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Oxidation of Piperazines by Bromamine-B in Acidic Buffer Medium: A Kinetic and Mechanistic Study.

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ABSTRACT

The kinetics of oxidation of piperazine and its derivatives, 1-methylpiperazine and 1-ethylpiperazine, by N-sodio-N-bromobenzenesulfonamide or bromamine-B (BAB) in pH 4.0 buffer has been investigated at 303K. The reaction rate shows a first-order each on $[BAB]_0$ and $[Piperazine]_0$, and an inverse fractional-order dependence on $[H^+]$. Additions of reaction product, benzenesulfonamide, or bromide ions and the variation of ionic strength of the medium have no influence on the reaction rate. The reaction has been studied at different temperatures and activation parameters have been calculated. A general mechanism consistent with the preceding kinetic data has been proposed and the rate law derived. The protonation constants of piperazine and its substituted derivatives have been evaluated. The Hammett correlation of substituent effect shows a linear free energy relationship with $\rho = -0.75$ indicating that electron donating centers enhance the rate of reaction. An isokinetic temperature of $\beta = 393$ K indicates that enthalpy factors control the reaction rate.

INTRODUCTION

The chemistry of a class of N-metallo-N-halo aryl sulfonamides, known as N-halo amines, attracted the attention of many investigators due to their diverse behavior. Their versatile nature is attributed to their ability to act both as electrophiles and nucleophiles [1]. As a result, these compounds interact with a wide range of functional groups in aqueous, partially aqueous and non-aqueous media in the presence of acids or bases, and the reduction products obtained are the respective sulfonamide and sodium halide [2]. The dominant members of the class of chloro compounds are chloramine-T (CAT) and chloramine-B (CAB). A review of the literature reveals that although the reaction of aromatic sulfonylhaloamines have been known and extensively investigated [1-7], there is not much information [8-11] available on the reaction of corresponding bromamines, bromamine-T and bromamine-B. Sodium N-bromobenzenesulfonamide or bromamine-B (BAB, $C_6H_5SO_2NBrNa \cdot 1.5 H_2O$) has gained importance as a mild oxidant and it is readily prepared by brominating chloramine-B. Bromamine-B is found to be a most potential oxidant among these N-halo amines. There are but a few reports [12-14] on the kinetics of oxidation of organic substrates by BAB as compared to the studies with haloamines as oxidants from a mechanistic view point.

Piperazine is a heterocyclic nitrogenous compound [15] and has chemical similarity with piperidine except that it has two opposing nitrogen atoms. In both animal and man, piperazine and its salts are known to be highly effective as anthelmintics [16]. It is used in the treatment of gout and is an excellent solvent for uric acid [16, 17]. Many uses of piperazine derivatives have been suggested [18]. The more important among these are as intermediates for tranquilizing agents and antihistamines, insecticides, fungicides, bactericides, analgesics, antispasmodics, filaricides and anthelmintics. Also some derivatives have been

investigated for the treatment of cancer also [19-20] radiation sickness^[21] and angina pectoris^[22]. The literature survey reveals that kinetic investigations of reaction of piperazines with iron(II) and cobalt(III) have been reported by Aravindakshan and Muraleedharan^[23]. Further there was no information available on oxidation of piperazine by oxidants including BAB with regards to the kinetic and mechanistic point of view. Therefore, studies on the mechanism and rate law for this redox system were absent. Hence, the oxidation of piperazines with BAB adds to the knowledge of redox chemistry. These facts prompted us to undertake the present kinetic investigation.

EXPERIMENTAL

Bromamine-B was prepared by the partial debromination of dibromamine B (DBB) which was obtained by the bromination of CAB using a reported method^[24]. Chloramine-B (30 g) was dissolved in 560 mL water to which liquid bromine (6 mL) was added drop wise with stirring. A yellow precipitate of DBB formed was washed with water, filtered, suction and dried in a vacuum desiccator. Dibromamine-B (31.5 g) was digested in batches with constant stirring in 50 mL of 4.0 M NaOH. The resulting mass was cooled in ice, filtered under suction and the product (BAB) was dried over anhydrous calcium chloride. The purity of BAB was tested iodometrically and through IR and NMR spectral data^[25]. An aqueous solution of BAB was prepared, standardized by iodometric method and preserved in an amber colored bottle, until used, to prevent its photo chemical deterioration.

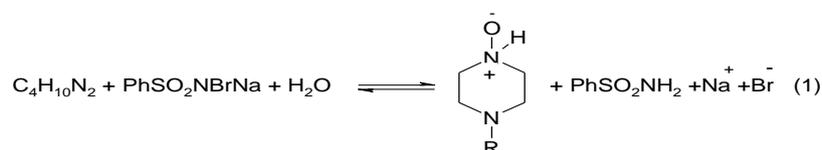
Piperazines (Spectrochem) of acceptable grades of purity were used without further purification. Fresh aqueous solutions of piperazine were prepared as required. All other chemicals used were of acceptable grades of purity. A constant ionic strength of the reaction mixture was maintained at 0.1 mol dm⁻³ by adding required amount of a concentrated NaClO₄ solution. Triply distilled water was employed for preparing aqueous solutions. A pH 4.0 buffer solution of acetic acid and sodium acetate was prepared^[26] and its pH value checked with a pH meter.

Kinetic Measurements

Kinetic runs were performed under pseudo-first order conditions of a large excess of the substrate over BAB at 303K. For each run requisite amounts of piperazine, NaClO₄ (to maintain a constant ionic strength), and a buffer of known pH were mixed in a stoppered Pyrex glass tube whose outer surfaces were coated black. Required amount of water was added to maintain a constant total volume. The tube was thermostated in a water bath at a given temperature. To this solution, was added a measured amount of pre-equilibrated BAB solution to give a known over all concentration. The reaction mixture was shaken for uniform concentration. The course of the reaction was monitored iodometrically by titration of unreacted BAB in known aliquots (5 mL each) of the reaction mixtures with drawn at regular time intervals. The reactions were followed for more than two half lives. The pseudo first- order rate constant (k') calculated from the linear plots of log[BAB] vs time. The regression analysis of the experimental data was carried out on origin 5.0 HP computer to obtain the regression coefficient, r .

Reaction Stoichiometry

Varying ratios of oxidant-to-piperazine in the presence of pH 4.0 buffer were equilibrated at 303K for 24 h. The unreacted BAB in the reaction mixture was determined iodometrically, indicated that one mole of piperazine consumed one mole of BAB to give the corresponding N-oxide which is stoichiometrically represented as in eq. (1).



Here R = H for piperazine, -CH₃ for 1-methylpiperazine and -C₂H₅ for 1-ethylpiperazine.

Product Analysis

The reaction mixture in the stoichiometric ratio in the presence of buffer medium was allowed to progress for 24 h at 303K. After completion of the reaction (monitored by TLC), the reaction mixture was neutralized and the products were extracted with ether. The organic products were subjected to spot tests and chromatographic analysis (TLC method). The products were piperazine oxide, 1-methyl piperazine oxide and 1-ethyl piperazine oxide. For example, the GC-MS data for piperazine obtained on a 17A Shimadzu gas

chromatograph with LCMS-2010A Shimadzu mass spectrometer showed a molecular ion peak at 102 amu (Figure 1) clearly confirming the formation of piperazine N-oxide. The reaction product, benzenesulfonamide (PhSO_2NH_2), was detected by TLC^[27] using light petroleum-chloroform-butan-1-ol (2:2:1= v/v/v) as the mobile phase and iodine as the detection agent ($R_f = 0.88$).

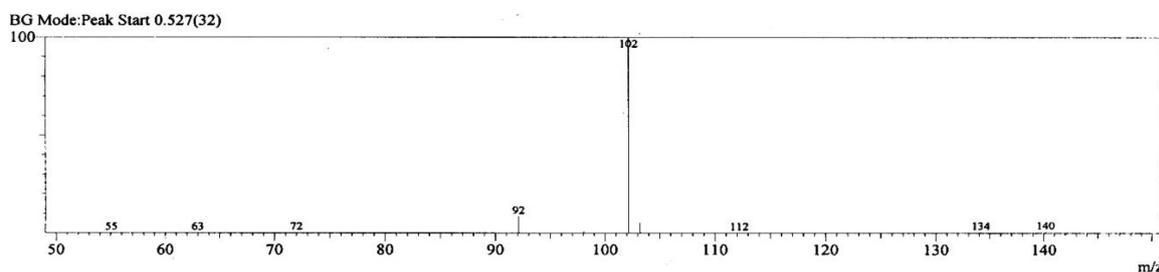


Figure 1: GC-Mass spectrum of piperazine-N-oxide with its molecular ion peak at 102 amu

RESULTS

The kinetics of oxidation of piperazine and its derivatives by BAB were investigated at several initial concentrations of the reactants in pH 4.0 buffer medium. Under comparable experimental conditions, the oxidation kinetic behavior was compared for all three piperazines.

Effect of Reactant Concentrations on the Rate

Under pseudo-first-order conditions of $[\text{piperazine}]_0 \gg [\text{BAB}]_0$ at constant $[\text{piperazine}]_0$, pH and temperature, plots of $\log[\text{BAB}]$ vs time were linear ($r > 0.9996$) showing a first-order dependence of the rate on $[\text{BAB}]_0$. The pseudo-first order rate constant k' obtained of 303K are listed in Table 1. The values of k' remain unaffected with a change in $[\text{BAB}]_0$ confirming the first-order dependence on $[\text{BAB}]_0$. The rate increased with increase in $[\text{piperazine}]_0$ (Table 1) and plots of $\log k'$ vs $\log[\text{piperazine}]$ were linear with unit slopes, indicating the first-order dependence of rate on $[\text{piperazine}]$.

Effects of pH and Halide Ion Concentration on the Rate

The reaction rate increased with increasing pH (Table 2) and plots of $\log k'$ vs $\log[\text{H}^+]$ were linear ($r > 0.9996$) with negative fractional slopes (-0.65 to -0.75), showing an inverse fractional-order dependence of the rate on $[\text{H}^+]$. Addition of Br ions in the form of NaBr did not alter the rate of the reaction, suggesting that bromine was not involved in the reaction rate equation.

Effect of Benzenesulfonamide and Ionic Strength on the Rate

Addition of benzenesulfonamide (PhSO_2NH_2) to the reaction mixture (3.0×10^{-4} - 7.0×10^{-4} mol dm^{-3}) had no effect on the rate, indicating that it is not involved in a pre-equilibrium to the rate determining step. The effect of ionic strength on the reaction rate was carried out in presence of 0.1 mol dm^{-3} sodium perchlorate, keeping all other experimental conditions constant. It was noticed that the ionic strength had negligible effect on the reaction rate.

Effect of Temperature on the Rate

The reaction was studied at different temperatures, 298 K to 313 K, while keeping the $[\text{BAB}]_0$ and other experimental conditions constant. The rate constants are presented in Table 3. The activation parameters (Table 3) were calculated from the slopes and intercepts of Arrhenius plots of $\log k'$ vs. $1/T$ ($r > 0.9996$).

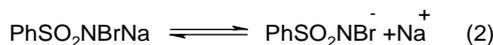
Test for Free radicals

Addition of the reaction mixture to the acryl amide monomer did not initiate polymerization indicating the absence of any free radicals produced *in situ* during the course of reaction.

DISCUSSION

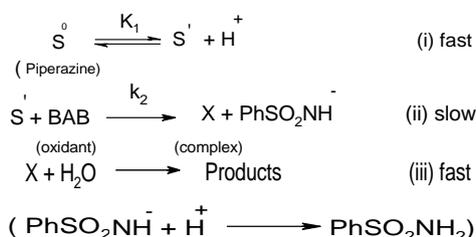
Reaction Mechanism

Pryde and Soper^[28], Morries *et al.*^[29] and Bishop and Jennings^[30] have shown the existence of similar equilibria in acid and alkaline solutions of N-metallo-N-halo aryl-sulphonamides. Bromamine-B ($\text{PhSO}_2\text{NBrNa}$) like its chlorine analogue chloramine-T behaves as a strong electrolyte in aqueous solutions forming different species as shown in eqs. (2) – (6).

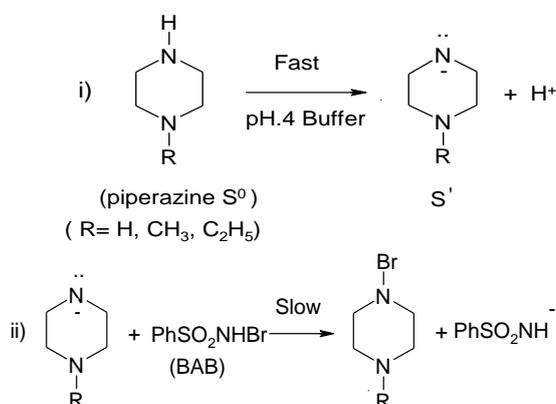


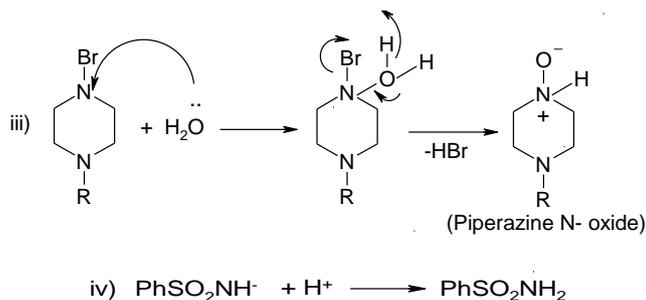
In acidic solutions, the probable oxidizing species are the free acid (PhSO_2NHBr), dibromamine-B ($\text{PhSO}_2\text{NBr}_2$), HOBr , and H_2OBr^+ . The involvement of $\text{PhSO}_2\text{NBr}_2$ in the mechanism leads to a second-order rate law, which is contrary to the experimental observations equation (5). As eq. (4) indicates a slow hydrolysis, if HOBr were the primary oxidizing species, a first-order retardation of the rate by the added PhSO_2NH_2 would be expected, which is contrary to the experimental results eq. (5). According Hardy and Johnston^[31], who has studied the pH-dependence of relative concentrations of the species present in acidified chloramine-T solution of comparable molarities, have shown that PhSO_2NHBr is the likely oxidizing species, in acid medium.

Furthermore, ultraviolet spectral measurements have shown that piperazine in aqueous solutions has a sharp absorption band at 235 nm, while BAB exhibits a peak around 340 nm both in the presence of pH 4.0 buffer and water. A mixture of BAB and piperazine in the absence of buffer shows a λ_{max} around 330 nm. This indicates no direct reaction between BAB and piperazine and no deprotonation from BAB. However, piperazine in the presence of pH 4.0 buffer showed a λ_{max} of 380 nm, which is a larger shift in λ_{max} indicating the formation of intermediate S' due to deprotonation of the substrate, piperazine. Based on the preceding discussion the following **Scheme 1** is proposed for the reaction



Scheme 1. A detailed mode of oxidation of piperazines by BAB in acidic medium: Structures of intermediates are depicted in **Scheme 2**.





Scheme 2. A reaction pathway for the oxidation of piperazines by BAB in acidic medium

Rate Law Derivation

From the slow step of Scheme 1,

$$\text{Rate} = k_2[S'][\text{BAB}] \quad (7)$$

$$S^o = \frac{[S'][H^+]}{K_1} \quad (8)$$

$$[S]_t = [S^o] + [S'] \quad (9)$$

Combination of eqs. (8) and (9) leads to eq. (10)

$$[S] = \frac{[S'][H^+]}{K_1} + S' = \frac{[S']\{[H^+] + K_1\}}{K_1}$$

$$[S'] = \frac{K_1[S]_t}{[H^+] + K_1} \quad (10)$$

By substituting for $[S']$ from eq. (10) in eq. (7), one gets

$$\text{rate} = \frac{k_2 K_1 [S]_t [\text{BAB}]}{[H^+] + K_1} \quad (11)$$

The rate law (eq. (11)) obtained from Scheme 1 is in good agreement with the experimental results, where a first-order dependence each on $[\text{BAB}]_0$ and $[\text{piperazine}]_0$ and inverse fractional order on $[\text{H}^+]$.

Since, $\text{rate} = k'[\text{BAB}]$, eq. (11) can be transformed as,

$$k' = \frac{k_2 K_1 [S]_t}{[H^+] + K_1}$$

or

$$\frac{1}{k'} = \frac{[H^+]}{k_2 K_1 [S]_t} + \frac{1}{k_2 [S]_t} \quad (12)$$

Based on eq. (12), plots of $1/k'$ vs. $[\text{H}^+]$ at constant $[\text{BAB}]_0$, $[\text{piperazine}]_0$ and temperature have been found to be linear (Figure 2: $r > 0.9951$) for all piperazines. The deprotonation constants (K_1) and protonation constants (K_p) of the substrate and the reaction constant (k_2) were calculated from the slope and intercept of these plots for the standard runs with $[\text{BAB}]_0 = 5.0 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{piperazine}]_0 = 1.0 \times 10^{-2} \text{ mol dm}^{-3}$, $[\text{H}^+] = 1.0 \times 10^{-4} \text{ mol dm}^{-3}$ at 303K. Further the values of protonation constant of the substrate ($K_p = 1/K_1$) were also determined. These values are presented in Table 4.

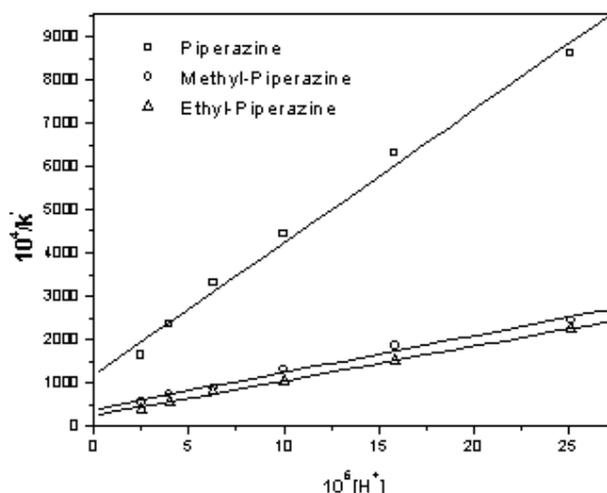


Figure 2: Plots of $1/k$ vs. $[H^+]$: experimental conditions are as in Table 2.

Structure Reactivity Correlation

Structural modification of a reactant molecule may influence the rate or equilibrium constant of a reaction through inductive, polar, steric and resonance effects, which can be used to probe into the reaction mechanism. Out of a number of empirical models proposed in describing the relationship between structure and reactivity, the most successful and extensively investigated is the linear free energy relationship^[32] with Hammett equation as the most prominent example. Hammett treatment describes the substituent effects on the rate and equilibria of aromatic molecules. In the present system, structure reactivity relationship is ascertained by utilizing different groups ($R = H, CH_3, C_2H_5$) at position one on the nitrogen atom of the piperazine ring and tested to fit the results into Hammett equation^[33]. The Hammett plot of $\log k'$ vs. σ is reasonably linear ($r = -0.9251$). From the plot, the value of the reaction constant ρ is found to be -0.75 signifying that the electron releasing groups in the piperazine ring enhance the rate. The positive inductive effect of the substituent increases the electron density on nitrogen of piperazine and subsequently the lone pair of electrons of nitrogen of piperazine easily attacks the electrophilic bromine of the reactive oxidizing species to form N-bromopiperazine as the transition state (Scheme 2). Furthermore, the positive inductive effect of the substituent in the present system increases in the order, $H < CH_3 < C_2H_5$, justifying the observed reactivity trend of piperazine $<$ 1-methylpiperazine $<$ 1-ethylpiperazine for piperazines oxidations.

Isokinetic Relationship

The largest activation for the slowest reaction (Table 3) indicates that the reaction is enthalpy controlled, within the reaction series. The variation in the rate may be caused by changes in either the enthalpy or entropy of activation or both, among the recognized categories. Rate changes caused by changes in both enthalpy and entropy of activation quantities in a parallel fashion represent one of the important categories. In this class, enthalpy and entropy of activation are correlated by linear relationship $\Delta H^\ddagger = \Delta H^\ddagger_0 + \beta \Delta S^\ddagger$, which is the isokinetic relationship and β is the isokinetic temperature. When the experimental temperature $T < \beta$, the reaction rate is controlled mainly by the enthalpy change. In the present case of the piperazines oxidations, the two activation parameters are linearly related as shown by plotting ΔH^\ddagger vs ΔS^\ddagger (Figure 3: $r = 0.9937$). From the slope, the value of isokinetic temperature (β) computed is found to be 393K. The calculated value of β is higher than the experimental temperature of 303K. This suggests that the reaction is enthalpy controlled. The existence of isokinetic relationship is of significance and is very valuable tool to the mechanistic chemist when used as supportive evidence along with other types of data. The large negative value of ΔS^\ddagger indicates a more ordered activated complex and the near constancy of ΔG^\ddagger shows an identical mechanistic pathway in the oxidation of all the three piperazines studied. Furthermore, the independent nature of the rate towards the addition of benzenesulfonamide, halide ion and neutral salts substantiates the proposed mechanism and the rate law derived.

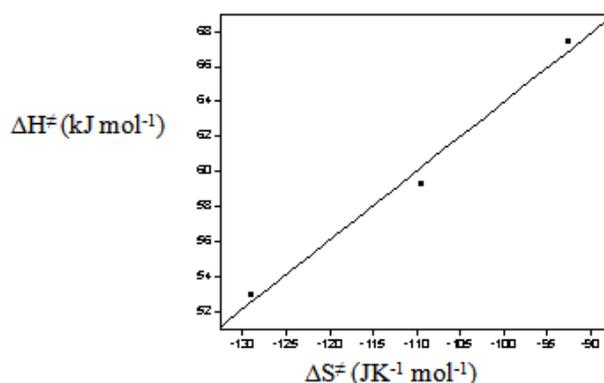
Figure 3: Isokinetic plot of ΔH^\ddagger vs. ΔS^\ddagger

Table 1: Effect of varying concentration of reactants on the reaction rate. pH= 4.0, Temperature = 303 K

$10^4[\text{BAB}] \text{ mol dm}^{-3}$	$10^2[\text{Piperazine}] \text{ mol dm}^{-3}$	$10^4 k' \text{ (s}^{-1}\text{)}$		
		Piperazine	1-Methylpiperazine	1-Ethylpiperazine
3.0	1.0	2.23	7.66	9.12
4.0	1.0	2.23	7.32	9.50
5.0	1.0	2.27	7.67	9.53
6.0	1.0	2.17	7.48	9.41
7.0	1.0	2.25	7.62	9.34
5.0	5.0	1.25	4.12	4.69
5.0	7.0	1.55	5.52	6.30
5.0	10.0	2.25	7.67	9.55
5.0	12.0	2.63	9.21	10.72
5.0	15.0	3.38	11.8	14.58
5.0	20.0	4.56	16.7	18.20

Table 2: Effect of varying pH on the reaction rate. $[\text{Piperazine}]_0 = 1.00 \times 10^{-2} \text{ mol dm}^{-3}$, $[\text{BAB}]_0 = 5.00 \times 10^{-4} \text{ mol dm}^{-3}$, Temperature = 303 K

pH	$[\text{H}^+] \times 10^5$	$10^4 k' \text{ (s}^{-1}\text{)}$		
		Piperazine	1-Methylpiperazine	1-Ethylpiperazine
3.6	25.11	1.16	4.10	4.46
3.8	15.85	1.58	5.42	6.60
4.0	10.00	2.25	7.67	9.60
4.2	6.30	3.01	11.5	12.6
4.4	3.98	4.26	13.5	17.7
4.6	2.51	6.11	18.2	25.8

Table 3: Effect of varying temperature on the reaction rate and activation parameters of the oxidation of piperazines by BAB in buffer medium $[\text{Piperazine}] = 1.0 \times 10^{-2} \text{ mol dm}^{-3}$, $[\text{BAB}]_0 = 5.0 \times 10^{-4} \text{ mol dm}^{-3}$. pH = 4.0

Substrate	$k' \times 10^4 \text{ (s}^{-1}\text{)}$				$\Delta H^\ddagger \text{ (kJ mol}^{-1}\text{)}$	$\Delta S^\ddagger \text{ (JK}^{-1}\text{mol}^{-1}\text{)}$	$\Delta G^\ddagger \text{ (kJ mol}^{-1}\text{)}$	$E_a \text{ (kJ mol}^{-1}\text{)}$
	298	303	308	313				
Piperazine	1.46	2.25	3.66	5.61	67.38	-92.52	95.65	69.93
1-Methylpiperazine	4.89	7.67	10.71	16.60	59.30	-109.44	92.74	61.84
1-Ethylpiperazine	6.92	9.67	13.58	20.00	52.69	-129.0	92.10	55.23

Table 4: Values of protonation and deprotonation constants for the oxidation of Piperazines by BAB in buffer medium at 303 K

Substrate	$10^{-5}K_1 \text{ (mol dm}^{-3}\text{)}$	$10^4K_P \text{ (dm}^{-3} \text{ mol}^{-1}\text{)}$	$k_2 \text{ (s}^{-1}\text{)}$
Piperazine	2.25	4.44	0.13
1-Methylpiperazine	5.00	1.93	0.23
1-Ethylpiperazine	5.50	1.81	0.25

CONCLUSIONS

Kinetics of oxidation of piperazines using Bromamine-B as oxidant was carried out in acid medium. A mechanism has been proposed and the rate law derived. The Hammett correlation of substituent effect shows a linear free energy relationship with $\rho = -0.75$ indicating that electron donating centers enhance the rate of reaction. An isokinetic study indicates that enthalpy rather than entropy factors control the reaction rate.

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