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Oxidation of Aspirin by N-Sodio-N-Bromobenzene Sulphonamide (Bromamine-B) in Acid Medium; A Kinetic and Mechanistic Study

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The kinetics of the oxidation of aspirin (ASP) by bromamine-B (BAB) has been studied in aqueous perchloric acid at 303 K. Decarboxylation, bromination and loss of acetic acid gave the reaction product 2,4,6-tribromophenol and was identified by GC-MS. The rate shows first order dependence on [BAB], fractional order in [ASP] and inverse fractional order in $[H^+]$. The rate decreased with decreasing dielectric constant of the medium. The variation of ionic strength and the addition of the reaction product (benzene sulphonamide) and halide ions had no significant effect on the reaction rate. Thermodynamic parameters were evaluated. The solvent isotope effect was studied using D_2O.

INTRODUCTION

Aspirin (acetylsalicylic acid) is a nonsteroidal analgesic, anti-inflammatory and antipyretic agent. It is used in acute conditions such as headache, arthralgia, myalgia and other cases requiring mild analgesic. Aspirin is widely studied in medicine and several methods are suggested in the literature for its determination.[1, 2] A very few kinetic studies of aspirin hydrolysis are reported in literature.[3–5] It is therefore of interest to study the kinetic investigations of oxidation of this compound by bromamine-B. The chlorine compounds chloramine-T and chloramine-B are well known analytical reagents and mechanistic aspects of these reactions have been documented.[6, 7] However, information on the bromine analogues are very scanty.[8–12] Therefore, in the present paper, we report the mechanistic and kinetic aspects of oxidation of aspirin (ASP) by bromamine-B (BAB or $C_6H_5SO_2HBrNa{\cdot}1.5H_2O$) in perchloric acid medium at 303K.

RESULTS AND DISCUSSION

The kinetics of oxidation of aspirin by BAB was investigated in 10% acetic acid medium. Blank experiments with acetic acid, however, showed that there is slight decomposition of the solvent (< 2%) under the experimental conditions used. This was allowed in the calculation of the net reaction rate constant for the oxidation of aspirin.

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Effect of reactants: With the substrate in excess, at constant $[HClO_4]$ and $[ASP]_0$, plots of log [BAB] *vs.* time were linear, indicating a first-order dependence of rate on $[BAB]_0$. The pseudo-first-order rate constants (k′) obtained are given in Table-1. The rate increased with increasing $[ASP]_0$. A plot of log k′ *vs.* log $[ASP]_0$ was linear with a fractional slope (0.45) indicating fractional order dependence on the aspirin concentration (Table-1).

TABLE-1
EFFECT OF VARYING BAB, ASPIRIN AND $HClO_4$ CONCENTRATIONS ON THE RATE OF REACTION

10^4 [BAB] (mol dm^{-3})	10^3 $[ASP]_0$ (mol dim^{-3})	10^3 $[HClO_4]$ (mol dm^{-3})	$k' \times 10^4$ (s^{-1})
8.0	8.0	2.0	2.85
9.0	8.0	2.0	2.92
10.0	8.0	2.0	2.80
11.0	8.0	2.0	2.90
12.0	8.0	2.0	2.75
14.0	8.0	2.0	2.78
10.0	2.0	2.0	1.43
10.0	4.0	2.0	2.05
10.0	6.0	2.0	2.48
10.0	8.0	2.0	2.80
10.0	10.0	2.0	3.15
10.0	14.0	2.0	3.69
10.0	8.0	1.0	3.52
10.0	8.0	2.0	2.80
10.0	8.0	4.0	2.15
10.0	8.0	6.0	1.82
10.0	8.0	10.0	1.58
10.0	8.0	14.0	1.38
10.0	8.0	20.0	1.20

$\mu = 0.5$ mol dm^{-3}, Temperaure = 30°C

Effect of acid: The rate of reaction decreased with increase in $[HClO_4]$. The plot of log k′ *vs.* log $[HClO_4]$ was linear with a negative fractional order in $[HClO_4]$ (Table-2).

Effect of halide ions and benzene sulphonamide: The addition of Cl^- or

Br^- ions (5.0×10^{-4}–5.0×10^{-3} mol dm^{-3}) in the form of NaCl or NaBr did not alter the rate of the reaction. Addition of the reaction product, benzenesulphonamide (5.0×10^{-4}m–5.0×10^{-3} mol dm^{-3}) did not influence the rate of reaction.

TABLE-2
KINETIC AND THERMODYNAMIC PARAMETERS FOR THE OXIDATION OF ASPIRIN BY BAB IN PRESENCE OF PERCHLORIC ACID

Reactants	Order	Parameters	Values
[BAB]	1.00	Ea (kJ mol^{-1})	86.2 (82.3)
[ASP]	0.45	$\Delta H^{\#}$ (kJ mol^{-1})	83.7 (79.7)
		$\Delta S^{\#}$ (J K^{-1} mol^{-1})	–37.1 (–45.3)
$[HClO_4]$	–0.35	$\Delta G^{\#}$ (kJ mol^{-1})	94.9 (93.5)

Values in parentheses are the activation parameters for the rate limiting step.

Effect of ionic strength and dielectric constant of the medium: Variation of ionic strength of the medium by adding $NaClO_4$ (0.1–0.5 mol dm^{-3}) had no effect on the rate. The reaction was studied in aqueous methanol of different compositions (0–20% v/v). A plot of log k′ *vs* 1/D, where 'D' is the dielectric constant of the medium, was a straight line with a negative slope. Blank experiments indicated that methanol was very slowly oxidized by BAB under the experimental conditions. This was taken into account in the calcualtion of net reaction rate constant for the oxidation of ASP each time.

Solvent isotope studies: The solvent istope effect was studied in D_2O , the reaction was further retarded with $k' = 2.24 \times 10^{-4}$ s^{-1} in D_2O medium and 2.80×10^{-4} s^{-1} in H_2O, leading to a solvent isotope effect,

$$k'_{H_2O} / k'_{D_2O} = 1.25 \quad (1)$$

Pryde and Soper,[12] Morris *et al.*[13] and Bishop and Jennings[14] have shown the existence of similar equilibria in acid and alkaline solutions of N-metallo-N-haloarylsulphonamides. Bromamine-B, being analogous to CAT, behaves as a strong electrolyte in aqueous solutions forming different species as shown in equations (2)–(6).

$$RNBrNa \rightleftharpoons RNBr^- + Na^+ \quad (2)$$

$$RNBr^- + H^+ \rightleftharpoons RNHBr \quad (3)$$

$$RNHBr + H_2O \rightleftharpoons RNH_2 + HOBr \quad (4)$$

$$2RNHBr \rightleftharpoons RNH_2 + RNBr_2 \quad (5)$$

$$HOBr + H^+ \rightleftharpoons H_2OBr^+ \quad (6)$$

In acid solutions, the probable oxidizing species are the free acid (RNHBr), dibromamine-T ($RNBr_2$), HOBr and H_2OBr^+. The involvement of $RNBr_2$ in the mechanism leads to a second order rate dependence on $[BAB]_0$, according to equation (5), which is contrary to the experimental observations. As equation (4) indicates a slow hydrolysis, if HOBr were the primary oxidizing species of first

order, a retardation of the rate by the added RNH_2 would be expected. However, no such effect was noticed in this study. Hardy and Johnston[15] have studied the pH dependent relative concentrations of the species present in acidified BAB solutions of comparable molarities, and shown that RNHBr is the likely predominating oxidizing species in acid medium. Narayanan and Rao[16] and Subhashini *et al.*[17] have reported that monohaloamines can be further protonated at pH < 2, as in equations (7) and (8) for chloramine-T and chloramine-B, respectively;

$$p\text{-}CH_3C_6H_4SO_2NHCl + H^+ \rightleftharpoons p\text{-}CH_3C_6H_4SO_2\overset{+}{N}H_2Cl \quad (7)$$

$$C_6H_5SO_2NHCl + H^+ \rightleftharpoons C_6H_5SO_2\overset{+}{N}H_2Cl \quad (8)$$

Therefore in higher acidic conditions, for BAB, RNHBr is expected to be protonated as follows:

$$RNHBr + H^+ \rightleftharpoons \overset{+}{R}NH_2Br \quad (9)$$

In the present investigations, the retardation of the rate by H^+ ion indicates deprotonation of the species $\overset{+}{R}NH_2Br$ to monoprotonated oxidant RNHBr which is the active oxidizing species and Scheme-1 is proposed for the oxidation of ASP by BAB.

$$\overset{+}{R}NH_2Br \overset{K_1}{\rightleftharpoons} RNHBr + H^+ \quad \text{(fast)} \quad (10)$$

$$RNHBr + ASP \overset{K_2}{\rightleftharpoons} X \quad \text{(fast)} \quad (11)$$

$$X \overset{k_3}{\rightarrow} X' + RNH_2 \quad \text{(slow)} \quad (12)$$

$$X' + 2RNHBr \rightarrow X'' \quad \text{(fast)} \quad (13)$$

$$X'' + H_2O \rightarrow \text{Products} \quad \text{(fast)} \quad (14)$$

Scheme-1

Here the complexes X, X′ and X″ are defined in Scheme-II.

If $[BAB]_t$ represents the total concentration of the oxidant,

$$[BAB]_t = \overset{+}{R}NH_2Br + RNHBr + X \quad (15)$$

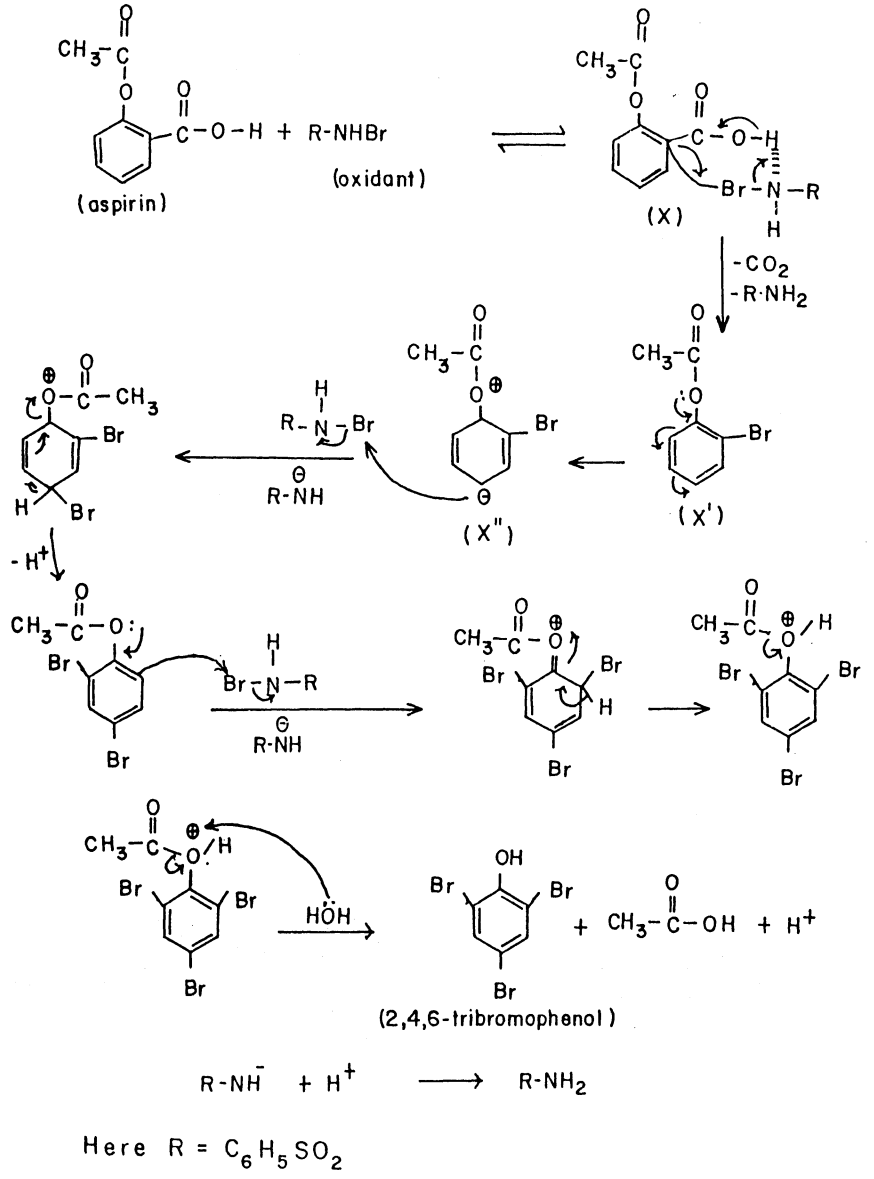
Scheme-1 leads to the rate law

$$\text{Rate} = \frac{k_3K_2K_1[BAB]_t[ASP]}{[H^+] + K_1\{1 + K_2[S]\}} \quad (16)$$

which is in agreement with the experimental results with a first order dependence on [BAB], a fractional order on [ASP] and an inverse fractional order in $[H^+]$.

A detailed mechanistic interpretation of the aspirin-oxidant reaction in acid medium is presented in Scheme-II. An electrophilic attack by the oxidant (RNHBr) through its positive bromine forms the complex X in the first step. Then complex X undergoes decarboxylation and *ortho*-bromination of aspirin forming the intermediate X′. The species X′ on intramolecular rearrangement and further bromination forms an acetyl-tribromo-cationic species intermediate of aspirin. The hydrolysis of the cationic species yields the products 2,4,6 -tribromophenol and acetic acid.

The change in the ionic strength of the medium does not alter the rate indicating that non-ionic species are involved in the rate limiting step. Solvent isotope studies in D_2O medium show a retardation of the rate. It is well known



Scheme II

that D_3O^+ is a stronger acid than the hydronium ion and hence this observation supports the proposed mechanism. The effect of varying solvent composition and dielectric constant (D) on the rate has been described in several studies. The negative dielectric effect,[18, 19] in the present studies, supports the interactions of two dipoles in the rate limiting step in Scheme-1. The fairly high positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated,[20] while the negative entropy of activation suggests the formation of the compact activated complex.

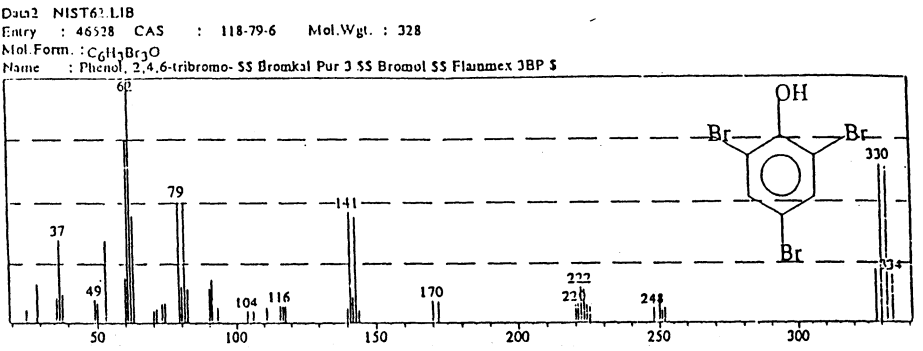


Fig. 1. Mass spectrum of 2,4,6-tribromophenol with its parent molecular ion peak at mass charge 33.

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