

## Oxidation of caffeine by sodium N-bromo-*p*-toluene sulphonamide in HCl medium

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Kinetics of oxidation of caffeine by sodium N-bromo-*p*-toluenesulphonamide (BAT) in HCl medium has been studied at 288 K. The rate shows a first order dependence on [BAT], fractional orders in [H<sup>+</sup>] and [Cl<sup>-</sup>] and is independent of [caffeine]. Addition of the reaction product, *p*-toluenesulphonamide and varying ionic strength of the medium have no effect on the rate. The rate constant decreases with decrease in the dielectric constant of the medium. The solvent isotope effect has been studied in D<sub>2</sub>O medium. Activation parameters have been evaluated from the Arrhenius plots. The proposed reaction mechanism and the derived rate laws are consistent with the observed kinetics.

Electrolytic oxidation<sup>1</sup> of caffeine in acidic solution has been earlier reported. The kinetics and mechanism of oxidation of caffeine by sodium N-chloro-*p*-toluenesulphonamide has been reported<sup>2</sup> from our laboratory. However, no information is available on the oxidation of caffeine by corresponding bromine analogues. As a part of our mechanistic studies on the oxidation of caffeine by N-bromoamines, we report herein the kinetics of oxidation of caffeine with sodium N-bromo-*p*-toluenesulphonamide (bromamine-T) in HCl medium at 288 K.

### Experimental

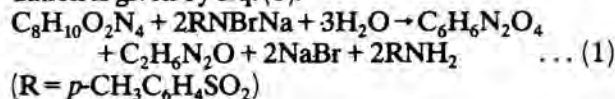
All solutions were prepared in doubly distilled water with AR grade chemicals. Bromamine-T (BAT) was prepared by the reported<sup>3</sup> procedure and its purity was checked by iodometry. An aqueous solution of BAT was prepared, standardised and preserved in brown bottles to prevent its photochemical deterioration. Caffeine (BDH) was recrystallised before use and aqueous solution of the substrate was prepared. Required ionic strength was maintained by adding NaClO<sub>4</sub> solu-

tion. Heavy water (D<sub>2</sub>O, 99.2%) was supplied by BARC, Bomaby, India.

The kinetic runs were made in glass stoppered pyrex boiling tubes coated black form outside. Mixtures containing requisite amounts of substrate. NaClO<sub>4</sub> and HCl were pre-equilibrated at 288 K. To this, aqueous solution of BAT of known concentration was added. The progress of the reaction was monitored iodometrically for two half lives by withdrawing aliquots of the reaction mixture at regular time intervals. The pseudo-first order rate constants calculated were reproducible within ± 3%.

### Stoichiometry and product analysis

Investigations under the conditions [BAT] ≫ [caffeine] revealed that one mole of caffeine reacts with two moles of BAT. The stoichiometry of oxidation is given by Eq. (1).



One of the reaction products, toluenesulphonamide (RNH<sub>2</sub>), was identified<sup>4</sup> by paper chromatography. Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl in ethanol as spray reagent (*R<sub>F</sub>* = 0.905). Methyl urea was identified<sup>5</sup> by TLC using ethyl acetate-chloroform-water (3:3:3) as the solvent. The colour was developed with 5% iron(III) chloride in 1% potassium hexacyanoferrate (III) (1:1). Alloxan was detected<sup>6</sup> as a purple spot after spraying with ammonium iron(II) sulphate solution.

### Results and discussion

With the substrate in excess, at constant [HCl] and [caffeine], plots of log[BAT] versus time were linear indicating a first order dependence of rate on [BAT]. The pseudo-first order rate constant (*k* = 1.03 × 10<sup>-3</sup> s<sup>-1</sup>) was unaffected by an increase in [caffeine], indicating that the rate was independent of substrate concentration.

At a fixed [BAT] and [substrate], the rate of reaction increased with increase in [HCl] from 0.36 × 10<sup>-3</sup> to 6.19 × 10<sup>-3</sup> s<sup>-1</sup> in the range 0.005-0.04 mol dm<sup>-3</sup>. Plot of log *k* versus log[HCl] was linear with a slope of 1.40. When total [Cl<sup>-</sup>] in the reaction mixture was kept constant at 0.05 mol dm<sup>-3</sup> by adding NaCl and [H<sup>+</sup>] was varied using

HCl, the rate increased from  $1.38 \times 10^{-3}$  to  $4.80 \times 10^{-3} \text{ s}^{-1}$  with increase in  $[\text{H}^+]$  in the range 0.01-0.05 mol dm<sup>-3</sup> under the conditions,  $[\text{BAT}] = 10.0 \times 10^{-4}$  mol dm<sup>-3</sup>;  $[\text{caffeine}] = 10.0 \times 10^{-3}$  mol dm<sup>-3</sup> at 288 K. A plot of  $\log k$  versus  $\log[\text{H}^+]$  was linear with a fractional slope of 0.72. Under the same conditions, at fixed  $[\text{H}^+]$  (0.01 mol dm<sup>-3</sup>), the rate increased from  $1.04 \times 10^{-3}$  to  $4.58 \times 10^{-3} \text{ s}^{-1}$  with the addition of NaCl in the range 0.01-0.08 mol dm<sup>-3</sup>. A plot of  $\log k$  versus  $\log[\text{Cl}^-]$  was linear with a fractional slope of 0.68.

Addition of Br<sup>-</sup> ions in the form of NaBr ( $8 \times 10^{-4}$ - $30 \times 10^{-4}$  mol dm<sup>-3</sup>) had negligible effect on the reaction rate. Addition of the reaction product, *p*-toluenesulphonamide ( $8 \times 10^{-4}$ - $30 \times 10^{-4}$  mol dm<sup>-3</sup>) had no effect on the rate indicating that it is not involved in a pre-equilibrium to the rate limiting step. Varying the ionic strength of the medium by adding NaClO<sub>4</sub> (0.1-0.5 mol dm<sup>-3</sup>) had no effect on the reaction rate.

The reaction was studied at different temperatures (283-298 K) and from the linear Arrhenius plots of  $\log k$  versus  $1/T$ , values of activation parameters for the reaction were computed. The rate constant at 283, 288, 293 and 298 K were 0.68, 1.04, 1.58 and  $2.15 \times 10^{-3} \text{ s}^{-1}$  respectively. The computed activation parameters were found to be  $E_a = 55.8$  kJ mol<sup>-1</sup>;  $\Delta H^\ddagger = 53.4$  kJ mol<sup>-1</sup>;  $\Delta S^\ddagger = -116.8$  JK<sup>-1</sup>mol<sup>-1</sup>;  $\Delta G^\ddagger = 87.3$  kJ mol<sup>-1</sup> and  $\log A = 9.9$ .

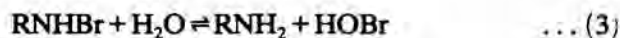
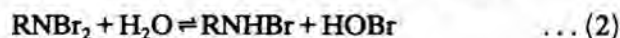
Solvent isotope effect was studied using D<sub>2</sub>O as solvent medium. The rate of reaction  $k_{\text{H}_2\text{O}}$  is  $1.04 \times 10^{-3} \text{ s}^{-1}$  and  $k_{\text{D}_2\text{O}}$  is  $1.53 \times 10^{-3} \text{ s}^{-1}$ .<sup>2</sup> The rate increased in D<sub>2</sub>O medium with a value of 1.47 for the inverse isotope effect.

Addition of methanol to reaction mixture (0-40% v/v) decreased the rate. Plot of  $\log k$  versus  $1/D$ , where  $D$  is the dielectric constant of the medium was linear with a negative slope. Blank experiments showed that oxidation of methanol by BAT during the experimental duration was negligible.

Addition of reaction mixture to acrylamide in an inert atmosphere did not initiate polymerisation of the latter showing the absence of free radicals in the reacting system.

Bromamine-T (RNBrNa) is analogous to CAT<sup>7</sup> and dissociates in aqueous solution giving RNBr<sup>-</sup> ion which can be protonated to give the free acid. The free acid has not been isolated but conductometric titration of CAT with cations has given ample proof<sup>8</sup> for its transformation in solution. BAT undergoes disproportionation giving rise to toluenesulphonamide (RNH<sub>2</sub>) and dibromamine-T

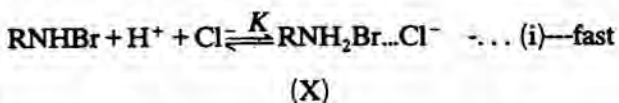
(RNBr<sub>2</sub>). The dibromamine-T and the free acid hydrolyse to give hypobromous acid (HOBr)



Finally HOBr ionizes as



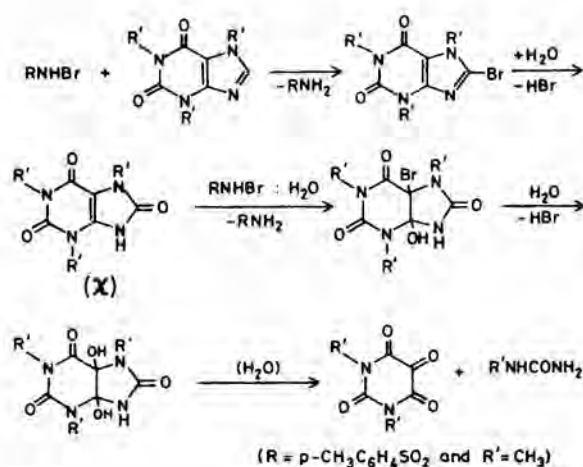
The possible oxidizing species in acidified BAT solutions are therefore RNHBr, RNBr<sub>2</sub>, HOBr and OBr<sup>-</sup> ion. If RNBr<sub>2</sub> were to be the reactive species, then the rate law predicts a second order dependence of rate on [BAT], which is contrary to the experimental observations. Equation (3) indicates that if HOBr is primarily involved, a first order retardation of rate by the added toluenesulphonamide is expected. However, no such effect was noticed. Hardy and Johnston<sup>9</sup> have shown that [RSO<sub>2</sub>NHBr] in aqueous bromamine-B ( $6 \times 10^{-3}$  mol dm<sup>-3</sup>) is high at pH 7 and is of the order  $4.1 \times 10^{-5}$  mol dm<sup>-3</sup> while [OBr<sup>-</sup>] =  $10^{-7}$  mol dm<sup>-3</sup>. Assuming the toluene derivative to be similar to the benzene derivative, a comparison with the concentration of species present in acidified CAT solution, calculated by Bishop and Jennings<sup>7</sup> would indicate that RNHBr is the likely oxidising species in acid medium. Recently Narayanan Rao<sup>10</sup> and Subhashini *et al.*<sup>11</sup> have reported that monohaloamine can be further protonated in acidic solution (pH < 2). The values of second protonation constants are 102 and  $61 \pm 5$  at 298K for CAT and CAB respectively. Since the rate of reaction is independent of [substrate], further protonation of RNHBr is likely in acid solution (pH < 2). The following mechanism as given in Scheme 1 is proposed.



Scheme 1

Assuming total concentration of BAT as  $[\text{BAT}]_T = [\text{RNHBr}] + [X]$ ,

$$[X] = \frac{K [\text{BAT}]_T [\text{H}^+][\text{Cl}^-]}{1 + K [\text{H}^+][\text{Cl}^-]} \quad \dots (5)$$



Scheme 2

Since,

$$\frac{-d[\text{BAT}]}{dt} = k_1[\text{X}] = \frac{Kk_1[\text{BAT}]_T[\text{H}^+][\text{Cl}^-]}{1 + K[\text{H}^+][\text{Cl}^-]}$$

$$k' = \frac{Kk_1[\text{H}^+][\text{Cl}^-]}{1 + K[\text{H}^+][\text{Cl}^-]}$$

where  $k'$  = observed rate constant

$$\frac{1}{k'} = \frac{1}{Kk_1[\text{H}^+][\text{Cl}^-]} + \frac{1}{k_1} \quad \dots (6)$$

A linear plot of  $1/k'$  versus  $1/[\text{H}^+]$  at constant  $[\text{Cl}^-] = 0.06 \text{ mol dm}^{-3}$  gives  $k_1 = 10 \times 10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  and  $K = 278.0 \text{ dm}^3 \text{ mol}^{-1}$ .

A detailed mechanism of oxidation of caffeine by BAT is given in Scheme 2. The first step is the electrophilic attack by RNHBr at C-8 to form chlorocaffeine, followed by solvolysis to X. Addition to the C<sub>5</sub>-C<sub>6</sub> double bond solvolysis and hydrolysis gives alloxan and methyl urea.

The negative dielectric constant effect observed in the present studies clearly supports the dipole-

dipole nature of interaction at the rate determining step in the proposed reaction scheme. Since  $\text{D}_3\text{O}^+$  is about three times stronger<sup>12</sup> than  $\text{H}_3\text{O}^+$  for acid catalysed reaction, the inverse isotope effect ( $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}}$ ) must be greater than unity. The observed value (1.47) for solvent isotope effect is in agreement with these facts.

The proposed mechanism is also supported by the moderate values of energy of activation. The fairly high positive value of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the negative entropy of activation suggests the formation of the compact activated complex. The constancy of rate constant on addition of neutral salt or reaction product ( $\text{RNH}_2$ ) also supports the proposed mechanism.

The rates are found to be higher<sup>5</sup> with bromamine-T than chloramine-T. This could be attributed to the difference in electrophilic nature of the halogen cations,  $\text{Br}^+$  and  $\text{Cl}^+$ , involved in the oxidation process and the ease with which these species can be formed in reactions.

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