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OXIDATIVE CONVERSION OF CHLOROPROCAINE HYDROCHLORIDE TO O-CHLORO-P-AMINOBENZOIC ACID BY BROMAMINE - B IN ALKALINE MEDIUM: STUDY OF KINETIC, MECHANISTIC, AND REACTIVITY

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Abstract

In this study, rate = k[oxidant]o [CPL]o [NaOH]x is the rate law applied, At 298 K, BAB kinetically oxidized the chloroprocaine hydrochloride. An appropriate rate law and mechanism were discovered using experimental data. The products of oxidation were found. Decomposition constants and composition activation parameters were computed. Kinetic modeling and mechanical routes have been computed for this redox system. This approach has a lot of industrial promise because of its mild reaction conditions, excellent product yields, and ease of use and experimentation.

Keyword: Kinetic, chloroprocaine hydrochloride, Kinetic modeling

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1. Introduction

Chloroprocaine (CP) is the preferred local anaesthetic for surgical procedures and labour and delivery due to its minimal maternal and foetal toxicity, rapid onset, and short duration of action [1]. 2-Chloroprocaine is a short-acting amino-ester local anaesthetic [2]. It has been

successfully used for spinal anaesthesia since its introduction in 1952. Following many instances of neurological impairments in patients who received excessive intrathecal CP during epidural labour analgesia, the medicine was withdrawn from the market in the 1980s. Animal studies established the safety of the preservative-free formulation, which has been thoroughly evaluated in both voluntary trials and clinical practise, demonstrating a favourable safety and efficacy profile. When compared to bupivacaine, 2-chloroprocaine (2-CP) demonstrated faster offset times to the end of anaesthesia, independent ambulation, and hospital discharge. These data imply that 2-CP may be a viable option to modest dosages of long-acting local anaesthetics in ambulatory surgery. Additionally, the safety profile suggests that 2-CP may be a viable alternative to intrathecal short- and intermediate-acting local anaesthetics such as lidocaine and mepivacaine, which frequently produce temporary neurological symptoms [3].

Arylhalosulfonamides, commonly known as organic haloamines, are versatile redox titrators [4]. N-anions that are bases, nucleophiles, and nucleosides are all examples of organic haloamines that can be used [5]. The two most important chloramine compounds are sodium N-chloro-p-toluene sulfonamide (CAT) and sodium N-chlorobenzenesulfonamide (NCBS). Every one of these reactions has a mechanistic basis. Initially, research concentrated on CPH oxidation using CAT in alkaline medium. These redox systems were shown to be extremely slow in kinetic measurements in several experimental setups. Then we contemplated using BAB as an oxidant and carried on with the hypothesis reactions, which we enjoyed. Thus, BAB is a potent oxidant in the conversion of CPH to O-Chloro-P-Aminobenzoic Acid [6]. Using an alkaline media, BAB may quickly oxidise CPH to p-aminobenzanoic acid, diethylamine, and glycolic acid.The kinetics and mechanics of CPL with BAB reactions in alkaline medium are being studied for the first time.The purpose of this research programme is to conduct oxidation-kinetic studies with the following objectives: (i) accumulating kinetic data, (ii) classifying oxidation products, (iii) developing rigorous kinetic models, (iv) formulating elegant systems, (v) identifying various reactive species, and (vi) deriving thermodynamic parameters.

Materials and Methods

2.1. Material and reagents

The appropriate evaluations for pure chloroprocaine hydrochloride obtained from Sigma – Aldrich and Chloramine-B obtained from (E. Merck). Bromamine – B is synthesised via

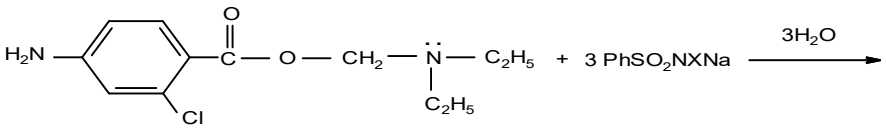
bromination of CAB. The reaction product is identified as Dibromamine-B, which is followed by partial debromination to yield bromamine-B [7,8]. BAB's purity is determined iodometrically using its active bromine content, and the 13C FT-NMR spectrum confirms the compound's identity. There were solvent isotope investigations utilizing 99.4 % pure D2O from the Bhabha Atomic Research Centre in India. Double-distilled water was used throughout, as well as analytical grade chemicals.

Kinetic procedure

Pyrex bubble cylinders with a darkened external surface were used to preserve the pseudo-first-order condition at 30±0.1°Cunderneath the conditions ([CPH]o>>[BAB]o). After 30 minutes at 30±0.1°C (to keep the volume constant (50 ml) for all runs), oxidant and imperative readings of NaOH substrates were taken. When the reaction was initiated, the purposeful dose of BAB in the liquid was increased rapidly while it was shaken to keep a constant concentration. BAB unconsumed in known quantities (5ml each) was added to the reaction mixture to determine the reaction's progress, which was measured using iodometric titrations. They were tracked for over two-thirds of their lifetimes. After using straight plots of log [BAB] versus time graphing is done to calculate the pseudo first-order rate constant (k',s-1), the results had a 94% repeatability rate. A scientific calculator, the fx-350TL, was used to calculate it.

Stoichiometry

At 293 K, multiple groups of reaction combinations comprising varying concentrations of oxidant and substrate and NaOH is present in concentrations of 5.8x10-4mol dm-3 were held for 24 hours . Iodometric analysis of BAB that was not consumed indicates that three moles of oxidant are required to convert one mole of CPH to the equivalent p-aminobenzoic acid, diethylamine, and glycolic acid, showing a 1:3 stoichiometry. The stoichiometry observed is



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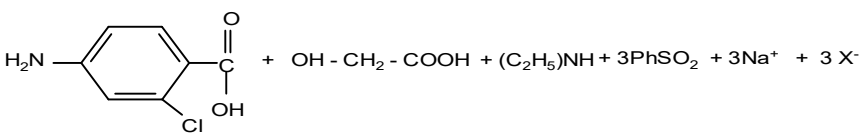


Equation 1: Three products that result from oxidation in the reaction: p-aminobenzoate, diethylamine, and glycolic acid.

Product analysis

Alkali was employed to neutralise the reaction products, and ether was used to remove them. Spot tests [9] and chromatographic analysis (TLC method) were performed on the organic compounds, which demonstrated that CPL was oxidized, and it is confirmed by GC–MS. The Shimadzu 17A gas chromatograph and Shimadzu QP-5050A electron-sway mass spectrometer was used to acquire the GC–MS findings. There are 171, 73, and 76 amu peaks of molecular ions indicating o-chloro-p-aminobenzoic acid, which is shown in Figure 1, diethylamine in Figure 2. and glycolic acid in Figure 3. As a result of the prevailing kinetic conditions, it was concluded that these compounds did not go through any more oxidation processes. Ethanol was used to extract BAB, which was then separated by TLC, utilising a dissolvable oil ether-CHCl3-1-butanol framework, with iodine as the spray reagent (Rf =0.88). The existence of benzenesul fonamide was further confirmed by the molecular ion signal at 157 amu.

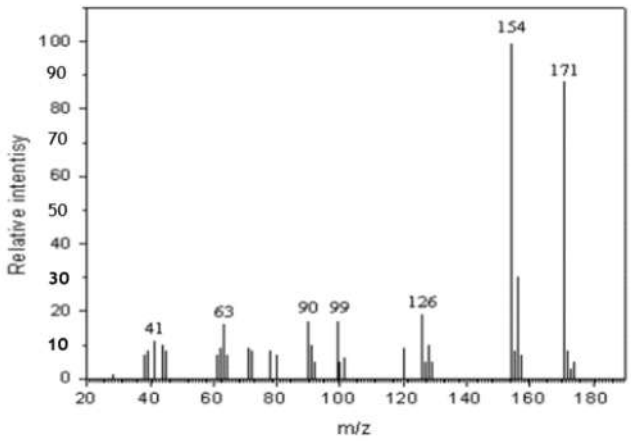


Figure 1. GC-Mass spectrum of o-chloro-p-aminobenzoic acid with its peak at 171 amu

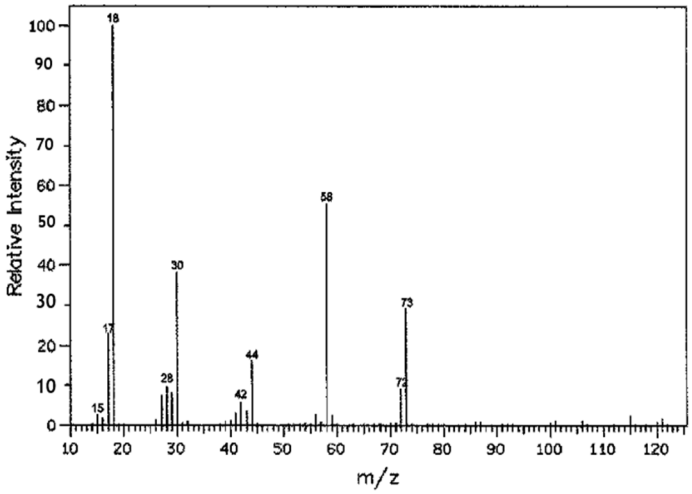


Figure 2. GC-Mass spectrum of diethylamine with peak at 73 amu

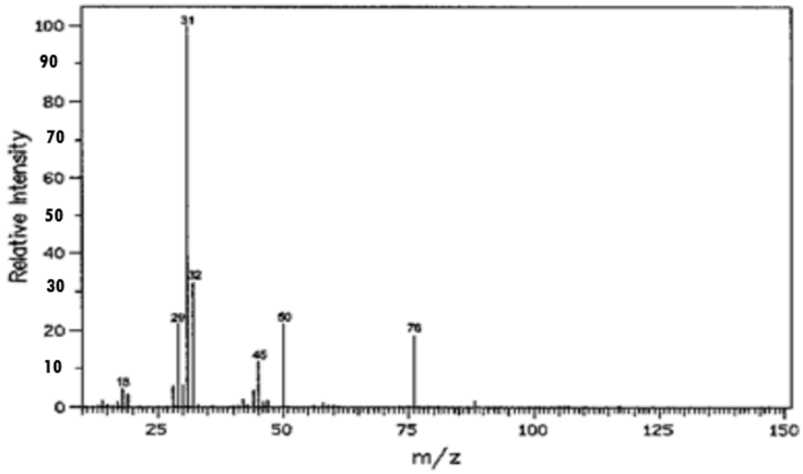


Figure 3. GC – Mass spectrum of glycolic acid with its peak at 76 amu

Kinetic Results

Bromamine - B converts chloroprocaine hydrochloride to o-chloro p-aminobenzoic acid in alkaline media by maintaining [CPL] = 1.8X 10^{-2} mol dm^{-3}; [BAB] = 2.0 X 10^{-3} mol dm^{-3}; [NaOH] = 5.8 X 10^{-4} mol dm-^{3}

Effect of reactant rate on the reaction constant

The kinetic run was carried out with a stoichiometric excess of substrate at constant [NaOH] and [CPL]. Plots of log [BAB] versus time were linear with a slope equal to unity, suggesting that the reaction rate is first order dependent on [BAB]. Table 1 shows the significance of the

pseudo first order rate constant k' below the identical investigational environments. Increases in [CPL] have improved the amount of influence on the rate, demonstrating that [CPL] is first–order dependent on the rate. In addition to that k' versus $[CPL]_o$ plots were also linear, indicating a first-order dependence on $[CPL]_o$ and the transitory existence of intermediates created. The reaction rate declined as [NaOH] increased (Table 1), and a plot of log $k^{/}$ vs log $[OH^-]$ was linear (figure 5) with a negative slope of 0.35, indicating a rate dependency on [NaOH] on a fractional order basis.

Table 1. Effect of concentrations of BAB, CPL, NaOH on the rate at 293K

10^3 $[BAB]_o$ (mol dm^{-3})	10^2[CPL] (mol dm^{-3})	10^4[NaOH] (mol dm^{-3})	10^4K' (mol dm^{-3})
0.5	1.8	5.8	1.46
1.0	1.8	5.8	1.54
2.0	1.8	5.8	1.58
4.0	1.8	5.8	1.61
6.0	1.8	5.8	1.59
2.0	0.6	5.8	0.69
2.0	1.2	5.8	1.24
2.0	1.8	5.8	1.58
2.0	3.4	5.8	2.83
2.0	6.4	5.8	4.51
2.0	1.8	0.8	5.2
2.0	1.8	2.4	4.87
2.0	1.8	6.8	3.54
2.0	1.8	12	1.96
2.0	1.8	20	0.59

[CPL] = 1.8X 10^{-2} mol dm^{-3}; BAB] = 2.0 X 10^{-3} mol dm^{-3}; [NaOH] = 5.8 X 10^{-4} mol dm^{-3}

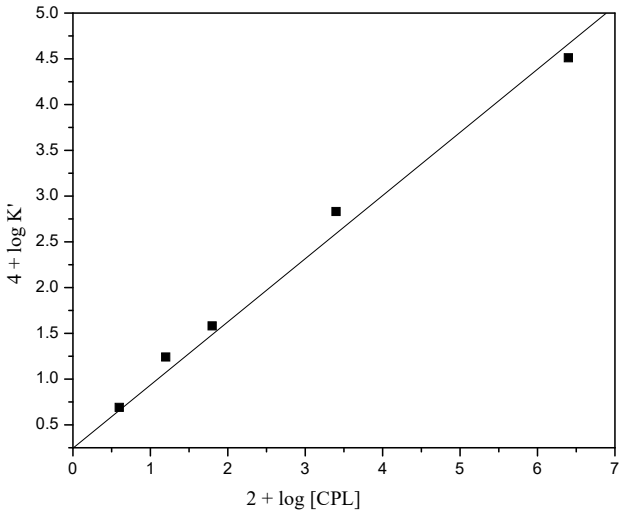


Figure 4. Plot of 2 + log [CPL] versus 4+log k/.

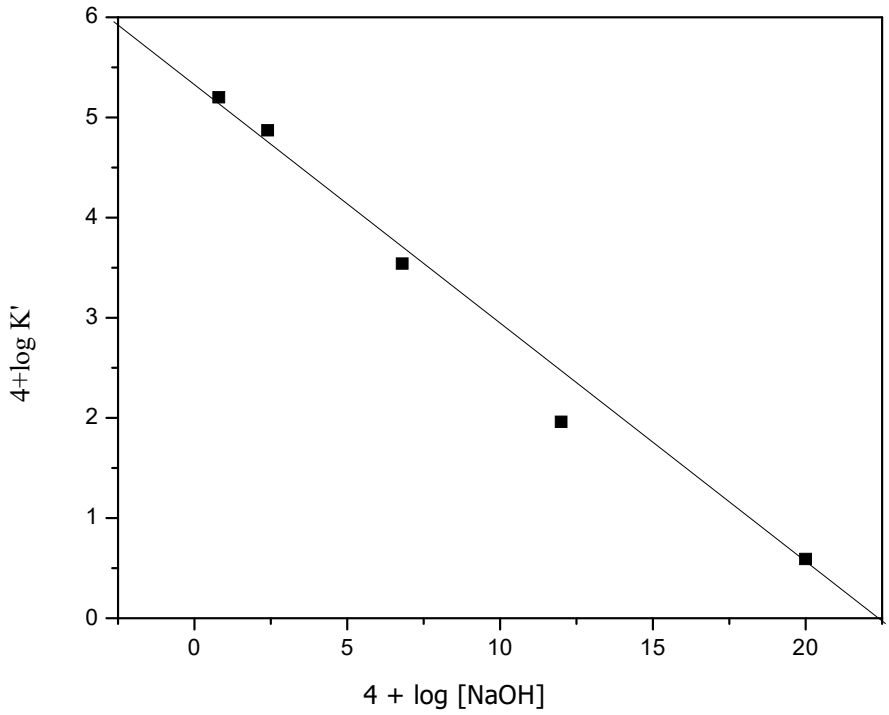


Figure 5. Plot of 4 + log [NaOH] versus 4+log k/.

The result of concentration of benzenesulfonamide,

When varied amounts of the reaction mixture are used, the addition of benzenesulfonamide ($PhSO_2NH_2$) has no effect on the rate (4.8×10^{-3} mol dm^{-3}). This shows that $PhSO^2NH^2$ is not involved in any reaction prior to the rate-determining step. Changes in halide ion concentration

affect reaction rate. When [OH^-] was kept constant using NaOH, adding NaCl or NaBr had no influence on the reaction rate.

Effect of the medium dielectric permittivity on the reaction rate

The dielectric permittivity of the reaction medium was changed by adding methanol (0–30% v/v). The rate dropped as the dielectric permittivity of the reaction mixture increased, as indicated in Table 2. In Figure 6, where D denotes the medium's dielectric permittivity, there was a linear connection with a negative slope.

Table 2. An experiment at 298 K shows how dielectric constant affects reaction rate

% CH_3OH	D	$10^3K'$ (mol dm^{-3})
0	76.73	1.58
10	72.37	1.35
20	67.48	1.18
30	62.71	0.771
40	58.06	0.23

[CPL] = 1.8X 10^{-2} mol dm^{-3}; BAB] = 2.0 X 10^{-3} mol dm^{-3} ; [NaOH] = 5.8 X 10^{-4} mol dm^{-3}

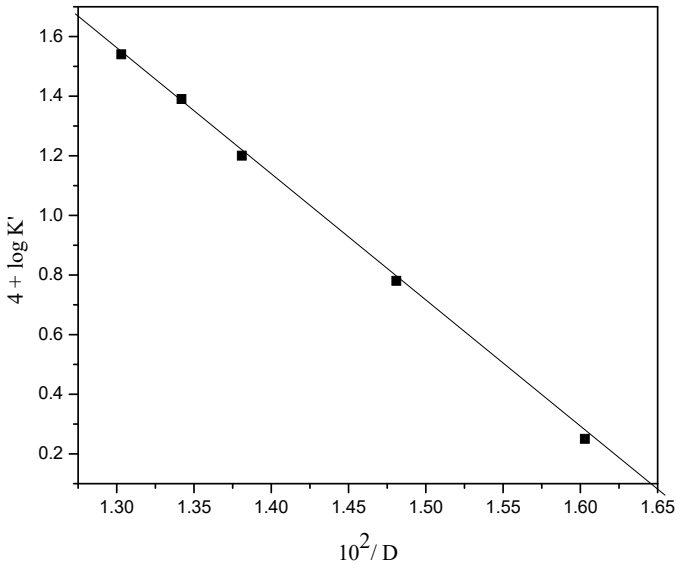


Figure 6. Plot of 10^2/D versus 4+log k/.

Inhibition of a reaction by temperature

When all other factors were held constant, the reaction was examined at various temperatures (288-313 K). A plot of log k/ vs. 1/T with an Arrhenius coefficient of 0.9934 was used to determine the activation parameters Ea, $\Delta H^{\neq}$, $\Delta S^{\neq}$, $\Delta G^{\neq}$ and log A which are displayed in Table 3.

Table 3. Temperature dependence of chloroprocaine hydrochloride reaction rate as well as stimulation factors in alkaline media around 303 K

Temperature	$10^4\ k'(s^{-1})$
288	1.16
293	1.58
298	2.12
303	2.68
313	2.89
E_a(kJ mol^{-1})	35.5
$\Delta H^{\neq}$ (kJ mol^{-1})	31.8
$\Delta S^{\neq}$(JK^{-1} mol^{-1})	-192
$\Delta G^{\neq}$(kJ mol^{-1})	88.5

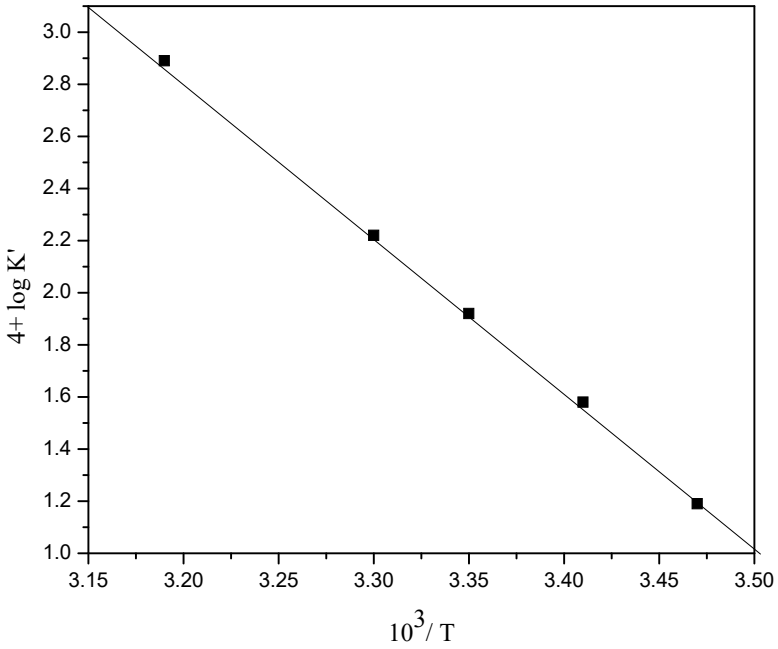


Figure 7. Plot of 103 / T versus 4 + log k/.

Study of Polymerization

To confirm that there were no free radical species formed in the reaction sequence, we added the reaction mixture to the monomer solution in an aqueous acrylamide.

Result and Discussion

Reactive groups of BAB in alkaline medium

Due to the comparable chemical characteristics of organic haloamines, it is predicted that their solutions will exhibit similar equilibria [11-13]. Bromamine-B, like chloramine-T and chloramine-B, operates as a solid electrolyte in both acidic and alkaline environments. In alkaline medium bromamine and dibromamine solutions($TsNBr_2$) does not exist. During the reaction in alkaline media, the oxidising species $PhSO_2NHBr$, $PhSO_2NBr$, and OBr^- might be converted to the more reactive oxidising species HOBr. Hardy and Johnston [14] established the following equilibria in an alkaline solution of BAB. If HOBr is the dominant oxidising species, the addition of benzenesulphonamide should result in first order rate retardation. However, this effect was not found. The retarding effect of the OH^- ion on the reaction rate indicates that several chloroanimometric reactions which are due to the synthesis of conjugate

acid, $PhSO_2NHBr$, and $PhSO_2NBr$ during the retarding step [15,16]. The inverse-fractional-order dependence of the rate on $[OH^-]$ and the absence of influence on the ratio of additional benzene sulphonamide strongly suggest that $PhSO_2NHBr$ is the most effective reactive species in the present investigation. To account for the observed kinetics, the following mechanism is proposed (Scheme 1):

$$PhSO_2N^-Br + H_2O \overset{K_1}{\rightleftharpoons} PhSO_2NHBr + OH^- \quad \text{(i) fast}$$

$$PhSO_2NHBr + S \xrightarrow{k_2} X \quad \text{(ii) slow \& rds}$$

$$X + 2PhSO_2NHBr \xrightarrow{k_3} \text{Products} \quad \text{(iii) fast}$$

Scheme 1

The rate law for Scheme 1 can be deduced as follows:

$$[BAB]t = [PhSO_2NBr^-] + [PhSO_2NHBr] \qquad (1)$$

By exchanging for $[PhSO_2NCl^-]$ from symmetry (i) of Scheme 6.1 in Equation (6.2) and resolving for $[PhSO_2NHBr]$, one gets

$$PhSO_2NHBr = \frac{K_1k_2\,[BAB]_t\,[H_2O]}{K_1[H_2O] + [OH^-]} \qquad (2)$$

As of System 1's slow/rate-determining stage,

$$\text{Rate} = k_2[PhSO_2NHBr]\,[CPL] \qquad (3)$$

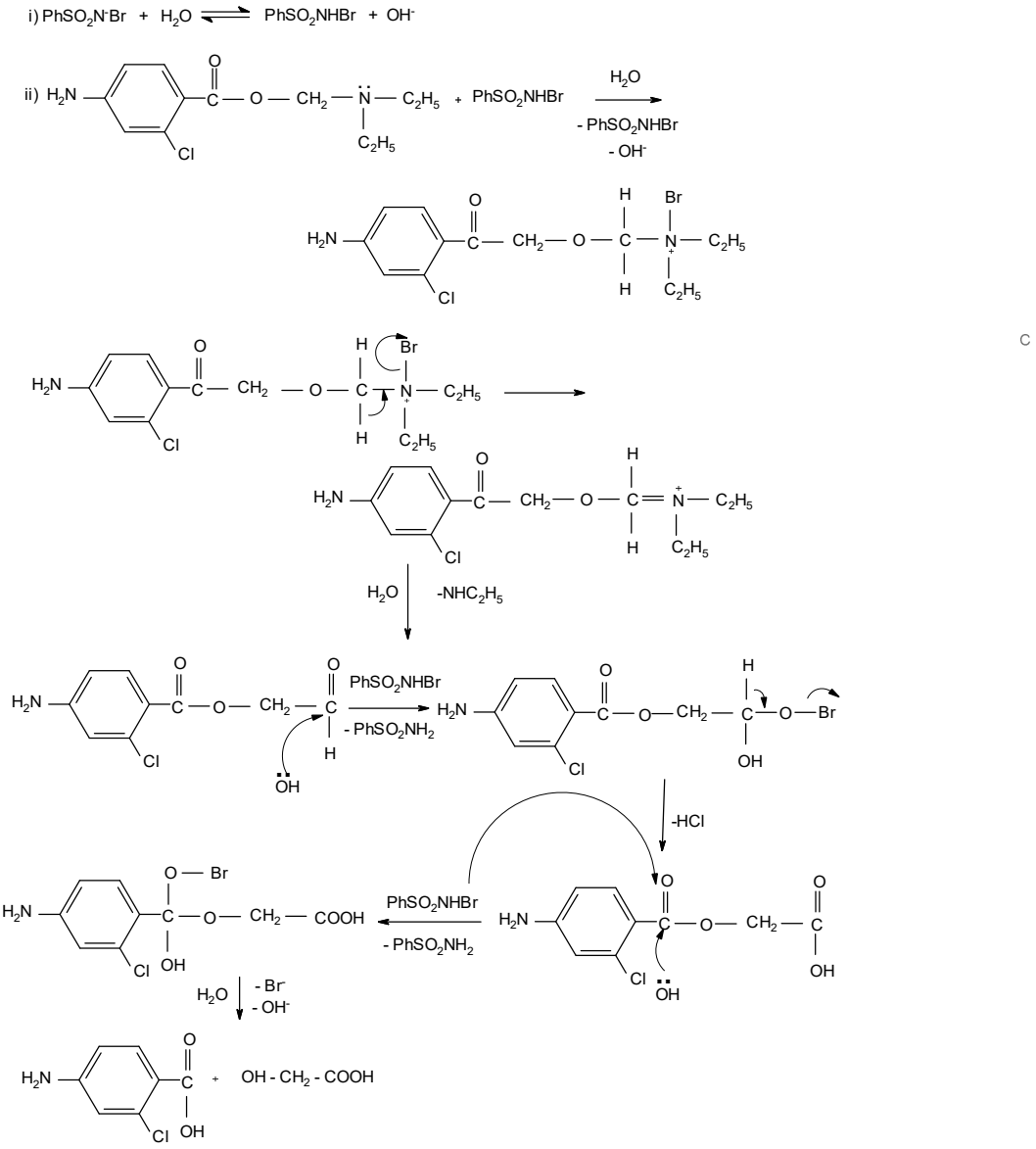
Substituting for $[PhSO_2NHBr]$ from Eqn (6.3) into Eqn (6.4), yields the following rate law:

$$\text{Rate} = \frac{K_1k_2\,[BAB]_t\,[CPL]\,[H_2O]}{K_1[H_2O] + [OH^-]} \qquad (4)$$

Rate law (4) is in good agreement with the observed experimental results.

Considering the foregoing, Scheme 2 can be constructed to account for the experimental data about the oxidation of CPL with BAB in alkaline media. In Scheme 2, an initial equilibrium phase (step(i)) involves the hydrolysis of BAB's anionic form, $PhSO_2NBr^-$, to generate the conjugate acid $PhSO_2NHBr$ in an OH^-retarding process. The following sluggish and rate-determining phase involves the assault of a lone pair of electrons on the nitrogen atom on the

bromine atom of the conjugate acid, resulting in the development of an intermediate complex (X) and the exclusion of p-benzenesulfonamide ($PhSO_2NH_2$). By a series of rapid steps (step(iii)), in the presence of a molecule of H_2O and another two moles of $PhSO_2NHBr$, this intermediate complex releases the final products, o- chloro-aminobenzoic acid, diethylamine, and glycolic acid.



Scheme 2: A detailed mechanism for the oxidation of CPL by BAB in NaOH medium

Reaction rate effects of dielectric and solvent isotope

Numerous articles have described the effect of the solvent on the reaction kinetics. An ion-dipole system with a zero angle of approach was explored by Amis [17]. The authour revealed that the slope of a log $k^{/}$ vs 1/D plot is undeviating, and that the slope of a log $k^{/}$vs 1/D plot is negative. The current study's log $k^{/}$ vs 1/D plot (Figure 6) confirms the rate-determining

mechanism outlined in Scheme 2, which involves a negative ion and a dipole. The influence of medium dielectric constant on reaction rate constant is theoretical. After attaining equilibrium, we explored acid-base catalysis processes in aqueous medium in heavy water (D_2O). Because the breaking of the C-H bond is required for most organic compound oxidation reactions, such processes are influenced by deuterium isotopic impact, which reveals the origin of the rate-determining phase. In the current study, studies with solvent isotopes showed that D_2O accelerates reaction rates. Because D_3O^+ besides OD^- ions remain more acidic also basic than H_3O^+ and OH^- ions, the rate of reaction rises in D_2O medium [18-21].The witnessed isotope consequence of $k^{/}(H_2O) / k^{/}(D_2O) < 1$ in the solvent is due to the higher acidity of D^3O^+ compared to H_3O^+. However, the rate rise of D_2O is minor equated to the projected value, which remains 2-3 intervals bigger. It is being connected to the rate dependence on [NaOH]. As a result of this discovery, the hypothesised mechanism is supported.

Effect of Ionic Strength of the Medium on the Reaction Rate

The effect of ionic strength on reaction rate will reveal details almost the charges intricate in the reaction. The influence of ionic strength (μ) on the rate of a reaction (k') between two ions (Z_A and Z_B) is provided by the equation [22].

$$\log k' = \log k_0 + 1.018\, ZAZB\mu^{1/2} \qquad (5)$$

k_0 is the rate constant for infinite dilution. A straight line with a slope of 1.018 ZAZB and an intercept=log k_o is obtaine when a plot of log k′ versus $\mu^{1/2}$ is done. The sign ZAZB determines the direction of the slope. When the responding species are of the same sign, the rate increases. The rate of reaction between ions of opposing signs reduces with ionic strength. The ionic pressure of the medium should have no effect on the rate constant of a neutral molecule. Adding $NaClO_4$ to the reaction mixture had no influence on rate in CPL. According to the Bronsted-Bjerrum principle [46], one of the reactive species is a neutral molecule, as shown in Scheme 2.

Conclusions

The rate law used in this investigation is rate = k[oxidant]o $[CPL]_o$ $[NaOH]_x$, wherever x equals 0.35. BAB oxidised the chloroprocaine hydrochloride kinetically at 298 K. Using experimental data, a suitable mechanism and rate law were found. We detected the oxidation products. We calculated decomposition constants and composition activation parameters. The mechanical pathways and kinetic modelling have been calculated for this redox system. In addition to

gentle reaction conditions, superior product yields, operational and experimental simplicity, shows that this method has great industrial potential.

References:

[1] **Rudolph, H., and De Jong, M. D** (1981). **American Journal of Obstetrics and Gynecology**, The chloroprocaine controversy, **Volume. 140, Number. 3**: Page. 237-239.

[2] **Bernards, C., Hostetter, L., Barash, P., Cullen, B., R. Stoelting, M. Cahalan, Stock** (2013). Ortega, Clinical Anaesthesia, Philadelphia Lippincott,

[3] **D Ghisi, D., and Bonarelli**, **S.,** (2015). **Ambulatory Anesthesia**, Ambulatory surgery with chloroprocaine spinal anesthesia: a review, **Volume. 2**, Page. 111-120.

[4] **Malcolm Campbell, M., and Johnson, G.,** (1978). **Chemical Reviews**, Chloramine T and related N-halogeno-N-metallo reagents, **Volume 78, Number. 1**: Page. 65-79.

[5] **Iyengar, T. A., Puttaswamy, Mahadevappa, D. S**., (1990). **Carbohydrate Research,** Oxidation of some aldopentoses by chloramine-B in alkaline medium: a kinetic and mechanistic study, **Volume 204**, Page. 197-206.

[6] **Puttaswamy and Shubha, J. P.,** (2009). **Bulletin of the Korean Chemical Society**, N-Oxidation of Pyrazines by Bromamine-B in Perchloric Acid Medium: Kinetic and Mechanistic Approach, Volume 30, Page. 1939 – 1945.

[7] **Shubha., J P, Manjunatha, R., and Puttaswamy**, (2014), **IOSR Journal of Applied Chemistry**, Kinetics and Mechanism of Oxidation of Coumarin and Substituted Coumarins by Chloramine-B in Hydrochloric Acid Medium, **Volume 7**, Page. 96-103.

[8] **Viswanathan, S. N., Pranesh, S. J., and Swamy, P**., (2019), **Chemistry Africa**, Comparative Study on the Oxidation Kinetics of Structural Isomers by Acidified N-Bromo-Benzenesulfonamide: A Mechanistic Determination, Volume 2, Page. 435–441.

[9] **Feigl, F.,** (1975), Spot Tests in Organic Analysis, Elsevier, Amsterdam.

[10] **G Akerlof,** (1932), Journal of the American Chemical Society, Dielectric constants of some organic solvent-water mixtures at various temperatures, Volume 154, Number 11, Page. 4125–4139.

[11] **Pryde, B. G. and Soper, F. G.,** (1931), Journal of the Chemical Society, CCVIII. —The direct interchange of chlorine in the interaction of p-toluenesulphonamide and N-chloroacetanilide, Page. 1514-1518

[12] **Duke and Frederick, R**, (1948), **Journal of The American Chemical Society**, Kinetics of the Oxidation of Acetone by Selenious Acid, **Volume 70, Number 1:** Page. 419-421.

[13] **Yathirajan, H. S., Raju, C. R., Mohana, K. N., Shashikanth, S., and Nagaraja, P,** (2003), **Turkish Journal of Chemistry**, Kinetics and Mechanism of Oxidation of L-Isoleucine and LOrnithine Hydrochloride by Sodium N-Bromobenzenesulphonamide in Perchloric Acid Medium, **Volume 27, Number 5**: Page. 571 – 580.

[14] **Hardy, F. E., and Johnston, J. P.,** (1973), **Journal of the Chemical Society, Perkin Transactions,** The interaction of N-bromo-N-sodiobenzenesulphonamide (bromamine B) with p-nitrophenoxide ion, **Volume 2, Number 6:** Page. 742-746

[15] **Shubha, J. P., Manjunath., R and Puttaswamy,** (2014), **IOSR Journal of Applied Chemistry**, Kinetics of oxidation of chloroprocaine hydrochloride by N-halo-p-toluene sulfonamides in acid medium: A Mechanistic approach, **Volume 7, Number 5:** Page. 96-103.

[16] **Higuchi, K., Ikeda, K. and Hussain, A.,** (1968), **Journal of the Chemical Society B: Physical Organic**, Mechanism and thermodynamics of chlorine transfer among organochlorinating agents. Part III. Autocatalytic pathway between N-chloro-succinimide and chloramine-T, Page. 1031-1036.

[17] **Amis, E. S.,** (1966), Solvent effects on reaction rates and mechanism, Academic Press, New York.

[18] **A. Kohen, A., Limbach, H. H.,** (2006), Isotope Effects In Chemistry and Biology, CRC Press: Florida,

[19] Moelwyn Hughes, E. A., (1947), The Kinetics Of Reactions In Solution, Clarender Press: Oxford.

[20] Benson, S. W., (1960), The Foundations Of Chemical Kinetics", McGraw-Hill: New York.

[21] Frost, A. A., Pearson, R. G., (1961), Kinetics and mechanism, Wiley: New York.

[22] K. J. Laidler, K. J., (1995), Chemical Kinetics, Tata McGraw-Hill, New Delhi.