Kinetics and Mechanism of oxidation of Miglitol by Bromamine –T (BAT) in HCl medium using RuCl$_3$ as catalyst

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ABSTRACT

Kinetics and oxidation of Miglitol (MIG) by sodium -N- bromo - p- toluenesulphonamide (bromamine – T or BAT) in hydrochloric acid medium using RuCl$_3$ as catalyst at 303K have been studied. The rate is first order in [BAT]$_o$, fractional order in [MIG], fractional order in RuCl$_3$, fractional order in [H$^+$] and negative fractional order in [PTS]. Addition of 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. 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 acryl amide solution did not initiate polymerization, showing the absence of free radicals species. Oxidation products were identified. Protonated oxidant H$_2$O$^+$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: Miglitol, Bromamine –T, RuCl$_3$, mechanistic, oxidation, hydrochloric acid.

INTRODUCTION

Aromatic N- halosulphonamides behave as mild oxidants, halogenating agents containing a strong polarized N-linked halogen which is in +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].

Transition metal ions form complexes [10,11] and act as catalyst in oxidation and reduction reactions due to its multiple oxidation states. Osmium, ruthenium, palladium, manganese, chromium, iridium act as catalyst and has drawn considerable interest [12]. By using few transition metal ions as homegenous catalyst, kinetics of oxidation of some molecules have been studied [13-20]. Miglitol is an alpha – glucosidase inhibitor used for lowering blood glucose levels in people with diabetes mellitus [21,22]. Literature survey revealed no information available on the kinetics of oxidation of this drug by any oxidants. Hence Kinetics and mechanism of oxidation of Miglitol(2*R*,3*R*,4*R*,5*S*)-1-(2-hydroxyethyl)-2-(hydroxymethyl) piperidine-3,4,5-triol) with BAT in hydrochloric acid medium at 303K using RuCl$_3$ as catalyst have been studied and reported in the article.

EXPERIMENTAL SECTION

Bromamine – T was obtained [6] 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 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

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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, ^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.

Miglitol (Biocon, India) and p – Toluenesulphonamide(E.Merck) was used without further purification and aqueous solution of desired strength was prepared freshly each time. Purity of Miglitol and p- Toluenesulphonamide was checked by its M.P 113°C (Lit. 114 °C) and 139-144°C (Lit. 138-143°C)respectively. IR spectrum agreed with the literature. 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[23] 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([MIG]$_o$ >> [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, $RuCl_3$ 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 bromamine – T and Miglitol in presence of 1×10^{-2} mol dm^{-3} HCl and 2×10^{-5} mol dm^{-3} $RuCl_3$ catalyst at 303K were equilibrated for 24 h. Determination of unreacted BAT showed 1:1 stoichiometry

$$C_8H_{17}NO_5 + TsNBrNa \longrightarrow C_8H_{13}NO_5 + TsNH_2 + H_2 + Na^+ + Br^- \quad ....(1)$$

Product Analysis:
Reduction product of BAT, p – toluenesulphonamide was detected by thin layer chromatography [24] 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°C) and IR spectra. Oxidation product 3,4,5-trihydroxy-1-(2-oxoethyl)piperidine-2-carbaldehyde was detected by spot tests [25] and was confirmed by IR spectroscopy. Strong peak for aldehyde was observed at 1625cm^{-1}.

RESULTS AND DISCUSSION

1. Effect of Reactants
With substrate in excess, at constant [MIG]$_o$, [H$^+$], [RuCl$_3$] 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 variation in [BAT]$_o$ (Table I), confirming first order dependence on [BAT]$_o$. Under identical experimental conditions, an increase in [MIG]$_o$ leads to increase in $k^/$ (Table I). A plot of log $k^/$ vs log [MIG] was linear (Fig I) with a slope of 0.32 indicating a fractional order dependence on [MIG]. When [HCl] was increased, at constant [MIG], [BAT], [RuCl$_3$] and temperature resulted in increase in rate of the reaction (Table I). A plot of log $k^/$ vs log [HCl] was linear (Fig II) with a slope of 0.91, showing a fractional order dependence on [HCl]. By varying the concentrations of RuCl$_3$ lead to increase in the rate of the reaction (Table I) and a plot of log $k^/$ vs log [RuCl$_3$] was linear (Fig III) with a slope of 0.57, indicating a fractional order dependence on [RuCl$_3$].Catalytic constant k_c was found to be 0.9889×10^1.

2. Effect of halide ions and p- Toluene sulphonamide
At constant [H$^+$], addition of NaCl or NaBr (1×10^{-3} mol dm^{-3} to 10×10^{-3} mol dm^{-3}) did not affect the rate of the reaction (Table II). Hence the dependence of the rate on [HCl] reflected the effect of [H$^+$] only on the reaction.

Addition of reduction product of the oxidant PTS (1×10^{-3} mol dm^{-3} to 15×10^{-3} mol dm^{-3}) decreased the rate of the reaction (Table II). A plot of log $k^/$ vs log PTS was linear(Fig IV) with a negative slope of 0.62, showing a negative fractional order on [PTS] which indicates that PTS is involved in fast pre equilibrium to the rate limiting step.

Table I: Effect of varying [BAT], [MIG], [RuCl₃] and [HCl] on the reaction rate

10^4[BAT]$_o$	10^3[MIG]	10^3[HCl]	10^6[RuCl$_3$]	10^4k$^/$
mol dm^{-3}	mol dm^{-3}	mol dm^{-3}	mol dm^{-3}	s^{-1}
5.0	10.0	5.0	20.0	2.45
10.0	10.0	5.0	20.0	2.55
20.0	10.0	5.0	20.0	2.60
10.0	5.0	5.0	20.0	1.03
10.0	10.0	5.0	20.0	2.55
10.0	15.0	5.0	20.0	3.47
10.0	20.0	5.0	20.0	4.21
10.0	10.0	2.0	20.0	1.16
10.0	10.0	3.0	20.0	1.64
10.0	10.0	5.0	20.0	2.55
10.0	10.0	10.0	20.0	5.39
10.0	10.0	5.0	10.0	1.50
10.0	10.0	5.0	20.0	2.55
10.0	10.0	5.0	30.0	3.38
10.0	10.0	5.0	40.0	4.66

Table II: Effect of concentration of halide ions, PTS, NaClO₄ on the oxidation [MIG] by BAT

10^3[conc]	PTS	NaCl	NaClO$_4$	NaBr
mol dm^3	10^4k$^/$(s^{-1})	10^4k$^/$(s^{-1})	10^4k$^/$(s^{-1})	10^4k$^/$(s^{-1})
1.0	4.20	2.25	2.40	2.34
5.0	3.19	2.45	2.72	2.55
10.0	2.00	2.55	2.32	2.62
15.0	1.31	2.34	2.46	2.33

3. Effect of ionic strength and dielectric constant

Variation of ionic strength using NaClO$_4$ (1×10^{-3} mol dm^{-3} to 10×10^{-3} mol dm^{-3}) solution[26] did not affect the rate of the reaction (Table II) 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 of the rate in the reaction (Table III). Plot of (1/ D) vs logk$^/$ was found to be linear with a positive slope (Fig V). Values of D for MeOH – OH mixtures were taken from the literature[23]. 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.

Table III: Effect of varying 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	2.55
10	72.37	1.38	5.03
20	67.38	1.48	10.23
30	62.71	1.60	25.86

4. Effect of temperature

Reaction was studied over a range of temperature 293K to 323K by varying the concentration of Miglitol and keeping other experimental conditions constant (Table IV). It was found that the rate increased with increase in temperature (Fig VI)

From the linear Arrhenius plot of log k$^/$ vs 1/T (Fig VII), values of activation parameters like energy of activation (Ea) , enthalpy of activation($\Delta H^{\neq}$), entropy of activation($\Delta S^{\neq}$) , free energy of activation($\Delta G^{\neq}$) were computed.(Table V)

Table IV: Effect of [MIG] on different temperatures in acidic medium

10^3 [MIG] mol dm^3	10^4k$^/$(s^{-1})		
	293K	303K	313K
5.0	1.01	1.63	2.23
10.0	1.73	2.55	3.63
50.0	2.29	3.47	4.46

Table V: Effect of temperature and values of Activation parameters for the oxidation of MIG by BAT

Temperature (K)	$10^4 k\,(s^{-1})$	Activation parameters
293 303 313 323	1.95 2.55 4.66 10.66	$E_a = 55.794\ (56.388)$ kJ mol^{-1} $\Delta H^{\neq} = 53.321(53.826)$ kJ mol^{-1} $\Delta G^{\neq} = 31.784(30.905)$ kJ mol^{-1} $\Delta S^{\neq} = -115.070(-100.91)$ kJ mol^{-1} $\log A = 6.0729(6.169)$

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

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

6. Catalytic activity
Moelwyn- Hughes[27] have pointed the relationship between catalyzed and uncatalyzed rate constants.
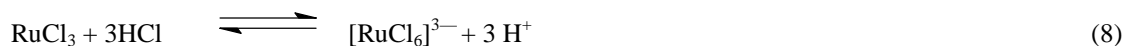
$$k_T = k_u + K_c[\text{Ru(III)}]^x$$

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). Catalytic constant was found to be 0.988×10^1. 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 (Table V).

Pyrde and soper[28], Morris et al[29] and Bishop and Jennings[30] 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 – 7)
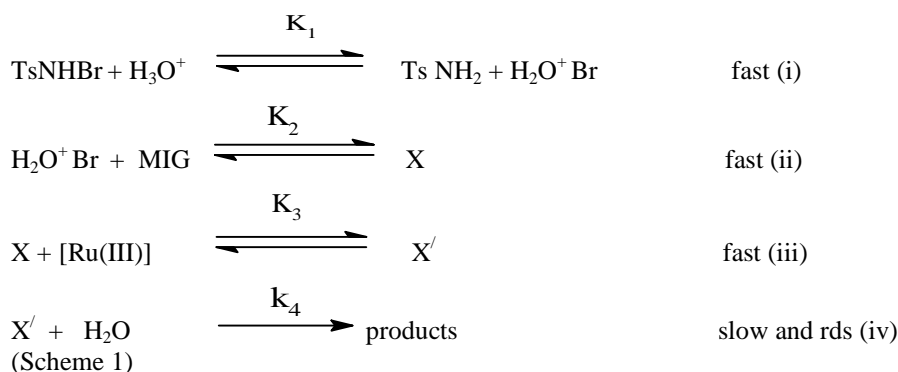
TsNBrNa $\rightleftharpoons$	TsNBr$^-$ + Na$^+$	(2)

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

TsNBr$^-$ + H$^+$ $\rightleftharpoons$	TsNHBr	(3)
2 TsNHBr $\rightleftharpoons$	TsNH$_2$ + TsNBr$_2$	(4)
TsNHBr + H$_2$O $\rightleftharpoons$	TsNH$_2$ + HOBr	(5)
TsNHBr + H$^+$ $\rightleftharpoons$	Ts N$^+$H$_2$ Br	(6)
TsN$^+$H$_2$ Br + H$_2$O $\rightleftharpoons$	TsNH$_2$ + H$_2$O$^+$Br	(7)
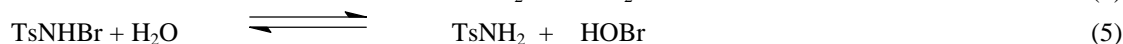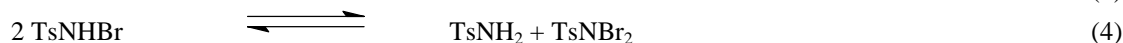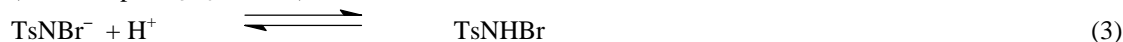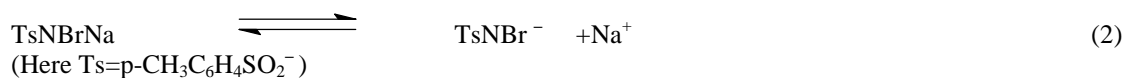
The possible oxidizing species in acid medium are TsNHBr, TsNBr$_2$, HOBr, H$_2$O$^+$ Br. If TsNBr$_2$ were to be the reactive species, then the rate law predicts a second order dependence of rate on [BAT]$_o$, (Eq 4) which is contrary to the experimental observations. First order retardation of rate was observed by adding PTS. Hence, Eqs (6) and (7) play a dominant role in the oxidation of miglitol by BAT. In aqueous solution of [RuCl$_3$], Ru(III)[31-34] can exist as [RuCl$_6$]$^{3-}$, [RuCl$_5$(H$_2$O)]$^{2-}$, [RuCl$_4$(H$_2$O)$_2$]$^-$, [RuCl$_3$(H$_2$O)$_3$], [RuCl$_2$(H$_2$O)$_4$]$^+$, [RuCl(H$_2$O)$_5$]$^{2+}$ and [Ru(H$_2$O)$_6$]$^{3+}$. Literature survey reveals that the active catalyst species may be assumed to be either [RuCl$_6$]$^{3-}$ or [RuCl$_5$(H$_2$O)]$^{2-}$ ion as shown in the following equilibria [Eqs. (8) and (9)]:

RuCl$_3$ + 3HCl $\rightleftharpoons$	[RuCl$_6$]$^{3-}$ + 3 H$^+$	(8)
[RuCl$_6$]$^{3-}$ + H$_2$O $\rightleftharpoons$	[RuCl$_5$(H$_2$O)]$^{2-}$ + Cl$^-$	(9)
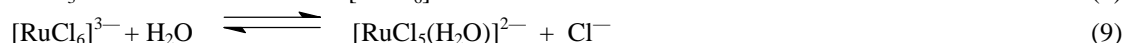
Singh et.al[35, 36] used the above equilibria in Ru(III) catalyzed reaction in HClO$_4$ solution. In present case since there was no effect of chloride ion on the reaction rate, Eq 9 does not play a role in the reaction and hence the complex ion, [RuCl$_6$]$^{3-}$ is assumed to be the reactive catalyst species.

Hardy and Johnston [37] 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.

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

$$TsNHBr + H_3O^+ \underset{}{\overset{K_1}{\rightleftharpoons}} Ts\,NH_2 + H_2O^+\,Br \qquad\qquad \text{fast (i)}$$

$$H_2O^+\,Br + MIG \underset{}{\overset{K_2}{\rightleftharpoons}} X \qquad\qquad\qquad\qquad \text{fast (ii)}$$

$$X + [Ru(III)] \underset{}{\overset{K_3}{\rightleftharpoons}} X^/ \qquad\qquad\qquad\qquad \text{fast (iii)}$$

$$X^/ + H_2O \xrightarrow{k_4} products \qquad\qquad\qquad \text{slow and rds (iv)}$$
(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 MIG oxidation by BAT in acid medium is proposed. The reactive $H_2O^+\,Br$ species interacts with the substrate, miglitol 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 $X^/$. The fractional order in [Ru(III)] supports the fast pre – equilibrium, step(iii), 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

$$[BAT]_t = [TsNHBr] + [H_2O^+\,Br] + [X] + [X^/]\ldots\ldots\ldots\ldots..(10)$$

From the above, the following rate law can be derived:

$$Rate = \frac{-d[BAT]}{dt} = \frac{K_1K_2K_3k_4[BAT]_t[MIG][H_3O^+][Ru(III)]}{[TsNH_2] + K_1[H_3O^+] + K_1K_2[MIG][H_3O^+]\,(1 + K_3[Ru(III)])} \qquad \ldots(11)$$

$$\frac{1}{k} = \frac{TsNH_2}{K_1K_2K_3k_4[BAT]_t[MIG][H_3O^+][Ru(III)]} + \frac{1}{K_2K_3k_4[BAT]_t[MIG][Ru(III)]} + \frac{1}{K_3k_4[BAT]_t[Ru(III)]} + \frac{1}{k_4[BAT]_t} \qquad \ldots(12)$$

Rate law Eq 11 is in agreement with the experimental results.

Variation 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.
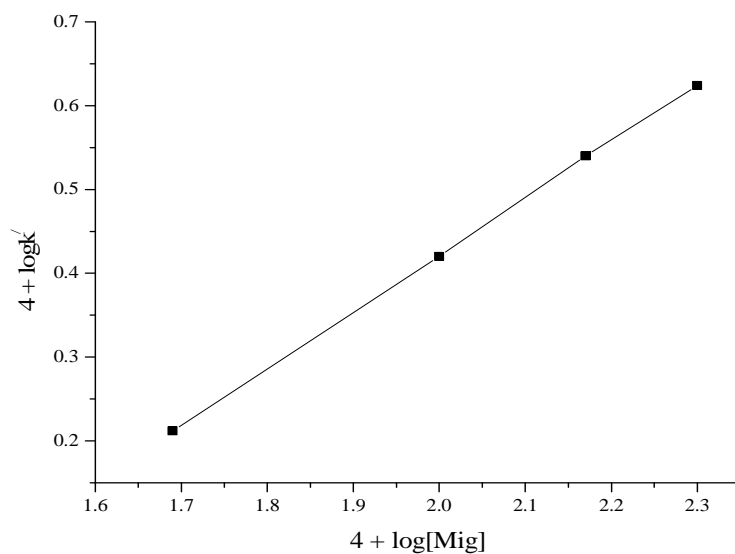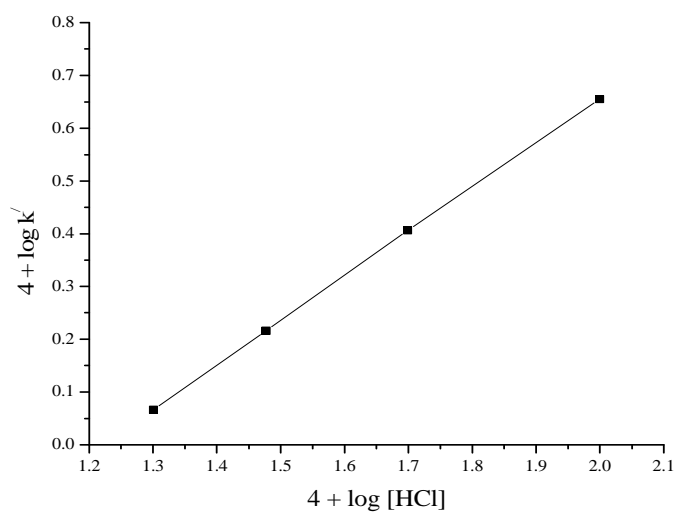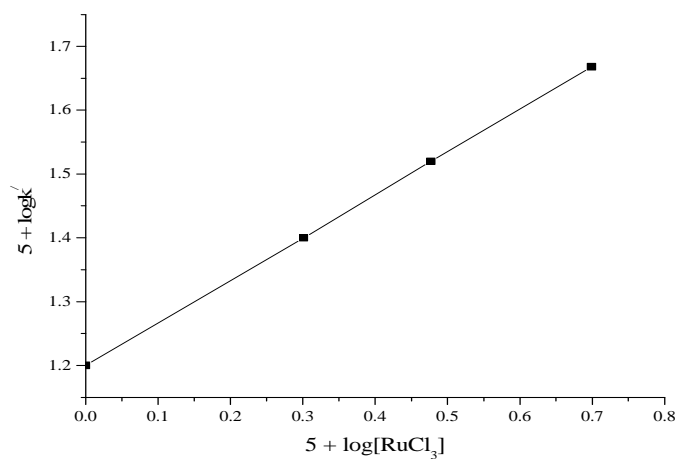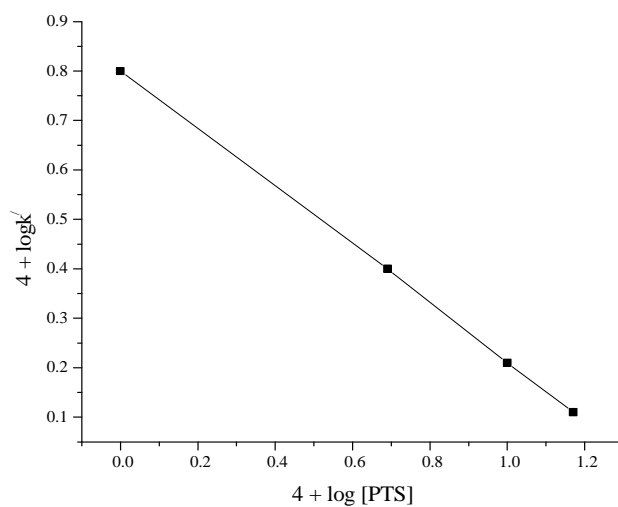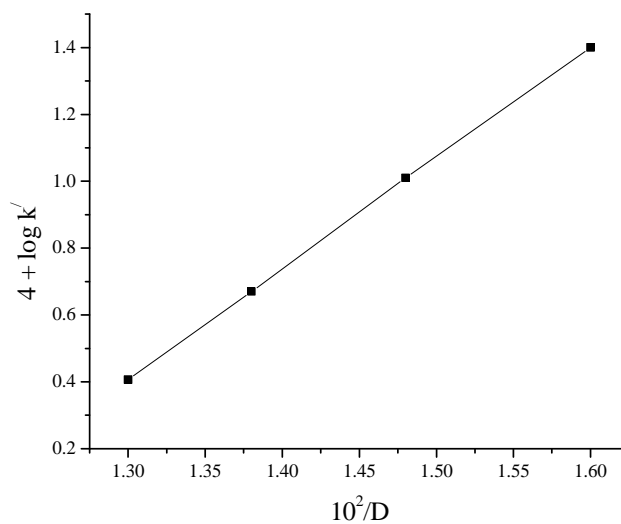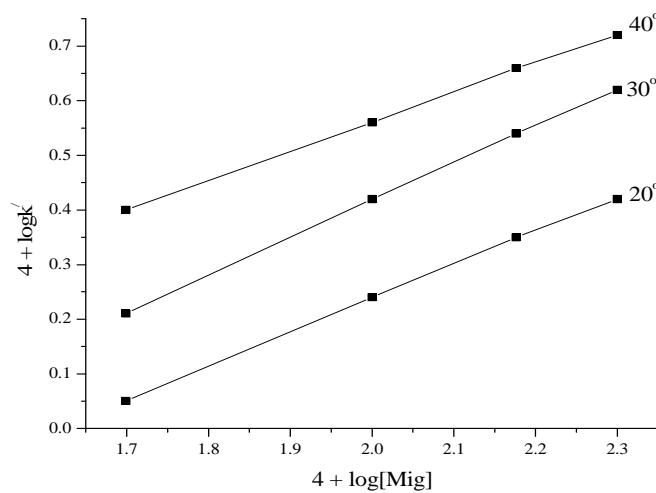
Fig I: Effect of [MIG] on the reaction rate

Fig II: Effect of [HCl] on the rate of the reaction

Fig III: Effect of [RuCl₃] on the rate of the reaction

Fig IV: Effect of [PTS] on the rate of the reaction

Fig V: Effect of dielectric constant on the rate of the reaction

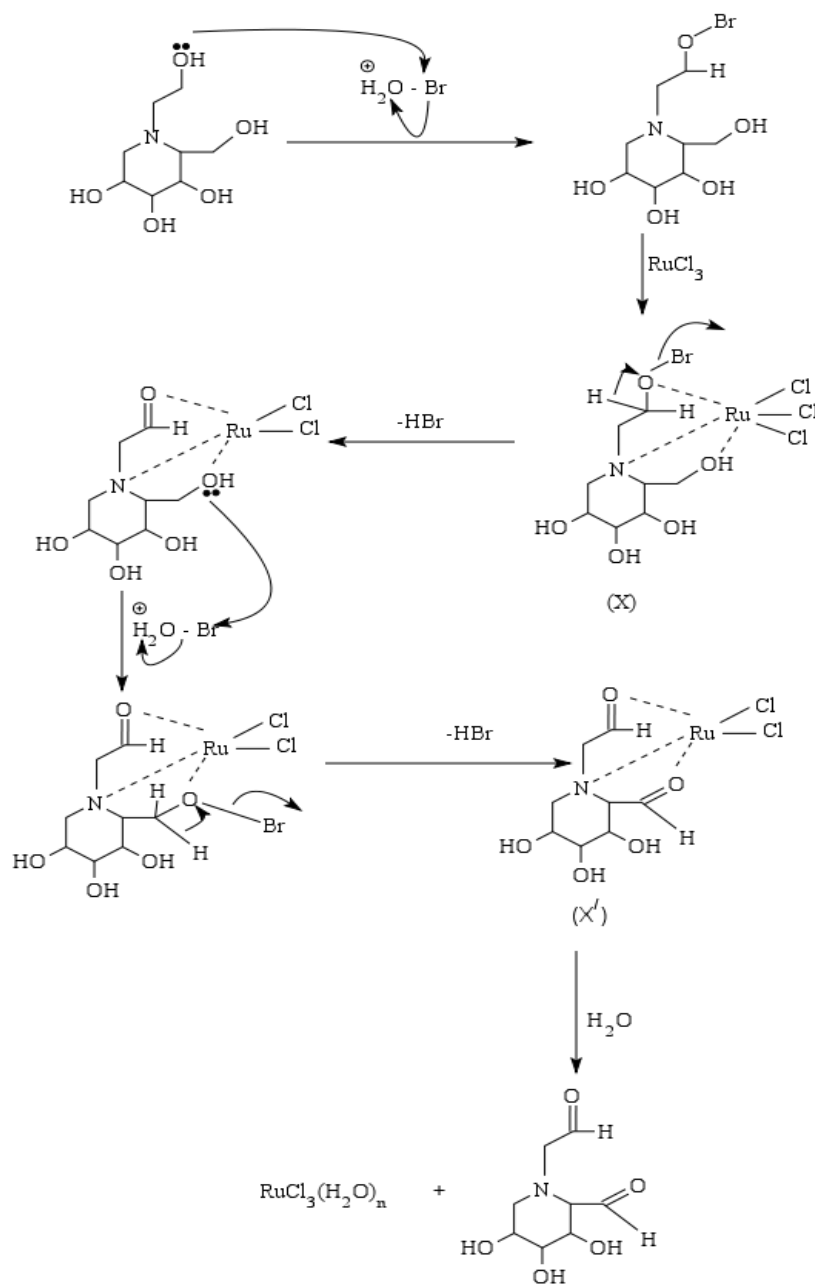**Fig VI: Effect of [MIG] on the rate of the reaction at different temperatures**
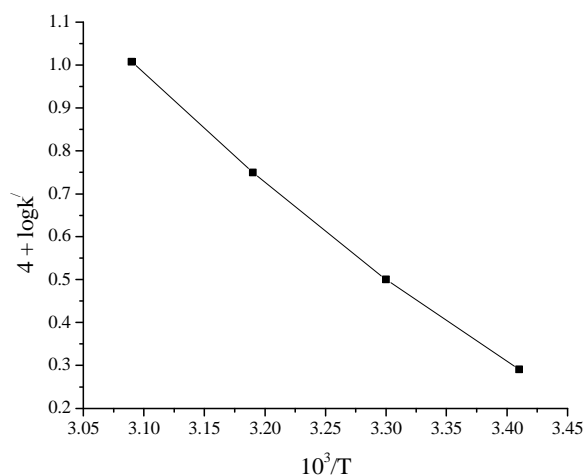
Scheme2: Mechanism of Oxidation of [MIG] with [BAT] in presence of RuCl₃ as catalyst

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Fig VII: Effect of Temperature in acidic medium

CONCLUSION

Kinetics and oxidation Miglitol by sodium – N – bromo – p – toluenesulphonamide (Bromamine-T or BAT) in aqueous HCl in presence of RuCl$_3$ as catalyst have been studied at 303K. Activation parameters were computed. Major oxidation product was identified as 3,4,5-trihydroxy-1-(2-oxoethyl)piperidine-2-carbaldehyde. H$_2$O$^+$Br is the reactive species which reacts with the substrate. Based on kinetic results and reaction stoichiometry, a suitable mechanism has been proposed.

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