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Mechanistic investigation of oxidation of paracetamol by sodium N-chlorobenzenesulphonamide in acid medium

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Abstract. Oxidation of paracetamol (PAM) by sodium N-chlorobenzenesulphonamide (chloramine-B or CAB) in $HClO_4$ medium at 30°C was studied. The rate is first order in $[CAB]_0$ and fractional order each in $[PAM]_0$ and $[H^+]$. Variation of ionic strength and addition of the reaction product benzenesulphonamide or halide ions had no significant effect on the reaction rate. The solvent isotope effect was studied using D_2O. Decrease in dielectric constant of the medium increases the rate. Activation parameters for the overall reaction have been computed. Michaelis–Menten type of kinetics has been proposed and activation parameters for the rate-limiting step have also been computed. 4-Amino-2,6-dichlorophenol was identified as the oxidation product of PAM. A mechanism consistent with the observed results is proposed and discussed.

Keywords. Paracetamol; kinetics of oxidation; chloramine-B; sodium N-chlorobenzenesulphonamide.

1. Introduction

Considerable attention has centred around the chemistry of N-metallo-N-arylhalosulphonamides, generally known as organic haloamines, because of their versatility, and their behaviour both as bases and nucleophiles. Chloramine-T (CAT), a by-product in saccharin manufacture, is well-known as an analytical reagent, and the mechanistic aspects of its reactions have been well-documented [1–3]. The benzene analogue sodium N-chlorobenzenesulphonamide or chloramine-B ($C_2H_5SO_2NClNa.\ 1{\cdot}5\ H_2O$; CAB) is gaining importance as a mild oxidant [4–6]. It can be easily prepared from benzenesulphonamide and chlorine.

Although the oxidation of organic and inorganic substrates with CAB has been studied, little attention has been focussed on CAB's reactions with pharmaceuticals, particularly with respect to the oxidation kinetics of antipyretics. The substrate, paracetamol (4′-hydroxyacetanilide or 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 drug in the literature. We therefore wished to study the oxidation kinetics of this drug by N-haloamine to see if we could understand the

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mechanisms of metabolic conversion of paracetamol in biological systems and also identify the reactive species of the oxidant in aqueous acid. The results are discussed in this communication.

2. Experimental

Chloramine-B was prepared[7] by passing chlorine through a solution of benzenesulphonamide in 4 mol dm^{-3} NaOH for an hour. The product was collected, dried and recrystallized from water (m.p. 170°C with decomposition). Its purity was checked by iodometry for its active chlorine content and also by its ^1H and ^{13}C-NMR spectra. An aqueous solution of CAB 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 the high ionic strength (I = 0·5 mol dm^{-3}) of the medium. Heavy water (D_2O, 99·2%) was supplied by the Bhabha Atomic Research Centre, Mumbai. Triple-distilled water was used throughout where required.

2.1 *Kinetic measurements*

The reaction was carried out under pseudo-first order condition ([PAM]>>[CAB]) 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 thermostatted at 30°C for thermal equilibrium. A measured amount of CAB, also thermostatted at the same temperature, was rapidly added to the mixture. The progress of the reaction was monitored up to two half-lives by iodometric determination of unreacted CAB 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[CAB] vs time plots were reproducible to within ± 3–4%.

2.2 *Stoichiometry and product analysis*

Reaction mixtures containing varying ratios of CAB to PAM ([CAB]>>[PAM]) in the presence of 0·02 mol dm^{-3} $HClO_4$ were equilibrated at 30°C for 24 h. Estimation of the unreacted CAB showed a 1:2 stoichiometry:

$$C_8H_9NO_2 + 2PhSO_2NClNa + 2H_3O^+ \rightarrow C_6H_5NOCl_2 + 2PhSO_2NH_2 + CH_3COOH + H_2O + 2Na^+. \quad (1)$$

The reduction product of CAB, benzenesulphonamide ($PhSO_2NH_2$), was recrystallized from dichloromethane/petroleum ether (m.p. = 149–150°C, lit. m.p. = 150–152°C. An *Rf* 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-dichlorophenol, was subjected to elementary analysis and Beilstein's test, and the functional groups were identified by the usual tests. It was further confirmed by its m.p. 168–169°C (Lit. m.p. 167–170°C).

3. Results

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

Under pseudo-first order conditions of [PAM]>>[CAB] at constant $[H^+]$ and temperature, plots of log[CAB] vs time were linear indicating first-order dependence of rate on $[CAB]_0$. The rate constant k' was not affected by a change in $[CAB]_0$ (table 1). Values of k' increased with increase in $[PAM]_0$ (table 1) and the plot of $\log k'$ vs $\log[PAM]_0$ was linear with a slope of 0·49 indicating fractional-order dependence of rate on $[PAM]_0$. Further, a plot of k' vs $[PAM]_0$ was linear, with an intercept confirming the fractional-order dependence on $[PAM]_0$. 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 fractional-order dependence of rate on $[H^+]$.

Addition of the reaction product, benzenesulphonamide (PSO_2NH_2; 0·0005–0.003 mol dm^{-3}) and halide ions Cl^- or Br^- ions in the form of NaCl or NaBr (0·0005–0·003 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 the 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 CAB under the experimental conditions. This was taken into account in the calculation of net reaction rate constant for the oxidation of PAM in each case.

The reaction was studied at different temperatures and the activation parameters for the composite reaction were computed (table 2) from the linear Arrhenius plot of log k' vs $1/T$. The rate constants at 298, 303, 308 and 313 K were 1·20, 1·97, 3·34 and $5·75 \times 10^{-4}$ s^{-1} respectively. The solvent isotope effect was studied in D_2O wherein the reaction rate was further increased with $k' = 2·12 \times 10^{-4}$ s^{-1} in D_2O medium and $1·97 \times 10^{-4}$ s^{-1} in H_2O leading to a solvent isotope effect, $k'(H_2O)/k'(D_2O) = 0·93$. 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.

Table 1. Effect of varying concentrations of oxidant, substrate and acid on the rate of reaction.
$I = 0·5$ mol dm^{-3}, temperature = 30°C

10^3 $[CAB]_0$ (mol dm^{-3})	10^2 $[PAM]_0$ (mol dm^{-3})	10^2 $[HClO_4]$ (mol dm^{-3})	$k' \times 10^4$ (s^{-1})
0·8	2·0	2·0	2·02
1·0	2·0	2·0	1·97
1·2	2·0	2·0	1·95
1·4	2·0	2·0	1·99
1·6	2·0	2·0	2·00
1·0	0·5	2·0	0·98
1·0	1·0	2·0	1·45
1·0	4·0	2·0	2·70
1·0	6·0	2·0	3·50
1·0	2·0	0·5	0·81
1·0	2·0	1·0	1·20
1·0	2·0	4·0	3·05
1·0	2·0	6·0	4·10

Table 2. Kinetic and thermodynamic parameters for the oxidation of paracetamol by CAB in acid medium.

Thermodynamic parameters	Ea (kJ mol^{-1})	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	$\Delta G^{\#}$ (kJ mol^{-1})
Composite reaction	81·4	78·9	−55·8	97·8
Rate-limiting step	68·1	65·6	−93·1	93·8

4. Discussion

Chloramine-B is analogous to chloramine-T and exhibits similar equilibria in aqueous acidic and basic solutions[9]. In general, CAB undergoes a two electron change in its reactions. The reduction of CAB/$PhSO_2NH_2$ is *p*H dependent and decreases with increase in *p*H of the medium (values are 1·14 V at *p*H 0·65 and 0·50 V at *p*H 12 for CAT). Depending on the *p*H of the medium, CAB furnishes different types of reactive species in solution, such as $PhSO_2NHCl$, $PhSO_2NCl_2$, HOCl and H_2OCl^+ in acidic solutions[9–11]:

$$PhSO_2NClNa \rightleftharpoons PhSO_2NCl^- + Na^+, \tag{2}$$

$$PhSO_2NCl^- + H^+ \overset{K_a}{\rightleftharpoons} PhSO_2NHCl,\ K_a = 1{\cdot}5 \times 10^{-5} \text{ at } 25°C, \tag{3}$$

$$2PhSO_2NHCl \overset{K_d}{\rightleftharpoons} PhSO_2NH_2 + PhSO_2\,NCl_2,\ K_d = 0{\cdot}113 \text{ at } 25°C, \tag{4}$$

$$PhSO_2NCl_2 + H_2O \overset{K_h}{\rightleftharpoons} PhSO_2NHCl + HOCl, \tag{5}$$

$$PhSO_2NHCl + H_2O \overset{K'_h}{\rightleftharpoons} PhSO_2NH_2 + HOCl,\ K'_h = 1{\cdot}5 \times 10^{-5} \text{ at } 25°C, \tag{6}$$

$$HOCl \rightleftharpoons H^+ + OCl^-, \tag{7}$$

$$HOCl + H^+ \rightleftharpoons H_2OCl^+. \tag{8}$$

Therefore, the probable reactive species in acid solution of CAB are $PhSO_2NHCl$, $PhSO_2NCl_2$, HOCl and H_2OCl^+. The first-order dependence of rate on $[CAB]_0$ and the addition of $PhSO_2NH_2$ (benzenesulphonamide) having no effect on the reaction rate, both indicate that $PhSO_2NCl_2$ and HOCl may not be the reactive species [(4) and (6)] and, further, that these species are present in very low concentrations[9] at the experimental 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 in the rate-limiting step could be the conjugate acid, $PhSO_2NHCl$. Further, protonation of monochloromines (RNHCl) at *p*H < 2 according to (9) has been reported[12,13].

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

Here, when R = *p*-$CH_3C_6H_4SO_2$–, $K = 1{\cdot}02 \times 10^2$ at 25°C, while with R = $C_6H_5SO_2$–, $K = 61 \pm 5$ at 25°C for CAT and CAB respectively. Hence, it is likely that $PhSO_2NHCl$ is further protonated in acid media. Based on the preceding discussion and observed kinetic results, a mechanism is proposed for the oxidation of PAM by CAB in acid medium (scheme 1).

$$PhSO_2NHCl + H^+ \overset{K_1}{\rightleftharpoons} PhSO_2\overset{+}{N}H_2Cl \qquad \text{(i) fast}$$

$$PhSO_2\overset{+}{N}H_2Cl + PAM \overset{K_2}{\rightleftharpoons} X \qquad \text{(ii) fast}$$

$$X \xrightarrow{k_3} X' \qquad \text{(iii) slow \& r.l.s.}$$

$$X' + PhSO_2\overset{+}{N}H_2Cl \xrightarrow{k_4} \text{Products} \qquad \text{(iv) fast}$$

Scheme 1.

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 CAB in acid medium is proposed. In this the protonated oxidant species $PhSO_2\overset{+}{N}H_2Cl$ formed from $PhSO_2NHCl$ and H^+ reacts with the substrate in a fast equilibrium step to form the substrate–CAB complex (X). This decomposes in a rate-limiting step to the products. Two moles of the oxidant is consumed to yield the ultimate products.

Step (iii) of scheme 1 determines the overall rate,

$$\text{rate} = -\text{d}\,[\text{CAB}]/\text{d}t = k_3\,[\text{X}]. \quad (10)$$

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

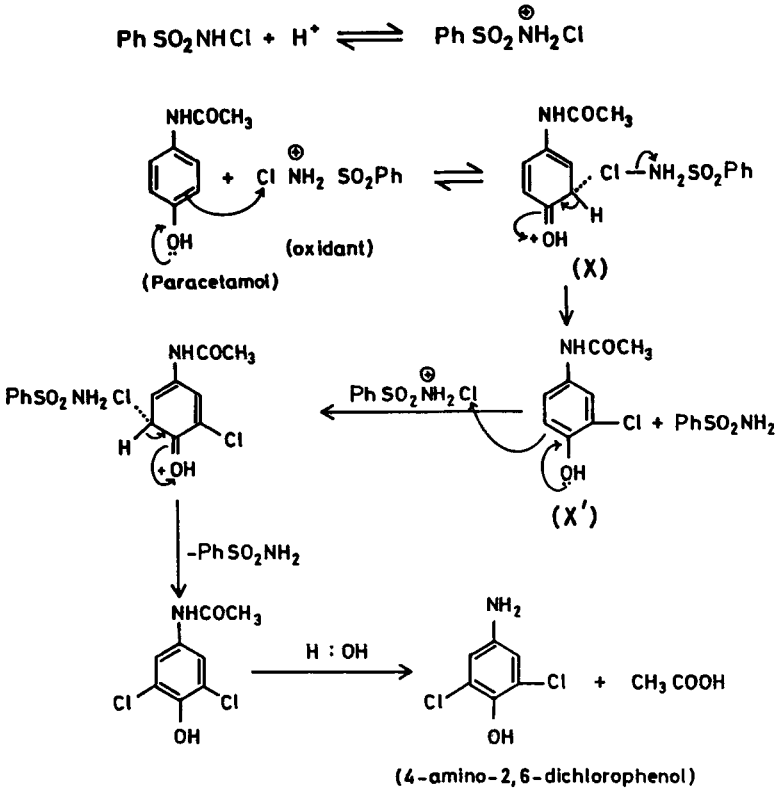
$$[CAB]_t = [PhSO_2NHCl] + [PhSO_2\overset{+}{N}H_2Cl]\,[X],$$

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

$$\text{rate} = \frac{-\text{d}[\text{CAB}]}{\text{d}t} = \frac{K_1K_2k_3[\text{CAB}]_t[\text{PAM}][\text{H}^+]}{1 + K_1[\text{H}^+] + K_1K_2[\text{PAM}][\text{H}^+]}. \quad (11)$$

Rate law (11) is in agreement with experimental results and can be written as,

$$\frac{1}{k'} = \frac{1}{K_2k_3[\text{PAM}]}\left\{\frac{1}{K_1[\text{H}^+]} + 1\right\} + \frac{1}{k_3}. \quad (12)$$



Scheme 2.

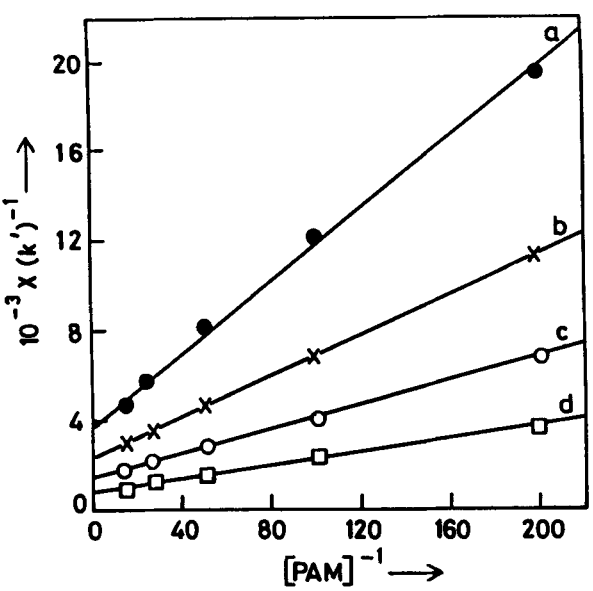


Figure 1. Double reciprocal plots of $1/k'$ vs 1/[PAM] at (a) 298, (b) 303, (c) 308 and (d) 313 K. $[CAB]_0 = 0{\cdot}001$ mol dm^{-3}; $[HClO_4] = 0{\cdot}02$ mol dm^{-3} and $I = 0{\cdot}5$ mol dm^{-3}.

Since the rate was fractional in $[PAM]_0$, Michaelis–Menten kinetics [14] were adopted to study the effect of $[PAM]_0$ on the rate at different temperatures, and by plotting $1/k'$ vs $1/[PAM]_0$ (figure 1), values of k_3 obtained were $10^4\ k_3(s^{-1})$, 2·78 (298 K), 4·35 (303 K), 7·14 (308 K) and 12·5 (313 K). Activation parameters (table 2) for the rate-limiting step were computed from the linear Arrhenius plot of log k_3 vs $1/T$.

Rate increases with decrease in dielectric constant of the medium indicating a charge dispersal in the transition state which is less polar than the reactants [15]. It is interesting that the rate increased only slightly in D_2O medium, contrary to expectations [16] in proton-catalysed reactions. It is well-known that D_3O^+ is a stronger acid than H_3O^+ (~2–3 times greater) and hence a rate increase of the same magnitude is expected in D_2O. However, it is 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 isotope effect $[k'(H_2O)/k'(D_2O) < 1]$ resulting in a net effect, $k'_H/k'_D \geq 1$. Magnitude is smaller and 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 fewer degrees of freedom.

The reduction product ($PhSO_2NH_2$) does not influence the rate, showing that it is not involved in pre-equilibrium. 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. Addition of halide ions has no effect on the rate indicating that no interhalogen or free chlorine is formed. All these observations also confirm the proposed mechanism.

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