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SPECTROPHOTOMETRIC KINETIC INVESTIGATION OF OXIDATION OF AMITRIPTYLINE BY N-BROMO-P-BENZENESULPHONAMIDE IN ACIDIC BUFFER (pH= 1.2) MEDIUM

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ABSTRACT

Oxidation of amitriptyline by sodium N-bromobenzenesulphonamide (BAB) has been studied in acidic buffer medium pH 1.2 has been kinetically studied at 303K. Oxidation of amitriptyline was followed spectrophotometrically at λ_{max}= 410 nm. The reaction rate shows a first order dependence on [oxidant], [substrate] and inverse fractional order dependence in [H^+]. Addition of halide ions and the reduction product of benzenesulphonamide and variation of ionic strength and dielectric constant of the medium do not have any significant effect on the reaction rate. The reaction was studied at different temperatures and activation parameters were evaluated. Mechanisms proposed and the derived rate law is consistent with the observed kinetics.

KEYWORDS: Oxidation, Amitriptyline, Bromamine-B, acidic buffer, kinetics.

INTRODUCTION

Amitriptyline is a tricyclic antidepressant (TCA). It is the most widely used TCA and has at least equal efficacy against depression.[1] Amitriptyline is used for a number of medical conditions including depressive disorders, anxiety disorders, attention deficit hyperactivity disorder, migraine prophylaxis, eating disorders, bipolar disorder, post herpetic neuralgia and insomnia.[2] Amitriptyline is used in ankylosing spondylitis for pain relief. It is also used as a preventive for patients with recurring biliary dyskinesia.[3] It is also used in the treatment of nocturnal enuresis (bed wetting) in children. Amitriptyline may be prescribed for other conditions such as cyclic vomiting syndrome, post-traumatic stress disorder (PTSD). The symptoms and the treatment of an overdose are largely the same as for the other TCAs. The british national formulary notes that amitriptyline can be particularly dangerous in overdose. Breyer-pfaff et al[4] have reported comparative N-glucuronidation kinetics of ketotifen and amitriptyline by expressed human UDP glucuronosyltransferases and liver microsomes. Amitriptyline (AT) the most widely used tricyclic antidepressant was reported by Ursula et al.[5] Diansong et al[6] have been reported the role of human UGT2B10 in N-glucuronidation of tricyclic antidepressants, amitriptyline, imipramine, clomipramine and trimipramine. Abbar Jyothi et al[7] have reported ruthenium(III) catalyzed oxidative degradation of amitriptlyine-A tricyclic antidepressant drug by permanganate in aqueous acidic medium. Ledesma et al[8] have reported study of the mechanisms involved in the adsorption of amitriptyline from aqueous solution on to activated carbons. Vijaya et al[9] have reported the design and invitro evaluation of hydroxyl propyl methylcellulose based transdermal films of amitriptyline hydrochloride. Lamani Shekappa et al[10] have been reported the oxidation of tricyclic antidepressant agent amitriptyline by permanganate in sulphuric acid medium by kinetic and mechanistic approach. Recently amitriptyline has been demonstrated to act as an agonist of the TrKA and TrKB receptors.[11] Further there was no information available on oxidation of amitriptyline by BAB, we have recently studied the kinetics of the reaction of bromomine-B with amitriptyline.

Aromatic N-halosulphonamides are mild oxidants containing a strongly polarized N-linked halogen in its +1 oxidation state. The prominent member of this group chloramine-T (CAT) is a well known analytical reagent and the mechanistic aspects of many of its reactions have been documented.[12-17] Bromamine-B (BAB) (p-$C_6H_5SO_2NBrNa.3H_2O$) is a haloamine containing a positive bromine has been recently introduced as an oxidimetric titrant in aqueous medium.

However information on the bromine analogues is very scanty. In the present investigation we report studies on the kinetic and mechanistic aspects of oxidation of amitriptyline by bromamine-B in acidic buffer medium in the temperature range 298-313K.

MATERIAL AND METHODS

Experimental

Bromamine-B was prepared and purified using the procedure of Ahmed and Mahadevappa.[18] Aqueous solution of BAB were prepared, standardized by the iodometric method and stored in amber colored bottles. Analar grade amitriptyline was used and aqueous solution of the substrate was prepared. Whenever required, all other chemicals used were of acceptable grades of purity. A constant ionic strength of the reaction mixture was maintained, by adding a concentrated $NaClO_4$. Triply distilled water was used for preparing aqueous solutions. A pH 1.2 buffer solution by using of potassium chloride and hydrochloric acid was prepared[19] and its pH value was checked with pH meter.

Kinetic Measurement

The Kinetic runs were performed under pseudo-first order condition of $[\text{Amitriptyline}]_0 << [\text{BAB}]_0$. Mixture containing requisite amount of solutions of the amitriptyline $NaClO_4$ and buffer of known pH were taken in stoppered pyrex glass tubes, whose outer surface were coated black to eliminate photochemical effects. A required amount of pH 1.2 buffer solution was added to maintain a constant volume for all runs. The tube was thermostated in a water bath set at a given temperature. To this solution was added a measured amount of pre equilibrated BAB solution to give a known overall concentration. The reaction mixture was periodically shaken for uniform concentration. The progress of the reaction was monitored by withdrawing aliquots of the reaction mixture at regular time intervals and by spectrophotometrically measured the unreacted amitriptyline for two half-lives. The pseudo first-order rate constants $k^{'}$ calculated were reproducible with in ± 3.0%. The regression analysis of the experiment was carried out on an origin 5.0 HP computer to obtain regression coefficientr.

Stoichiometry

Reaction mixtures containing different composition of amitriptyline and BAB were equilibrated at 303K in an acidic buffer (hydrochloric acid + potassium chloride) of pH 1.2 for 24 hours. The iodometric determination of unreacted BAB in the reaction mixture showed that one mole of BAB was consumed by a mole of amitriptyline.

$$C_{20}H_{23}N + PhSO_2NBrNa + H_2O \longrightarrow C_{20}H_{23}NO + PhSO_2NH_2 + NaBr \quad \dots (1)$$

Product analysis

The reaction product of BAB, benzenesulphonamide was identified by TLC using petroleum ether-chloroform-butanol (2:2:1 v/v) solvent system for ascending irrigation and iodine as developing reagent (R_f = 0.88).[20] Amitriptyline N-oxide is the oxidation product of amitriptyline was confirmed by GC-MS analysis. Mass spectral data for the amitriptyline N-oxide was obtained in a 17A Shimadzu gas chromotograph with LCMS-2010A Shimadzu mass spectrometer. The Mass spectra showed a parent molecular ion peak at 293amu (Fig.1) confirming the formation of amitriptyline N-oxide in the reaction mixture of amitriptyline and BAB.

RESULTS AND DISCUSSIONS

Effects of varying reactant concentrations on the rate

The stoichiometry of the amitriptyline-bromamine-B reaction was found to be of 1:1 ratio, under pseudo first order conditions of [BAB] >> [AT] at constant [BAB], pH and temperature. The plot of log (A_0/A_t) versus time was linear indicating a first order dependence of the reaction rate on [AT]. A_o and A_t are the absorbances of the reaction mixture at time intervals of zero and t respectively. The pseudo-first order rate constants k' obtained at 30^0C are independent of [AT], further confirming the first order dependence on [AT] (Table1). At constant pH, [AT], ionic strength and temperature, the rate increased with increasing [BAB] (Table1). Further a plot of log k' versus log [BAB] was linear with first order dependence on [BAB] (Fig. 2).

Effects of pH and halide ions concentration on the rate

At constant $[BAB]_o$ $[AT]_o$ and temperature the rate of the reaction increased with decrease in $[H^+]$ (Table 2). The plots of log k' versus log $[H^+]$ were linear (r>-0.9970) with negative fractional slope indicating an inverse fractional order of approximately -0.79 with $[H^+]$. Addition of Cl^- or Br^- ions in the form of NaCl or NaBr at constant $[H^+]$ and ionic strength did not affect the rate, suggesting that chloride or bromide ions were not involved in the reaction rate.

Effects of [BSA] and Ionic strength on the rate

The addition of benzenesulfonamide [2.0 $\times 10^{-4}$ M to 20.0 $\times 10^{-4}$ M] had no effect on the rate, indicating that it is not involved in a pre-equilibrium to the rate determining step. The variation of ionic strength of the medium using $NaClO_4$ **(**0.02-0.20M**)** had no effect on the rate.

Effects of Dielectric constant and Temperature on the rate

The variation of the solvent composition using MeOH (5.0 to 20.0% v/v) did not affect the rate. The reaction was studied at varying temperatures 303K-318K. The activation parameters namely energy of activation (Ea), enthalpy of activation (($\Delta H^{\neq}$), entropy of activation and free energy of activation ($\Delta G^{\neq}$) were obtained from the Arrhenius plots of log k' versus 1/T. The kinetic and activation parameters obtained are presented in (Table 3).

Test for free radicals

The addition of the reaction mixture to aqueous acrylamide monomer solutions in the dark did not initiate polymerization, indicating the absence of insitu formation of free-radical species in the reaction sequence.

DISCUSSION

The existence of similar equilibria in acid and alkaline solutions of N-metallo-N-haloarylsulphonamides were reported by Pryde and Soper,[21,22] Morris et al[23] and Bishop and Jennings.[24] Bromamine-B analogous to CAB behaves as strong electrolyte in aqueous solutions forming different species[25] as shown in equations 2 to 6.

$$PhSO_2NBrNa \rightleftharpoons PhSO_2NBr^- + Na^+ \quad \dots (2)$$

$$PhSO_2NBr^- + H^+ \rightleftharpoons PhSO_2NHBr \quad \dots (3)$$

$$PhSO_2NHBr + H_2O \rightleftharpoons PhSO_2NH_2 + HOBr \quad \dots (4)$$

$$2PhSO_2NHBr \rightleftharpoons PhSO_2NH_2 + PhSO_2NBr_2 \quad \dots (5)$$

$$HOBr + H^+ \rightleftharpoons H_2O^+Br \quad \dots (6)$$

In acidic solutions, the probable oxidizing species are the free acid ($PhSO_2NHBr$), dibromamine-B ($PhSO_2NHBr_2$), HOBr and H_2O^+Br. If $PhSO_2NHBr_2$ were the reactive species, then the rate law would predict a second order dependence of rate on [BAB], which is contrary to experimental observation. As equation (4) indicates a slow hydrolysis, if HOBr is primary oxidizing species, a first order retardation of rate by the added $PhSO_2NH_2$ (benzenesulphonanide) is expected, however no such effect was noticed. Narayana and Rao[26] and Subhashini et al.[27] have reported that monohaloamines can be further protonated at pH < 2 as shown in equations 7 and 8 for chloramine-T and chloramine-B respectively.

$CH_3C_6H_4SO_2NHCl + H^+ \rightleftharpoons CH_3C_6H_4SO_2N^+H_2Cl$ … (7)

$C_6H_5SO_2NHCl + H^+ \rightleftharpoons C_6H_5SO_2N^+H_2Cl$ ... (8)

The second protonation constants for CAT and CAB are 102 and 61±5 respectively at 25°C. Gupta[28] suggests that the value could be lower than those reported by the above workers.

In the present case, inverse fractional order in $[H^+]$ suggests that the protonation of $PhSO_2N^+H_2Br$ results in the generation of $PhSO_2NHBr$, which is likely to be the active oxidizing species involved in the mechanism of amitriptyline oxidation. Based on the preceding discussion following mechanism (Scheme 1) is proposed for the reaction.

Scheme -1

$PhSO_2N^+H_2Br \overset{K_1}{\rightleftharpoons} PhSO_2NHBr + H^+$ fast … (i)

$PhSO_2NHBr + S \overset{k_2}{\rightleftharpoons} X$ slow … (ii)

$X + H_2O \xrightarrow{k_3} \text{Product}$ … (iii)

$\text{rate} = k_2\,[PhSO_2NHBr]\,[S]$ … (9)

The total effective concentration of $[BAB]_t$ is given by

$[BAB]_t = [PhSO_2N^+H_2Br] + [PhSO_2NHBr]$ …(10)

From step (i)

$$K_1 = \frac{[PhSO_2NHBr]\,[H^+]}{[PhSO_2N^+H_2Br]} \quad ...(11)$$

$$\therefore\ [PhSO_2N^+H_2Br] = \frac{[PhSO_2\,NHBr][H^+]}{K_1} \quad ...(12)$$

Substitute equation (12) in (10)

$$[BAB]_t = \frac{[PhSO_2NHBr][H^+]}{K_1} + [PhSO_2NHBr]$$

$$\therefore\ [BAB]_t = [PhSO_2NHBr]\left\{\frac{[H^+]+1}{K_1}\right\}$$

$$[PhSO_2NHBr] = \frac{K_1[BAB]_t}{[H^+]+K_1} \qquad ...(13)$$

Since rate = $k_2\,[PhSO_2NHBr]\,[S]$

This equation leads to the following rate law

$$\text{rate} = \frac{k_2\ K_1[BAB]_t\ [S]}{[H^+]+K_1} \qquad ...(14)$$

This is in good agreement with the experimental data, including a first order in substrate, oxidant and an inverse fractional order in $[H^+]$.

Since rate = $k_{obs}\,[BAB]_t$, equation (14) can be transformed in to equation (15)

$$k_{obs} = \frac{k_2\ K_1[S]}{[H^+]+K_1} \qquad \ldots (15)$$

$$\frac{1}{k_{obs}} = \frac{[H^+]+K_1}{k_2\ K_1[S]} \qquad \ldots(16)$$

Or

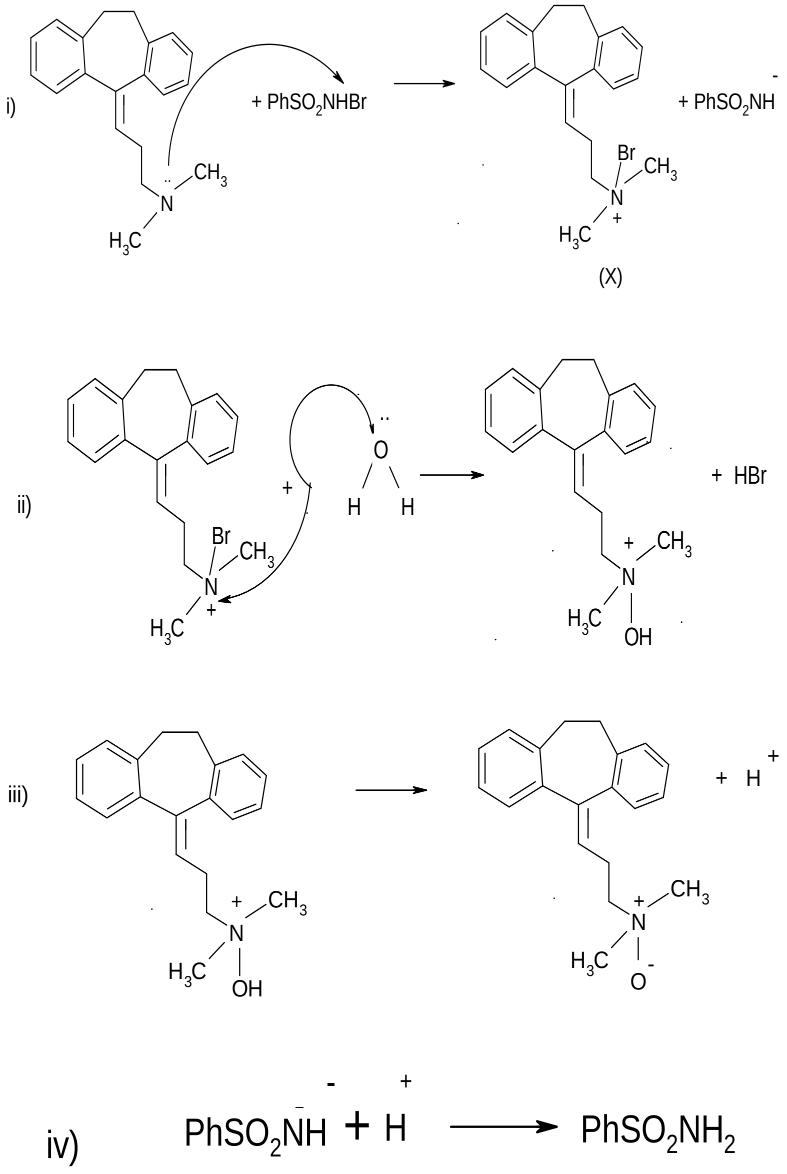
$$\frac{1}{k_{obs}} = \frac{[H^+]}{k_2\ K_1[S]} + \frac{1}{k_2\ [S]} \qquad \ldots(16)$$

A plot of ${}^{1}/_{k_{obs}}$ versus $[H^+]$ at constant [substrate], [BAB] and temperature from equation (16) was found to be linear with

$$\text{Slope} = \frac{1}{k_2\ K_1[S]} \quad \text{and Intercept} = \frac{1}{k_2\ [S]} \qquad \ldots(17)$$

The value of K_1 deprotonation constant (0.13) and k_2 (1.075) were calculated from the slope and intercept of the plots. Further more the protonation constant $K_P = 1/K_1$ (7.54) of

$PhSO_2NHBr$ was evaluated. The values of protonation constant $K_P = 7.54$ almost equal to that of values suggested by Narayan et al.[18] and Subhashini et al.[19] Therefore constancy of K_P values form a strong indirect evidence for the existence of the reacting species $PhSO_2N^+H_2Br$. The moderate value of enthalpy of activation ($\Delta H^{\neq}$) is supportive of the proposed mechanism in Scheme 1 and 2. The highly negative entropy of activation ($\Delta S^{\neq}$) indicates the formation of rigid transition state.



Scheme 2. A reaction path for the oxidation of Amitriptyline by BAB in buffer medium.

Table 1: Effect of varying reactant concentration on the rate.

Buffer pH = 1.2; μ = 0.1 mol dm^{-3}; λ_{max} = 410 nm. T = 303K.

[BAB] x 10^{3} mol dm^{-3}	10^{4}[Amitriptyline] mol dm^{-3}	10^{5}k′ (sec^{-1})
1.0	1.0	7.94
2.0	1.0	15.8
3.0	1.0	23.0
4.0	1.0	33.9
5.0	1.0	43.8
6.0	1.0	57.5
3.0	0.6	25.0
3.0	0.8	23.0
3.0	1.0	24.5
3.0	1.2	22.0
3.0	1.5	23.0

Table 2: Effect of varying pH on the rate of reaction.

$[AT]_0$ = 1.0 × 10^{-4} mol dm^{-3}; [BAB] = 3.0 × 10^{-3} mol dm^{-3}; μ = 0.1 mol dm^{-3}; T = 303K.

pH	[H^{+}]	k x 10^{5}(sec^{-1})
1.0	0.100	15.1
1.1	0.079	18.6
1.2	0.060	23.0
1.3	0.050	25.1
1.4	0.039	31.6
1.5	0.031	39.0

Table 3: Activation parameters for the oxidation of amitripyline by BAB in buffer medium.

Ea (kJ mol^{-1})	ΔH$^{\neq}$ (kJ mol^{-1})	ΔS$^{\neq}$ (JK^{-1} mol^{-1})	ΔG$^{\neq}$ (kJ mol^{-1})
50.48	47.94	- 156.41	95.94

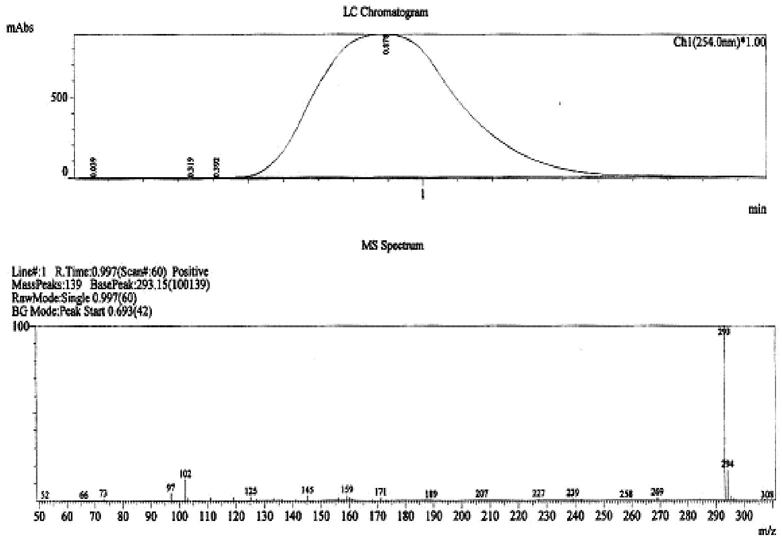


FIG. 1 GC-Mass Spectra of Amitriptyline N-Oxide with Molecular Peak (293).

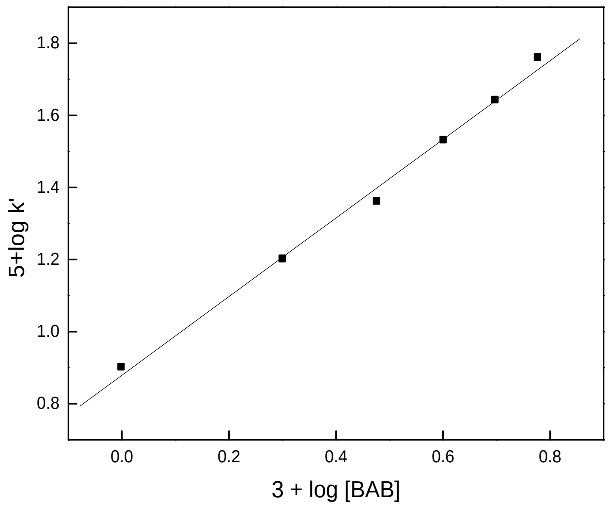


FIG.2 Plot of log k' versus[BAB]

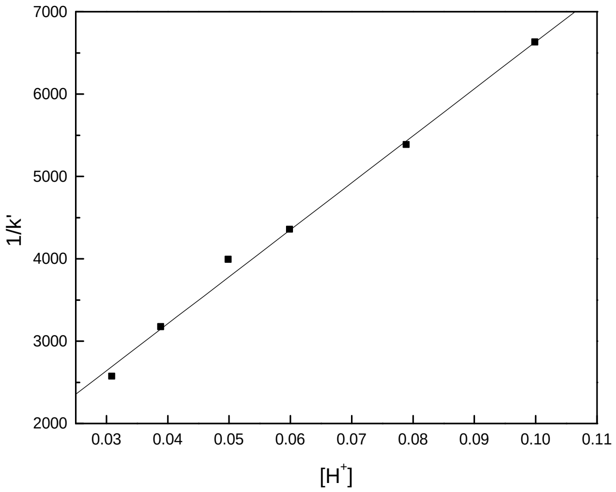


FIG.3 Plot of 1/k' versus [H$^+$]

CONCLUSION

Spectrophotometric kinetics and oxidation of amitriptyline by sodium-N-bromobenzenesulphonamide (BAB) in buffer medium has been studied at 303K. Activation parameters were computed. Major oxidation product amitriptyline-N-oxide was detected by mass spectral studies. Bromamine-B is the reactive species which reacted with substrate to give corresponding product. Based on kinetic results and reaction stoichiometry, a suitable mechanism and rate law has been proposed.

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