Research Journal of Pharmaceutical, Biological and Chemical Sciences

Kinetic and mechanistic studies on the Oxidation of Voglibose by Bromamine –T in HCl medium

R Ramachandrappa[1], Diwya[2], Pushpa Iyengar[2][*]

[1]Department of Chemistry, Jyoti Nivas College, Koramangala Industrial Layout, Bangalore - 560095, Karnataka.
[2]Acharya institute of Technology, Soldevanahalli, Hesarghatta Road, Bangalore-560 090, Karnataka, India.

ABSTRACT

Kinetics and oxidation of Voglibose VB, [(1S,2S,3R,4S,5S') – 5 – (1,3 – dihydroxypropan – 2 - ylamino) – 1 – (hydroxymethyl)cyclohexane- 1,2,3,4 – tetraol] by Bromamine – T (BAT) in hydrochloric acid medium have been studied at 303K. The rate is first order in $[BAT]_o$, fractional order in both $[VB]_o$ and $[H^+]$. Addition of NaCl, NaBr and PTS did not affect the rate of the reaction. Hence the dependence of rate on [HCl] reflected the effect of $[H^+]$ only on the reaction. Variation in ionic strength did not affect the rate of the reaction indicating that non – ionic species are involved in the rate limiting step. The dielectric effect is positive. 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 acrylamide solution did not initiate polymerization, showing the absence of free radical species. Oxidation products were identified. Protonated oxidant $C_6H_5 – CH_3SO_2NH_2Br^+$ is the oxidizing species which reacts with the substrate. Based on kinetic results, reaction stoichiometry and oxidation products, a suitable mechanism have been proposed.
Keywords: Kinetics, Mechanism, Voglibose, Bromamine – T

Corresponding author
Email: pushpaiyengar@yahoo.co.in

INTRODUCTION

Aromatic N- halosulphonamides behave as mild oxidants, halogenating agents containing a strong polarized N- linked halogen which is in the +1 state. Bromamine – T (sodium N- bromo- p- toluenesulphonamide or BAT) can be easily prepared by the 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 [1-9].

Voglibose (VB), [(1S,2S,3R,4S,5S') – 5 – (1,3 – dihydroxypropan – 2 - ylamino) – 1 – (hydroxymethyl)cyclohexane- 1,2,3,4 – tetraol] is an alpha-glucosidase inhibitor used for lowering post-prandial blood glucose levels in people with diabetes mellitus [10,11]. Reaction kinetics of similar compounds have been studied. Literature survey revealed no reports on the oxidation of this drug specially the kinetic and mechanistic aspects of Voglibose by Bromamine - T in HCl medium. In view of this, kinetics and mechanistic studies on the oxidation of Voglibose in HCl medium is studied at 303K.

MATERIALS AND METHODS

Experimental

Bromamine – T was obtained [6] by the 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 micro burette, with constant stirring at room temperature. Separated Dibromamine-T (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 then by its mass spectrum, UV, IR, ^{1}H 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.

Voglibose (Biocon, India) and p – Toluenesulphonamide(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 was altered by the addition of methanol in varying proportions (v/v) and values of permittivity of methanol – water mixtures reported in literature [12] 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([VB]$_o$ >> [BAT]$_o$) at constant temperature 303K, in a glass – stoppered pyrex boiling tubes coated black on the

outside to eliminate photochemical effects. Oxidant and the requisite amounts of substrate, HCl solutions 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. The reaction was studied for more than two half- lives. Pseudo – first order rate constants ($k^{/}$) calculated from the linear plots of log [BAT] versus time were reproducible within ± 3-4 %.

Stoichiometry

Reaction mixture containing various ratios of BAT to VB in presence of 1x 10^{-2} mol dm^{-3} HCl at 303K, under the condition [BAT] >> [VB], were equilibrated for 24 h. Determination of unreacted BAT showed 1:2 stoichiometry.

$$C_{10}H_{21}NO_7 + 2TsNBrNa + 2\ H_3O^+ \longrightarrow C_{10}H_{17}NO_8 + 2TsNH_2 + 2H_2O + 2Na^+ + 2Br^- \quad ………(1)$$
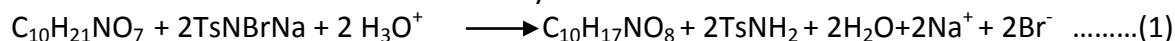
Product Analysis

Reduction product of BAT, p- toluenesulphonamide, was detected by thin layer chromatography[13] 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 melting point 137 - 138ºC (lit.m.p.137 - 140ºC) and IR spectra. Oxidation product of Voglibose was confirmed to be 1,2,3,4 – tetrahydroxy – 5 – [1 – hydroxy – 3 – oxopropano – 2 - yl) amino] cyclohexane – 1 – carbaldehyde by spectroscopic techniques and spot tests [14]. A strong peak for aldehyde was observed at $1625cm^{-1}$.

<div align="center">

RESULTS

</div>

Effect of Reactants

Kinetics of oxidation of VB by BAT was investigated at various initial concentrations of the reactants in acid medium. With substrate in excess, at constant Voglibose $[VB]_o$,$[H^+]$ and temperature, plots of log [BAT] vs time was linear indicating a first order dependence of rate on $[BAT]_o$. Rate constant $k^{/}$ was not affected by change in $[BAT]_o$ (Table 1) confirming the first order dependence on $[BAT]_o$. Under identical experimental conditions, an increase in $[VB]_o$ lead to increase in $k^{/}$ (Table 1) at constant $[BAT]_o$, [HCl] and temperature. A plot of log $k^{/}$ vs log [VB](Fig 1) was linear with a slope of 0.25 indicating a fractional order dependence on [VB]. When [HCl] was increased, the rate of the reaction also increased (Table 1). A plot of log $k^{/}$ vs log [HCl] (Fig 2) was linear with a positive fractional slope of 0.34, showing a fractional order dependence on $[H^+]$.

Table 1 - Effect of reactant concentrations on the reaction rate at 303K

10^4[BAT]$_o$ mol dm^{-3}	10^3[VB] mol dm^{-3}	10^4[HCl] mol dm^{-3}	10^4k$^/$ s^{-1}
5.0	10.0	20.0	4.20
10.0	10.0	20.0	.4.11
15.0	10.0	20.0	3.98
20.0	10.0	20.0	4.00
10.0	5.0	20.0	3.33
10.0	10.0	20.0	4.11
10.0	20.0	20.0	4.86
10.0	50.0	20.0	6.20
10.0	10.0	5.0	2.31
10.0	10.0	10.0	3.25
10.0	10.0	20.0	4.11
10.0	10.0	50.0	6.00

Table 2 - Temperature dependence and values of Activation parameters

Temperature (K)	10^4k$^/$(s^{-1})	Activation parameters	
		Parameter	Value
293	1.13(2.17)	Ea(kJ mol^{-1})	65.5 (56.31)
303	4.11(5.00)	$\Delta H^{\neq}$ (kJ mol^{-1})	62.9 (53.79)
313	7.66(10.0)	$\Delta G^{\neq}$ (kJ mol^{-1})	42.4 (31.95)
323	20.5(22.3)	$\Delta S^{\neq}$ (JK^{-1} mol^{-1})	-137.6 (- 103.2)
		logA	7.8 (6.03)

Note: values in parenthesis are the decomposition constants and activation parameters for the rate determining step.

Table 3 - Effect of Dielectric constant of the medium on the reaction rate.

[MeOH] (%v/v)	D	10^2/D	10^4k$^/$ (s^{-1})
0	76.93	1.30	4.11
10	72.37	1.38	7.00
20	67.38	1.48	10.47
30	62.71	1.60	20.25

[BAT] = 1x10^{-2} mol dm^{-3}, [VB] = 10x10^{-2} mol dm^{-3}, T =303K, [HCl] = 2x10^{-2} mol dm^{-3}

Table 4 - Effect of [VB] and temperature on the reaction rate.

10^2 [VB] mol dm^3	293K	10^4k$^/$(s^{-1}) 303K	313K
5.00	0.77	3.33	4.84
10.0	1.132	4.11	7.66
50.0	2.62	5.00	9.09

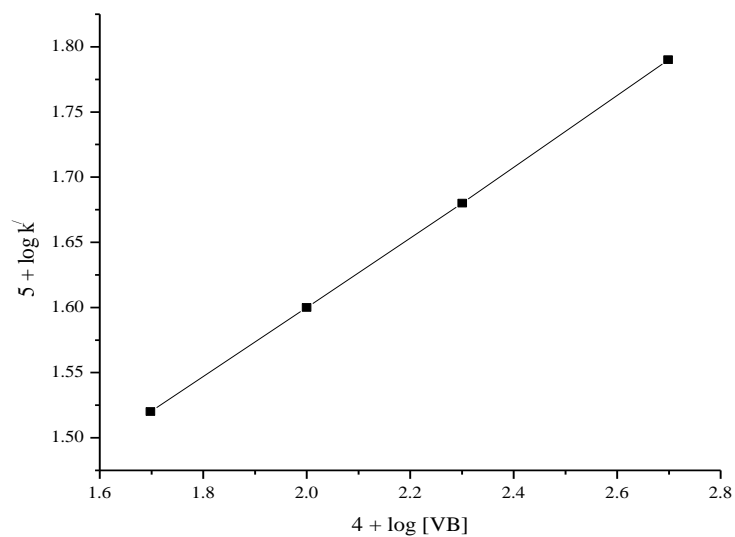[BAT] = 1x10^{-2} mol dm^{-3}, T =303K, [HCl] = 2x10^{-2} mol dm^{-3}

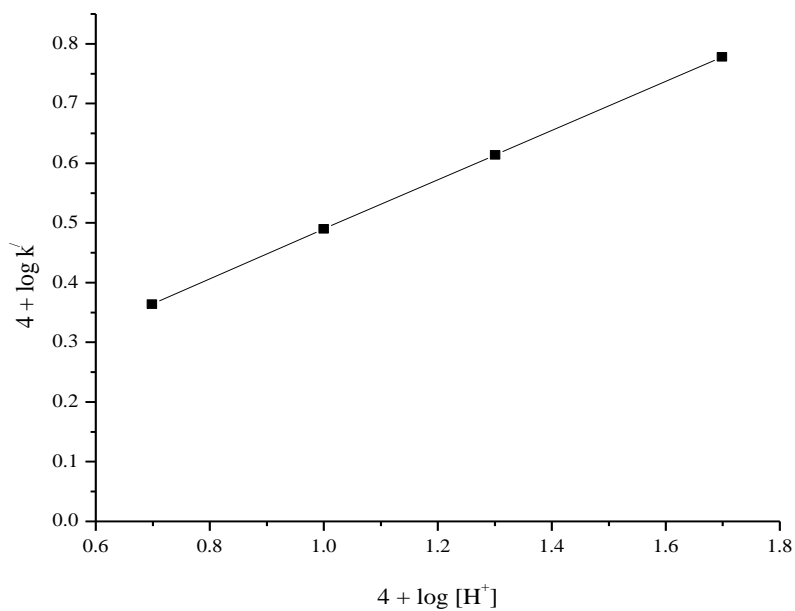**Figure 1 Effect of [VB] on the reaction rate**

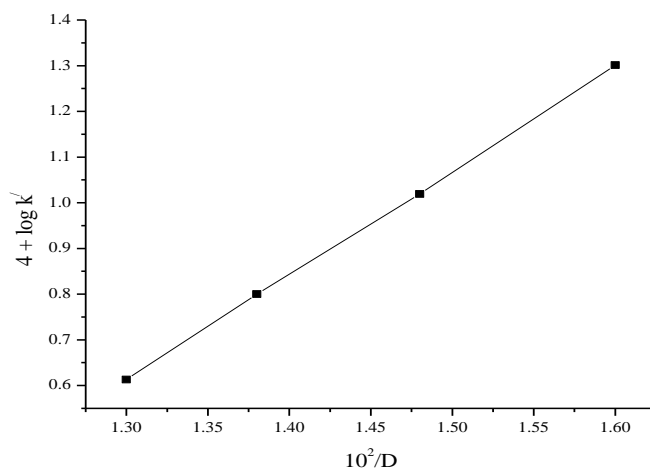**Fig 2 Effect of [HCl] on the reaction rate**

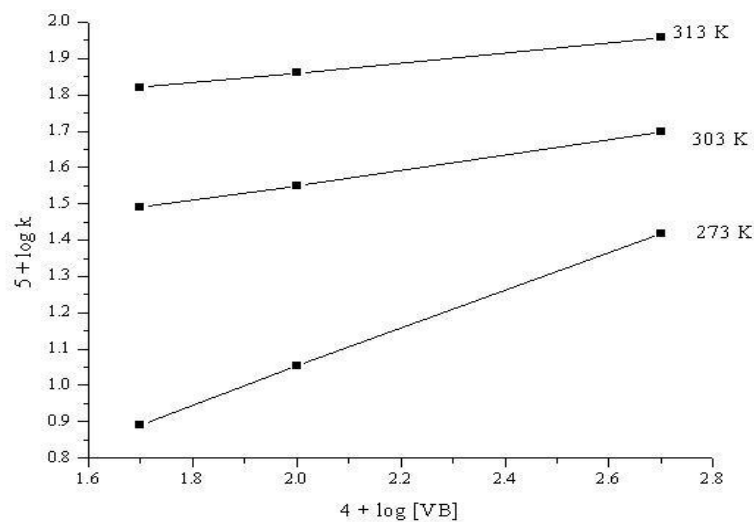**Fig 3 Effect of Dielectric constant of the medium on the reaction rate.**
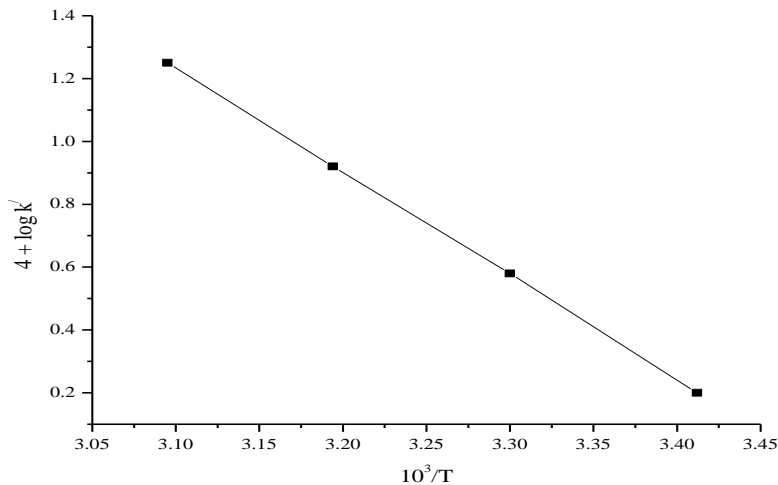

Fig 4 Effect of [VB] and temperature on the reaction rate

Fig 5 Effect of temperature on the reaction rate

(B) 1/ k$^/$ versus 1/ [VB]
Plot of 1/ k$^/$ vs 1/[VB] and1/ k$^/$ vs 1/[H$^+$] to calculate the activation parameters
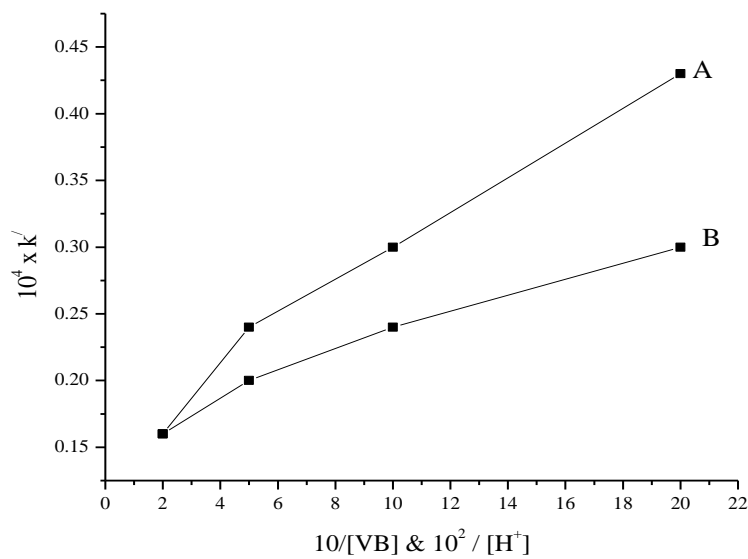

Fig 6 – Plots of   (A) 1/k$^/$ versus 1 / [H$^+$]

Effect of halide ions and p- Toluene sulphonamide

At constant [H$^+$], addition of NaCl or NaBr (1.0x10^{-3} mol dm^{-3} to 5.0x10^{-3} mol dm^{-3}) did not affect the rate of the reaction. Hence the dependence of rate on [HCl] reflected the effect of [H$^+$] only on the reaction. Addition of reduction product of the oxidant, p-toluenesulphonamide (PTS; 1.0x10^{-3} mol dm^{-3} to 5.0x10^{-3} mol dm^{-3}) did not affect the rate which indicates its non – involvement in pre - equilibrium with the oxidant.

Effect of ionic strength and dielectric constant

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 to 30% v/v) to the reaction mixture. Addition of methanol resulted in an increase in rate of the reaction. A plot of (1/D) vs logk' was linear with a positive slope (Fig 3). Blank experiments showed that MeOH was oxidized slowly (~3%) with BAT under the experimental conditions. This was corrected for the calculations in the reaction for the rate constant.
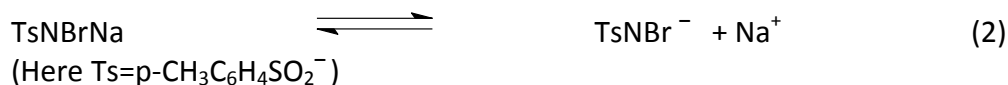
Effect of temperature

Reaction was studied by varying the temperature from 293K to 313K (Fig 4) and keeping other experimental conditions constant .It was found that the rate increased with increase in temperature. From the linear Arrhenius plot (Fig 5), activation parameters like energy of activation (Ea), enthalpy of activation (ΔH$^{\neq}$), entropy of activation (ΔS$^{\neq}$), free energy of activation (ΔG$^{\neq}$) and logA were computed (Table 2)**.**

Test for free radicals

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

DISCUSSION

Pyrde and soper [15] Morris et al [16] and Bishop and Jennings [17] have shown the existence of similar equilibrium in acid and alkaline solutions of N- metallo – N – haloarylsulphonamides. 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)
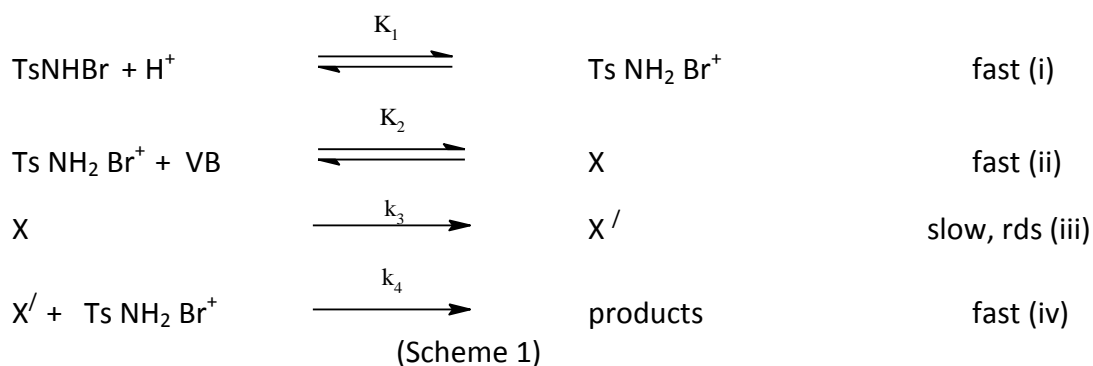
TsNBrNa $\rightleftharpoons$ TsNBr$^-$ + Na$^+$ (2)
(Here Ts=p-CH$_3$C$_6$H$_4$SO$_2{}^-$)

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

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

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

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

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

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

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 the 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 Voglibose. Hardy and Johnston [18] 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, Narayan and Rao [19] and Subhashini et al [20] have reported that monochloramines can be further protonated at pH<2. Hence it is likely that $TsNHBr$ is further protonated in acid media [21]. In present case, acceleration of H^+ ion indicates that $TsNH_2^+Br$ is the active oxidizing species.

Based on the preceding discussion and kinetic results, a mechanism (Scheme 1) is proposed for the oxidation of VB by BAT in acid medium.

$$TsNHBr + H^+ \overset{K_1}{\rightleftharpoons} Ts\ NH_2\ Br^+ \qquad \text{fast (i)}$$

$$Ts\ NH_2\ Br^+ + VB \overset{K_2}{\rightleftharpoons} X \qquad \text{fast (ii)}$$

$$X \overset{k_3}{\longrightarrow} X^/ \qquad \text{slow, rds (iii)}$$

$$X^/ + Ts\ NH_2\ Br^+ \overset{k_4}{\longrightarrow} products \qquad \text{fast (iv)}$$

(Scheme 1)

X and $X^/$ represents the complex intermediate species, whose structures are shown in Scheme 2 in which a detailed mechanistic interpretation of VB oxidation by BAT in acid medium is proposed. In this, the protonated oxidant species $TsNH_2\ Br^+$ formed from $TsNHBr$ and H^+ 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$^/$ reacts with another mole of oxidant to yield the final products

Mechanism of Oxidation of [VOG] with [BAT]
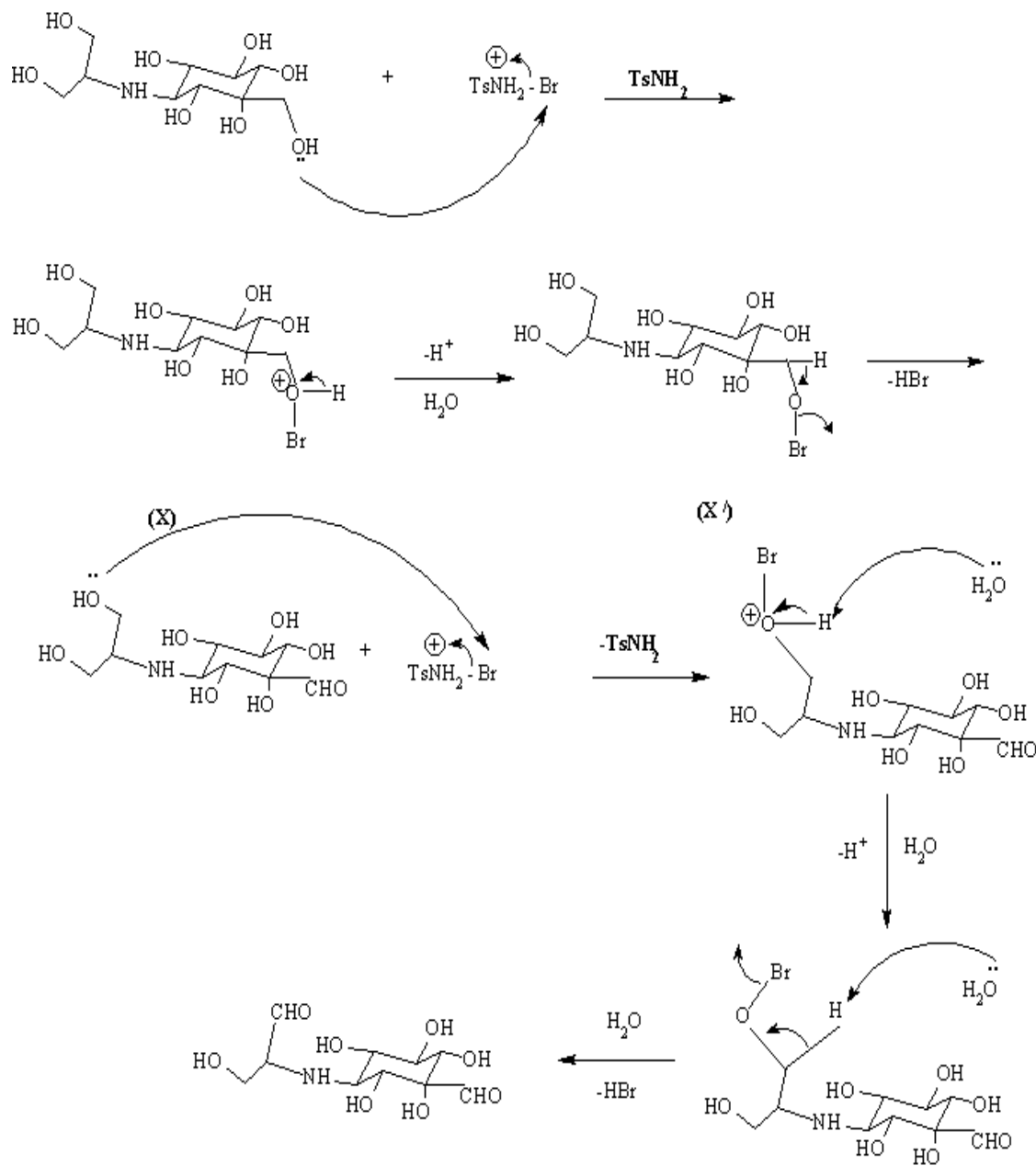
Scheme 2

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

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

If [BAT]$_t$ represents total BAT concentration in solution, then

$$[BAT]_t = [Ts\,NHBr] + [TsNH_2\,Br^+] + [X] \quad \text{.......................(10)}$$

From the above, solving for [X] and substituting its value in (9), the rate law (11) can be derived:

$$\text{Rate} = \frac{-d[BAT]}{dt} = \frac{K_1 K_2 k_3 [BAT]_t [VB][H^+]}{1 + K_1[H^+] + K_1 K_2 [VB][H^+]} \quad \ldots\ldots\ldots\ldots(11)$$

Rate law (11) is in agreement with the experimental results and it can be transformed as

$$\frac{1}{K^1} = \frac{1}{K_2 k_3 [VB]} \left\{ \frac{1}{K_1[H^+]} + 1 \right\} + \frac{1}{k_3} \quad \ldots\ldots\ldots(12)$$

From the double reciprocal plots of $1/k^/$ vs $1/[VB]$ and $1/k^/$ vs $1/[H^+]$ (Fig 6) values of formation constants K_1, K_2 and decomposition constant, k_3 was found to be $5.714 \times 10^{-4} s^{-1}$.

Since a fractional order in $[VB]_o$ was observed, Michaelis – Menten kinetics were adopted [22]. 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 2.

Reduction product $TsNH_2$ (PTS) does not influence the rate showing that it is not involved in pre equilibrium. Change in ionic strength of the medium does not alter the rate indicating the involvement of non-ionic species 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 the 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 the compact activated complex with less degrees of freedom.

ACKNOWLEDGEMENT

REFERENCES

[1]   Puttaswamy , RV Jagadeesh. Applied Catalysis 2005; 292(18): 259-271.
[2]   Puttaswamy, R Ramachandrappa & NM Made Gowda. Synthesis and Reactivity in Inorganic and Metal-Organic Chemistry 2002; 32(7): 1263-1280.
[3]   Puttaswamy, JP Shubha. AIChE Journal 2009; 55(12): 3234–3240.
[4]   Devi J, Kothari S et al. Indian J Chem 1996; 73: 243 – 246.
[5]   T Asha Iyengar and DS Mahadevappa. Journal of Chemical Sciences 1993; 105: 63-70.

[6]   Nair CG, Lalithakumari R, Senan PI. Talanta 1978; 25(9): 525-7.
[7]   Puttaswamy and RV Jagadeesh. Ind Eng Chem Res 2006; 45 (5), pp 1563–1570
[8]   Puttaswamy, RV Jagadeesh, NM Made Gowda. International Journal of Chemical Kinetics 2005; 37(11): 700–709.
[9]   PR Rangaraju, TV Venkatesha, R Ramachandrappa et.al. RJPBCS 2011; 2(4): 101
[10]   Ryuzo Kawamori, Naoko Tajima, Yasuhiko Iwamoto et.al. The Lancet 2009; 373: 1607 - 1614
[11]   Yasuda K, Shimowada K, Uno M, et.al. Diabetes Res Clin Pract 2003; 59(2): 113-22.
[12]   Akerloff G, J Am chem Soc 1932; 54: 4125.
[13]   Mahadevappa DS & Gowda NMM. Talanta, 1975; 22: 771.
[14]   Feigl F. Spot tests in organic analysis, (Elsevier, Amsterdam), 1966; pp.141, 142, 213.
[15]   Pyrde BG & Soper FG. J chem Soc 1926; 1582; ibid 1931; 1510.
[16]   Morris JC, Salazar JA & Wineman MA. J Am chem Soc 1948; 70: 2036.
[17]   Bishop E & Jennings VJ. Talanta, 1958; 1: 197.
[18]   Hardy FF & Johnston JP. J chem Soc; Perkin tran 1973; 2: 742.
[19]   Narayan SS & Rao VRS. Radiochemica Acta 1983; 32: 211.
[20]   Subashini M, Subramaniam M & Rao VRS. Talanta, 1985; 32: 1082.
[21]   R Ramachandrapppa, Puttaswamy, SM Mayanna, NMM Gowda. Int J Chem Kinet 1998; 30: 407.
[22]   Laidler KJ. Chemical kinetics, (Tata- McGraw Hill, Bombay), 1965; 474.