



Oxidation of Tranexamic Acid by Bromamine – T in HCl Medium Catalyzed by RuCl₃: A Kinetic and Mechanistic Approach

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Abstract

Kinetics and oxidation of tranexamic acid (TX) [trans -4-(aminomethyl) cyclohexanecarboxylic acid] by sodium -N- bromo - p- toluenesulphonamide (bromamine – T or BAT) in hydrochloric acid medium using RuCl₃ as catalyst at 303K have been studied. The rate was first order in [BAT]₀, fractional order in [TX], first order in RuCl₃, fractional order in [H⁺] and [PTS]. Addition of NaCl and NaBr did not affect the rate of the reaction which indicates that the rate of the reaction depends only on [H⁺]. Variation of ionic strength did not affect the rate of the reaction indicating that non – ionic species are involved in the rate limiting step. 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 acryl amide solution did not initiate polymerization, showing the absence of free radical species. Oxidation products were identified. Protonated oxidant H₂O⁺Br is the reactive species which reacts with the substrate. Based on kinetic results, reaction stoichiometry and oxidation products, a suitable mechanism have been proposed.

Key Words: Reaction kinetics, mechanism, tranexamic acid, bromamine – T.

Introduction

Aromatic N- halosulphonamides behave as mild oxidants and halogenating agents containing a strong polarized N- linked halogen which is in +1 state. Bromamine – T (sodium N-bromo- p- toluenesulphonamide or BAT; p – CH₃C₆H₄SO₂NBrNa.3H₂O) 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 oxidant¹⁻⁸. Kinetic study has also been carried out using other oxidant⁹.

Tranexamic acid, (TX) [trans – 4 – (aminomethyl) cyclohexanecarboxylic acid] is an antifibrinolytic agent and has applications in pharmaceuticals^{10,11}. Its kinetics and oxidation study is very important. Kinetics and mechanistic study of tranexamic acid by Bromamine - B in alkaline medium catalyzed by Palladium (II) has been studied¹². Literature survey revealed no information in the kinetics of oxidation of this drug by this oxidant. Hence, kinetics and mechanism of oxidation of tranexamic acid with BAT in HCl medium catalyzed by RuCl₃ at 303K have been studied.

Material and Methods

Bromamine – T was obtained by partial debromination of dibromamine – T (DBT)⁶. 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

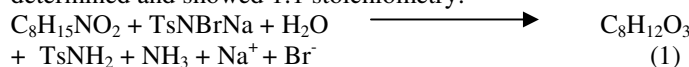
the absorbed bromine was completely eliminated and then vacuum dried for 24 h. About 20g of DBT was dissolved with stirring in 30ml of 4 mol dm⁻³ NaOH at room temperature and the resultant aqueous solution was cooled in ice, pale yellow crystals of BAT formed were filtered under suction, washed quickly with minimum amount of ice cold water and dried over P₂O₅. The product was confirmed to be bromamine – T by qualitative analysis and then by its mass spectrum, UV, IR, ¹H and ¹³C- spectral data¹³. An aqueous solution of BAT was prepared afresh, standardized by iodometric method and preserved in brown bottles to prevent its photochemical deterioration.

Tranexamic acid (Biocon, India) 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 was altered by the addition of methanol in varying proportions (v/v) and values of permittivity of methanol – water mixtures reported in literature¹⁴ 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 ([TX]₀ >> [BAT]₀) 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, RuCl₃ 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. 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 $\pm 3-4 \%$.

Stoichiometry: Various ratios of substrate ie Tranexamic acid ($10 \times 10^{-2} \text{ mol dm}^{-3}$) and bromamine – T (1×10^{-2}), in presence of HCl ($10 \times 10^{-2} \text{ mol dm}^{-3}$) and RuCl_3 ($2 \times 10^{-5} \text{ mol dm}^{-3}$) catalyst at 303K were equilibrated for 24 h. Unreacted BAT was determined and showed 1:1 stoichiometry.



Product Analysis: Reduction product of BAT, p – toluenesulphonamide was detected by thin layer chromatography using light petroleum – chloroform – 1 butanol (2:2:1 v/v/v) as the solvent and iodine as the reducing agent¹⁵. Further it was confirmed by its MP ($138-143^\circ$), IR and NMR spectra. Oxidation product 4 – formylcyclohexane – 1 – carboxylic acid was detected by spot tests ie. Schiff's reagent test, 2, 4- dinitrophenyl hydrazine test and was confirmed by IR spectroscopy^{16,17}. Strong peak for -CHO group was observed at 1725cm^{-1} .

Results and Discussion

Effect of Reactants: With substrate in excess, at constant $(\text{TX})_0$, (H^+) , (RuCl_3) and temperature, plots of $\log (BAT)$ vs time were linear, indicating a first order dependence of rate on $(BAT)_0$. Rate constant k' was unaffected by variation in $(BAT)_0$ as shown in table 1, confirming first order dependence on $(BAT)_0$. In table 1, increase in concentration of TX, lead to increase in k' under identical experimental conditions. Plot of $\log k'$ vs $\log (TX)$ was linear with a positive slope of 0.633 indicating a fractional order dependence on (TX). Increase in (HCl), lead to increase in reaction rate, as reported in table 1. Plot of $\log k'$ vs $\log (HCl)$ was linear with a positive slope of 0.433 indicating a fractional order dependence on (H^+) . Concentration of RuCl_3 was varied keeping other parameters constant, lead to increase in rate of the reaction as shown in table 1. Plot of $\log k'$ vs $\log [\text{RuCl}_3]$ was linear with a positive slope of 1.233 indicating a fractional order dependence on $[\text{RuCl}_3]$. Catalytic constant K_c was found to be 1.99×10^2 .

From the above discussion figure 1 and figure 2 were drawn.

Effect of halide ions and p- Toluene sulphonamide: Under identical experimental conditions, addition of NaCl and NaBr ($2 \times 10^{-3} \text{ mol dm}^{-3}$ to $10 \times 10^{-3} \text{ mol dm}^{-3}$) did not affect the reaction rate as reported in table 2. Hence it reflected that rate depends only on (H^+) .

Addition of reduction product of the oxidant PTS ($1 \times 10^{-3} \text{ mol dm}^{-3}$ to $10 \times 10^{-3} \text{ mol dm}^{-3}$) decreased the rate of the reaction. The data have been summarized in table 2. In figure 3, plot of $\log k'$ vs $\log \text{PTS}$ is linear with a negative slope of 0.438 showing fractional order on (PTS) which indicates that PTS is involved in fast pre - equilibrium to the rate limiting step.

Effect of ionic strength and dielectric constant: Variation of ionic strength using NaClO_4 solution ($2 \times 10^{-3} \text{ mol dm}^{-3}$ to $50 \times 10^{-3} \text{ mol dm}^{-3}$) did not affect the reaction rate, indicating that non – ionic species are involved in rate limiting step as seen in table 2. A plot of $(1/D)$ vs k' is a straight line¹⁸. Dielectric constant (D) of the medium was varied by adding methanol (0 – 30% v/v) to the reaction mixture. Addition of MeOH lead to decrease in reaction rate as reported in table 3. In figure 4, plot of $(1/D)$ vs $\log k'$ is linear with a negative slope of 1.05. Values of D for MeOH- OH mixtures were taken from the literature¹⁴. Blank experiments with methanol showed that there was slight decomposition (~3%) of solvent under the experimental conditions. This was corrected for the calculations of net reaction for the rate constant.

Effect of temperature: Reaction was studied over a range of temperature (293K to 323K) by varying the concentration of TX at constant experimental conditions. Rate increased with increase in temperature as shown in figure 5. From figure 6 which is the linear Arrhenius plot of $\log k'$ vs $1/T$, values of activation parameters like energy of activation (E_a), enthalpy of activation (ΔH^\ddagger), entropy of activation (ΔS^\ddagger), free energy of activation (ΔG^\ddagger) were computed. Results obtained from the above discussion are tabulated in table 4 and table 5.

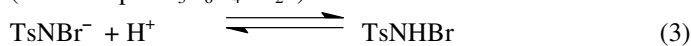
Test for free radicals: Addition of reaction mixture to aqueous acrylamide solution did not initiate polymerization, showing the absence of free radicals species.

Catalytic activity: The relationship between catalyzed and uncatalyzed rate constants is $k_T = k_u + K_c[\text{Ru(III)}]^x$ where k_T is the observed rate constant in presence of Ru(III), k_u is the rate constant in absence of catalyst, K_c is the catalytic constant, x is the order with respect to Ru(III)¹⁹. Catalytic constant was found to be 1.99×10^2 . Values of K_c were evaluated at different temperature. Plot of $\log K_c$ vs $1/T$ (plot not shown) was linear and thermodynamical parameters were calculated which is reported in table 5.

Existence of similar equilibrium in acid and alkaline solutions of N- metallo – N – haloarylsulphonamides was reported²⁰⁻²². Bromamine-T is analogous to CAT in aqueous solution behaving as strong electrolyte forming different species of the following types (2 – 7)



(Here $\text{Ts} = \text{p-CH}_3\text{C}_6\text{H}_4\text{SO}_2^-$)



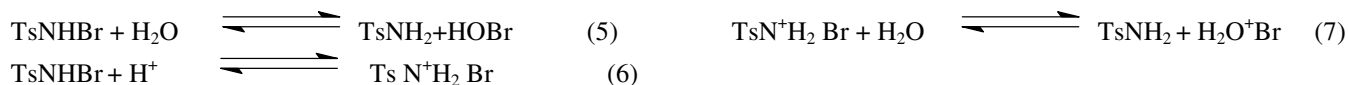


Table-1
Effect of varying [BAT], [TX], [RuCl₃] and [HCl] on the reaction rate at 303K

$10^3[\text{BAT}]_0$ mol dm ⁻³	$10^3[\text{TX}]_0$ mol dm ⁻³	$10^3[\text{HCl}]$ mol dm ⁻³	$10^6[\text{RuCl}_3]$ mol dm ⁻³	$10^4k'$ s ⁻¹
5.0	10.0	20.0	20.0	3.30
10.0	10.0	20.0	20.0	3.29
15.0	10.0	20.0	20.0	3.31
20.0	10.0	20.0	20.0	3.32
10.0	5.0	20.0	20.0	2.93
10.0	10.0	20.0	20.0	3.33
10.0	20.0	20.0	20.0	5.19
10.0	30.0	20.0	20.0	6.30
10.0	10.0	5.0	20.0	1.33
10.0	10.0	10.0	20.0	2.44
10.0	10.0	20.0	20.0	3.34
10.0	10.0	30.0	20.0	4.44
10.0	10.0	20.0	10.0	1.66
10.0	10.0	20.0	20.0	3.33
10.0	10.0	20.0	30.0	5.93
10.0	10.0	20.0	40.0	8.66

Table-2
Effect of concentration of halide ions, PTS, NaClO₄ on the oxidation [TX] by BAT

$10^3[\text{conc}]$ mol dm ³	PTS $10^4k'(\text{s}^{-1})$	NaCl $10^4k'(\text{s}^{-1})$	NaClO ₄ $10^4k'(\text{s}^{-1})$	NaBr $10^4k'(\text{s}^{-1})$
5.0	10.96	3.31	3.34	3.21
10.0	7.585	3.32	3.32	3.21
50.0	6.025	3.30	3.33	3.42
100.0	5.011	3.34	3.13	3.12

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

MeOH (% v/v)	D	$10^2/D$	$10^4 k'(\text{s}^{-1})$
0	76.93	1.30	3.33
10	72.37	1.38	2.75
20	67.38	1.48	2.21
30	62.71	1.60	1.72

Table-4
Effect of [TX] on different temperatures in acidic medium

$10^3[\text{TX}]$ mol dm ³	$10^4k'(\text{s}^{-1})$		
	293K	303K	313K
5.0	1.66	2.93	2.77
10.0	2.22	3.33	4.66
20.0	3.73	5.19	7.04
30.0	5.01	6.30	9.77

Table-5
Effect of temperature and values of Activation parameters for the oxidation of TX by BAT

Temperature (K)	$10^4 k' (s^{-1})$	Activation parameters
293	2.22	$E_a = 40.687(39.060) \text{ kJ mol}^{-1}$
303	3.33	$\Delta H^\ddagger = 38.125(36.498) \text{ kJ mol}^{-1}$
313	4.66	$\Delta G^\ddagger = 53.520(50.267) \text{ kJ mol}^{-1}$
323	10.66	$\Delta S^\ddagger = -49.986(-44.697) \text{ kJ mol}^{-1}$
		$\log A = 3.554(3.278)$

Note: Values in the parenthesis were calculated by plotting $\log K_c$ vs $1/T$.

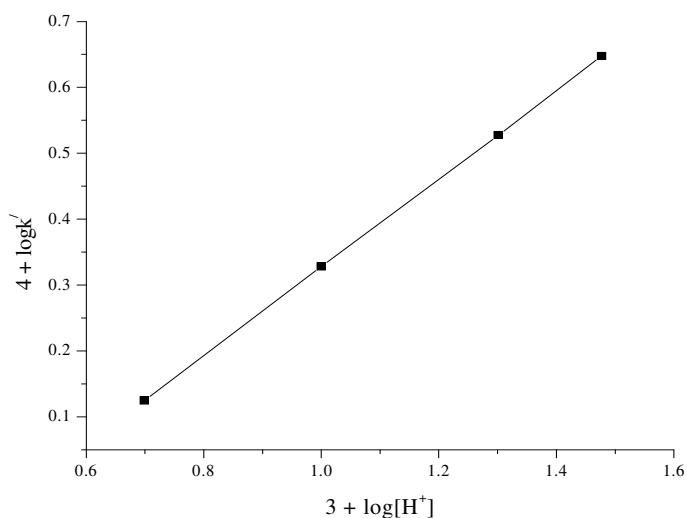


Figure-1
Effect of [HCl] on the rate of the reaction

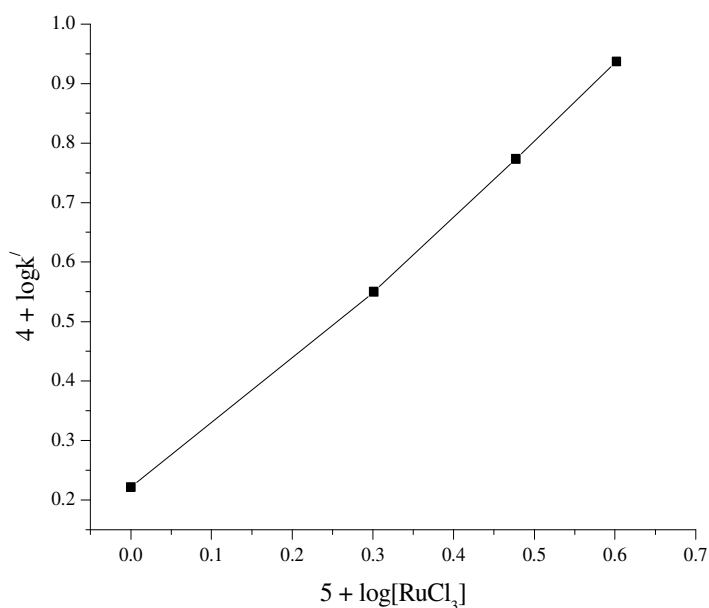


Figure-2
Effect of [RuCl₃] on the rate of the reaction

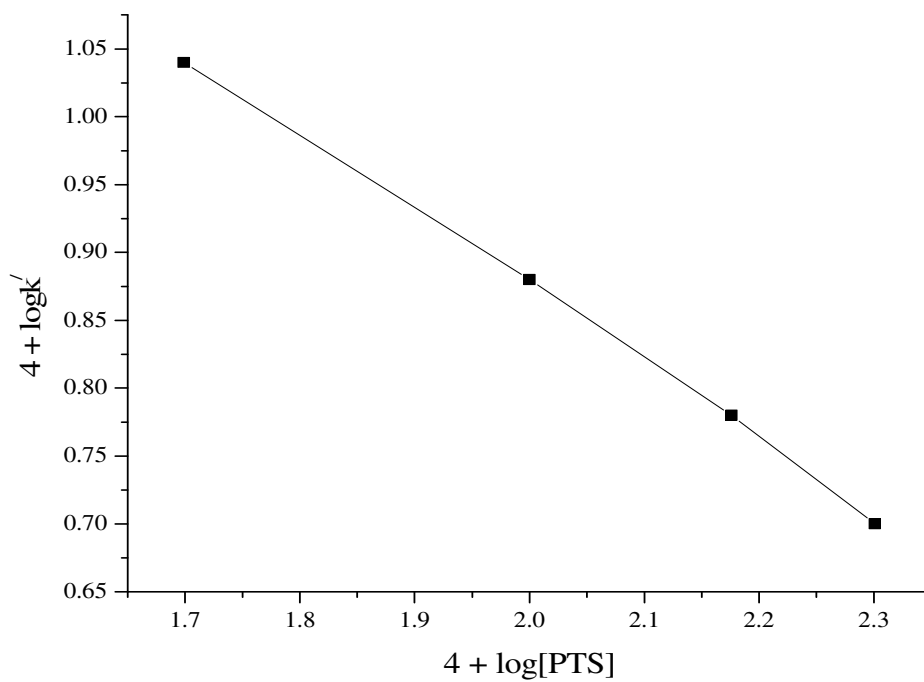


Figure-3
Effect of [PTS] on the rate of the reaction

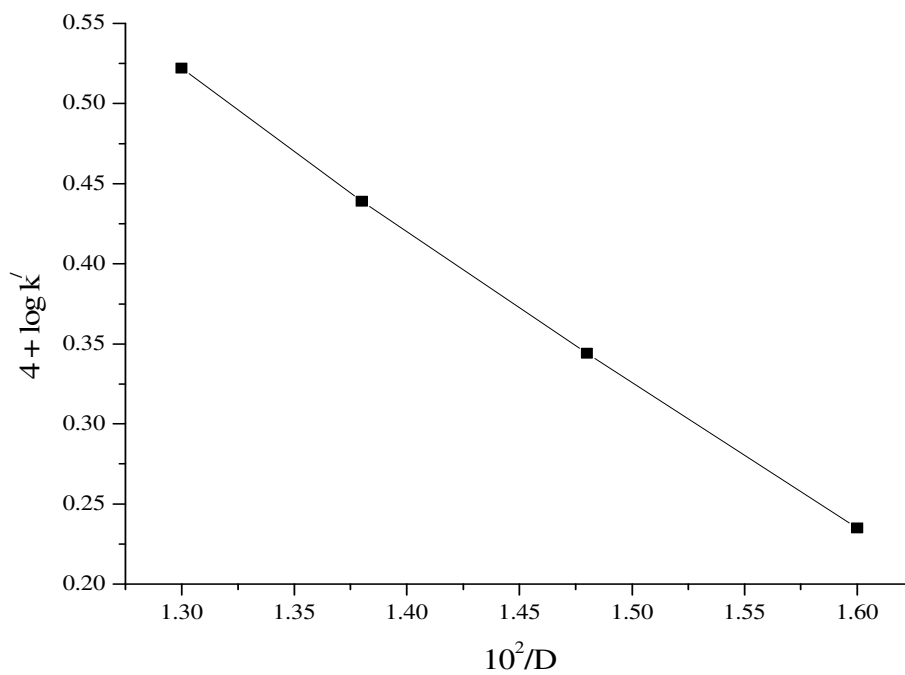


Figure-4
Effect of dielectric constant on the rate of the reaction

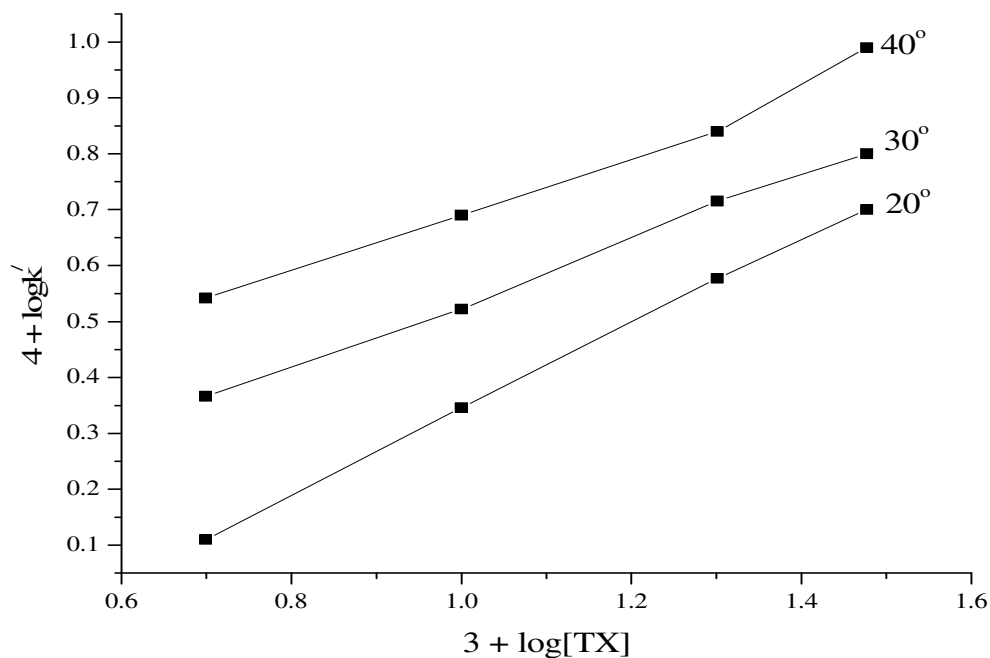


Figure-5
Effect of [TX] on the rate of the reaction at different temperatures

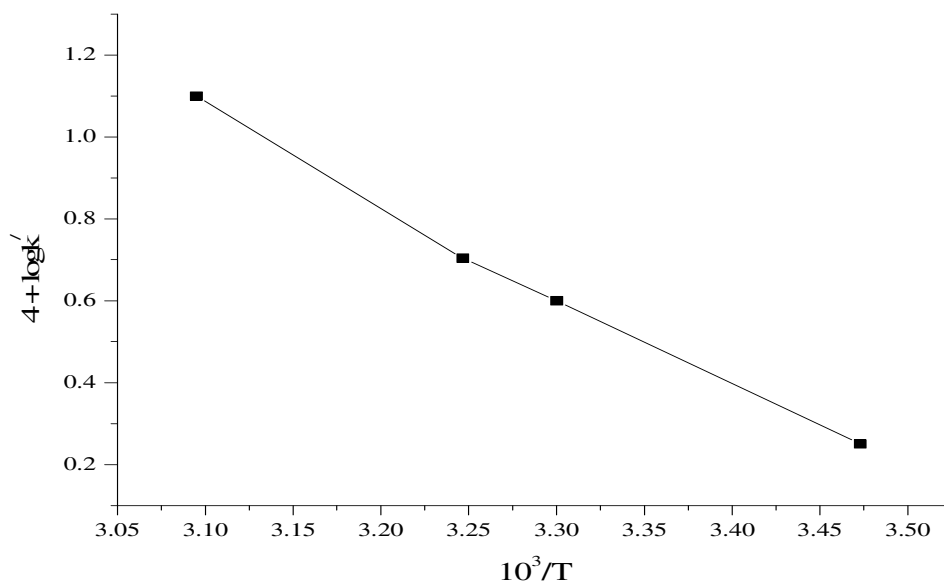
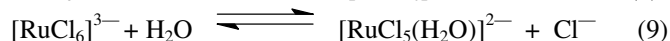
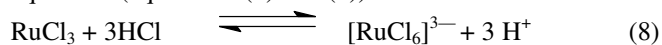


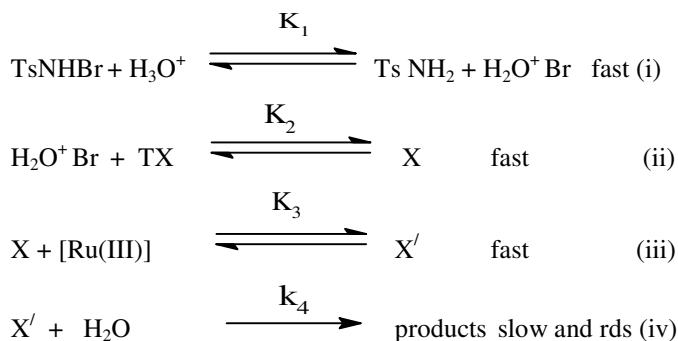
Figure-6
Effect of Temperature on the reaction rate in acidic medium

possible oxidizing species in acid medium are TsNHBr, TsNBr₂, HOBr, H₂O⁺ Br. If TsNBr₂ were to be the reactive species, then the rate law predicts a second order dependence of rate on [BAT]₀, which is contrary to the experimental observations. First order retardation of rate was observed by adding PTS. Hence, equations (6) and (7) play a dominant role in the oxidation of tranexamic acid by BAT. In aqueous solution of [RuCl₃], Ru(III) can exist as [RuCl₆]³⁻, [RuCl₅(H₂O)]²⁻, [RuCl₄(H₂O)₂]⁻, [RuCl₃(H₂O)₃], [RuCl₂(H₂O)₄]⁺, [RuCl(H₂O)₅]²⁺ and [Ru(H₂O)₆]³⁺²³⁻²⁶. Literature survey reveals that the active catalyst species may be assumed to be either [RuCl₆]³⁻ or [RuCl₅(H₂O)]²⁻ ion as shown in the following equilibria (equations. (8) and (9)):



The above equilibria in reactions catalysed by Ru(III) was used^{27,28}. In present case since there was no effect of chloride ion on the reaction rate, equation 9 does not play a role in the reaction and hence the complex ion, [RuCl₆]³⁻ is assumed to be the reactive catalyst species. pH dependent relative concentration of the species present in acidified CAT solutions of comparable molarities have been studied which shows that its acid form is likely oxidizing species in acid medium²⁹.

Based on the preceding discussion and observed kinetic results, a mechanism (scheme 2) is proposed for the oxidation of TX by BAT in acid medium.



Scheme-1

In scheme 1, X and X' represents the intermediate species, whose structures are shown in scheme 2 in which a detailed mechanistic interpretation of TX oxidation by BAT in acid

medium is proposed. The reactive H₂O⁺Br species interacts with the substrate, tranexamic acid in a fast step (ii) to form the bromo intermediate X. Furthermore, X reacts with the active catalyst species, [Ru(III)], in a fast pre – equilibrium step (iii) to form the metal complex X'. Fractional order in [Ru(III)] supports the fast pre – equilibrium, step(ii), in the mechanism. Finally X' hydrolyses in the slow- rate limiting step forming end products.

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

$$[\text{BAT}]_t = [\text{TsNHBr}] + [\text{H}_2\text{O}^+\text{Br}] + [\text{X}] + [\text{X}'] \quad (10)$$

Rate law equation 11 is in agreement with the observed kinetic orders. Proposed schemes and derived the rate law are also supported by following observations: Addition of methanol decreases the reaction rate. Limiting case of zero angle approach between two dipoles or an ion-dipole system has shown that plot of logk' vs 1/D is linear with a negative slope for a reaction between a negative ion and a dipole or between two dipoles, while a positive slope results for a positive ion – dipole interaction reported³⁰. Negative dielectric effect observed in this experiment reveals the presence of dipole-dipole interaction.

Reduction product TsNH₂ (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 that 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 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.

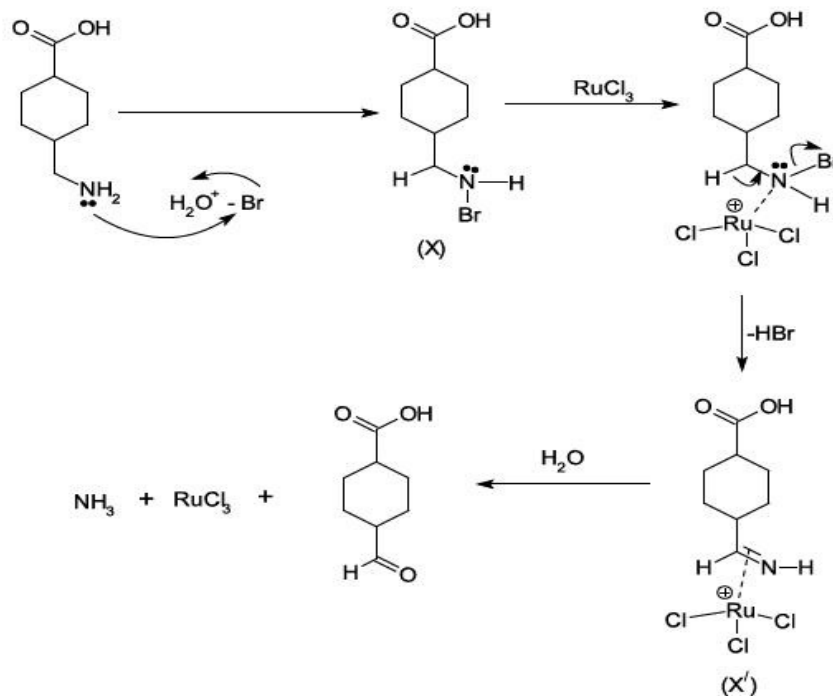
Conclusion

Kinetics and oxidation tranexamic acid by sodium – N – bromo – p – toluenesulphonamide (bromamine-T or BAT) in aqueous HCl in presence of RuCl₃ as catalyst have been studied at 303K. Activation parameters were computed. Major oxidation product was identified as 4 – formylcyclohexane – 1 – carboxylic acid. H₂O⁺Br is the reactive species which reacts with the substrate. Based on kinetic results and reaction stoichiometry, a suitable mechanism has been proposed.

From the above, following rate law can be derived:

$$\text{Rate} = \frac{-d[\text{BAT}]}{dt} = \frac{K_1 K_2 K_3 k_4 [\text{BAT}]_t [\text{TX}] [\text{H}_3\text{O}^+] [\text{Ru(III)}]}{[\text{TsNH}_2] + K_1 [\text{H}_3\text{O}^+] + K_1 K_2 [\text{TX}] [\text{H}_3\text{O}^+] (1 + K_3 [\text{Ru(III)}])} \quad (11)$$

$$\frac{1}{k} = \frac{\text{TsNH}_2}{K_1 K_2 K_3 k_4 [\text{BAT}]_t [\text{TX}] [\text{H}_3\text{O}^+] [\text{Ru(III)}]} + \frac{1}{K_2 K_3 k_4 [\text{BAT}]_t [\text{TX}] [\text{Ru(III)}]} + \frac{1}{K_3 k_4 [\text{BAT}]_t [\text{Ru(III)}]} + \frac{1}{k_4 [\text{BAT}]_t} \quad (12)$$



Scheme-2
Mechanism of Oxidation of [TX] with [BAT] in presence of RuCl₃ as catalyst

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