Kinetics and Mechanism of Oxidation of Aspirin by Bromamine-T, *N*-Bromosuccinimide, and *N*-Bromophthalimide

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Received 6 March 1997; accepted 10 October 1997

ABSTRACT: The kinetics of the oxidation of aspirin (ASP) by bromamine-T (BAT), *N*-bromosuccinimide (NBS), and *N*-bromophthalimide (NBP) has been studied in aqueous perchloric acid at 303 K. The oxidation reaction follows identical kinetics with first-order in [oxidant], fractional-order in [ASP], and inverse fractional-order in [H^+]. Under identical experimental conditions the extent of oxidation with different oxidizing agents is in the order: NBS > BAT > NBP. The rate decreased with decreasing dielectric constant of the medium. The variation of ionic strength and the addition of the reaction products and halide ions had no significant effect on the reaction rate. The solvent isotope effect was studied using D_2O. Kinetic parameters were evaluated by studying the reaction at different temperatures. The reaction products were identified by GC–MS. The proposed reaction mechanism and the derived rate law are consistent with the observed kinetic data. Formation and decomposition constants for ASP-oxidant complexes have been evaluated. Decarboxylation, bromination, and loss of acetic acid gave 2,4,6-tribromophenol. © 1998 John Wiley & Sons, Inc. Int J Chem Kinet: 30: 407–414, 1998

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 analgesia. Aspirin is widely studied in medicine and several methods are suggested in the literature for its determination [1,2]. Very few kinetics of aspirin hydrolysis are reported in the literature [3,5]. It is therefore of interest to investigate the kinetics of its reaction with oxidizing agents. The kinetics and mechanism of oxidation of a number of organic and inorganic substrates using bromamine-T (BAT), *N*-bromosuccinimide (NBS), and *N*-bromophthalimide (NBP) have been studied extensively [6–12]. The present article reports our study on the kinetics and mechanism of oxidation of aspirin (ASP) by BAT, NBS, and NBP in perchloric acid medium.

EXPERIMENTAL

Bromamine-T was obtained by partial debromination of dibromamine-T (DBT) in 4 M NaOH [13]. The purity of BAT obtained was checked iodometrically and

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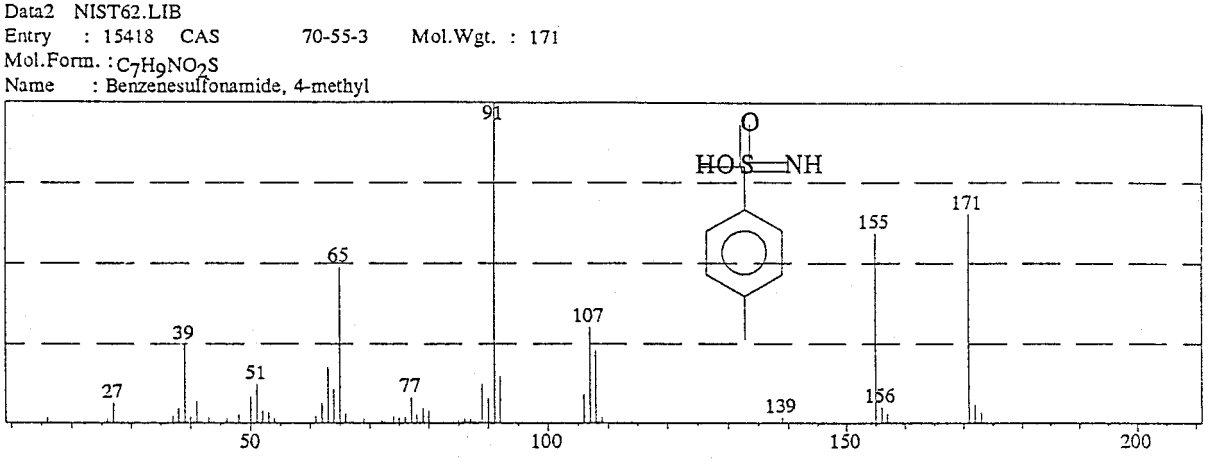


Figure 1 Mass spectrum of *p*-toluenesulfonamide with its parent molecular ion peak at mass/charge 171.

through its mass, UV, IR, and ^{1}H and ^{13}C NMR data. An aqueous solution of BAT was prepared, standardized by the iodometric method, and preserved in brown bottles. *N*-Bromosuccinimide, from Loba, Bombay, India, was used without further purification. The purity was checked iodometrically and by its IR spectrum. *N*-Bromophthalimide was prepared by the reported method [14]. The purity was checked iodometrically and by its IR spectrum. Aqueous solutions of NBS and NBP were always prepared afresh, standardized, and used.

Aspirin (Merck) was used without further purification. A solution of the compound was prepared in acetic acid-water [10:90] mixture. All solutions were prepared using AR chemicals and double distilled water. A constant ionic strength of the medium was maintained using a concentrated solution of sodium perchlorate.

Kinetic Measurement

The reaction was carried out in glass-stoppered Pyrex boiling tubes whose outer surface was coated black to eliminate photochemical effects. Requisite amounts of the solutions of ASP and $NaClO_4$, $HClO_4$, and water (to keep the total volume constant for all runs) were taken in the tube and thermostated at 303 K for thermal equilibrium. A measured amount of the oxidant solution, also thermostated at the same temperature, was rapidly added to the mixture with stirring in the boiling tube. The progress of the reaction was monitored by iodometric determination of the unreacted oxidant in measured aliquots of the reaction mixture withdrawn at different intervals of time. The course of the reaction was studied for two half-lives. The pseudo-first-order rate constants (**k′**) calculated were reproducible (± 3%).

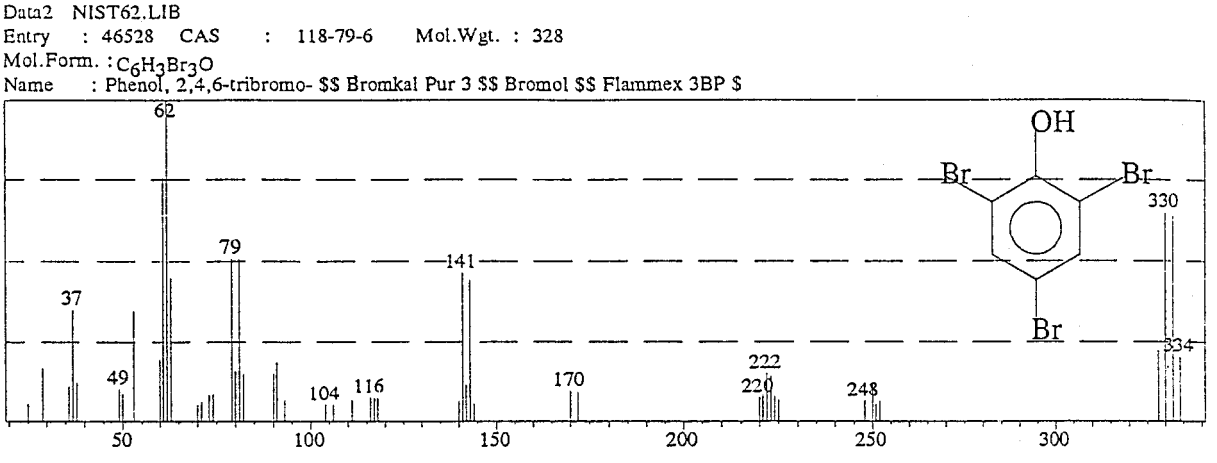


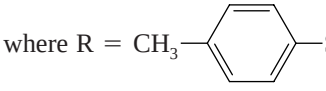
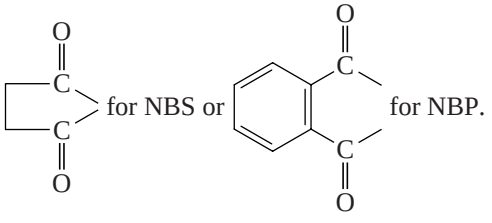
Figure 2 Mass spectrum of 2,4,6-tribromophenol with its parent molecular ion peak at mass/charge 331.

Stoichiometry and Product Analysis

Various ratios of ASP and the oxidant were equilibrated in the presence of $HClO_4$ for 24h (303 K) under the condition $[oxidant]_o \gg [aspirin]_o$. Determination of the unreacted oxidant in the reaction mixtures showed that one mole of ASP consumed 3 moles of oxidant, conforming to the following stoichiometry:

$$\underset{\text{(ASP)}}{C_9H_8O_4} + 3\ R{-}NHBr\ (\text{BAT}) + H_2O \longrightarrow C_6H_3OBr_3 + 3\ R{-}NH_2 + CO_2 \quad (1)$$

$$\underset{\text{(ASP)}}{C_9H_8O_4} + 3\ R'{=}NBr\ (\text{NBS/NBP}) + H_2O \longrightarrow C_6H_3OBr_3 + 3\ R'{=}NH + CO_2 \quad (2)$$

where R =  for BAT and R′ =  for NBS or for NBP.

The reduction product of BAT, *p*-toluenesulfonamide (PTS), was identified by paper chromatography using benzyl alcohol saturated with water as the solvent system with ascending irrigation and using 0.5% vanillin in 1% HCl in EtOH as the spray reagent (R_f = 0.905). The GC–MS data were obtained on a 17A Shimadzu gas chromatograph with a QP-5000 Shimadzu mass spectrometer. The GC had a capillary column with 250°C oven temperature, 200°C interface temperature, and approximately 150°C column temperature. The mass data were obtained using the electron impact method. The mass spectrum showing an M^+ parent ion peak at 171 amu clearly confirms PTS (Fig. 1). Succinimide and phthalimide were detected by methods reported elsewhere [9–12]. The oxidation product of ASP, 2,4,5-tribromophenol, was confirmed by IR and MS spectral studies (Fig. 2).

RESULTS

The kinetics of oxidation of ASP by BAT, NBS, and NBP was investigated at several initial concentrations of the reactants in $HClO_4$ medium. The same oxidation behavior was observed for all the three oxidants (OX).

Table I Effect of Varying Reactant Concentrations on the Reaction Rate[a]

		$k' \times 10^4/s^{-1}$		
10^4 [Oxidant]/M	10^3 $[ASP]_O$/M	NBS	BAT	NBP
8.0	8.0	5.70	4.85	1.88
9.0	8.0	5.80	4.80	1.95
10.0	8.0	5.78	4.90	1.97
11.0	8.0	5.84	4.98	1.85
12.0	8.0	5.90	4.70	1.90
10.0	2.0	1.92	1.90	0.63
10.0	4.0	3.24	3.20	0.92
10.0	6.0	4.50	4.05	1.42
10.0	8.0	5.78	4.90	1.97
10.0	10.0	6.60	5.70	2.45
10.0	12.0	7.67	6.40	2.82
10.0	14.0	8.80	7.75	3.38

[a] $[HClO_4] = 2.00 \times 10^{-3}$ M; μ = 0.50 M; and Temp. = 303 K.

Table II Effect of Perchloric Acid Concentration on the Reaction Rate[a]

	$\mathbf{k}' \times 10^4/s^{-1}$		
10^3 $[HClO_4]$/M	NBS	BAT	NBP
1.0	7.40	5.70	2.5
2.0	5.78	4.90	1.97
4.0	4.43	4.58	1.45
6.0	3.90	3.98	1.22
8.0	3.54	3.60	1.10
10.0	3.24	3.29	1.02
12.0	3.08	2.95	0.92
14.0	2.92	2.70	0.80

[a] $[Oxidant]_O = 1.00 \times 10^{-3}$ M; $[ASP]_O = 8.00 \times 10^{-3}$ M; μ = 0.50 M; and Temp. = 303 K.

Table III Effect of Dielectric Constant (D) of the Medium on the Rate of Reaction

% MeOH		$k' \times 10^4/s^{-1}$		
(v/v)	D[a]	NBS	BAT	NBP
0.0	76.73	5.78	4.90	1.97
10	72.37	4.30	3.50	1.65
20	67.48	2.52	2.35	1.21
30	62.71	1.45	1.65	0.72
40	58.06	0.85	1.05	0.50

$[Oxidant]_O = 1.00 \times 10^{-3}$ M; $[ASP]_O = 8.00 \times 10^{-3}$ M; $[HClO_4] = 2.00 \times 10^{-3}$ M; μ = 0.50 M; and Temp. 303 K.

[a] Values of D are from the literature, ref. [15].

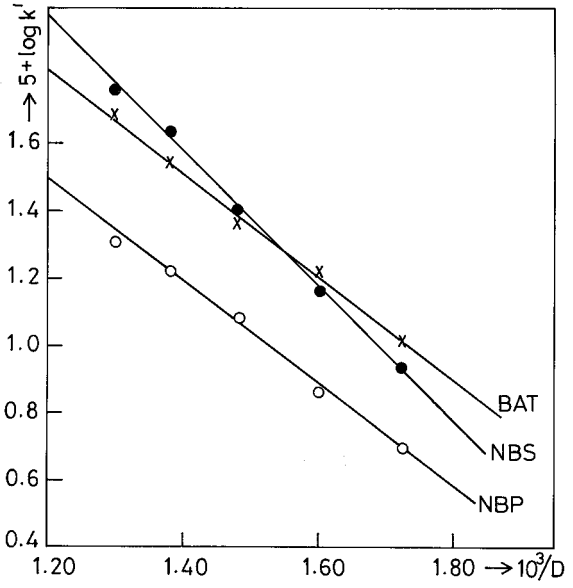


Figure 3 Plots of log k' vs. 1/D at 303 K.

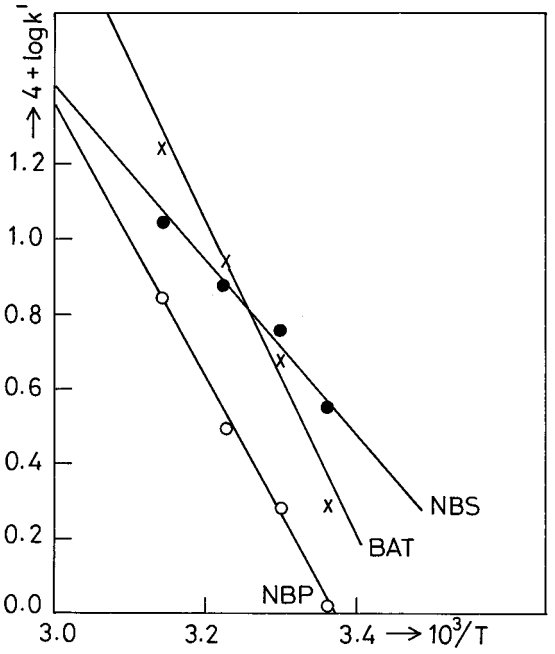


Figure 4 Arrhenius plots of log k' vs. 1/T.

At constant acid concentration with the substrate in excess, plots of log $[OX]_o/[OX]$ vs. time were linear indicating a first-order dependence of the rate on [OX]. The pseudo-first-order rate constants (k') obtained are given in Table I.

The rate increased with increasing $[ASP]_o$ (Table I). Plots of log k' vs. log $[ASP]_o$ were linear with slopes (ca. 0.6) with all the three oxidants, thus indicating a fractional-order dependence on the substrate concentration. The rate of reaction decreased with increase in $[HClO_4]$ (Table II). Plots of log k' vs. log $[HClO_4]$ were linear with negative fractional slopes indicating a negative fractional order (ca. -0.3) in $[H^+]$.

The variation of the ionic strength ($\mu = 0.10 - 0.60$ M) of the medium using sodium perchlorate or the addition of the reaction products (*p*-toluenesulfonamide or succinimide or phthalimide) ($1.0 \times 10^{-2} - 4.0 \times 10^{-2}$ M) had no effect on the reaction rate. The addition of Cl^- or Br^- ions ($1.0 \times 10^{-2} - 4.0 \times 10^{-2}$ M), in the form of NaCl or NaBr, had no significant effect on the rate. The reaction was also studied in aqueous MeOH of different compositions (0–40% v/v). It was observed that an increase in MeOH content retarded the rate of reaction (Table III). The values of the dielectric constant (D) of water-MeOH mixtures of different compositions are available in the literature [15]. Plots of log k' vs. 1/D were linear (Fig. 3) with negative slopes supporting a rate-limiting step with charge dispersal. Blank experiments performed

Table IV Effect of Temperature on the Rate of Reaction

Temperature (K)	$k' \times 10^4/s^{-1}$		
	NBS	BAT	NBP
297	3.38	1.82	1.05
303	5.78	4.90	1.97
310	7.67	9.00	3.15
318	11.04	17.0	7.02

$[Oxidant]_o = 1.00 \times 10^{-3}$ M; $[ASP]_o = 8.00 \times 10^{-3}$ M; $[HClO_4] = 2.0 \times 10^{-3}$ M; and $\mu = 0.50$ M.

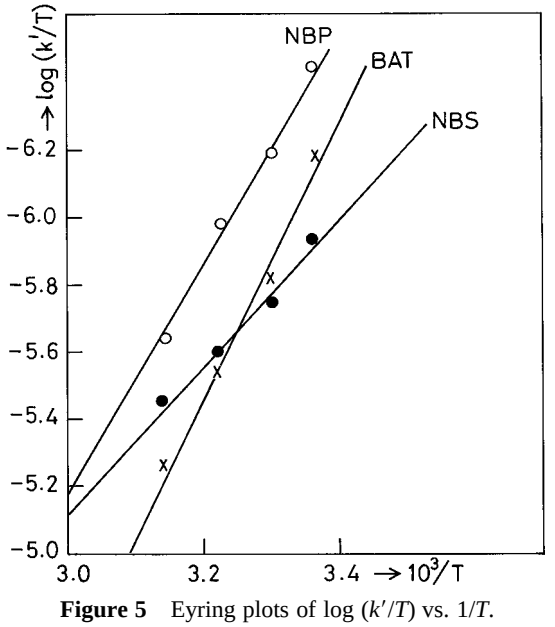


Figure 5 Eyring plots of log (k'/T) vs. 1/T.

Table V Kinetic and Activation Parameters for the Oxidation of ASP by NBS, BAT, and NBP

Oxidant	E_a (kJ mol^{-1})	$\Delta H^{\neq}$ (kJ mol^{-1})	$\Delta S^{\neq}$ (JK^{-1} mol^{-1})	$\Delta G^{\neq}$ (kJ mol^{-1})	log A
NBS	44.7 (38.3)	42.3 (35.7)	−170.0 (−180.4)	94.1 (91.1)	5.1 (6.3)
BAT	73.0 (69.9)	70.4 (67.3)	−77.4 (−79.3)	94.1 (91.7)	9.9 (9.8)
NBP	98.8 (72.6)	95.9 (70.0)	+2.87 (−75.1)	96.2 (93.1)	13.7 (13.0)

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

showed that MeOH was not oxidized significantly by the oxidants under the present experimental conditions.

Solvent isotope studies were performed in D_2O medium at 303 K using BAT as the probe. Values of k'_{D_2O} and k'_{H_2O} were found to be $4.08 \times 10^{-4}s^{-1}$ and $4.90 \times 10^{-4}s^{-1}$, respectively, leading to a solvent isotope effect $k'_{H_2O}/k'_{D_2O} = 1.20$.

The reactions were studied at different temperatures (297–318 K) (Table IV). The activation parameters, energy of activation (E_a), enthalpy of activation ($\Delta H^{\neq}$), entropy of activation ($\Delta S^{\neq}$), and free energy of activation ($\Delta G^{\neq}$), and frequency factor (A) were obtained from the Arrhenius and Eyring plots which were linear (Figs. 4 and 5). The activation parameters obtained are presented in Table V.

Constancy of the rate constant at different $[Hg(OAc)_2]$ in the case of NBS, showed that $Hg(OAc)_2$ functions only as a bromide-ion trapping agent and not as a catalyst. The addition of reaction mixture to aqueous acrylamide solution did not initiate polymerization showing the absence of free radical species (proper control experiments were also performed).

DISCUSSION

Pryde and Soper [16], Morris et al. [17], and Bishop and Jennings [18] have shown the existence of similar equilibria in acid and alkaline solutions of *N*-metallo-*N*-haloarylsulfonamides. Bromamine-T ((*p*-$MeC_6H_4SO_2NBrNa \cdot 3H_2O$ or RNBrNa), like its chlorine analog chloramine-T, behaves as a strong electrolyte in aqueous solutions forming different species as shown in eqs. (3–7).

$$RNBrNa \rightleftharpoons RNBr^- + Na^+ \quad (3)$$

$$RNBr^- + H^+ \rightleftharpoons RNHBr \quad (4)$$

$$RNHBr + H_2O \rightleftharpoons RNH_2 + HOBr \quad (5)$$

$$2\ RNHBr \overset{K'_d}{\rightleftharpoons} RNH_2 + RNBr_2 \quad (6)$$

$$HOBr + H^+ \rightleftharpoons H_2OBr^+ \quad (7)$$

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 law according to eq. (6), which is contrary to the experimental observations. As eq. (5) indicates a slow hydrolysis, if HOBr were the primary oxidizing species, a first-order retardation of the rate by the added RNH_2 would be expected contrary to the experimental result. Hardy and Johnston [19], who have studied the pH dependent relative concentrations of the species present in acidified bromamine-B solutions of comparable molarities, have shown that its acid form is the predominant species. Extending the same argument to bromamine-T, it is safe to assume that the acid form RNHBr is the likely oxidizing species in acid medium. Narayanan and Rao [20] and Subhashini et al. [21] have reported that monohaloamines can be further protonated at pH < 2 as in the following eqs. (8) and (9) for chloramine-T (*p*-$MeC_6H_4SO_2NHCl$) and chloramine-B ($C_6H_5SO_2NHCl$), respectively:

$$p\text{-}MeC_6H_4SO_2NHCl + H^+ \rightleftharpoons (p\text{-}MeC_6H_4SO_2NH_2Cl)^+ \quad (8)$$

$$C_6H_5SO_2NHCl + H^+ \rightleftharpoons (C_6H_5SO_2NH_2Cl)^+ \quad (9)$$

Therefore, in higher acidic conditions, RNHBr of BAT and R′NBr of NBS and NBP can be protonated as follows:

$$\underset{(OX)}{RNHBr} + H^+ \rightleftharpoons \underset{(OXH^+)}{(RNH_2Br)^+} \quad (10)$$

$$\underset{(OX)}{R'NBr} + H^+ \rightleftharpoons \underset{(OXH^+)}{(R'NHBr)^+} \quad (11)$$

In the present investigations, the retardation of the rate by H^+ ion indicates that the unprotonated oxidant (OX) is the active oxidizing species. This is being supported by the similar kinetic parameters observed in the oxidation of ASP (or S) by the three oxidants, BAT, NBS, and NBP in acid medium. Hence, a general mechanism (Scheme I) is proposed for the observed kinetics.

$OXH^+ \overset{K_1}{\rightleftharpoons} OX + H^+$ fast (i)

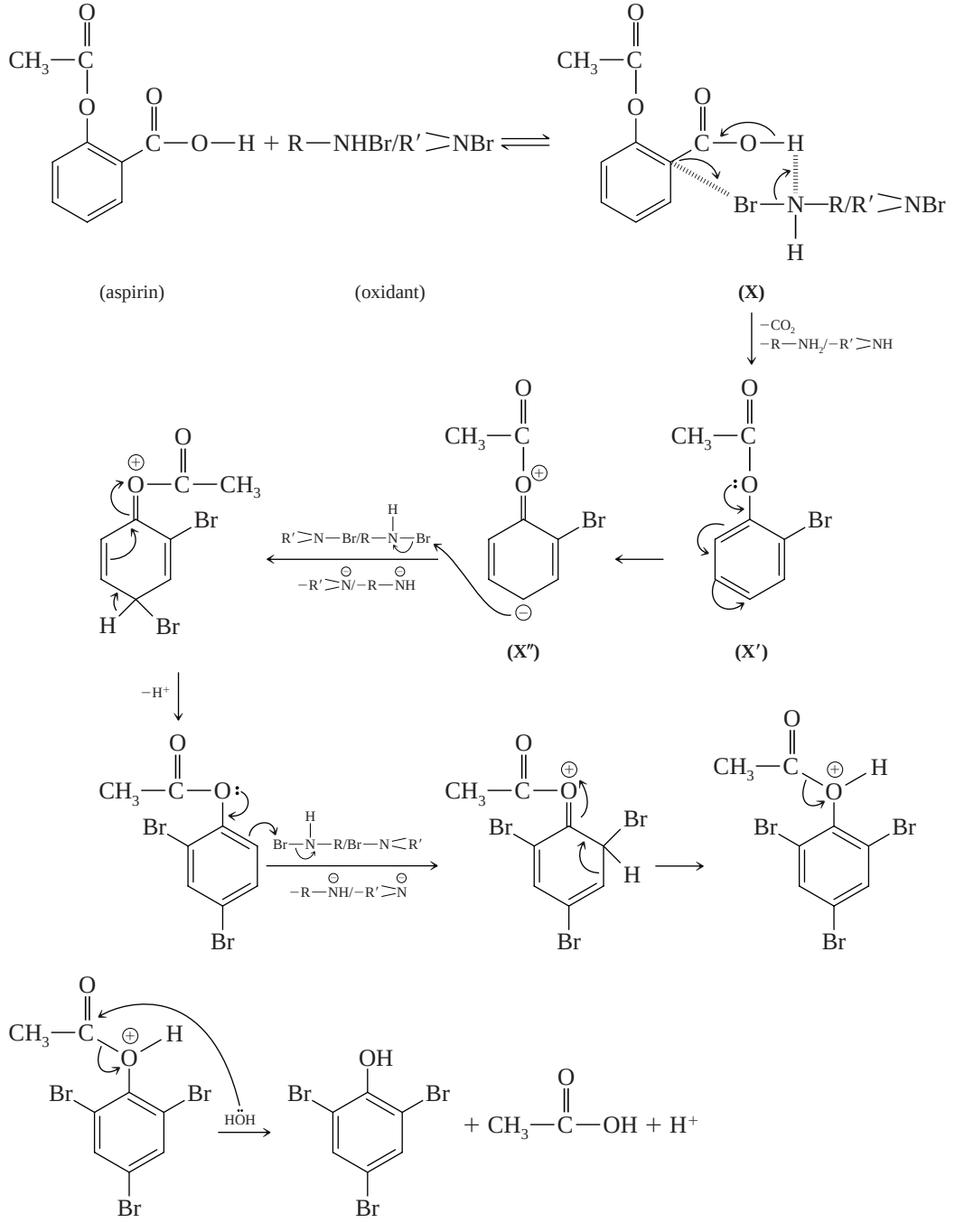
$OX + S \overset{K_2}{\rightleftharpoons} X$ fast (ii)

$X \xrightarrow{k_3} X' + RNH_2$ or $R'NH$ slow (iii)

$X' + 2\,OX + H_2O \longrightarrow \longrightarrow \longrightarrow$ Products fast (iv)

Scheme I

Here the complexes X and X′ are as defined in Scheme II.



$R—NH^-/-R'\!>\!N^- + H^+/H^+ \longrightarrow R—NH_2/R'\!>\!NH$

Here R and R′ are as in eqs. (1) and (2).

Scheme II

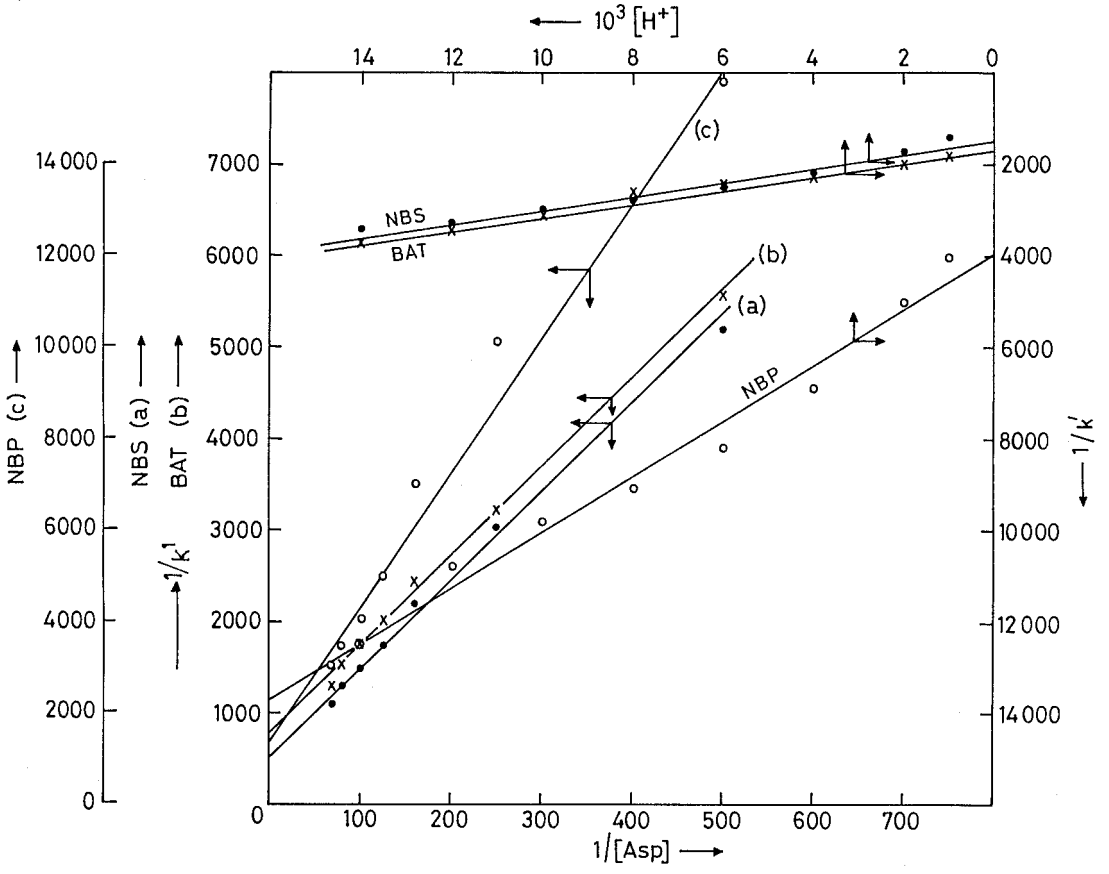


Figure 6 Plots of $1/k'$ vs. 1/[ASP] and $1/k'$ vs. $[H^+]$ at 303 K.

The total concentration of OX, from Scheme I, is given by eq. (12),

$$[OX]_t = [OXH^+] + [OX] + [X] \qquad (12)$$

which leads to the following rate law:

$$\text{Rate} = -d[OX]/dt = \frac{K_1K_2k_3[OX]_t[S]}{[H^+] + K_1\{1 + K_2[S]\}} \qquad (13)$$

The rate law (eq. (13)) is in agreement with the experimental data including a first-order in [oxidant], a fractional-order in [ASP or S], and an inverse fractional-order in $[H^+]$.

Since rate $= k_{obs}[OX]_t$, eq. (13) can be transformed as,

$$\frac{1}{k^1} = \frac{1}{k_{obs}} = \frac{1}{K_2k_3[S]}\left\{\frac{[H^+]}{K_1} + 1\right\} + \frac{1}{k_3} \qquad (14)$$

The plots of $1/k'$ vs. 1/[S] and $1/k'$ vs. $[H^+]$ at constant temperature and other reaction conditions, from eq. (14), were linear (Fig. 6). From the slopes and intercepts of these plots, values of formation constants K_1 and K_2 and decomposition constant k_3 were calculated (Table VI). The near constant values of K_1, K_2, and k_3 support the proposed general mechanism for the oxidation of aspirin by all the three oxidants. Since the rate was fractional in $[S]_o$, Michaelis–Menten kinetics were adopted. The effect of $[S]_o$ on the rate at different temperatures (297–318 K) was shown by the plots $1/k'$ vs. 1/[S]. Using the calculated k_3 values, activation parameters for the decomposition step (step iii of Scheme I) were evaluated using the Arrhenius

Table VI The Values of K_1, K_2, and k_3 Determined from Double Reciprocal Plots[a]

Oxidant	$K_1 \times 10^3$/M	K_2/M	$k_3 \times 10^3/s^{-1}$
NBS	5.72	72.73	1.82
BAT	7.52	100.0	1.25
NBS	3.87	79.4	0.66

[a] Calculated from the plots of $1/k'$ vs. 1/[ASP] and $1/k'$ vs. $[H^+]$ at 303 K using eq. (14) under conditions given in Tables I and II.

and Eyring plots of log k_3 vs. 1/T and ln (k_3/T) vs. 1/T, respectively. These data are also presented in Table V. A detailed mechanistic interpretation of the aspirin-oxidant reaction in acid medium is presented in Scheme II. In each case, an electrophilic attack by the oxidant (RNHBr of BAT or R′NBr of NBS/NBP) through its positive bromine forms the complex X in the first step. In the second step, X undergoes decarboxylation and ortho bromination of aspirin forming the intermediate X′. The species X′ on intramolecular rearrangement and further brominations forms an acetyl-tribromocationic intermediate of aspirin. The hydrolysis of the cationic species yields the products, 2,4,6-tribromophenol and acetic acid.

The reduction products (RNH_2 or R′NH) do not influence the rate showing that it is not involved in a preequilibrium. The change in the ionic strength of the medium does not alter the rate indicating that nonionic 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 that D_3O^+ is a stronger acid than the hydronium ion [22] 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. For the limiting case of zero angle of approach between two dipoles or an anion-dipole system, Amis [23] has shown that a plot of log k_{obs} 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 negative dielectric effect, in the present studies, supports the interaction of two dipoles in the rate limiting step in Scheme I [19].

Under comparable conditions, it was observed that the rate of oxidation of ASP increases in the order: NBS > BAT > NBP. This is mainly due to electronic factor. The E_a is highest for the slowest reaction and vice versa, indicating that it is enthalpy controlled (Table V). The moderate E_a values support the proposed mechanism while low values of $\Delta S^{\neq}$ indicate the formation of rigid associative transition states. The near constancy of $\Delta G^{\neq}$ values suggest that the oxidation of ASP by all the three oxidants occurs by a similar mechanism.

Our thanks to Professor M. A. Pasha, Department of Chemistry, Bangalore University, for helpful discussions.

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