IJBPAS, June, 2012, 1(5): 696-708

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

OXIDATION OF THIAMINE HYDROCHLORIDE BY BROMAMINE–T IN HCl MEDIUM: A KINETIC AND MECHANISTIC APPROACH

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ABSTRACT

Kinetics and oxidation of thiamine hydrochloride (TM, vitamin B_1) (2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl)methyl]-4-methyl-thiazol-5-yl] ethanol) by sodium – N – bromo – p – toluenesulphonamide (Bromamine-T or BAT) in aqueous HCl have been studied at 303K. The reaction was first order dependence in $[BAT]_o$, fractional order in $[TM]_o$ and inverse fractional order in [HCl]. Dielectric effect was positive. Addition of PTS, NaCl and NaBr did not affect the rate of the reaction. Variation of ionic strength did not affect the rate of the reaction indicating that non – ionic species are involved in the rate limiting step. Rate increased with increase in temperature from 293K to 323K. From the linear Arrhenius plot, activation parameters were computed. Addition of reaction mixture to aqueous acrylonitrile solution did not initiate polymerization, showing the absence of free radicals species. The stoichiometry of the reaction was found to be 1:1 and oxidation products were identified. TsNHBr was the reactive species which reacts with the substrate. Based on kinetic results and reaction stoichiometry, a suitable mechanism has been proposed.

Keywords: Oxidation, Mechanism, Bromamine-T, Thiamine Hydrochloride.

INTRODUCTION

Thiamine hydrochloride (TM, vitamin B_1) (2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl) methyl]-4-methyl-thiazol-5-yl] ethanol) which belongs to thoiazolium group is biologically very important. Its deficiency causes beri – beri in man and polyneutrics in birds **[1, 2]**.

Aromatic N- halosulphonamides behave as mild oxidants, halogenating agents containing strong polarized N- linked halogen which is in +1 state. Bromamine – T (sodium N- bromo-p- toluenesulphonamide or BAT; p – $CH_3C_6H_4SO_2NBrNa.3H_2O$) can be easily prepared by bromination of Chloramine – T (CAT) and is found to be a better oxidizing agent than CAT. Literature survey reveals that several work have been carried out with BAT as oxidant **[3-11]**.

Kinetics of oxidation of thiamine by other oxidants have been carried out **[12, 13]**. Hence Kinetics of oxidation of thiamine hydrochloride (2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl) methyl]-4-methyl-thiazol-5-yl]ethanol) with BAT in HCl medium at 303K have been studied and reported in this article.

MATERIALS AND METHODS

Bromamine – T was obtained **[8]** by partial debromination of Dibromamine – T (DBT). To a solution containing 20g of CAT in 400ml of water, about 4 ml of liquid bromine was added drop-wise from a microburette, with constant stirring at room temperature. Separated DBT was filtered under suction, washed thoroughly with ice cold water until all the absorbed bromine was completely eliminated and then vacuum dried for 24 h. About 20g of DBT was dissolved with stirring in 30ml of 4 mol dm^{-3} NaOH at room temperature and the resultant aqueous solution was cooled in ice, pale yellow crystals of BAT formed were filtered under suction, washed quickly with minimum amount of ice cold water and dried over P_2O_5. The product was confirmed to be Bromamine – T by qualitative analysis and by its mass spectrum, UV, IR, ^1H and ^{13}C- spectral data. An aqueous solution of BAT was prepared afresh, standardized by iodometric method and preserved in brown bottles to prevent its photochemical deterioration.

Thiamine hydrochloride (E.Merck) and p-Toluenesulphonamide (E.Merck) was used without further purification and aqueous solution of desired strength was prepared freshly each time. All other chemicals used were of analytical grade. Permittivity of the reaction medium **[14]** was altered by addition of methanol in varying proportions (v/v) and values of permittivity of methanol – water mixtures reported in literature were employed. Double distilled water was used in preparing all aqueous solutions throughout the studies

Kinetic Procedure

All reactions were carried out under pseudo – first order conditions ($[TM]_o >> [BAT]_o$) at constant temperature 303K, in a glass – stoppered pyrex boiling tubes coated black on outside to eliminate photochemical effects. Oxidant and the requisite amounts of substrate, HCl solution and water (for constant total volume) taken in separate boiling tubes were thermally equilibrated at 303K. Reaction was initiated by rapid addition of measured amount of BAT to the mixture and was shaken intermittently. Progress of the reaction was monitored by iodometric determination of unconsumed BAT in known aliquots (5ml each) of the reaction mixture at regular intervals of time. Reaction was studied for more than two half-lives. The pseudo – first order rate constants ($k^{/}$) calculated from the linear plots of log $[BAT]_o$ versus time were reproducible within ± 3-4 %.

Stoichiometry and Product Analysis: Reaction mixture containing various ratios of bromamine - T to Thiamine hydrochoride in presence of $5x10^{-2}$ mol dm^{-3} HCl at 303K, under the condition $[TM]_o >> [BAT]_o$, were equilibrated for 24h. Determination of unreacted BAT showed 1:1 stoichiometry.

$$C_{12}H_{17}N_4OS^+Cl^-.HCl+TsNBrNa + H_3O^+ \longrightarrow$$

$$C_{12}H_{15}N_4OS^+Cl^-.HCl +TsNH_2+H_2O+NaBr \quad (1)$$

Reduction product of BAT, p–toluene sulphonamide was detected by thin layer chromatography **[15]** using light petroleum – chloroform – 1 butanol (2:2:1 v/v/v) as the solvent and iodine as the reducing agent. Further it was confirmed by its MP (138-143°), IR and NMR spectra. Oxidation product (2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl) methyl]-4-methyl-thiazol-5-yl] ethanol) was detected using Schiff's reagent **[16]** and 2, 4- dinitrophenyl hydrazine test and was confirmed by IR spectroscopy. Strong peak for -CHO group was observed at $1725cm^{-1}$.

RESULTS

Oxidation of TM by BAT in HCl medium have been kinetically investigated at 303K.

1. Effect of Reactants on the Reaction Rate

With substrate in excess, at constant $[TM]_{o,}$ $[H^+]$ and temperature, plots of log [BAT] vs time were linear indicating a first order dependence of rate on $[BAT]_{o.}$ Rate constant

$k^{/}$ was unaffected by change in $[BAT]_o$ **(Table1)** confirming first order dependence on $[BAT]_{o.}$ Increase in $[TM]_o$, lead to increase in rate of the reaction **(Table1)** at constant $[BAT]_{o,}$ [HCl] and temperature. Plot of log $k^{/}$ vs log [TM] **(Figure 1)** was linear with a positive slope of 0.5 indicating fractional order dependence on [TM]. The rate decreased with increase in [HCl] **(Table 1)**. Plot of log $k^{/}$ vs log [HCl] **(Figure 2)** was linear with a negative slope of 0.58, showing an inverse fractional order dependence on $[H^+]$

2. Effect of Halide Ions and p- Toluene Sulphonamide on the Rate

Addition of NaCl or NaBr($10x10^{-2}$ mol dm^{-3} to 30 $x10^{-2}$ mol dm^{-3}) did not affect the rate of the reaction. Hence it reflected that the rate of the reaction depends only on $[H^+]$. Addition of reduction product of the oxidant, p- toluenesulphonamide (PTS; $1.0x10^{-3}$ mol dm^{-3} to $4.0x10^{-3}$ mol dm^{-3}) did not affect the rate, which indicates its non–involvement in pre-equilibrium with the oxidant.

3. Effect of Ionic Strength and Dielectric Constant on the Rate

Variation in ionic strength using $NaClO_4$ solution ($1.0x10^{-3}$ mol dm^{-3} to $5.0x10^{-3}$ mol dm^{-3}) did not affect the rate of the reaction indicating that non–ionic species are involved in the rate limiting step.

Dielectric constant (D) of the medium was varied by adding methanol (0-30% v/v) to the reaction mixture. Addition of methanol resulted in an increase in the reaction rate **(Table 2)**. Plot of (1/D) vs log$k^{/}$ **(Figure 3)** was linear with a positive slope (0.90). Values of D for MeOH – OH mixtures were taken from literature **[14]**.

Blank experiments showed that MeOH oxidized slowly (~3%) under the experimental conditions. This was corrected for the calculation of rate constant.

4. Effect of Temperature on the Reaction Rate

Reaction was studied over a range of temperature 293K to 323K by varying the concentration of Thiamine hydrochloride **(Figure 4)**, keeping other experimental conditions constant. It was found that the rate increased with increase in temperature **(Table 3)**.

From the linear Arrhenius plot **(Figure 5)**, activation parameters like energy of activation (Ea), enthalpy of activation ($\Delta H^{\neq}$), entropy of activation ($\Delta S^{\neq}$), free energy of activation ($\Delta G^{\neq}$) and logA were computed **(Table 4).**

5. Test for Free Radicals

Addition of reaction mixture to aqueous acrylonitrile solution did not initiate polymerization, showing absence of free radical species.

Table 1 - Effect of Reactant Concentrations on the Reaction Rate at 303K

10^4[BAT]$_o$	10^3[TM]$_o$	10^3[HCl]$_o$	$10^4k^/$
mol dm $^{-3}$	mol dm $^{-3}$	mol dm $^{-3}$	s^{-1}
5.0	10.0	50.0	4.526
10.0	10.0	50.0	4.536
20.0	10.0	50.0	4.540
30.0	10.0	50.0	4.500
60.0	10.0	50.0	4.550
10.0	1.0	50.0	1.520
10.0	5.0	50.0	3.190
10.0	10.0	50.0	4.536
10.0	20.0	50.0	6.032
10.0	30.0	50.0	7.310
10.0	10.0	1.0	10.992
10.0	10.0	25.0	7.197
10.0	10.0	50.0	4.536
10.0	10.0	100.0	2.878
10.0	10.0	200.0	2.360
10.0	10.0	300.0	2.144

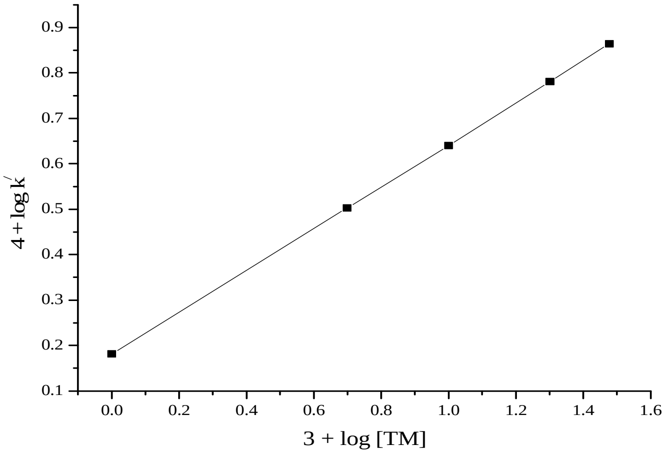


Figure 1: Effect of [TM] on the Reaction Rate

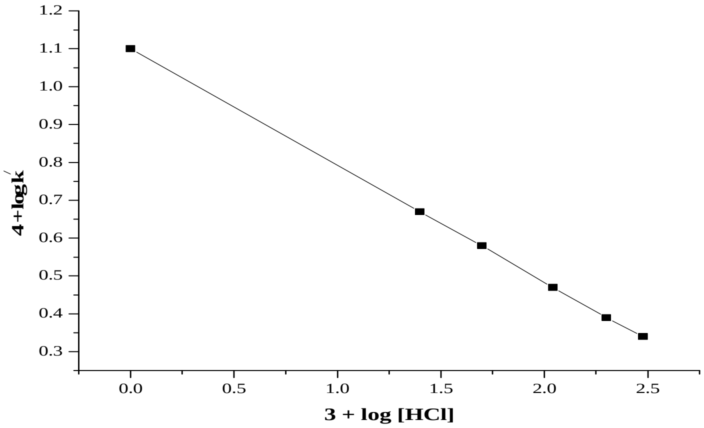


Figure 2: Effect of [HCl] on the reaction rate

Table 2: Effect of Dielectric Constant of the Medium on the Reaction Rate

MeOH (% v/v)	D	10^2/D	10^4 $k^/(s^{-1})$
0	76.93	1.30	4.536
10	72.37	1.38	5.300
20	67.38	1.48	6.438
30	62.71	1.60	7.548

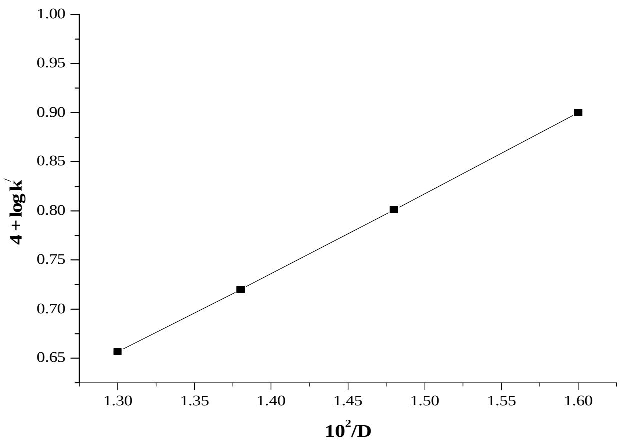


Figure 3: Effect of Dielectric Constant of the Medium on the Reaction Rate

Table 3 - Effect of [TM] and Temperature on the Reaction Rate

10^3 [TM] mol dm^3	$10^4k^/(s^{-1})$		
	293K	303K	313K
5.00	1.659	3.190	10.000
10.0	2.269	4.536	12.022
50.0	3.019	6.032	15.205

Table 4: Temperature Dependence and Values of Activation Parameters

Temperature (K)	$10^4k^/(s^{-1})$	Activation parameters	
		Parameter	Value
293	1.35(1.56)	Ea(kJ mol^{-1})	90.02(93.67)
298	2.44(3.65)	$\Delta H^{\neq}$ (kJ mol^{-1})	87.52(89.01)
303	4.53(5.13)	$\Delta G^{\neq}$ (kJ mol^{-1})	65.42(69.24)
313	7.44(7.89)	$\Delta S^{\neq}$ (JK^{-1} mol^{-1})	-218.63(-220.73)
323	10.90(11.23)	logA	12.16(12.30)

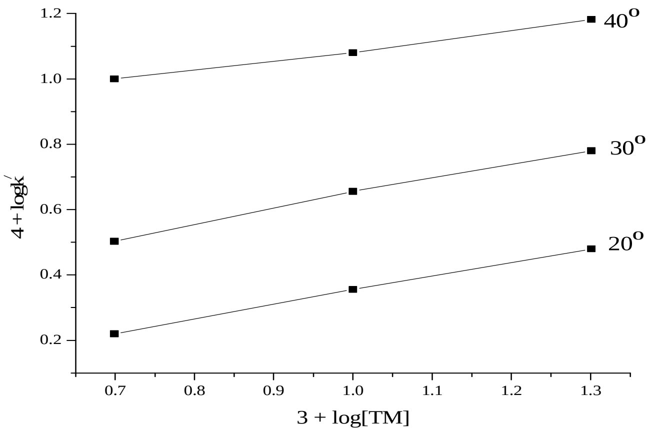


Figure 4: Effect of [TM] and Temperature on the Reaction Rate

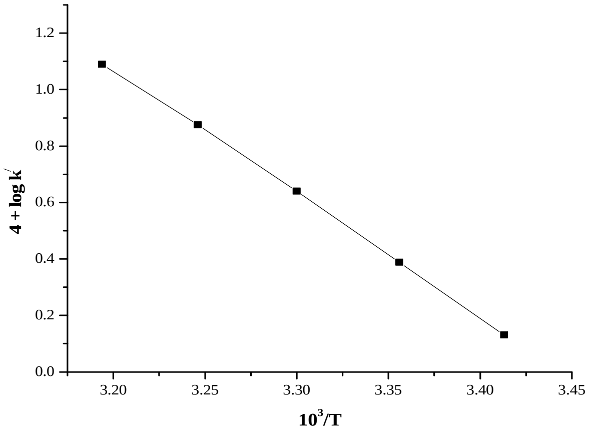


Figure 5: Effect of Temperature on the Reaction Rate

DISCUSSION

Existence of similar equilibrium in acid and alkaline solutions of N-metallo–N–haloarylsulphonamides have been shown **[17-19]**. Bromamine- T is analogous to CAT and behaves like a strong electrolyte in aqueous solutions, forming different types of reactive species as shown in equations (2 – 8)

$TsNBrNa \rightleftharpoons TsNBr^{-} + Na^{+}$ (2)

(Here Ts=p-$CH_3C_6H_4SO_2^{-}$)

$TsNBr^{-} + H^{+} \rightleftharpoons TsNHBr$ (3)

$$2\ TsNHBr \rightleftharpoons TsNH_2 + TsNBr_2 \quad (4)$$

$$TsNHBr + H_2O \rightleftharpoons TsNH_2 + HOBr \quad (5)$$

$$TsNBr_2 + H_2O \rightleftharpoons TsNHBr + HOBr \quad (6)$$

$$HOBr \rightleftharpoons H^+ + OBr^- \quad (7)$$

$$HOBr + H^+ \rightleftharpoons H_2O^+Br \quad (8)$$

Therefore, the possible oxidizing species in acid medium are TsNHBr, $TsNBr_2$, HOBr and possibly H_2O^+Br. If $TsNBr_2$ were to be the reactive species, then the rate law predicts a second order dependence of rate on $[BAT_o]$, which is contrary to the experimental observations. If HOBr is primarily involved, a first order retardation of rate by added PTS is expected, since no such effect is noticed, HOBr can be ruled out as oxidizing species. Hence TsNHBr is responsible for the oxidation of TM. Hardy and Johnston **[20]** have studied the pH dependent relative concentration of the species present in acidified CAT solutions of comparable molarities and have shown that its acid form is likely oxidizing species in acid medium.

Further, Monochloramines can be further protonated at pH<2 **[21, 22]**. Hence it is likely that TsNHBr is further protonated in acid media [**15]**. In present case, TsNHBr is the active oxidizing species.

Based on the preceding discussion and kinetic results, mechanism **(Scheme1)** is proposed for the oxidation of TM by BAT in HCl medium.

Scheme 1

$$TsNH_2\,Br^+ \overset{K_1}{\rightleftharpoons} TsNHBr + H^+ \quad \text{(i) fast}$$

$$TsNHBr + TM \overset{K_2}{\rightleftharpoons} X \quad \text{(ii) fast}$$

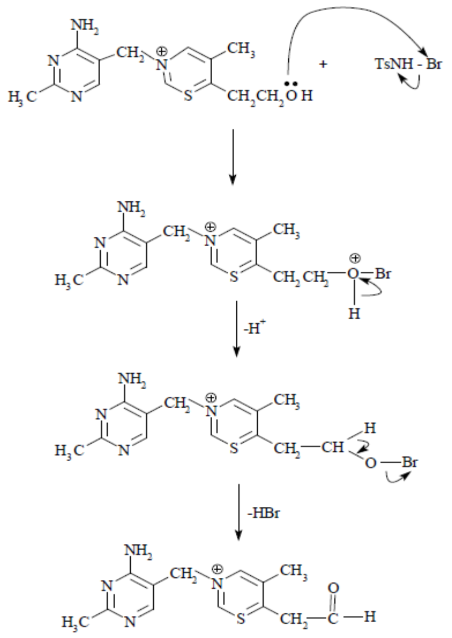
$$X \xrightarrow{k_3} X^{/} \quad \text{(iii) slow, rds}$$

$$X^{/} \xrightarrow{k_4} \text{Products} \quad \text{(iv) fast}$$

X and $X^{/}$ represents complex intermediate species, whose structures are shown in Scheme 2 in which a detailed mechanistic interpretation of TM oxidation by BAT in acid medium is proposed.In this, the oxidant species TsNHBr formed from dissociation of $TsNH_2Br^+$ reacts with the substrate in a fast equilibrium step to form substrate – BAT complex (X).

This gives another intermediate complex ($X^{/}$) in a rate limiting step. $X^{/}$ will give the final products.

Scheme 2: Mechanism of Oxidation of [TM] with [BAT]



Step (iii) of Scheme 1 determines the overall rate,

$$\text{Rate} = \frac{-d[\text{BAT}]}{dt} = k_3[\text{X}] \qquad \text{....(9)}$$

If $[\text{BAT}]_t$ represents total BAT concentration in solution, then

$[\text{BAT}]_t$ = [Ts NHBr] + $[\text{TsNH}_2\ \text{Br}^+]$+ [X]…(10)

From the above, solving for [X] from the above equation and scheme 1

$$[\text{X}] = \frac{K_1K_2[\text{BAT}]_t[\text{TM}]}{[\text{H}^+] + K_1(1 + K_2[\text{TM}])} \qquad \text{....(11)}$$

By substituting for [X] from Equation (11) into Equation (9), the following rate law is obtained

$$\text{Rate} = \frac{-d[\text{BAT}]}{dt} = \frac{K_1K_2k_3[\text{BAT}]_t[\text{TM}]}{[\text{H}^+] + K_1(1 + K_2[\text{TM}])} \qquad (12)$$

Rate law (12) is in good agreement with the experimental results, where in a first order dependence of rate on $[\text{BAT}]_o$, fractional order on [TM] and inverse fractional order on $[\text{H}^+]$. Since rate = $k^/[\text{BAT}]_o$, rate law (12) can be transformed into Equations 13- 14

$$k^/ = \frac{K_1K_2k_3[\text{TM}]}{[\text{H}^+] + K_1 + K_1K_2[\text{TM}]} \qquad (13)$$

$$\frac{1}{k^/} = \frac{[\text{H}^+]}{K_1K_2k_3[\text{TM}]} + \frac{1}{K_2k_3[\text{TM}]} + \frac{1}{k_3} \qquad (14)$$

From the slopes and intercepts of $1/k^/$ vs 1/[TM] and $1/k^/$ vs $[\text{H}^+]$ (Figures not shown), values of formation constants $K_1 = 1.15 \times 10^{-4}$ mol dm^{-3},$K_2 = 2.3 \times 10^{-4}$ $\text{dm}^3\ \text{mol}^{-1}$ and decomposition constant k_3 were calculated and found to be $0.7 \times 10^{-4}\ \text{s}^{-1}$.

Since a fractional order in $[\text{TM}]_o$ was observed, Michaelis – Menten kinetics were adopted. The substrate concentration was varied at different temperatures and k_3 was calculated at each temperature from the double reciprocal plots. Activation parameters for the rate limiting step were evaluated from a plot of log k_3 vs 1/T and data are summarized in **Table 4**.

Effect of solvent on the reaction kinetics has been described by Laidler **[23]** and Amis **[24]**. In the present investigation, a plot of log$k^{/}$ vs 1/D was linear with a positive slope. Reduction product $TsNH_2$ (PTS) does not influence the rate showing its non-involvement in pre-equilibrium step. Change in ionic strength of the medium does not alter the rate, which indicates that non-ionic species are involved in the rate limiting step. Addition of halide ions had no effect on the rate indicating that no interhalogen or free bromine is formed. Proposed mechanism is further supported by moderate values of energy of activation and other activation parameters. Fairly high positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the large negative entropy of activation suggests the formation of compact activated complex with less degrees of freedom.

CONCLUSION

Kinetics and oxidation of thiamine hydrochloride by sodium – N – bromo – p – toluenesulphonamide (Bromamine-T or BAT) in aqueous HCl have been studied at 303K. Activation parameters were computed. Major oxidation product was identified as (2-[3-[(4-Amino-2-methyl-pyrimidin-5-yl)methyl]-4-methyl-thiazol-5-yl] ethanal). TsNHBr is the reactive species which reacts with the substrate. Based on kinetic results and reaction stoichiometry, a suitable mechanism has been proposed.

ACKNOWLEDGEMENT

We are grateful to the Principal and management of Jyoti Nivas College, Bangalore, for permission to carry out research at Jyoti Nivas College. We thank Mohammad Afzal Pasha and Puttaswamy, Dept of Chemistry, Bangalore University, Bangalore for helpful discussions.

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