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Mechanism of Oxidation of Paracetamol by Bromamine-B in Acid Medium: A Kinetic Approach

PUTTASWAMY* and NIRMALA VAZ.
Department of Post Graduate Studies in Chemistry
Central College, Bangalore University, Bangalore-560 001, India

The kinetics of oxidation of paracetamol (PAM) by sodium N-bromobenzenesulfonamide (bromamine-B or BAB) in $HClO_4$ medium has been studied at 303 K. The reaction is of first-order in [BAB] and of fractional-order each with respect to [PAM] and $[H^+]$. The variation of ionic strength and the addition of the reaction product, benzenesulfonamide, and halide ions had no significant effect on the reaction rate. Decrease in dielectric constant of medium increases the rate and the solvent isotope effect was studied using D_2O. The rates were determined at different temperatures and the activation parameters for the overall reaction have been computed. Michaelis-Menten type of kinetics is observed and activation parameters for the rate-limiting step have also been computed. 4-Amino-2,6-dibromophenol was identified as the oxidation product of PAM. Mechanism (scheme) consistent with the observed kinetic data has been proposed and discussed.

INTRODUCTION

Considerable attention has centred around the chemistry of N-metallo-N-arylhalosulfonamides generally known as organic haloamines, because of their versatility in behaving like mild oxidants, halogenating agents and N-anions, which act as both bases and nucleophiles. The important chlorine compounds of this group, chloramine-T (CAT) and chloramine-B (CAB), are well known as analytical reagents for the determination of diverse substrates. Mechanistic aspects of many of these reactions have been documented[1–3]. However, meagre information exists in the literature[4–6] on the bromine analogues, bromamine-T (BAT) and bromamine-B (BAB). Sodium N-bromo-benzenesulfonamide or bromamine-B ($C_6H_5SO_2NBrNa1{\cdot}5H_2O$) is becoming important as a mild oxidant and is found to be a better oxidizing agent then the chloro compounds.

Although the oxidation of organic and inorganic substrates with BAB has been studied, a little attention is focussed on BAB's reactions with pharmaceuticals, particularly with respect to the oxidation kinetics of antipyretics. The substrate, paracetamol (4-acetamidophenol) is a well-known drug that finds extensive applications in pharmaceutical industries. It is an antipyretic-analgesic compound, which is extremely useful in therapeutics. There is hardly any reference to the kinetics of oxidation of this important drug in the literature. Hence, we thought

it is worthwhile to make a study of the oxidation kinetics of this drug by N-haloamine and this investigation may throw some light on the mechanisms of metabolic conversion of paracetamol in biological system and also to identify the probable reactive species of the oxidant in aqueous acid. Therefore, we have for the first time made a detailed study on the oxidation kinetics of paracetamol (PAM) by BAB in acid medium; the results and also plausible mechanisms are discussed in this communication.

EXPERIMENTAL

Materials: Bromamine-B was prepared[7] by passing bromine through a solution of benzenesulfonamide in 4 mol dm^{-3} NaOH for 1 h. The product was collected, dried and recrystallized from water (m.p. 443 K with decomposition). Its purity was checked by iodometry for its active bromine content and also by its ^1H and ^{13}C NMR spectra. An aqueous solution of BAB was standardized iodometrically and stored in brown bottles to arrest photochemical deterioration. An aqueous solution of paracetamol (Merck) was freshly prepared whenever required. All other chemicals were of AnalaR grade. Concentrated $NaClO_4$ solution was used throughout to maintain a constant high ionic strength ($I = 0.50$ mol dm^{-3}) of the medium to swamp the reaction. Heavy water (D_2O, 99.2%) was supplied by the Bhabha Atomic Reasearch Centre, Mumbai, India. Triple-distilled water was used throughout.

Kinetic measurements: The reaction was carried out under pseudo-first-order condition ([PAM] $\gg$ [BAB]) in glass-stoppered pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effects. Solutions containing appropriate amounts of substrate, $HClO_4$, $NaClO_4$ and water (for constant volume) were taken in the tube and thermostated at 303 K for thermal equilibrium. A measured amount of BAB, also thermostated at the same temperature, was rapidly added to the mixture. The progre of the reaction was monitored up to two half-lives by iodometric determination of unreacted BAB in a measured aliquot (5 mL each) of the reaction mixture at different intervals of time. Pseudo-first-order rate constants (k) calculated from log [BAB] *vs.* time plots were reproducible within ± 3–4%. Regression analysis of data was carried out on an fx-100w calculator to obtain the regression coefficient 'r'.

Stoichiometry and product analysis: Reaction mixtures containing varying ratios of BAB to PAM in the presence of 4.0×10^{-2} M $HClO_4$ were equilibrated at 303 K for 24 h. Estimation of the unreacted BAB showed a 1 : 2 stoichiometry:

$$C_8H_9NO_2 + 2PhSO_2NBrNa + 2H_3O^+ \longrightarrow C_6H_5NOBr_2 + 2PhSO_2NH_2 + CH_3COOH + H_2O + 2Na^+ \quad (1)$$

The reduction product of BAB, benzensulfonamide ($PhSO_2NH_2$) was recrystallized from dichloromethane/petroleum ether (m.p. 422–423 K; lit. m.p. = 423–425 K). R_f value of 0.36 was determined from TLC using (CH_2Cl_2 + $CHCl_3$, 7 : 3 v/v) as the solvent system and iodine as the spray reagent. Acetic

acid was identified by spot tests[8]. The oxidation product of paracetamol, 4-amino-2,6-dibromophenol, was detected by elementary analysis Beilsteins test and functional groups were identified by usual tests. It was further confirmed by its m.p. 441–442 K (lit. m.p. = 440–443 K).

RESULTS AND DISCUSSION

The kinetics of oxidation of paracetamol by BAB was investigated at several initial concentrations of the reactants in $HClO_4$ medium.

Under pseudo-first-order conditions of [PAM] ≫ [BAB] at constant $[H^+]$ and temperature, plots of log [BAB] *vs.* time were linear (r >0.9925) indicating a first-order dependence of rate on [BAB]. The rate constant, k, was not afffected by a change in [BAB], (Table-1). Values of k increased with increase in [PAM] (Table-1) and the plot of log k *vs.* log [PAM] was linear (r = 0.9995) with a slope of 0.45 indicating a fractional-order dependence of rate on [PAM]. Further, a plot of k *vs.* [PAM], was linear (r = 0.9998) with an intercept, confirming the fractional-order dependence on [PAM]. The rate increased with increase in $[HClO_4]$ (Table-1) and a plot of log k *vs.* log $[H^+]$ was linear with a slope of 0.66 indicating a fractional-order dependence of rate on $[H^+]$.

TABLE-1
EFFECT OF VARYING CONCENTRATIONS OF OXIDANT, SUBSTRATE AND ACID ON THE RATE OF REACTION

10^4 [BAB] (mol dm^{-3})	10^2 [PAM] (mol dm^{-3})	10^2 $[HClO_4]$ (mol dm^{-3})	$k \times 10^4$ (s^{-1})
6.0	1.0	4.0	4.65
8.0	1.0	4.0	4.58
10.0	1.0	4.0	4.60
12.0	1.0	4.0	4.52
14.0	1.0	4.0	4.68
10.0	0.4	4.0	3.04
10.0	1.0	4.0	4.60
10.0	2.0	4.0	6.25
10.0	3.0	4.0	7.75
10.0	4.0	4.0	9.05
10.0	1.0	1.0	1.52
10.0	1.0	2.0	2.70
10.0	1.0	4.0	4.60
10.0	1.0	10.0	9.45
10.0	1.0	20.0	15.60

I = 0.5 mol dm^{-3}; Temperature = 303 K.

Addition of the reaction product, benzenesulfonamide ($PhSO_2NH_2$; 5.0×10^{-4} 3.0×10^{-3} mol dm^{-3}) and halide ions Cl^- or Br^- in the form of NaCl or NaBr ($5.0 \times 10^{-4} - 3.0 \times 10^{-3}$ mol dm^{-3}) or variation of ionic strength of medium (0.1–0.8 mol dm^{-3}) had no significant effect on the rate. Addition of methanol to reaction mixture (0–40% v/v) increased the rate and the plot of log k *vs.* 1/D, where D is the dielectric constant of medium, gave a straight line with positive slope. Blank experiments showed that methanol was very slightly oxidized (< 2%) by BAB under the experimental conditions. This was taken into account in the calculation of net reaction rate constant for the oxidation of PAM each case.

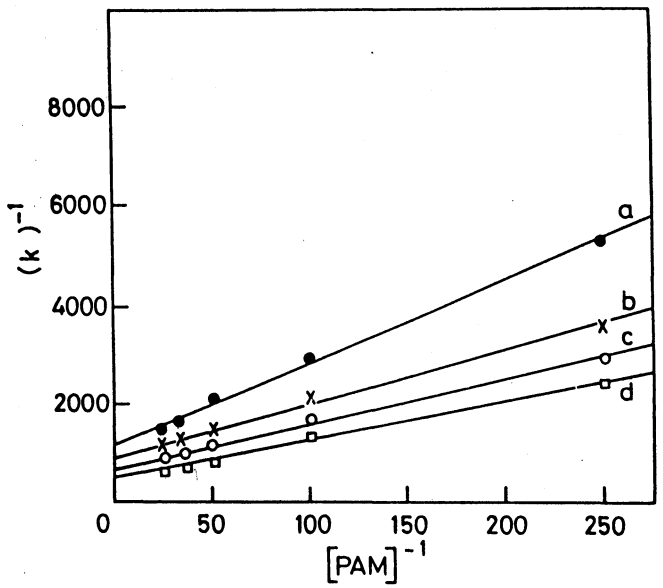


Fig. 1 Double reciprocal plots of 1/k *vs.* 1/[PAM] at (a) 298 K (b) 303 K (c) 308 K and (d) 313 K; [BAB] = 1.0×10^{-3} mol dm^{-3}; [$HClO_4$] = 4.0×10^{-2} mol dm^{-3}; I = 0.5 mol dm^{-3}

The reaction was studied at different temperature (298–313 K), keeping other experimental conditions constant. From the linear Arrhenius plot of log k *vs.* 1/T ($r = 0.9805$), values of composite activation parameters, energy of activation (E_a), enthalpy of activation ($\Delta H^{\#}$), entropy of activation ($\Delta S^{\#}$) and free energy of activation ($\Delta G^{\#}$) were computed. These are sumarized in Table-2. As a dependence of the rate on H^+ ion concentration was noted, solvent isotope studies of the rate variation in D_2O medium revealed that $k(H_2O) = 4.60 \times 10^{-4}$ s^{-1} and $k(D_2O) = 5.05 \times 10^{-4}$ s^{-1}. The solvent isotope effect $k(H_2O)/k(D_2O) = 0.91$.

TABLE-2
TEMPERATURE DEPENDENCE AND ACTIVATION PARAMETERS FOR THE OXIDATION OF PARACETAMOL BY BAB

Temperature (K)	$k \times 10^4 (k_3 \times 10^4)$ (s^{-1})	Activation parameters	
298	3.30 (8.33)	E_a (kJ mol^{-1})	40.2 (35.0)
303	4.60 (10.5)	$\Delta H^{\#}$ (kJ mol^{-1})	37.7 (32.5)
308	5.52 (12.5)	$\Delta G^{\#}$ (kJ mol^{-1})	94.3 (92.1)
313	6.34 (16.6)	$\Delta S^{\#}$ (kJ mol^{-1})	−186 (−195)

Values in parentheses are the decomposition constants and activation parameters for the ratelimiting step.

Absence of free radicals in the reaction mixture was shown by the negative test with acrylamide, as no polymerization was initiated even after 1 h in a nitrogen atmosphere.

Bromamine-B is analogous to CAT and CAB and exhibits similar equilibria in aqueous acidic and basic solutions[9]. In general, BAB undergoes a two-electron change in its reactions. The oxidation potential of BAB-$PhSO_2NH_2$ is pH dependent and decreases with increase in pH of the medium (E_0 is 1.14 V at pH 0.65 and 0.50 V at pH 12 for CAT). Depending on the pH of the medium BAB furnishes different types of reactive species in solution[9-11].

$$PhSO_2NBrNa \rightleftharpoons PhSO_2NBr^- + Na^+ \quad (2)$$

$$PhSO_2NBr^- + H^+ \rightleftharpoons PhSO_2NHBr \quad (3)$$

$$2PhSO_2NHBr \rightleftharpoons PhSO_2NH_2 + PhSO_2NBr_2 \quad (4)$$

$$PhSO_2NBr_2 + H_2O \rightleftharpoons PhSO_2NHBr + HOBr \quad (5)$$

$$PhSO_2NHBr + H_2O \rightleftharpoons PhSO_2NH_2 + HOBr \quad (6)$$

$$HOBr \rightleftharpoons H^+ + OBr^- \quad (7)$$

$$HOBr + H^+ \rightleftharpoons H_2O^+Br \quad (8)$$

Therefore, the probable reactive species in acid solution of BAB are $PhSO_2NHBr$, $PhSO_2NBr_2$, HOBr and H_2O^+Br. The first-order dependence of rate on [BAB] and addition of $PhSO_2NH_2$ (benzenesulfonamide) having no effect on the reaction rate indicates that $PhSO_2NBr_2$ and HOBr may not be the reactive species [(4) and (6)], and further, that these species are present in very low concentrations[9] at the experimetal conditions employed. The absence of ionic strength effects indicates the involvement of a neutral species in the rate-limiting step. Hence, the effective oxidizing species could be the conjugate acid, $PHSO_2NHBr$. Further, protonation of monochloramines (RNHCl) at pH < 2 according to equation (9) has been reported[12, 13].

$$RNHCl + H^+ \overset{K}{\rightleftharpoons} RNH_2Cl \quad (9)$$

Here, when $R = p\text{-}CH_3C_6H_4SO_2^-$, $K = 1.02 \times 10^2$ at 298 K while with

$R = C_6H_5SO_2^-$, $K = 61 \pm 5$ at 298 K for CAT and CAB respectively. Extending the same argument for bromamines, it is likely that $PhSO_2NHBr$ of BAB could be further protonated in acid media. Based on the preceding discussion and observed kinetic results, the following mechanism (Scheme-1) is proposed for the oxidation of PAM by BAB in acid medium:

$$PhSO_2NHBr + H^+ \underset{}{\overset{K_1}{\rightleftharpoons}} PhSO_2NH_2Br^+ \quad \text{(i)} \qquad \text{fast}$$

$$PhSO_2NH_2Br^+ + PAM \overset{K_2}{\rightleftharpoons} X \quad \text{(ii)} \qquad \text{fast}$$

$$X \xrightarrow{k_3} X' \quad \text{(iii) slow and rate limiting step}$$

$$X' + PhSO_2NH_2Br^+ \xrightarrow{k_4} \text{Products} \quad \text{(iv)} \qquad \text{fast}$$

Scheme I

In Scheme 1, X and X′ represent the intermediate species whose structures are shown in Scheme 2 where a detailed mechanistic interpretation of PAM oxidation by BAB in acid medium is proposed, in which, the protonated oxidant species $PhSO_2NH_2Br^+$ reacts with the substrate in a fast equilibrium step to form the substrate-BAB complex (X). This decomposes in a rate-limiting step to the products. A total of two moles of the oxidant is consumed to yield the ultimate products.

Step (iii) of Scheme 1 determines the overall rate:

$$\text{rate} = -d[BAB]/dt = k_3[X] \tag{10}$$

If $[BAB]_t$ represents total BAB concentration in solution. then

$$[BAB]_t = [PhSO_2NHBr] + [PhSO_2NH_2Br^+][X]$$

from which, solving for [X] and substituting its value in (10), rate law (11) can be derived:

$$\text{rate} = \frac{-d[BAB]}{dt} \frac{K_1K_2k_3[BAB]_t[PAM][H^+]}{1 + K_1[H^+] + K_1K_2[PAM][H^+]} \tag{11}$$

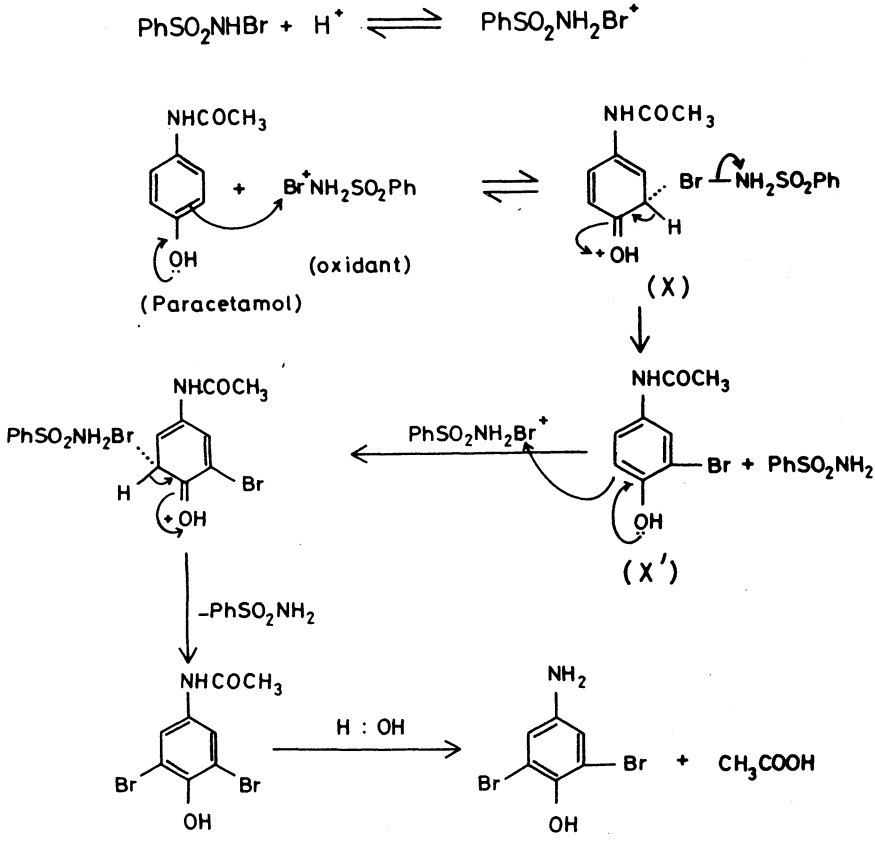
Rate law (11) is in agreement with experimental results and it can be transformed as

$$\frac{1}{k} = \frac{1}{K_2k_3[PAM]} \left\{\frac{1}{K_1[H^+]} + 1\right\} + \frac{1}{k_3} \tag{12}$$

Since a fractional order was noticed in [PAM], the Michaelis-Menten kinetics[14] was adopted to study the effect of [PAM] on the rate at different temperatures (298–313 K). The decomposition constants k_3 (step (iii) of Scheme 1) were calculated at different temperatures using equation (12). Using these k_3 values, activation parameters for the rate-limiting step (r.l.s) were also evaluated from the linear Arrhenins plot of log k_3 *vs.* 1/T ($r = 0.9873$). These data are given in Table-2.

The effect of varying solvent composition and dielectric constant (D) on the rate has been described in several studies. For a limiting case of zero angle approach between two dipoles or an anion-dipole system, Amis[15] has shown that a plot of log k *vs.* 1/D gives a straight line. It gives a negative slope for a reaction between an anion and a dipole or between two dipoles and a positive slope for a reaction between a cation and a dipole. The positive dielectric effect, in the present studies, supports the involvement of ion-dipole interaction in the rate-limiting step.

It is interesting that the rate increased only slightly in D_2O medium, contrary to expectations[16] in proton catalyzed reactions. It is well known that D_3O^+ is a stronger acid than H_3O^+ (*ca.* 2–3 times greater) and hence a rate increase of the same magnitude is expected in D_2O. However, it could be noted that the rate decreases in D_2O when O—H/O—D exchange takes place and the O—H/O—D bond is cleaved during the reaction. This could be due to the hydrolysis step wherein the normal kinetic isotope effect [$k_H/k_d > 1$] counterbalances the solvent



Scheme 2 (4-amino-2,6-dibromophenol)

isotope effect [$k(H_2O)/k(D_2O) < 1$] resulting in a net effect, $k_H/k_D \geq 1$. The magnitude is smaller which can be attributed to the fractional order dependence on [H^+].

The proposed mechanism is also supported by the moderate values of energy of activation and other activation parameters. The fairly high positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the large negative entropy of activation suggests the formation of the compact activated complex with less degrees of freedom.

The reduction product ($PhSO_2NH_2$) does not influence the rate showing that it is not involved in a pre-equilibrium. The change in ionic strength of the medium does not alter the rate indicating that non-ionic species are involved in the rate-limiting step. Addition of halide ions has no effect on the rate indicating that no interhalogen or free bromine is formed. All these observations are also in conformity with the proposed mechanism.

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