\,[\mathrm{TCH}]}{1 + K_1\,[\mathrm{TCH}]}, \tag{12}$$

$$\frac{1}{k'} = \frac{1}{K_1 k_2\,[\mathrm{TCH}]} + \frac{1}{k_2}. \tag{13}$$

Based on rate law (13), a plot of $1/k'$ versus 1/[TCH] at constant $[\mathrm{CAB}]_o$, $[H^+]$, and temperature was found to be linear (Figure 2; $r = 0.9934$). From the intercept and slope of this plot, the formation constant (K_1) and the decomposition constant (k_2) of the substrate-oxidant species were found to be 10.9 $\mathrm{dm^3\ mol^{-1}}$ and $6.67 \times 10^{-3}\ \mathrm{s^{-1}}$, respectively.

3.1. Michaelis-Menten Kinetics. Since the rate was fractional-order in $[\mathrm{TCH}]_o$, Michaelis-Menten type of kinetics [13] was adopted. The TCH was varied in the concentration range of 0.5×10^{-2}–$4.0 \times 10^{-2}\ \mathrm{mol\,dm^{-3}}$ at different temperatures (283–313 K), with all other experimental conditions being held constant. Based on (13), plots of $1/k'$ versus 1/[TCH] were found to be linear ($r > 0.9851$).

For a reaction involving a fast preequilibrium H^+ or OH^- ion transfer, the rate increases in D_2O since D_3O^+ and OD^- are 2 to 3 times stronger acids and stronger bases [12–14], respectively, than H_3O^+ and OH^- ions. The reverse holds good for reactions involving retardation of rate by H^+ or OH^- ions. In the present case, solvent isotope studies show that $k'\,(H_2O)/k'\,(D_2O) \approx 1$ and this is generally correlated with the fact that the negligible effect of $[H^+]$ on the rate of reaction. Hence the observed solvent isotope effect supports the proposed mechanism and the derived rate expression.

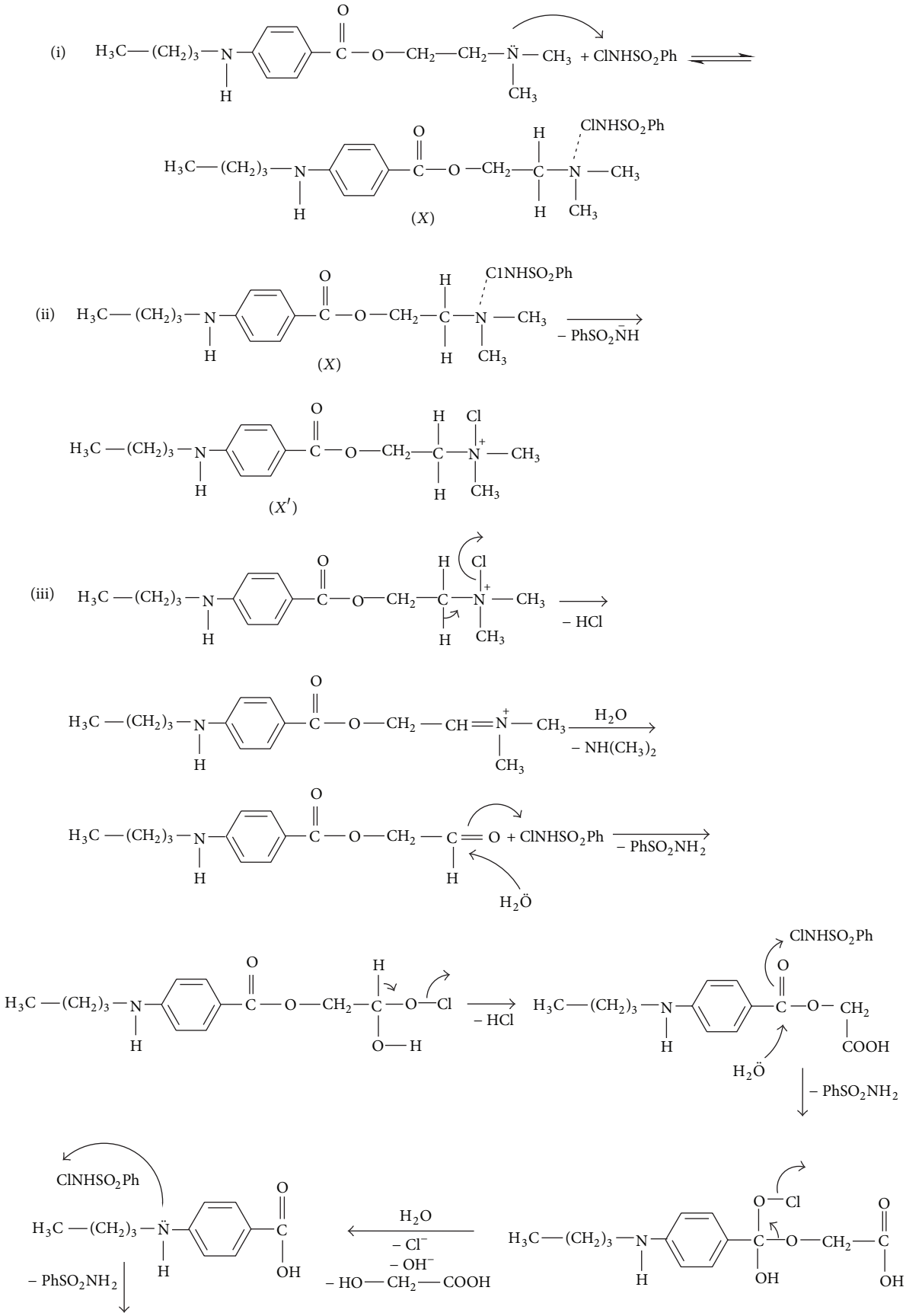
The effect of varying solvent composition on the reaction kinetics has been described in detail in the well-known monographs [15–25]. For a limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis [23] has shown that a plot of $\log k'$ versus $1/D$ gives a straight line 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-limiting step of Scheme 2.

The influence of the ionic strength of the medium on the rate is negligible indicating that nonionic species are involved in the rate limiting step. The reaction product, benzenesulfonamide ($PhSO_2NH_2$), does not influence the rate showing that it is not involved in a preequilibrium. 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.

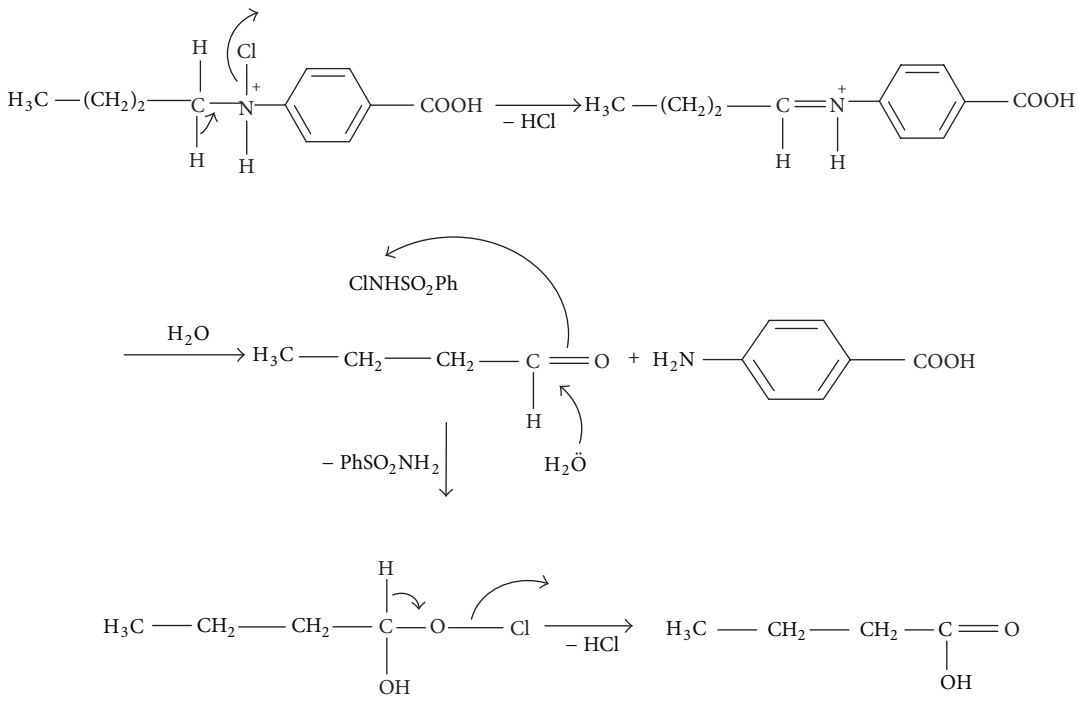
The proposed mechanism is also supported by the moderate values of energy of activation and other activation parameters. The fairly high positive value of free energy of activation indicates that the transition state is highly solvated, while the large negative $\Delta S^{\neq}$ suggests the formation of a compact activated complex with a reduction in the degrees of freedom of molecules.

4. Conclusion

The kinetics of oxidation of tetracaine hydrochloride by CAB has been studied at 303 K. The reaction follows the rate law rate $= k[\mathrm{CAB}]_o[\mathrm{TCH}]^x$, where x is less than unity. On the basis of experimental results, a suitable mechanism and appropriate rate law have been derived.



Scheme 2: Continued.



Scheme 2: Detailed mechanistic interpretation of oxidation of tetracaine hydrochloride by CAB in $HClO_4$ medium.

Conflict of Interests

The authors do not have any conflict of interests.

Acknowledgments

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