Mechanistic Investigation of Oxidation of Phenyl-propanolamine with *N*-Bromobenzenesulfonamide in Alkaline Medium: A Kinetic Approach

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Abstract: The kinetics of oxidation of phenylpropanolamine (PPA) with sodium *N*-bromobenzenesulfonamide or bromamine–B (BAB) has been investigated in alkaline medium at 308 K. The oxidation reaction obeys the rate law, $- d[BAB]/dt = k [BAB] [PPA]^x [OH^-]$, where x is less than unity. The variation of ionic strength of the medium, addition of the reduction product, benzenesulfonamide, and chloride ion had no pronounced effect on the reaction rate. Decrease of dielectric permittivity of the medium by increasing the CH_3CN content increased the rate. The reaction was studied at different temperatures and the activation parameters have been evaluated from the Arrhenius plot. The stiochiometry of the reaction was found to be 1:1, and the oxidation product of phenylpropanolamine was identified as benzaldehyde and ethylideneamine. The rate decreased in D_2O medium and the normal isotope effect k' (H_2O) / k' (D_2O) is 2.18. Proton inventory studies have been made in H_2O – D_2O mixtures. Formation and decomposition constant of BAB-PPA complexes in the reaction scheme have been determined. The conjugate acid, $C_6H_5SO_2NHBr$ is assumed to be the reactive species. The proposed mechanism and the derived rate law are consistent with the observed experimental results.

Keywords: Phenylpropanolamine, Oxidation kinetics, Alkaline medium, Bromamine-B.

Introduction

The chemistry of *N*-metallo-*N*-aryl halosulfonamides, generally known as organic haloamines is of interest due to their diverse behavior. Their versatile nature is due to their ability to act as sources of halonium cations, hypohalite species and nitrogen anions, which act as both electrophiles and nucleophiles. The manohaloamines are two-electron oxidants while dihaloamines undergo four-electron change. As a result, these compounds react with a wide range of functional groups and affect a variety of molecular changes. The important member of this group is chloramine-T (CAT), which is a by-product of saccharin manufacture. Although mechanistic aspects of many reactions of chloramine-T and

chloramine-B (CAB) have been well documented[1-6], similar studies on bromine analogues are scanty. Bromamine–B ($C_6H_5SO_2NBr$ Na. 1.5 H_2O), the bromine analogue of CAB, is gaining importance as a mild oxidant and is found to be a better oxidizing agent than chloro-compounds. However, a little information exists in the literature on BAB reactions[7-10], particularly with respect to the oxidation kinetics of pharmaceuticals, which may throw some light on the mechanism[11] of the metabolic conversion in biological systems. In view of this, there is a considerable scope for the study of BAB to get better insight of the speciation of BAB reaction models and understanding its redox chemistry in solution.

Phenylpropanolamine (PPA) is a drug of the phenylethylamine family used as a decongestant and also as an appetite suppressant. Although this drug does enhance weight loss[12-14], the precise mechanism is unclear. PPA reduces food intake, body weight and carcass lipid in rats[15]. In veterinary medicine, it is used to control urinary incontinence in dogs.

In the light of the available information and of our continued interest on mechanistic studies of haloaminometric reactions in general, and medicinal compounds in particular the present investigation was under taken. The present paper reports for the first time the detailed kinetics of oxidation of phenylpropanolamine with BAB in presence of NaOH medium at 308 K. The objectives of the present investigation are to (i) elucidate the reaction mechanism in alkaline solution, (ii) put forward appropriate rate law, (iii) ascertain the reactive species and (iv) identify the reaction products.

Experimental

Bromamine-B was prepared[16] by partial debromination of dibromamine-B (DBB), which in turn was prepared by the bromination of chloramine-B (CAB). DBB (31.5g) was added in small quantities at a time and with constant stirring a 50 mL of 4M sodium hydroxide. The mass was cooled in ice, filtered under suction and the product was dried over anhydrous $CaCl_2$. The available bromine was determine by iodometry (found: 27.9%; requires: 28.04%). It was further characterized by IR, ^1H and ^{13}C NMR spectroscopy. An aqueous solution of BAB was standardized iodometrically and was preserved in brown bottles to prevent photochemical deterioration. Pharmaceutical grade phenylpropanolamine hydrochloride (supplied by Cipla India Ltd., Mumbai, India) was used as received. All other chemicals used were of analytical grade. Ionic strength of the reaction mixture was kept constant ($\mu = 0.2$ mol dm^{-3}) using a concentrated solution of $NaClO_4$ in order to swamp the reaction. Solvent isotope studies was made with D_2O (99.4%) supplied by the Bhabha Atomic Research Centre, Trambay, India. Doubly distilled water was used for preparing all aqueous solutions.

Kinetic measurements

The kinetic runs were carried out under pseudo-first-order conditions ([substrate]>> [oxidant]) at constant temperature in glass stoppered Pyrex boiling tubes coated black on the outside to eliminate photochemical effects. Mixtures containing the requisite amounts of PPA, NaOH, $NaClO_4$ and water (to maintain a constant total volume for all runs) were placed in the tube and thermally equilibrated in a water bath set at a given temperature (308 ± 0.1K). To this was added a measured amount of a pre-equilibrated standard BAB solution to give a known concentration. 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 constant, k' calculated were reproducible within ±4 %. Regression analysis of the experimental data to obtain regression coefficient, r, was calculated using a fx-570M statistical calculator.

Stoichiometry and product analysis

Reaction mixtures containing varying compositions of BAB and PPA were kept at 308 K in presence of 0.013 mol dm^{-3} NaOH for 24 h. The iodometric determination of unreacted BAB in the reaction mixture showed that one mole of BAB was consumed per mole of the PPA according to equation (1):

$$C_9H_{13}NO + RNClNa \longrightarrow C_7H_6O + C_2H_5N + RNH_2 + Na + Cl^- \qquad (1)$$

where $R = C_6H_5SO_2$.
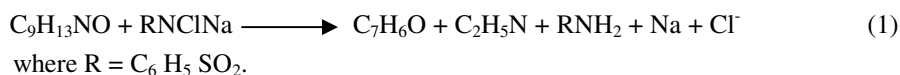
The products in the reaction mixture were extracted several times with diethyl ether. The combined ether extract was evaporated and subjected to column chromatography on silica gel (60 – 200 mesh) using gradient elusion (from dichloromethane to chloroform). The reduction product of BAB, benzenesulfonamide was detected by paper chromatography[17]. Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl solution in ethanol as spray reagent ($R_f = 0.88$). It was further confirmed by its IR spectral data. The oxidation products of phenylpropanolamine were found to be benzaldehyde, and ethylidene amine and detected by spot test[18]. Benzaldehyde was identified by preparing 2, 4-DNP derivative. Further it was confirmed by IR spectrum, which showed a band at 1703 cm^{-1} for >C=0 stretching and at 2846 cm^{-1} for aldehydic C-H stretching mode. IR spectra were recorded using FT-IR (JASCO) spectrometer using KBr pellets.

Results

The oxidation of PPA with BAB has been kinetically investigated at different initial concentrations of the reactants in the presence of NaOH at 308 K.

Effect of varying reactant concentrations on the rate

With the substrate in excess, at constant [NaOH], [PPA] ionic strength and temperature, the $[BAB]_0$ was varied. Plots of log [BAB] versus time were linear ($r > 0.997$) indicating a first-order dependence of the rate on $[BAB]_0$. The pseudo-first-order rate constant, k', calculated from the slopes are given in Table 1. Further, the values of k' are unaltered with variation of $[BAB]_0$ confirming the first-order dependence of the rate on $[BAB]_0$.Under similar experimental conditions, the reaction rate increased with increase in $[PPA]_0$ (Table 1). Plot of log k' versus $[PPA]_0$ was linear (Fig.1, $r = 0.996$) with a slope less than unity (0.35) indicating a fractional-order dependence on $[PPA]_0$. Further, plot of k' versus $[PPA]_0$ was linear ($r = 0.997$) having a Y-intercept, confirming the fractional-order dependence on $[PPA]_0$.

Effect of concentration of alkali on the rate

When the $[NaOH]_0$ was increased, keeping the other experimental conditions constant, the rate increased (Table 1). Plot of log k' versus log [NaOH] was linear (Fig. 2; $r = 0.995$) with a slope of unity indicating first-order dependence of rate on $[OH^-]$.

Effect of benzenesulfonamide and chloride ion on the rate

The reaction rate was unaffected by the addition of reduced product, benzenesulfonamide (2×10^{-4} to 8×10^{-4} mol dm^{-3}) indicating it was not involved in a pre-equilibrium with the oxidant. Also addition of Cl^- in the form of NaCl (2.0×10^{-2} to 8.0×10^{-2} mol dm^{-3}) had no significant effect on the reaction rate.
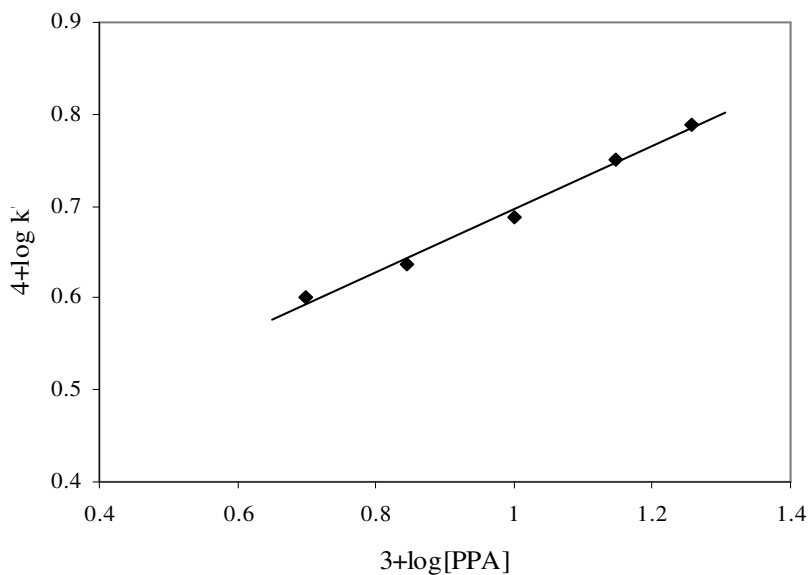
Figure 1. Plot of 4+log k' *versus* 3+log [PPA]

Table 1. Effect of varying concentrations of oxidant, substrate and alkali on the reaction rate at 308 K.

10^4 [CAB], mol dm^{-3}	10^3 [PPA], mol dm^{-3}	10^3 [NaOH], mol dm^{-3}	k' $\times 10^4$, s^{-1}
3.0	10.0	13.0	4.801
5.0	10.0	13.0	4.885
7.0	10.0	13.0	4.679
9.0	10.0	13.0	4.898
11.0	10.0	13.0	4.701
5.0	5.0	13.0	3.991
5.0	7.0	13.0	4.337
5.0	10.0	13.0	4.885
5.0	14.0	13.0	5.642
5.0	18.0	13.0	6.141
5.0	10.0	10.0	4.030
5.0	10.0	13.0	4.885
5.0	10.0	15.0	5.834
5.0	10.0	17.0	6.602
5.0	10.0	20.0	7.408
*5.0	10.0	13.0	4.901
**5.0	10.0	13.0	4.782
[a]5.0	10.0	13.0	4.802
[b]5.0	10.0	13.0	4.906

*At μ = 0.1 mol dm^{-3} and   ** at μ = 0.2 mol dm^{-3} a - [BSA] = 0.002 mol dm^{-3} and b - [BSA] = 0.006 mol dm^{-3}.
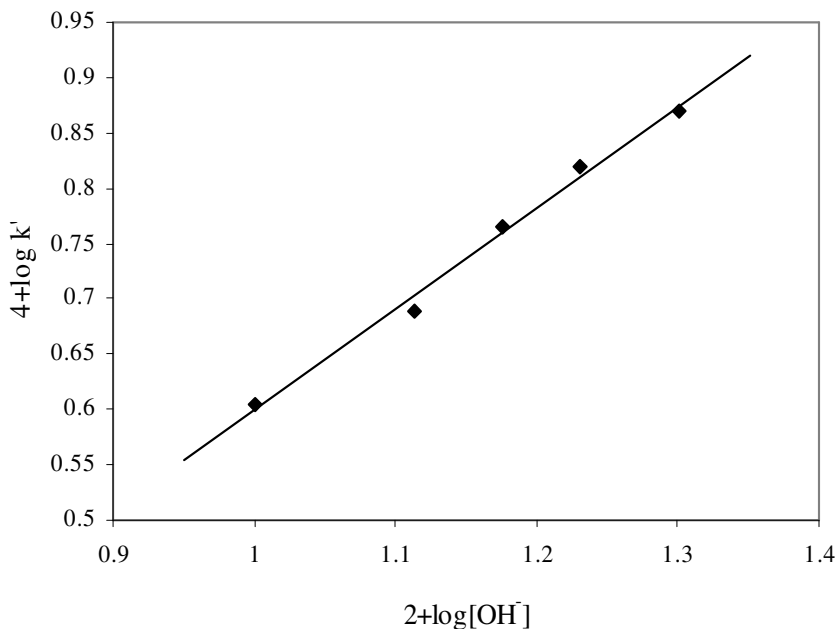
Figure 2. Plot of 4+log k' *versus* 2+log [OH⁻]

Effect of relative permittivity and ionic strength on the reaction rate

The effect of relative permittivity (D) of the medium on the rate has been studied by varying the CH_3CN – H_2O content in the reaction mixture with all other conditions kept constant. The values of relative permittivity were computed from the values of the pure liquids[19]. The rate constant, k' increases with decreasing relative permittivity of the medium. The plot of log k' versus 1/D gave a straight line (r = 0.998) with a positive slope. Blank experiments showed that, BAB did not oxidize PPA under the experimental conditions employed. The reaction rate remained unaffected by varying the ionic strength of the medium (by adding $NaClO_4$ solution). Hence no attempt was made to keep the ionic strength constant for kinetic runs.

Effect of solvent isotope on the rate

As the rate is dependent as [OH⁻], solvent isotope study in D_2O medium was made. The value of k' (H_2O) is 4.885×10^{-4} s⁻¹ and that of k' (D_2O) = 2.241×10^{-4} s⁻¹ leading to solvent isotope effect k' (H_2O) / k' (D_2O) = 2.18. Proton inventory studies were made in H_2O – D_2O mixtures and the results are shown in Table 3. The corresponding proton inventory plot for the rate constant k^n_{obs} in a solvent mixture containing deuterium atom fraction (n) is given in Fig.4.

Effect of temperature on the rate

The reaction was studied at different temperature (303 – 321 K) keeping other experimental conditions constant. The results are given in Table 2. From the linear Arrhenius plot of log k' versus 1/T (Fig. 3; r = 0.997), activation energy and other thermodynamic parameters were found to be E_a = 86.3 k J mol⁻¹; $\Delta H^{\neq}$ = 83.7 kJ mol⁻¹; $\Delta G^{\neq}$ = 78.0 kJ mol⁻¹ and $\Delta S^{\neq}$ = -37.5 JK⁻¹ mol⁻¹.

Table 2. Effect of varying temperature and dielectric permittivity on the rate

Temperature, K	CH_3CN, %, v/v	$k' \times 10^4$, s^{-1}
308	0	4.885
308	10	5.527
308	15	6.064
308	20	6.871
303	-	2.775
308	-	4.885
313	-	9.504
318	-	15.353
321	-	19.054

$[CAB] = 5 \times 10^{-4}$ mol dm^{-3}; $[PPA] = 10 \times 10^{-3}$ mol dm^{-3};
$[NaOH] = 13 \times 10^{-3}$ mol dm^{-3}; $\mu = 0.2$ mol dm^{-3}
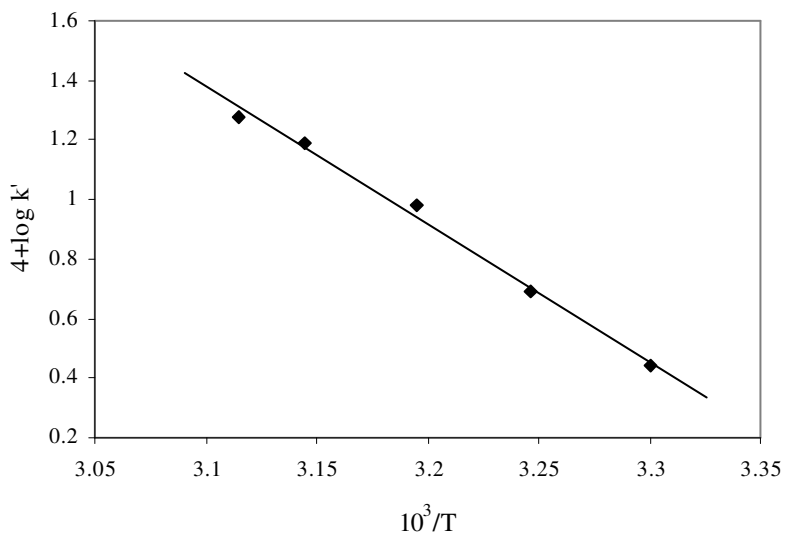
Figure 3. Plot of 4+log k' *versus* 10^3/T

Table 3. Proton inventory studies for the oxidation of PPA in H_2O-D_2O mixture at 308K

Atom fraction of D_2O, (n)	$k_{obs} \times 10^4$ s^{-1}
0.00	4.855
0.25	4.441
0.50	3.688
0.75	2.768
0.85	2.341

$[CAB] = 5 \times 10^{-4}$ mol dm^{-3}; $[PPA] = 10 \times 10^{-3}$ mol dm^{-3};
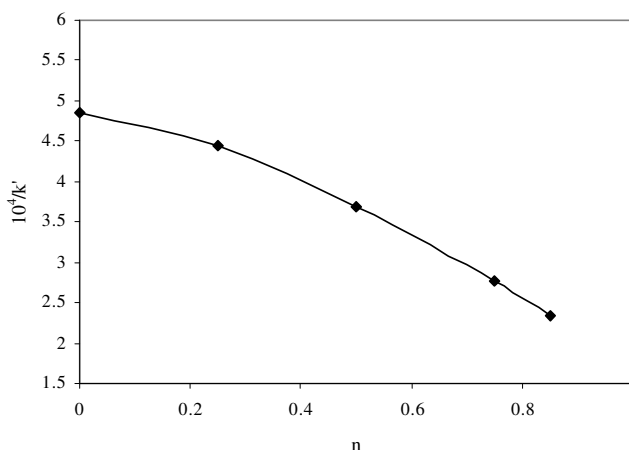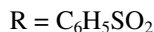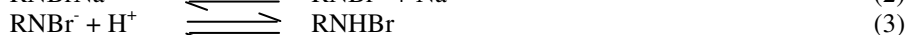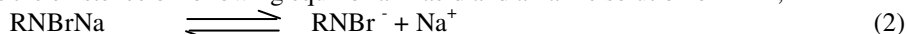$[NaOH] = 13 \times 10^{-3}$ mol dm^{-3}; $\mu = 0.2$ mol dm^{-3}

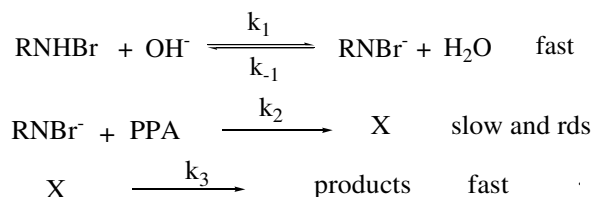**Figure 4**. Plot of $10^4/k'$ *versus* n.

Test for free radicals

The addition of aqueous acrylamide monomer solution to the reaction mixture in an inert atmosphere did not initiate polymerization indicating the absence of free radical species in the reaction sequence.

Discussion

The existence of similar equilibria in acid and alkaline solution of *N*-metallo-*N*-halo arylsulfonamide has been reported by Pryde and Soper [20], Morris *et.al.*[21], and Bishop and Jennings[22]. Bromamine-B like its chlorine analogues, chloramine-B and chloramine-T, behaves as a strong electrolyte in aqueous solution. The work of Hardy and Johnstan[11] indicates the existence of following equilibria in acid and alkaline solution of BAB,

$$RNBrNa \rightleftharpoons RNBr^- + Na^+ \qquad (2)$$
$$RNBr^- + H^+ \rightleftharpoons RNHBr \qquad (3)$$
$$RNHBr + H_2O \rightleftharpoons RNH_2 + HOBr \qquad (4)$$
$$2RNHBr \rightleftharpoons RNH_2 + RNBr_2 \qquad (5)$$
$$RNBr_2 + H_2O \rightleftharpoons RNHBr + HOBr \qquad (6)$$
$$HOBr \rightleftharpoons H^+ + OBr^- \qquad (7)$$
$$HOBr + H^+ \rightleftharpoons H_2OBr^+ \qquad (8)$$
$$RNBr^- + H_2O \rightleftharpoons RNHBr + OH^- \qquad (9)$$

$$R = C_6H_5SO_2$$

Thus the possible oxidizing species are $RNHBr$, $RNBr_2$, $HOBr$ and probably H_2OBr^+ in acid BAB solutions and $RNHBr$, $HOBr$ and $RNBr^-$ and OBr^- in alkaline BAB solutions. The oxidation potential of *N*-halosulfonamide system is pH dependent and decreases with increase in pH of the medium. In alkaline solutions of BAB, $RNBr_2$ does not exist at higher alkaline concentrations[22]. In very dilute alkali concentrations (pH < 11) the most likely species of BAB is $RNHBr$. Further, several workers[23-25] have observed the increasing effect of $[OH^-]$ on the rate of reaction. This has been attributed to the formation of $RNBr^-$ from the conjugate acid. In the present investigations, the negligible influence of added benzenesulfonamide on the rate suggests that, $RNHBr$ is the most likely oxidizing species in weak alkaline solution of BAB. A fractional-order dependence of rate as $[PPA]_0$ indicates a pre-equilibrium before the rate determining step. Bearing these facts in mind, the following mechanism (Scheme 1) is proposed to account the observed kinetics:

$$RNHBr + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RNBr^- + H_2O \quad\quad fast$$

$$RNBr^- + PPA \xrightarrow{k_2} X \quad\quad slow\ and\ rds$$

$$X \xrightarrow{k_3} \quad products \quad\quad fast$$

Scheme 1

In Scheme 1, X represents the complex intermediate species whose structure is shown in scheme 2, where a detailed mechanistic interpretation of PPA oxidation by BAB in alkaline medium is proposed.

From scheme 1   rate = k_2 [RNCl⁻] [PPA]   (10)

Applying steady state condition for RNCl⁻, it can be shown that,

$$[RNBr^-] = \frac{k_1[RNHBr][OH^-]}{k_{-1}[H_2O] + k_2[PPA]} \quad\quad (11)$$

Substituting for [RNBr⁻] from equation (11) into equation (10), the following rate law (equation 12) is obtained:

$$rate = \frac{k_1 k_2 [BAB][OH^-][PPA]}{k_{-1}[H_2O] + k_2[PPA]} \quad\quad (12)$$

The rate law (12) is in agreement with the experimentally observed results.

Since rate = k' [BAB], equation (12) can be transformed into equations (13) and (14).

$$k' = \frac{k_1 k_2 [OH^-][PPA]}{k_{-1}[H_2O] + k_2[PPA]} \quad\quad (13)$$

or

$$\frac{1}{k'} = \frac{k_{-1}[H_2O]}{k_1 k_2 [OH^-][PPA]} + \frac{1}{k_1[OH^-]} \quad\quad (14)$$

From the slopes and intercept of the linear double reciprocal plot of 1/k' versus 1/[PPA] (Fig. 5; r = 0.988) at fixed [OH⁻] , and [H₂O] = 55.5, the values of k_1 and k_{-1}/k_2 were found to be 6.056 x 10^{-2} dm⁻³ mol⁻¹ s⁻¹ and 1.036 x 10^{-4} respectively.

A change in solvent composition by varying the CH₃CN content in CH₃CN – H₂O affects the reaction rate. The general equation relating to the effect of dielectric constant to the reaction rate in a bimolecular reaction has been derived by Landskroener and Laidler[26]. For the limiting case of zero angle of approach between two dipoles, Amis [27] has shown that,

$$\ln k'_D = \ln k'_{D=\infty} - \frac{2\mu_1\mu_2}{DkTr^3} \quad\quad (15)$$

Where k'_D is a function of dielectric constant D, μ_1 and μ_2 are the dipole moments of reactions, r is the distance of approach for two dipoles, k is the Boltzmann constant and T is the absolute temperature. Equation (15) predicts a linear relation between log k' versus 1/D. The slope of the line should be negative for a reaction between two dipole molecules and positive for ion-dipole reactions. In the present case, the plot of log k' versus 1/D is linear with a positive slope, thus supporting the participation of ion-dipole species in the rate determining step.
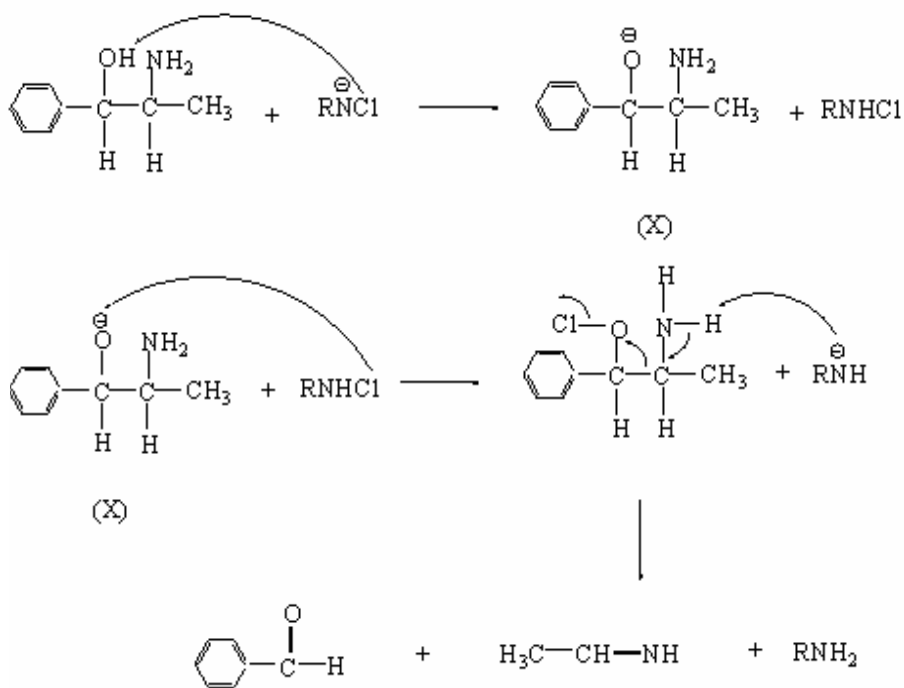
Scheme 2

The observed solvent isotope effect supports the proposed mechanism and the derived rate law. For a reaction involving a fast equilibrium H^+ or OH^- ion transfer, the rate increases in D_2O medium, since D_3O^+ and OD^- are stronger acid and stronger base respectively. In the present case, the observed solvent isotope effect of $k'(H_2O)/k'(D_2O) > 1$ is due to the greater basicity of OD^- compared to OH^-. However, the retardation of rate in D_2O is due to the hydrolysis step which tends to make the normal kinetic isotope effect. The proton inventory studies made in H_2O–D_2O mixture could throw light on the nature of the transition state. The dependence of the rate constant, k_{obs}^n on the deuterium atom fraction 'n' in the solvent mixture is given by the following form of Gross-Butler equation[28,29].

$$\frac{k_{obs}^0}{k_{obs}^n} = \frac{\pi TS\,(1-n+n\,\phi_i)}{\pi RS\,(1-n+n\,\phi_j)} \tag{16}$$

Where ϕ_i and ϕ_j are isotope fractionation factor for isotopically exchangeable hydrogen sites in the transition state (TS) and in the ground/reactant state (RS), respectively. The Gross-Butler equation permits the evaluation of ϕ_i when the value of ϕ_j is known. However, the curvature of proton inventory plot could reflect the number of exchangeable proton in the reaction [28]. Plot of k_{obs}^n versus n (Fig.4) is a curve in the present case, and this in comparison with the standard curves, indicate the involvement of a single proton or H-D exchange in the reaction sequence[30]. This proton exchange is indicative of the participation of hydrogen ion in the formation of transition state.
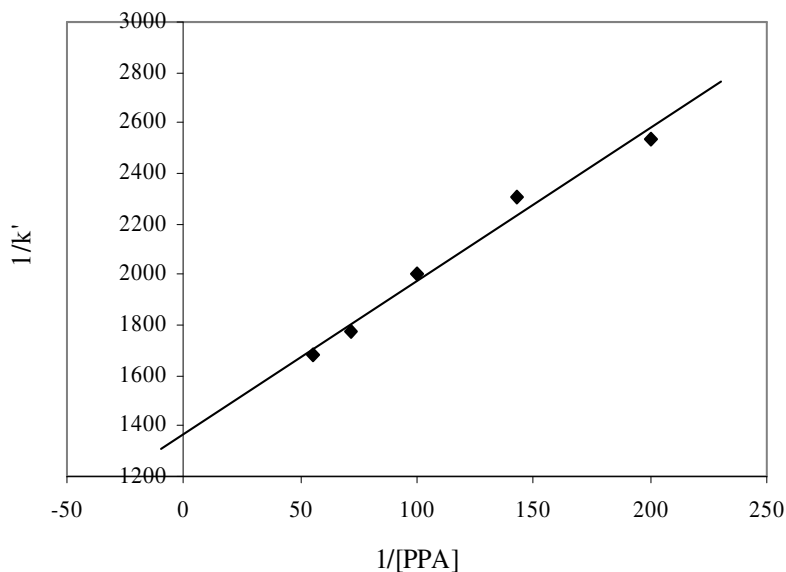
Figure 5. Plot of 1/ k' *versus* 1/[PPA]

The mechanism is further supported by the value of energy of activation and other thermodynamic parameters. The fairly high positive values of free energy of activation and enthalpy of activation indicates that, the transition state is highly solvated, while the negative entropy of activation suggests the formation of the compact activated complex with fewer degrees of freedom. The reduction product (RNH_2) did not influence the rate, showing that it is not involved in pre-equilibrium. Addition of Cl⁻ ion has no effect on the rate indicating that no free chlorine is formed in the reaction. All these observations also confirm the proposed mechanism and derived rate law.
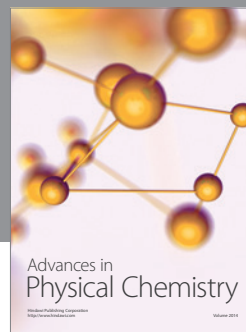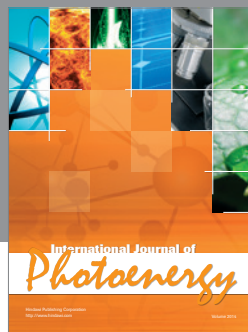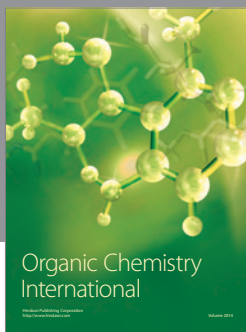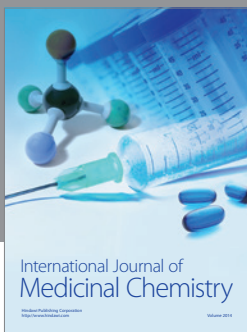
Acknowledgement

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