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OXIDATION STUDY OF PIPERAZINE BY N-CHLORO-P-TOLUENESULPHONAMIDE [CAT] IN ACIDIC BUFFER MEDIUM: KINETIC AND MECHANISTIC ASPECT

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***Abstract**:* Kinetics of oxidation of Piperazine by Chloramine-T (CAT) in buffer medium (pH 4.0) have been studied at 303K. Oxidation reaction follows first order kinetics with [CAT], [Piperazine] and inverse fractional order dependence on [H^+]. Addition of halide ions, toluenesulphonamide had no effect on the rate of the reaction indicating that non-ionic species are involved in the rate limiting step. Kinetic parameters were evaluated by studying the reaction at different temperature, oxidation products were identified. A common mechanism consistent with the kinetic data has been proposed. The protonation constant of substrate has been evaluated.

***Keywords*:** Piperazine, Chloramine-T, Kinetics, Reaction mechanism, Oxidation

1. Introduction

Piperazine is a heterocyclic nitrogenous compound [1] that has chemical similarity with piperidine as it has two opposing nitrogen atoms in the ring. In animals, including man, piperazine and its salts are known to be highly effective as anthelmintics [2]. It is used in the treatment of gout and is an excellent solvent for uric acid [2,3]. Many uses of piperazine derivatives have been suggested [4]. Their more important use is as intermediates for tranquilizing agents and antihistamines, insecticides, fungicides, bactericides, analgesics, antispasmodics, filaricides and anthelmintics. Some piperazines have been investigated for the treatment of

cancer [5,6], radiation sickness [7], and anginapectoris [8]. The literature survey shows that the kinetic investigations of reactions of piperazines with iron (II) and cobalt (III) have been reported by Aravindakshan et al. [9].

A prominent member of the class of N-haloarylsulphonamides is sodium N-chloro-p-toluenesulphonamide or chloramine-T (p-$CH_3C_6H_4SO_2NClNa_3H_2O$ or CAT), which is a by-product in the manufacture of saccharin Campbell and Johnson. CAT is the most widely studied haloamine containing positive chlorine which is implicated in the reaction of an array of functional groups of the substrates. Several studies on the mechanistic aspect of oxidation of diverse organic substrate including Piperazine by aromatic haloamines have been reported by us. An overview of literature showed a lack of data on the oxidation of Piperazine by CAT. In view of the above, we systematically studied kinetics of oxidation of Piperazine by CAT in presence of acid medium in order to understand the mechanistic aspects of these redox systems.

2. Experimental

The oxidant chloramine-T was prepared and purified using the method of Nair and Indrasenan [10]. The purity of CAT was analysed with the help of iodometric and spectroscopic data [10, 11]. Further an aqueous solution of CAT was standardized and preserved in amber-coloured bottles until use to prevent its photochemical deterioration. Piperazine also purchased from Sigma Aldrich was used as received without any further purification**.** Stock solutions of pH 4.0 buffer solution of acetic acid and sodium acetate was prepared [12] and its pH value checked with a pH meter. All other chemicals like TSA, NaCl, $NaClO_4$, methanol used were of analytical grade and all solutions were prepared using triple distilled water.

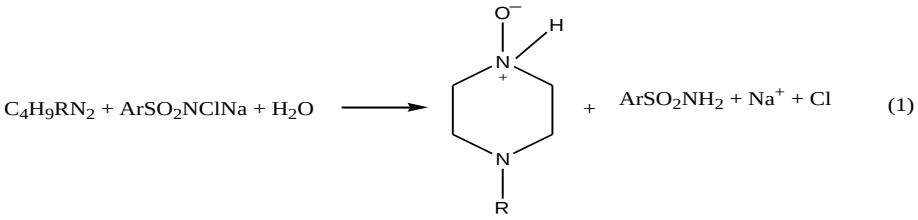
2.1 Kinetic Measurement

Kinetic examinations were made using iodometric titration. In the present work, kinetic runs were carried out in the temperatures ranging from 298K to 313K. A steady temperature was kept up within an exactness of ± 0.1K. The whole kinetic procedure was monitored under the pseudo-first-order conditions with an excess of Piperazine that contrasted with CAT at a steady pH = 4.0 at 303K. The known measure of Piperazine, buffer solutions and water were thermostats at 303K for 30 minutes. The oxidation responses were begun by the quick addition of the necessary amount of CAT into the response mix that contained Piperazine. The progress of the reaction was monitored by withdrawing aliquots of the reaction mixture at regular time intervals and by iodometrically titrate the unreacted CAT for over two half-lives. Plot of log $[CAT]_0$ vs time was used to calculate the pseudo first order rate constant k'. Regression coefficient (r) was calculated with the help of FX-991ms.

2. 2 Response Stoichiometry and Product Characterization

A different ratio of CAT was added to Piperazine in the pH 4.0 buffer at 303K. The remaining CAT in the response blend was estimated by iodometric titration. This examination demonstrates that Piperazine and the

oxidant CAT responded in an equal proportion of 1:1 to give the corresponding N- oxide at 303K as is given below.



2.3 Product analysis

The reaction mixture in the stoichiometric ratio in the presence of buffer medium was allowed to progress for 24 hours 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 N-oxide product to piperazine N-oxide, For example, the GC-MS data for piperazine N-oxide 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, p-toulenesulphonamide ($ArSO_2NH_2$), was detected by paper chromatography [13]. Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl in ethanol as spray reagent (R_f = 0.905).

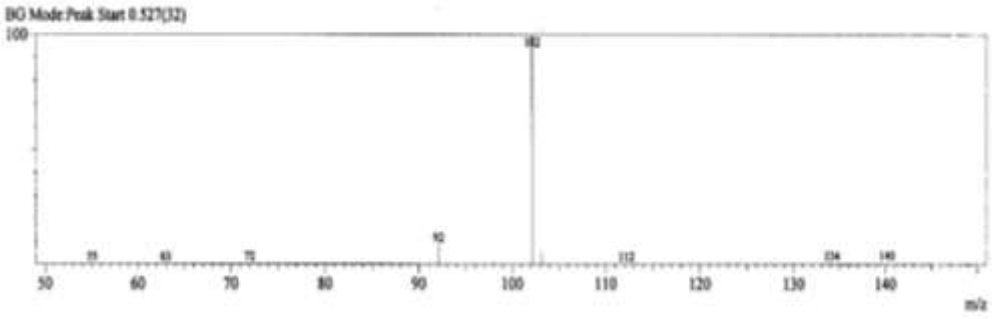


Fig. 1: GC-Mass spectrum of piperazine-N-oxide with its molecular ion peak at 102 amu

3. Results and Discussion

The kinetics of oxidation of Piperazine by CAT was investigated by several initial concentrations of the reactants in presence of buffer medium at 303K.

3.1 Consequence of modifying the concentration of PZ and CAT on the rate

Under pseudo first order conditions i.e. [PZ] >> [CAT], the values of rate constants were obtained by varying the concentration of CAT. The plot of log $[CAT]_0$ versus time was found to be linear indicating a first order dependence on CAT. The values of rate constant did not vary much with the variation in the concentration of CAT. This showed that the response is of first-order for [CAT]. During kinetic runs, upon increasing the concentration of PZ [(5.0 - 20.0) x 10^{-2} mol dm^{-3}], the rate of the response was seen to increase subsequently. Also, the order w.r.t oxidant was obtained by the plot of log [PZ] versus log k'. The nature of the graph was

linear and the order w.r.t to CAT was found to be 1.08 (Table 1, Figure 2, r= 0.996). This clearly indicated the first order dependence of rate on the concentration for [PZ].

Table 1. Effect of varying reactant concentrations on the reaction rate pH = 4.0; temperature = 303 K.

10^4 [CAT] (mol dm^{-3})	10^2[Piperazine]$_0$ (mol dm^{-3})	k′ × 10^6 sec^{-1}
3.0	1.0	1.88
4.0	1.0	1.88
5.0	1.0	1.88
6.0	1.0	1.88
7.0	1.0	1.88
5.0	5.0	0.90
5.0	7.0	1.14
5.0	10.0	1.88
5.0	12.0	2.27
5.0	15.0	3.35
5.0	20.0	4.17

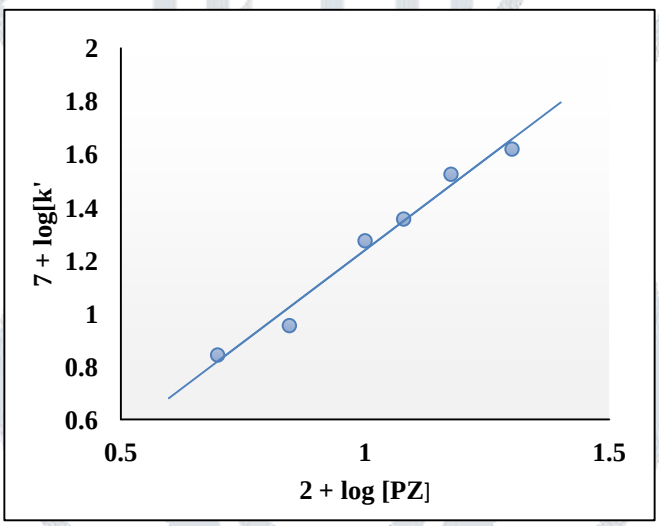


Fig. 2: Plot of log k′ Vs. log [PZ]

3.2 Consequence of changing the pH on the rate

It was seen that the rate of reaction increased when there was an increase in the pH and plot of log k′ versus log [H^+] was found to be linear with negative slope having a slope less than unity (-0.64 to -0.78) indicating an inverse fractional order dependence of the rate on [H^+]. The estimations of pseudo-first-order rate constants have been organized in Table 2, Figure 3.

Table 2. Effect of varying pH on the reaction rate [piperazine]$_0$= 1.00 × 10^{-2} mol·dm^{-3}; [CAT]$_0$ = 5.00 × 10^{-4} mol·dm^{-3}; temperature = 303 K.

pH	10^5 [H^+] (mol dm^{-3})	k′ × $10^6 s^{-1}$
3.6	25.11	0.84
3.8	15.85	1.32
4.0	10.00	1.88
4.2	6.305	2.72

4.4	3.981	3.86
4.6	2.511	4.60

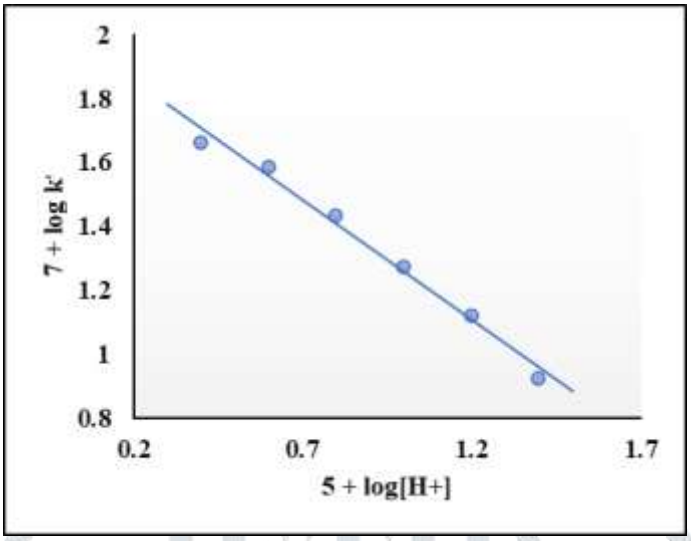


Fig. 3: Plot of log k′ Vs. log [H^+]

3.3 Consequence of halide ions on the rate

Addition of halide ion such as Cl^- in the form of NaCl ($3.0 \times 10^{-4} – 6.0 \times 10^{-4}$ mol dm^{-3}) has no influence on the rate of reaction, suggesting that chlorine was not involved in the rate equation and the dependence of the rate on [HCl] reflected the effect of [H^+] only.

3.4 Consequence of toluenesulphonamide on the rate

Toward the beginning of the response, including products toluenesulphonamide ($3.0 \times 10^{-4} – 7.0 \times 10^{-4}$ mol dm^{-3}) was added to the response blend. There was no noticeable impact on the response rate by the variety of concentration of toluenesulphonamide. This was seen by keeping all other experimental conditions constant.

3.5 Consequence of ionic strength on the rate

The effect of the concentration of sodium perchlorate from 0.1 to 1.0 mol dm^{-3}, the ionic strength of the response medium could be modified while other experimental conditions were kept steady in the acidic medium. It was seen that the rate of oxidation had negligible effect with an increased concentration of sodium perchlorate.

3.6 Consequence of adjusting the dielectric constant of the medium on the rate of reaction

Various quantities of methanol–water were added to the response blend by keeping other test conditions steady at 303K. This was done to change the dielectric constant (D) of the medium. The decrease in dielectric constant of the response medium was seen to increase the rate of the reaction. Under our empirical conditions, methanol–water mixture solvent did not undergo oxidation by CAT.

3.6 Consequence of modifying the temperature on the rate of reaction

The rates of response were researched at different temperatures from 298K to 313K by keeping the different parameters steady. The estimations of pseudo-first-order rate constants got at different temperatures have been displayed in Table 3. From the Arrhenius graph of log k versus 1/T, the estimations of different activation parameters, for example, Ea, $\Delta H^{\#}$, $\Delta S^{\#}$, $\Delta G^{\#}$, log A were assessed for the oxidation of Piperazine by CAT. The activation parameters acquired from the investigation are profoundly useful in understanding the actions controlling the transition state. The moderate estimation of activation parameters seen in the present case. For example, the vitality of actuation and other thermodynamic parameters bolster the proposed mechanism. The lower positive values of enthalpy of activation and free energy change show that the progression state is quite solvent and no significant bond breaking is noticed before reaching a transition state. Low enthalpy of activation with negative entropy of activation proposes that a small number of collisions become progressively stringent and the activated complex arrangement continues through the associative mechanism. The negative estimations of entropy change further as there is an increase in the degree of order on moving from an initial state to the transition state, which could be because of the more prominent levels in the solvent present in the activated complex.

Table 3. Effect of varying Temperature on the rate of reaction
$[Piperzine]_0 = 1.0 \times 10^{-2}$ mol dm^{-3}; $[CAT] = 5.0 \times 10^{-4}$ mol dm^{-3}; Buffer pH = 4.0; μ = 0.1 mol dm^{-3};

Temperature (K)	$10^3/T$	$k' \times 10^6$ sec^{-1}
298	3.355	1.17
303	3.300	1.88
308	3.246	3..08
313	3.194	7.11

3.7 Test for free radicals

Addition of reaction mixture to aqueous acrylamide monomer solutions did not initiate polymerization, indicating the absence of in situ formation of free radical species in the reaction sequence.

4. MECHANISM

Pryde and Sopper [14] Morris et al and Bishop and Jennings [15] have shown the existence of similar equilibria in acid of N-metallo-N-haloarylsulphonamides. Chloramine-T ($ArSO_2NClNa$) or $p\text{-}CH_3C_6H_4SO_2NClNa.3H_2O$) behaves as a strong electrolyte in aqueous solution forming different species as shown in equation (2) to (6).

$$ArNClNa \rightleftharpoons ArN^{-}Cl + Na^{+} \quad (2)$$

$$ArN^{-}Cl + H^{+} \rightleftharpoons ArNHCl \qquad ka = 2.82 * 10^{-5} \text{ at } 25^{0}C \quad (3)$$

$$2ArNHCl \rightleftharpoons ArNH_2 + ArNCl_2 \qquad k_d = 5.8 * 10^{-2} \text{at } 25^{0}C \quad (4)$$

$$ArNHCl + H_2O \rightleftharpoons ArNH_2 + HOCl \qquad k_h = 8 * 10^{-7} \text{at } 25^{0}C \quad (5)$$

$$ArNCl_2 + H_2O \rightleftharpoons ArNHCl + HOCl \quad (6)$$

$$HOCl \rightleftharpoons H^{+} + OCl^{-} \quad (7)$$

$$HOCl + H^{+} \rightleftharpoons H_2OCl^{+} \quad (8)$$

The possible oxidizing species in acidified CAT solutions are therefore, $ArSO_2NHCl$, $ArSO_2NCl_2$, HOCl and ClO^- ion. If the $ArSO_2NCl_2$ were to be the reactive species, then the rate law predicts a second order dependence of rate on $[CAT]_0$ from equation (4), which is contrary to experimental observations. Equation (6) indicates that hydrolysis is slight and if HOCl is primarily involved, a first-order retardation of rate by added $ArSO_2NH_2$ is expected. However, no such effect was noticed. Hardy and Johnston [16] who has studied the pH dependence of relative concentrations of the species present in acidified chloramine-T solution of comparable molarities have shown that $ArSO_2NHCl$ is the likely oxidizing species in acid medium.

Furthermore, ultraviolet spectral measurements showed that the aqueous piperazine solutions have a sharp absorption band at 235 nm, while the CAT solution exhibits a peak around 287 nm, both in pH 4.0 buffer solutions and water. A mixture of CAT and piperazine shows a λ_{max} around 330 nm which indicates no direct reaction between CAT and piperazines and no deprotonation from CAT. However, piperazine in the presence of pH 4.0 buffer shows a λ_{max} of 380 nm, which shows a longer shift indicating the formation of intermediate S´ due to deprotonation of the substrate. Based on the preceding discussion, scheme-1 below is proposed for the reaction.

$$S^0 \underset{\text{fast}}{\overset{K_1}{\rightleftharpoons}} S' + H^{+} \quad \text{------ (i)}$$

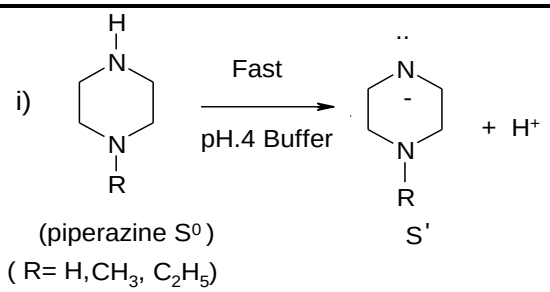
$$S' + CAT \xrightarrow[\text{slow}]{k_2} X + ArSO_2\bar{N}H \quad \text{------ (ii)}$$

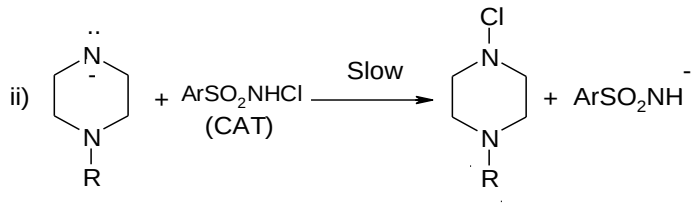
$$X + H_2O \longrightarrow \text{product} \quad \text{------ (iii)}$$

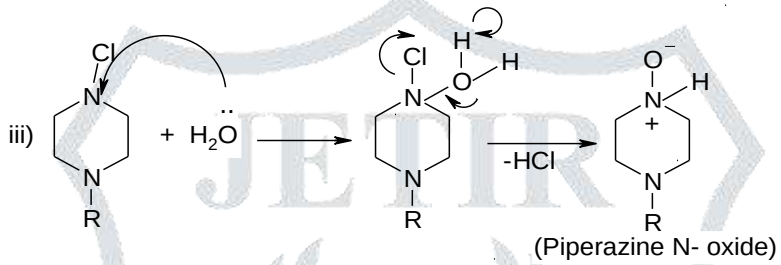
$$(ArSO_2\bar{N}H + H^{+} \longrightarrow ArSO_2NH_2)$$

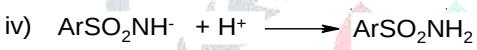
Scheme 1

A detailed mode of oxidation of piperazines by CAT in acidic buffer media and structures of intermediates are depicted in **Scheme 2**.









From the slow step of scheme 1,

$$\text{Rate} = k_2 [S'] [CAT] \qquad \text{---- (9)}$$

From step (i), we get

$$S^0 = \frac{[S'] [\overset{+}{H}]}{K_1} \qquad \text{----- (10)}$$

If $[S]_t$ is the total effective concentration of substrate, then

$$[S]_t = [S^0] + [S'] \qquad \text{---- (11)}$$

Substitution of eqn. (10) in eqn. (11) leads to eqn. (12),

$$[S]_t = \frac{[S'] [\overset{+}{H}]}{K_1} + [S'] \qquad \text{----- (12)}$$

$$[S]_t = \frac{[S'] \{[\overset{+}{H}] + K_1\}}{K_1} \qquad \text{-----(13)}$$

$$[S'] = \frac{K_1 [S]_t}{[\overset{+}{H}] + K_1} \qquad \text{-----(14)}$$

By substituting for [S´] from eq. (14) in eq. (9), we get

$$\text{rate} = \frac{k_2 K_1 [S]_t [CAT]}{[H^+] + K_1} \qquad \text{-----(15)}$$

The rate law (equation 15) obtained from scheme-1 is in good agreement with the experimental results, where a first-order dependence each on $[CAT]_0$ and $[Substrate]_0$ and inverse fractional order on $[H^+]$.

Since, rate = k´ [CAT], eq. (15) can be transformed as,

$$k' = \frac{k_2 K_1 [S]_t}{[H^+] + K_1} \qquad \text{-----(16)}$$

$$\frac{1}{k'} = \frac{[H^+]}{k_2 K_1 [S]_t} + \frac{1}{k_2 [S]_t} \qquad \text{-----(17)}$$

Based on eq. (17), plots of 1/k´v/s $[H^+]$ at constant $[CAT]_0$ $[Substrate]_0$ and temperature have been found to be linear. The deprotonation constant (K_1) and protonation constant (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 $[CAT]_0 = 5.0 \times 10^{-4}$ mol dm^{-3}, $[piperazine]_0 = 1.0 \times 10^{-2}$ mol dm^{-3}, $[H^+] = 1.0 \times 10^{-4}$ mol dm^{-3} at 303K. Further the values of protonation constant of the substrate $K_P = 1/K_1 = 44.456$ is also determined.

4. Conclusion

Kinetics of oxidation of three piperazines using chloramine-T as the oxidant was carried out in acid medium. The oxidation kinetics was studied by varying the ionic strength, dielectric constant of the medium. Finally, the reaction was studied at different temperatures and the products were isolated. Based on the observations made an appropriate rate law was derived and a possible mechanism was suggested.

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Conflict of Interest: The authors declare that there are no conflicts of interest.

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