MECHANISM OF OXIDATION OF CAFFEINE BY SODIUM N-CHLORO BENZENE SULPHONAMIDE: A KINETIC STUDY

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Abstract—The oxidation of caffeine by sodium N-chloro benzene sulphonamide (Chloramine-B, CAB) in HCl (0.02–0.10 M) over the temperature range 303–323 K shows first order dependence on [CAB], fractional orders in $[H^+]$ and $[Cl^-]$ and is independent of substrate concentration, ionic strength. Addition of the reaction product benzene sulphonamide have no influence on the reaction rate, which increases in D_2O a value of 1.41 for the inverse solvent isotope effect. On decreasing the dielectric constant of the medium by adding t-butanol, the rate decreases slightly. The kinetic data suggest a complex formation between $RNCl^-$ and HCl. Thermodyanamic parameters are evaluated. Rate expression and probable mechanism for the observed kinetics have been suggested.

The solution chemistry of organic haloamines is complex because of their ability to act as a source of several oxidising or chlorinating species. As a result they react with a wide range of functional groups affecting an array of molecular transformations. Aromatic sulphonyl haloamines are compounds with positive halogen. The well known N-haloamines are Chloramine-T (CAT) and Chloramine-B (CAB). The N–Cl bond in both CAT and CAB is highly polar and hence these two compounds are fairly strong electrophiles, since chlorine leaves as Cl^+ during reactions. Exhaustive investigations have been made on the kinetics and mechanism of oxidation of many substrates by CAT.[1–5] Review of the literature[1] reveals the absence of systematic kinetic investigations with CAB. Recently Mukherjee and Banerji[6] have reported on the kinetics and mechanism of oxidation of substituted benzyl alcohols in acetic acid medium by CAB.

Caffeine (1,3,7-trimethylxanthine) is a stimulant present in pharamaceuticals, food products, plant materials and drinks. Recently caffeine has been assayed by using CAT,[7] and no information is available about the mechanism, which may be important from a metabolic point of view. The present communication reports the kinetics and mechanism of oxidation of caffeine by CAB in HCl medium.
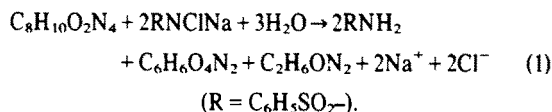
RESULTS

Oxidation of caffeine by CAB was carried out at 303 K in mineral acids (HCl, H_2SO_4 and $HClO_4$) of various concentrations. The reaction was facile in HCl and a detailed investigation was made on the kinetics and mechanism of oxidation of caffeine by CAB in HCl medium.

The oxidation of caffeine by CAB in HCl medium results in the formation of methylurea and alloxan. No detectable further oxidation of reaction products could be observed under the present experimental conditions.

Stoichiometry. Excess of CAB was allowed to react with 5×10^{-2} M caffeine in presence of various concentrations $(1 \times 10^{-2}$ M $– 1 \times 10^{-1}$ M) of HCl at 303 K. Unreacted CAB was estimated after 24 hr. Values of

$\Delta[CAB]/\Delta[Caffeine]$ in Table 1 suggest the overall reaction (1).

$$C_8H_{10}O_2N_4 + 2RNClNa + 3H_2O \rightarrow 2RNH_2$$
$$+ C_6H_6O_4N_2 + C_2H_6ON_2 + 2Na^+ + 2Cl^- \quad (1)$$
$$(R = C_6H_5SO_2–).$$

Rate laws. The kinetics of oxidation of caffeine $(1 \times 10^{-2}$ M) by CAB at constant concentration of HCl $(4 \times 10^{-2}$ M) was studied at several initial concentrations $(5 \times 10^{-4}–3 \times 10^{-3}$ M) of CAB. Plots of $[CAB]_t$ vs time are linear indicating a first-order dependence of rate on [CAB]. The constancy of rate constant (k^1) at different concentrations of CAB calculated from the integrated first-order rate equation (Table 2) gave further evidence for the first-order dependence of rate on [CAB].

The oxidation was carried out with different concentrations $(5 \times 10^{-3}–5 \times 10^{-2}$ M) of caffeine in 4×10^{-2} M HCl containing 1×10^{-3} M CAB. The reaction rate was independent of initial concentration of caffeine (Table 2) indicating zero-order with respect to [Caffeine].

The reactions were carried out with 1×10^{-3} M CAB and 1×10^{-2} M caffeine in the presence of various concentrations $(2 \times 10^{-2}–1 \times 10^{-1}$ M) of HCl at 303 K. The rate increased with increase in concentration of HCl. The reaction was fractional order (1.5) with respect [HCl]. In order to determine the order of the reaction with respect to $[H^+]$ and $[Cl^-]$, the reaction was also studied by varying both $[H^+]$ and $[Cl^-]$ ions (Table 3). Fractional order dependence of rate of reaction on each $[H^+]$ and $[Cl^-]$ was observed (Table 6).

Addition of benzene sulphonamide and change in ionic strength in the reaction medium had no effect on the rate of of oxidation (Table 2). The rate constants for the oxidation of caffeine by CAB in H_2O and D_2O were determined (Table 2) at 303 K. From these data inverse

Table 1. Stoichiometry of oxidation of caffeine by CAB

10[HCl]/M	0.1	0.2	0.3	0.4	0.5
$\Delta[CAB]/\Delta[Caffeine]$	1.92	1.95	1.94	2.01	1.00

Table 2. Effect of concentration of reactants on the rate at 303 K

10^3[CAB]/M	10^2[Caffeine]/M	10^4 k'/s
0.5	1.0	3.49
0.75	1.0	3.47
1.0	1.0	3.52
2.0	1.0	3.58
3.0	1.0	3.62
1.0	0.5	3.50
1.0	2.0	3.51
1.0	3.0	3.52
1.0	4.0	3.50
1.0	5.0	3.54
1.0	1.0	3.49*
1.0	1.0	3.59†
1.0	1.0	4.99‡

[HCl] = 4×10^{-2} M.
*2×10^{-3} M benzene sulfonamide.
†0.5 M NaClO$_4$.
‡in D$_2$O medium.

Table 3. Dependence of reaction rate on [H$^+$] and [Cl$^-$] at 303 K

10[HCl]/M	10[NaCl]/M	10^4 k'/s
0.2	0.8	5.12
0.4	0.6	7.67
0.6	0.4	10.15
0.8	0.2	12.21
1.0	—	14.39
0.4	—	3.51
0.4	0.2	4.82
0.4	0.4	6.14
0.4	0.6	7.42

[CAB] = 1×10^{-3} M, [Caffeine] = 1×10^{-2} M.

solvent isotope effect was calculated. At constant concentration of each of CAB (1×10^{-3} M), caffeine (1×10^{-2} M) and HCl (4×10^{-2} M), the reaction was carried out in the mixture of t-butanol and water of various compositions at 303 K. The reaction rate decreased slightly with increase in composition of t-butanol (Table 4).

Effect of temperature on the rate of oxidation of caffeine (1×10^{-2} M) by CAB (1×10^{-3} M) in presence of HCl (4×10^{-2} M) was studied (Table 5) from the Arrhenius plot, activation parameters (ΔH^+, ΔS^+ and ΔG^+) were calculated (Table 6). Entropy of activation was negative for the oxidation reaction.

DISCUSSION

Although the equilibria present in acidified CAT solutions have been clearly established,[8,9] no detailed in-

Table 4. Effect of solvent composition on the reaction rate at 303 K

% t-butanol	10	20	30	40	50
10^4 k'/s	3.39	3.24	3.01	2.76	2.59

[CAB] = 1×10^{-3} M, [Caffeine] = 1×10^{-2} M, [HCl] = 4×10^{-2} M.
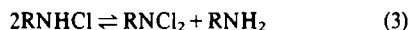
Table 5. Effect of temperature on the reaction rate

Temperature (K)	303	308	313	318	323
10^4 k'/s	3.52	5.72	8.68	11.83	16.77

[CAB] = 1×10^{-3} M, [Caffeine] = 1×10^{-2} M, [HCl] = 4×10^{-2} M.

Table 6. Kinetic and thermodynamic parameters for the oxidation of caffeine by CAB in HCl medium

Kinetic		Thermodynamic	
Reactants	Order w.r.t. (n)	Parameter	Values
[CAB]$_0$	1.00	E_a	60.86 kJ mol^{-1}
[Caffeine]	Zero	$\Delta H^‡$	58.31 kJ mol^{-1}
[HCl]	1.50	$\Delta G^‡$	79.65 kJ mol^{-1}
[H$^+$]	0.68	$\Delta S^‡$	-70.39 kJ mol^{-1}
[Cl$^-$]	0.82	A	1.39×10^9 s^{-1}

formation is available about the oxidative species present in acid solutions of CAB (RNClNa, where R=C$_6$H$_5$SO$_2$–). Zilberg[10] has shown that acidification of aqueous CAB gives dichloramine-B (RNCl$_2$) and benzene sulphonamide (RNH$_2$). Mogilevski et al.[11] have reported the presence of HOCl in acidified CAB solutions. Detailed conductometric and potentiometric investigations by Mahadevappa et al.[12,13] have shown that comparable equilibria exist in acidified CAT and CAB solutions and the conjugate acid of CAB is a fairly strong acid. One could expect the following equilibria in the acidified aqueous solution of CAB.

$$RNCl^- + H_3O^+ \rightleftharpoons RNHCl + H_2O \qquad (2)$$

$$2RNHCl \rightleftharpoons RNCl_2 + RNH_2 \qquad (3)$$

$$RNHCl + H_2O \rightleftharpoons RNH_2 + HOCl. \qquad (4)$$

Hence the probable oxidising species in acidified CAB solutions are RNHCl, RNCl$_2$ and HOCl.

In the present system if RNCl$_2$ were to be the active species, the rate law predicts a second order dependence[14] of rate on [CAB], which is contrary to the experimental observations. In the case of CAT solutions, Pryde and Soper[15] have shown that the direct interaction of conjugate acid with the substrate could be slow when compared with HOCl, which can attack at a faster rate. The reaction is also not retarded by the presence of RNH$_2$ (Table 2). It is shown[15,16] that HOCl gives Cl$_2$ in acidified chloride solution. RNHCl gives Cl$_2$ in higher acidic chloride solution[2,17] and both H$^+$ and Cl$^-$ ions suppress the hydrolysis[18] of Cl$_2$. Hence in the present system one can expect RNHCl or Cl$_2$ to be the effective oxidising species. Some experiments were carried out with Cl$_2$ water under identical conditions. It is found that kinetic data with Cl$_2$ are significantly greater than those with CAB (Fig. 1). Therefore, in the present system one could expect RNHCl to be the effective oxidising species.

The fractional order dependence of rate on [H$^+$] and [Cl$^-$] is indicative of the intermediate complex formation between CAB (RNCl$^-$) and HCl. But the structure of the complex (x) is not established. However a similar type of
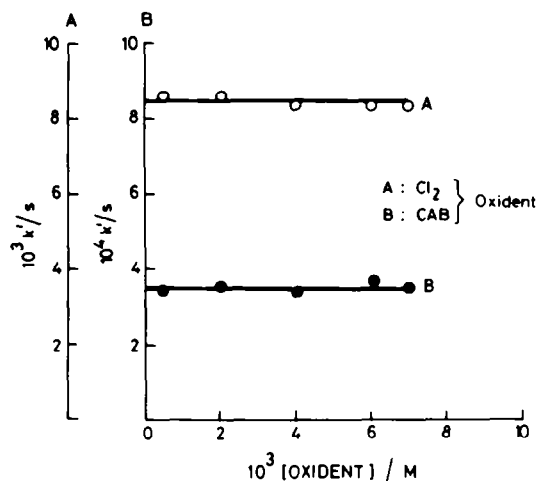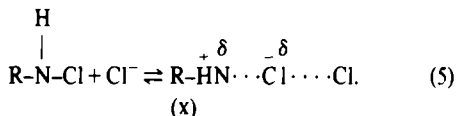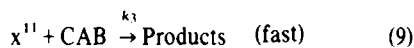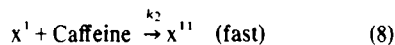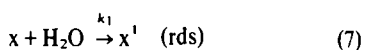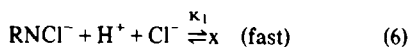
Fig. 1. Relationship between k_{CAB} and k_{Cl_2} at 303 K. [HCl] = 0.04 M, [Caffeine] = 1×10^{-2} M.

complex has been proposed for the oxidation of secondary alcohols[19] and benzyl alcohol[2] by N-chlorosuccinimide and CAT respectively in lower acidic chloride solutions.

$$\begin{array}{c} H \\ | \\ R-N-Cl + Cl^- \rightleftharpoons R-\overset{+}{H}N\cdots\overset{\delta}{Cl}\cdots\overset{-\delta}{Cl}. \\ (x) \end{array} \qquad (5)$$

The observed results indicate that the reaction is governed by the rate of disproportion of the complex at the rate determining step with the pre-equilibrium step involving the complex formation between $RNCl^-$ and HCl. Based on these facts, the following reaction scheme may be written.

$$RNCl^- + H^+ + Cl^- \overset{K_1}{\rightleftharpoons} x \quad \text{(fast)} \qquad (6)$$

$$x + H_2O \overset{k_1}{\rightarrow} x^1 \quad \text{(rds)} \qquad (7)$$

$$x^1 + \text{Caffeine} \overset{k_2}{\rightarrow} x^{11} \quad \text{(fast)} \qquad (8)$$

$$x^{11} + \text{CAB} \overset{k_3}{\rightarrow} \text{Products} \quad \text{(fast)} \qquad (9)$$

Assuming total concentration of CAB as $[CAB]_T = [RNCl^-] + [x]$, with $[Cl^-]_T \gg [CAB]_T$, one could obtain,

$$[x] = \frac{K_1[CAB]_T[H^+][Cl^-]}{1 + K_1[H^+][Cl^-]}$$

since,

$$-\frac{d[CAB]}{dt} = k_1[x] = \frac{K_1 k_1[H^+][Cl^-][CAB]_T}{1 + K_1[H^+][Cl^-]}$$

$$k^1 = \frac{K_1 k_1[H^+][Cl^-]}{1 + K_1[H^+][Cl^-]}$$

where k^1 = observed rate constant.

$$\frac{1}{k^1} = \frac{1}{K_1 k_1[H^+][Cl^-]} + \frac{1}{K_1} \qquad (10)$$

This equation predicts a linear relationship between $1/k^1$ and $1/[HCl]$ or $1/[Cl^-]$ {at constant $[H^+]$} or $1/[H^+]$ {at constant $[Cl^-]$}. The values of k_1 and K_1 computed independently from the above method are agree very well.

($k_1 = 2 \times 10^{-3}$, 2.2×10^{-3} and $K_1 = 1.2 \times 10^2$, 1.5×10^2).

The negative entropy of activation probably indicate the formation of a compact activated complex. The constancy of rate constant by the addition of $HClO_4$ and benzene sulphonamide supports the proposed mechanism. A slight negative dielectric constant effect (Table 4) probably supports dipole–dipole interaction[20] in rate determining step. Since D_3O^+ is about three times stronger than H_3O^+, for acid catalysed reactions, the inverse isotope effect $k_{D_2O}/K_{H_2O} > 1$. The observed value 1.41 indicates[21] the contribution of a primary isotope

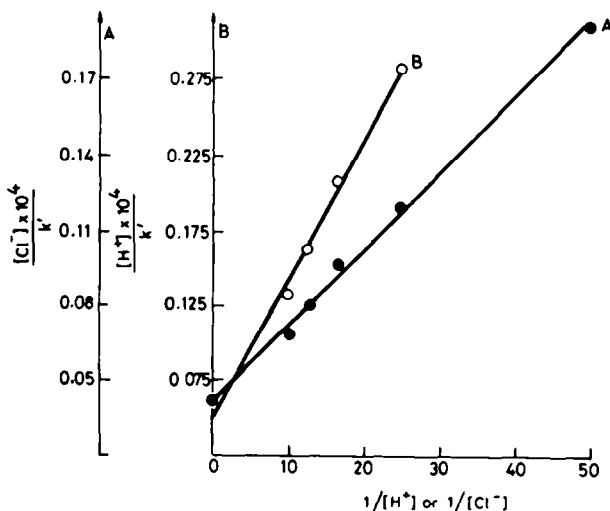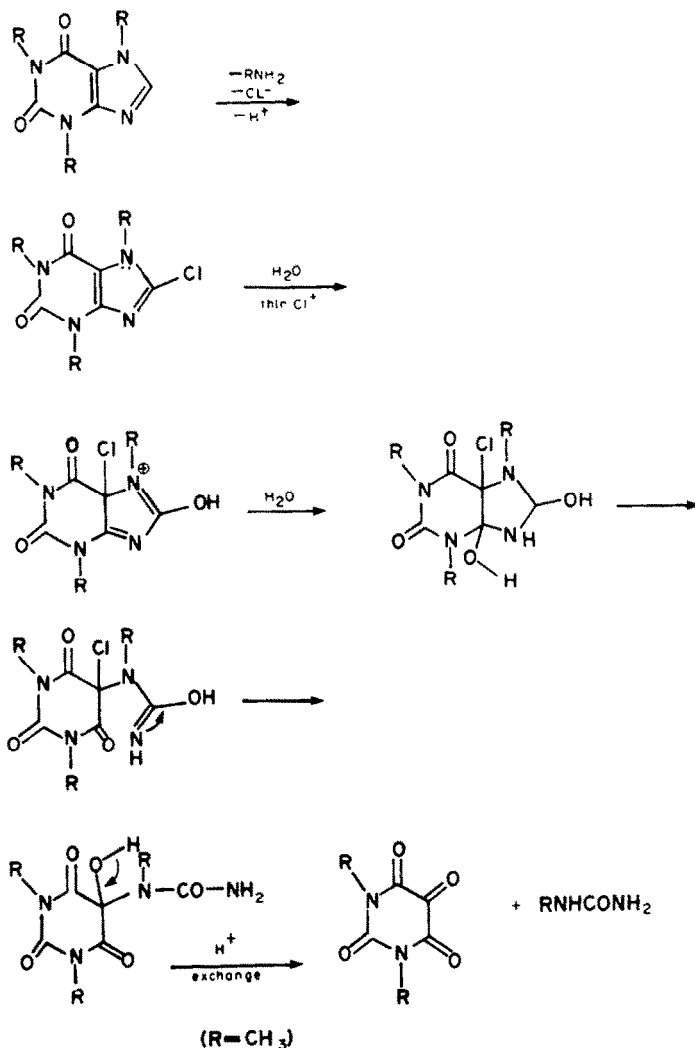Fig. 2. Double reciprocal plots of $1/k^1$ vs $1/[H^+]$ or $1/[Cl^-]$ at 303 K. [Caffeine] = 1×10^{-2} M, [CAB] = 1×10^{-3} M.

effect in the rate determining step (7), where a 0–D bond braking may be involved.

The electron flow during oxidation of caffeine is depicted as follows. The complex (x) may be expected to be electrophilic because of the central Cl atom which is bound to N and Cl. The nucleophilic attack by caffeine involves the unshared pair of electrons of the N of caffeine which are transferred ultimately to the N of CAB.

The first step is the electrophilic substitution:

^{13}C-NMR spectra. Caffeine (BDH) was recrystallised[23] before use. Solvent isotope experiments were performed in D_2O, supplied by the Bhabha Atomic Research Centre, Bombay, India. All reagents were of analytical grade.

Product analysis. The presence of benzene sulphonamide was identified by TLC[24] technique using a mixture of petroleum ether, chloroform and n-butanol (2:2:1 v/v) as the solvent, with iodine as the detecting reagent ($R_f = 0.88$). Alloxan was detected[25] as a purple spot after spraying with ammonium iron(II) sulphate solution. Methyl urea was identified by TLC[7] separation on silica gel plates using ethyl acetate-chloroform-water (3 + 3 +

(R═CH₃)

The 8-chloro caffeine undergoes substitution to form 8-hydroxy caffeine. The imidazole ring may be expected to undergo further electrophilic attack more readily because of the electron donating OH group. Thus two moles of CAB are used up. The intermediate cation cannot aromatise by H^+ loss and hence is readily attacked by H_2O to form the chloroydrin. Subsequent steps lead to H^+ exchange and SN_1 reactions.

EXPERIMENTAL

Materials. CAB was prepared[22] by bubbling Cl_2 gas through a solution of benzene sulphonamide in 4M NaOH at 343 K. The purity of the sample was checked by iodometric estimation of active chlorine and characterised by recording its FT ^{1}H and

4) as the solvent, and visualising with 5% iron(III) chloride-1% potassium hexacyanoferrate(III) (1 + 1).

Kinetic measurements. Experiments were carried out under pseudo-first-order conditions by keeping a large excess of (5 or more equiv) caffeine. The reactions were carried out at constant temperature 303 K (±0.1 K) and were followed iodometrically. The course of reaction was studied for two half lives. The pseudo-first-order rate constants obtained by plotting log [CAB] vs time, were reproducible with ± 5%.

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