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Research Article

RUTHENIUM(III) CATALYZED AND UNCATALYZED OXIDATION OF PREGABALIN BY ACIDIC CHLORAMINE-T: KINETIC AND MECHANISTIC APPROACH

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ABSTRACT

The kinetics of ruthenium (III) chloride (Ru(III)) catalyzed and uncatalyzed oxidation of an anticonvulsant drug, pregabalin (PG) by N-chloro-p-toluenesulfonamide or chloramine-T (CAT) in $HClO_4$ medium was investigated in the temperature range 293K -313K. The reaction showed a first order dependence on $[oxidant]_o$, fractional order dependence on $[PG]_o$ and inverse fractional order dependence on $[H^+]$ for both Ru(III) catalyzed and uncatalyzed reactions. The order with respect to Ru(III) concentration was unity. The reaction stoichiometry was found to be 1:2 for both the cases and oxidation products were identified. The products of reaction and halide ions have no significant effect on the rate in both the cases. The variation of ionic strength of the medium alters the rate in catalyzed reactions, but it has no effect on uncatalyzed reactions. The reaction rate was slightly decreased by the dielectric constant in both the cases. The reaction products were identified by the spot test, GC-MS and IR. The kinetics of Ru(III) catalyzed oxidation of PG by CAT has been compared with those of uncatalyzed reactions; The catalyzed reactions were found to be about 3-fold faster. The reaction constants involved in different steps of the mechanism were calculated for both the cases. The thermodynamic parameters were determined for both the cases. The catalytic constant (Kc) was also calculated for catalyzed reactions at different temperatures.

Key words: Ru(III) Catalyzed, Oxidation kinetics, Mechanism, Pregabalin, Chloramine-T.

INTRODUCTION

Pregabalin is described chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid. It binds with high affinity to the alpha 2-delta site in central nervous system tissues. It is a potent anti-epileptic drug[1], also called an anticonvulsant. It works by slowing down impulses in the brain that cause seizures. It is also used to treat pain caused by nerve damage in people with diabetes, neuropathic pain[2] associated with spinal cord injury.

The sodium salt of N-haloarylsulfonamides are used as versatile reagents[3] as they react with variety of functional groups performing a wide range of transformations[4,5]. Recently the kinetics and mechanism of oxidation of many organic substrates by these reagents have attracted the attention of chemists due to their ability to act as halonium cation, hypochlorous acid and N-anions, which can behave both as bases and neucleophiles[6]. These compounds contain positive halogen with +1 oxidation state which are mild oxidants. A prominent member of this class is sodium N-chloro-p-toluenesulfonamide or chloramine-T (CAT: $p\text{-}CH_3C_6H_4SO_2ClNa.3H_2O$). This reagent is mild, efficient, stable, non-toxic and inexpensive oxidant[7]. CAT is well known as an analytical reagent for the determination of diverse substrates and mechanistic interpretation of many of these reactions have been reported[8-12].

Ruthenium (III) chloride has been used in several redox reactions particularly in acidic medium[13-15] as it is known to be an efficient, non-toxic and homogeneous catalyst. Literature survey revealed that there is no information on the kinetics and mechanism of oxidation of PG by N-haloamines. Since, pregabalin is a potent anticonvulsant drug, this study might throw some light on the mechanistic behavior of this drug molecule. Hence, the title reaction was undertaken.

MATERIALS AND METHODS

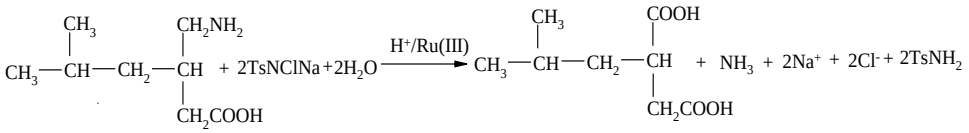
Pregabalin (Sigma Aldrich) was prepared by dissolving appropriate amount in double distilled water. The aqueous solution of CAT (E. Merck) was standardized iodometrically and stored in brown bottle to prevent photochemical deterioration. The Ru(III) solution was made by dissolving ruthenium chloride (s.d fine chemicals) in 0.5 mol dm^{-3} hydrochloric acid and its concentration was then assayed by EDTA titration[16,17]. All other reagents used were of analytical grade. Doubly distilled water was used throughout the studies.

Kinetics

The kinetics of oxidation of PG by CAT was followed under pseudo first order conditions of $[PG]_o >> [CAT]_o$ in both catalyzed and uncatalyzed reactions at 303 K. The uncatalyzed reaction was initiated by mixing previously thermostatted solutions of CAT to PG which also contained necessary amount of acid. The reaction in presence of catalyst was initiated by mixing CAT to PG which was also contained acid and Ru(III). The progress of reaction was monitored iodometrically by the determination of unreacted CAT in a measured aliquot (5ml) of the reaction mixture withdrawn into aqueous KI solution at regular intervals up to about two half-lives. The pseudo first order rate constants for catalyzed reactions (k_c) and uncatalyzed reactions (k_u) calculated from the plot of log [CAT] versus time were reproducible within ±3%.

Stoichiometry and Product Analysis

The kinetic runs were performed for the reaction mixture containing an excess of CAT over PG in presence of constant H^+ and ruthenium (III) concentration at 303 K. The iodometric titration of unreacted CAT showed that one mole of PG required two moles of CAT in both uncatalyzed and catalyzed reactions confirming the following stoichiometric equation.



(1)

Here, Ts = p-$CH_3C_6H_4SO_2$ –

The reaction mixture containing one mole of pregabalin and two moles of oxidant in presence of 0.6 x 10^{-3} mol dm^{-3} $HClO_4$ and 1.93 x 10^{-6} mol dm^{-3} Ru(III) were equilibrated under stirred condition at 303 K for about 24 hr. After completion of reaction (monitored by TLC), the reaction products were neutralized by NaOH. The reduction product of CAT, p-toluenesulfonamide (PTS or $TsNH_2$) was extracted by ethyl acetate and detected by paper chromatography[18]. It was further confirmed by its melting point 137-138 ^oC (lit. m.p 137 – 140 ^oC) and GC-mass spectrum. The GC-MS data was obtained on 17A Shimadzu Gas Chromatography with a QP-5050 mass spectrometer using electron input ionizer technique. The mass spectrum showing a molecular ion peak at 171 amu clearly confirms PTS. The main oxidation product was identified as 2-(2-methylpropyl) butanedioic acid by spot test[19]. It was further confirmed by IR spectrum which shows bonds at 1765 cm^{-1} and 1720 cm^{-1} corresponding to two C=O groups, a broad valley in the region 3101 cm^{-1} – 3512 cm^{-1} corresponding to two OH groups.

RESULTS AND DISCUSSION

Effect of Varying Substrate Concentration on Rate of Reaction

At a fixed concentration of H^+, CAT, Ru(III)(for catalyzed reactions) and temperature, where $[PG]_o >> [CAT]_o$, plots of log k_c or log k_u versus log [PG] ($R^2 > 0.9818$) (Figure 1) were linear with the slope of 0.36 for uncatalyzed reaction and the slope of 0.49 for catalyzed reaction, indicating less than unity order dependence on [PG] in both the cases under identical experimental conditions. The pseudo first order rate constants, k_c/k_u, are listed in Table 1.

Effect of Varying Oxidant Concentration on Rate of Reaction

The kinetic runs were performed under pseudo first order conditions of $[PG]_o >> [CAT]_o$ by varying the $[CAT]_o$ at constant concentration of all other ingredients for both catalyzed and uncatalyzed reactions. The linearity of plots of log [CAT] versus time indicate a first order dependence of reaction rate on $[CAT]_o$ for both Ru(III) catalyzed and uncatalyzed reactions. The pseudo first order rate constants (k_u and k_c:Ru(III), Table 1) remain unchanged with the variation of $[CAT]_o$. This confirms the unit order dependence of rate on $[CAT]_o$ in both the cases.

Effect of $[H^+]$ on Rate of Reaction

The effect of $[H^+]$ on the rate of reaction was studied by varying the amount of $HClO_4$ at constant $[CAT]_o$, $[PG]_o$, Ru(III)](for catalyzed reactions) and temperature. The rate was found to be decreased with increase in [$HClO_4$] (Table 1, Figure 2). The plots of log k_c or log k_u versus log $[H^+]$ were linear ($R^2 > 0.9440$) with negative slopes of 0.75 and 0.81 for catalyzed and uncatalyzed reactions respectively confirming negative fractional order dependence of rate on $[H^+]$ in both the cases.

Effect of Halide ions on Rate of Reaction

The reaction rates were studied by varying the [NaCl]/[NaBr] in the range 0.1 – 0.6 mol dm^{-3}. The rates remain unaltered with the added Cl^-/Br^- indicate that their effect is not significant on the rate of reaction in both catalyzed and uncatalyzed reactions.

Effect of Reduction Product on Rate of Reaction

Addition of reduction product, p-toluenesulfonamide (PTS; 1.0 x10^{-3} — 6.0x10^{-3} mol dm^{-3}) had no effect on the reaction rate indicating non-involvement of it in pre-equilibrium step in both the cases.

Effect of Ionic Strength on Rate of Reaction

Ionic strength of the medium was varied by adding $NaClO_4$ in the range 0.1 – 0.4 mol dm^{-3} keeping all other reactants concentrations constant and found that the rate was decreased with increase in ionic strength of the medium (I) for catalyzed reactions. The plot of log k_c versus $I^{1/2}$ was linear (R^2 =0.944) with a negative slope of 0.59 indicating that ionic species are involved in the rate determining step of catalyzed reactions. But the addition of $NaClO_4$ had no significant effect on the rate of uncatalyzed reactions. Hence, to swamp the reaction, the ionic strength of the medium was maintained at a concentration of 0.25 mol dm^{-3} for all kinetic runs of catalyzed reactions.

Effect of Dielectric Constant on Rate of Reaction

Dielectric constant (D) of solvent medium in the reaction mixture was varied by adding different portions of methanol (0 - 40% v/v) keeping other reaction conditions constant. The reaction rates found to decrease with increase in methanol content in case of both catalyzed and uncatalyzed reactions. The plots of log k_c or log k_u versus 1/D were linear ($R^2 > 0.9915$) (Figure 3) with slopes of -1.13 and -1.06 for catalyzed and uncatalyzed reactions respectively under similar experimental conditions. The values are depicted in Table 2.

Effect of Varying Catalyst Concentration on Rate of Reaction

As the concentration of Ru(III) was varied in the reaction mixture at constant [PG]o, [HClO4], [CAT]o and temperature, the rate was found to be increased with increase in [Ru(III)]. The order with respect to Ru(III) concentration was found to be unity from the linearity ($R^2 = 0.9897$) (Figure 4) plot of log k_c versus log [Ru(III)] (Table 1).

Effect of Temperature on Rate of Reaction

The influence of temperature on the rate of reaction was studied at different temperatures (293 K -313 K) and from Arrhenius plot of log k_c or log k_u versus 1/T ($R^2 > 0.9979$) (Figure 5),

values of activation parameters for both catalyzed and uncatalyzed reactions were calculated and tabulated in Table 3.

Test for Free Radicals

Tests were made to study the involvement of free radical species in the course of reactions by adding acrylamide to the reaction mixture. The reaction mixture fails to initiate the polymerization indicating the absence of free radical species in both catalyzed and uncatalyzed reactions.

RATE LAW AND MECHANISM
Mechanism for Uncatalyzed Reactions

CAT is a strong electrolyte in aqueous solution. In aqueous acidic solutions, it behaves as strong oxidizing agent and furnishes different species with the following equilibria[20-22].

$$TsNClNa \leftrightarrow TsNCl^- + Na^+ \quad (2)$$
$$TsNCl^- + H^+ \leftrightarrow TsNHCl \quad (3)$$
$$2TsNHCl \leftrightarrow TsNH_2 + TsNCl_2 \quad (4)$$
$$TsNHCl_2 + H_2O \leftrightarrow TsNHCl + HOCl \quad (5)$$
$$TsNHCl + H_2O \leftrightarrow TsNH_2 + HOCl \quad (6)$$

Where, Ts = $CH_3C_6H_4SO_2$

Hence, the possible oxidizing species of CAT in aqueous acid solutions are $TsNH_2Cl^+$, TsNHCl, $TsNCl_2$ and HOCl. As the reaction rate is not second order with respect to $[CAT]_o$ as from (4), the involvement of $TsNCl_2$ was ruled out as reactive species. There was no retardation of rate by the added PTS. Hence, HOCl is not primarily involved in the oxidation. Thus from above experimental facts TsNHCl is the most probable active oxidizing species for the oxidation of PG in the present system. Further, in acid medium TsNHCl is protonated to give $TsNH_2Cl^+$[23,24] and the protonation constant is found to be 1.02 x 10^2 at 298 K.

$$TsNHCl + H^+ \leftrightarrow TsNH_2Cl^+ \quad (7)$$

In the present study, there is retardation of rate by the added H^+ ions confirming the deprotonation of $TsNH_2Cl^+$ leading to the formation of TsNHCl, the active oxidizing species. In view of preceding discussions and experimental evidences, Scheme 1 has been proposed to predict the reaction mechanism for the oxidation of PG by CAT in $HClO_4$ medium at 303K.

$$TsNH_2Cl^+ \underset{}{\overset{K_1}{\rightleftharpoons}} TsNHCl + H^+ \qquad \text{(i) fast}$$

$$TsNHCl + PG \overset{K_2}{\rightleftharpoons} X \qquad \text{(ii) fast}$$

$$X \xrightarrow{k_3} X' \qquad \text{(iii) fast and r d s}$$

$$X' + TsNHCl \xrightarrow{k_4} \text{Products} \qquad \text{(iv) fast}$$

Scheme 1

Here, X and X/ are complex intermediate species whose structures are illustrated in Scheme 2, where a detailed mechanistic interpretation of PG – CAT system is depicted, it appears that $TsNH_2Cl^+$ deprotonates in the initial equilibrium step to give conjugate free acid TsNHCl as the reactive oxidizing species, which in turn reacts with pregabalin to form intermediate complex X in the next fast step. Further, in the rate limiting step the intermediate X on hydrolysis gives another intermediate X/ with the elimination of HCl and NH_3. In the next fast step, X/ reacts with another mole of CAT to give the final product, 2-(2-methylpropyl) butanedioic acid.
If $[CAT]_t$ is the total effective concentration of CAT, then

$$[CAT]_t = [TsNH_2Cl^+] + [TsNHCl] + [X] \quad (8)$$

Solving for $[TsNH_2Cl^+]$, [TsNHCl] and [X] from Scheme 1, substituting in (8) and simplifying, we get

$$rate = k_3[X] = \frac{K_1K_2k_3[CAT]_t[PG]}{[H^+] + K_1 + K_1K_2[PG]} \quad (9)$$

Equation (9) is in good agreement with the all observed experimental results.

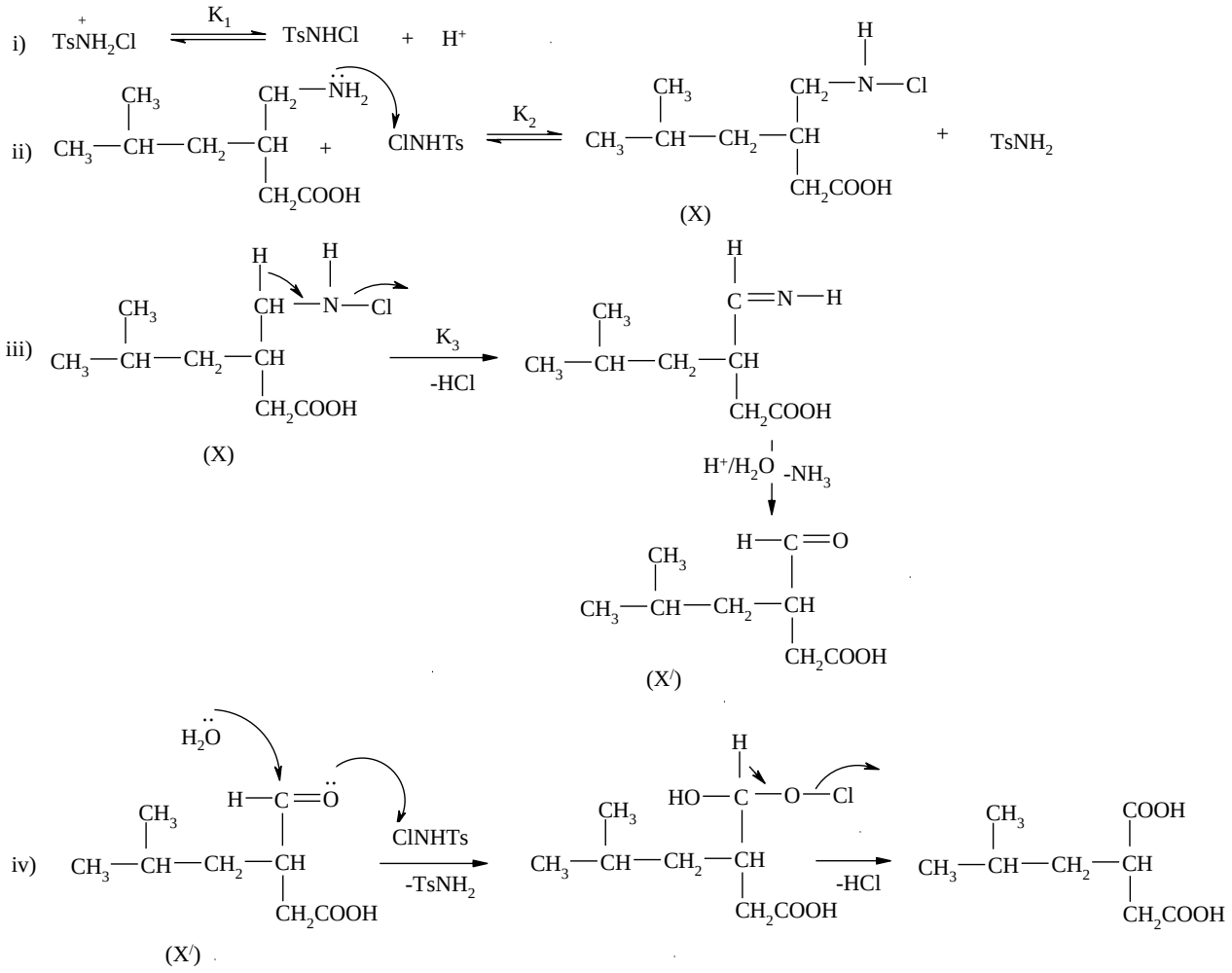
Since, rate = $k_u [CAT]_t$, Eq. (9) yields

$$k_u = \frac{K_1K_2k_3[PG]}{[H^+] + K_1 + K_1K_2[PG]} \quad (10)$$

On rearranging Eq. (10), we get

$$\frac{1}{k_u} = \frac{[H^+]}{K_1K_2k_3[PG]} + \frac{1}{K_2k_3[PG]} + \frac{1}{k_3} \quad (11)$$

The double reciprocal plot of $1/k_u$ >< 1/[PG] gives straight lines and positive intercept on y-axis proving the validity of rate law (9). From the slopes and intercepts, values of k_3 and K_1K_2 were calculated and found to be 1.85 x 10^{-3} s^{-1} and 1.16 respectively. The mechanism proposed is consistent with the observed negligible effects of p-toluenesulfonamide, ionic strength and halide ions on the reaction rate and also on the activation parameters.



Scheme 2, Detailed mechanistic interpretation of oxidation of pregabalin by CAT without Ru(III) catalyst

Mechanism for Ru(III) Catalyzed Reactions

It has been reported[25] that in acidic medium, Ru(III) chloride forms different intermediate complexes viz, $[RuCl_5(H_2O)]^{2-}$, $[RuCl_4(H_2O)_2]^{-}$, $[RuCl_3(H_2O)_3]$, $[RuCl_2(H_2O)_4]^{+}$ and $[RuCl(H_2O)_5]^{2}$ depending on the pH of solution. Under the experimental conditions in the present study, since there is no role of chloride ion on the reaction rate, $[RuCl_5(H_2O)]^{2-}$, is assumed to be the most likely homogeneous catalyst[26].

Spectral evidence for pregabalin – catalyst complex formation was taken from UV-visible spectra of both pregabalin and pregabalin -Ru(III) mixtures. A bathochromic shift of about 7 nm from 197 nm to 204 nm in the spectra of mixture of PG and Ru(III) was observed. This is also confirmed by Michelis-Menten plot ($1/k_c$ vs $1/[PG]$), which gives straight line with non-zero intercept. Such type of complex formation between substrate and catalyst has also been reported in other studies[27,28].

On the basis of preceding discussions viz, negligible effect of p-toluenesulfonamide ($TsNH_2$), first-order dependence of rate on each of $[CAT]_o$ and $[RuCl_3]$, an inverse fractional order on $[H^+]$ and fractional order on $[PG]_o$ the following Scheme 3 has been proposed.

$$TsNH_2Cl^{+} \underset{}{\overset{K_5}{\rightleftharpoons}} TsNHCl + H^{+} \quad \text{(i) fast}$$

$$TsNHCl + PG \overset{K_6}{\rightleftharpoons} X^{//} \quad \text{(ii) fast}$$

$$X^{//} + Ru(III) \xrightarrow{k_7} X^{///} \quad \text{(iii) fast and r d s}$$

$$X^{///} + TsNHCl \xrightarrow{k_8} Products \quad \text{(iv) fast}$$

Scheme 3

The structures of complex intermediate species ($X^{//}$ and $X^{///}$) are shown in Scheme 4, where in the mechanism for the oxidation of PG by CAT in presence of Ru(III) has been discussed. In the pre rate determining step, $TsNH_2Cl^{+}$ deprotonates to give the free acid TsNHCl as the reactive oxidizing species, which in turn reacts with pregabalin to form complex intermediate $X^{//}$. Further, in the rate limiting step, the intermediate $X^{//}$ combines with Ru(III) which facilitates the reaction. In the subsequent steps, $X^{//}$ gives another intermediate complex $X^{///}$ with the elimination of HCl, NH_3 and regenerating the catalyst. In the next fast step, $X^{///}$ reacts with another mole of CAT to give the final product, 2-(2-methylpropyl) butanedioic acid.

From slow step of Scheme 3, we get

$$rate = k_7[X^{//}] = \frac{K_5K_6k_7[CAT]_t[PG][Ru(III)]}{[H^+] + K_5 + K_5K_6[PG]} \quad (12)$$

Equation (12) is in good agreement with the all observed results.

Since, rate = $k_c[CAT]_t$, equation (12) yields

$$k_c = \frac{K_5K_6k_7[PG][Ru(III)]}{[H^+] + K_5 + K_5K_6[PG]} \quad (13)$$

On rearranging equation (13), we get

$$\frac{[Ru(III)]}{k_c} = \frac{[H^+]}{K_5K_6k_7[PG]} + \frac{1}{K_6k_7[PG]} + \frac{1}{k_7} \quad (14)$$

Based on the Eq. (14), the plots between $[Ru(III)]/k_c$ and $1/[H^+]$ or 1/[PG] yield straight lines with positive intercepts on y-axis and proves the validity of rate law (12). From the intercepts and slopes of such plots, the values of K_5, K_6 and k_7 are obtained and found to be 1.27 x 10^{-4} mol dm^{-3}, 4.94 x 10^3 dm^3 mol^{-1} and 3.7 x 10^2 dm^3 mol^{-1} s^{-1}. The derived rate law and proposed mechanism are well supported by all observed kinetic results. The high negative value of entropy of activation suggests that the intermediate complex is more ordered than reactants.

TABLE 1: EFFECT OF [PG], [CAT], [H^+] AND [RU(III)] ON REACTION RATE AT 303 K

$10^4[CAT]_o$ (mol dm^{-3})	$10^3[PG]_o$ (mol dm^{-3})	$10^3[H^+]$ (mol dm^{-3})	$10^6[Ru(III)]$ (mol dm^{-3})	10^4 *k'* (s^{-1})	
				Catalyzed	**uncatalyzed**
0.4	1.0	0.6	1.93	3.28	1.07
0.8	1.0	0.6	1.93	3.25	1.06
1.0	1.0	0.6	1.93	3.36	1.03
1.5	1.0	0.6	1.93	3.28	1.09
2.0	1.0	0.6	1.93	3.44	1.11
1.0	**0.2**	0.6	1.93	1.51	0.63
1.0	**0.5**	0.6	1.93	2.40	0.85
1.0	**1.0**	0.6	1.93	3.36	1.03
1.0	**2.0**	0.6	1.93	4.76	1.43
1.0	**3.0**	0.6	1.93	5.84	1.62
1.0	1.0	**0.2**	1.93	7.46	2.57
1.0	1.0	**0.4**	1.93	4.48	1.42
1.0	1.0	**0.6**	1.93	3.36	1.03
1.0	1.0	**0.8**	1.93	2.68	0.81
1.0	1.0	**1.0**	1.93	2.24	0.67
1.0	1.0	0.6	**0.48**	0.81	--
1.0	1.0	0.6	**0.96**	1.63	--
1.0	1.0	0.6	**1.93**	3.36	--
1.0	1.0	0.6	**3.86**	6.55	--
1.0	1.0	0.6	**5.78**	9.81	--

$[CAT]_o$ = 1.0 x 10^{-4} mol dm^{-3}; $[PG]_o$ = 1.0 x 10^{-3} mol dm^{-3}; $[HClO_4]$ = 0.6 x 10^{-3} mol dm^{-3}; [Ru(III)] = 1.93 x 10^{-6} mol dm^{-3}; T = 303 K.

TABLE 2: EFFECT OF VARYING DIELECTRIC CONSTANT OF MEDIUM ON REACTION RATE AT 303 K

%MeOH (v/v)	D	10^4 k' (s^{-1})	
		Catalyzed	uncatalyzed
0	76.73	3.36	1.03
10	72.37	2.74	0.84
20	67.48	2.10	0.67
30	62.71	1.58	0.52
40	58.06	1.12	0.37

$[CAT]_o$ = 1.0 x 10^{-4} mol dm^{-3}; $[PG]_o$ = 1.0 x 10^{-3} mol dm^{-3} $[HClO_4]$ = 0.6 x 10^{-3} mol dm^{-3}; [Ru(III)] = 1.93 x 10^{-6} mol dm^{-3}; T = 303 K.

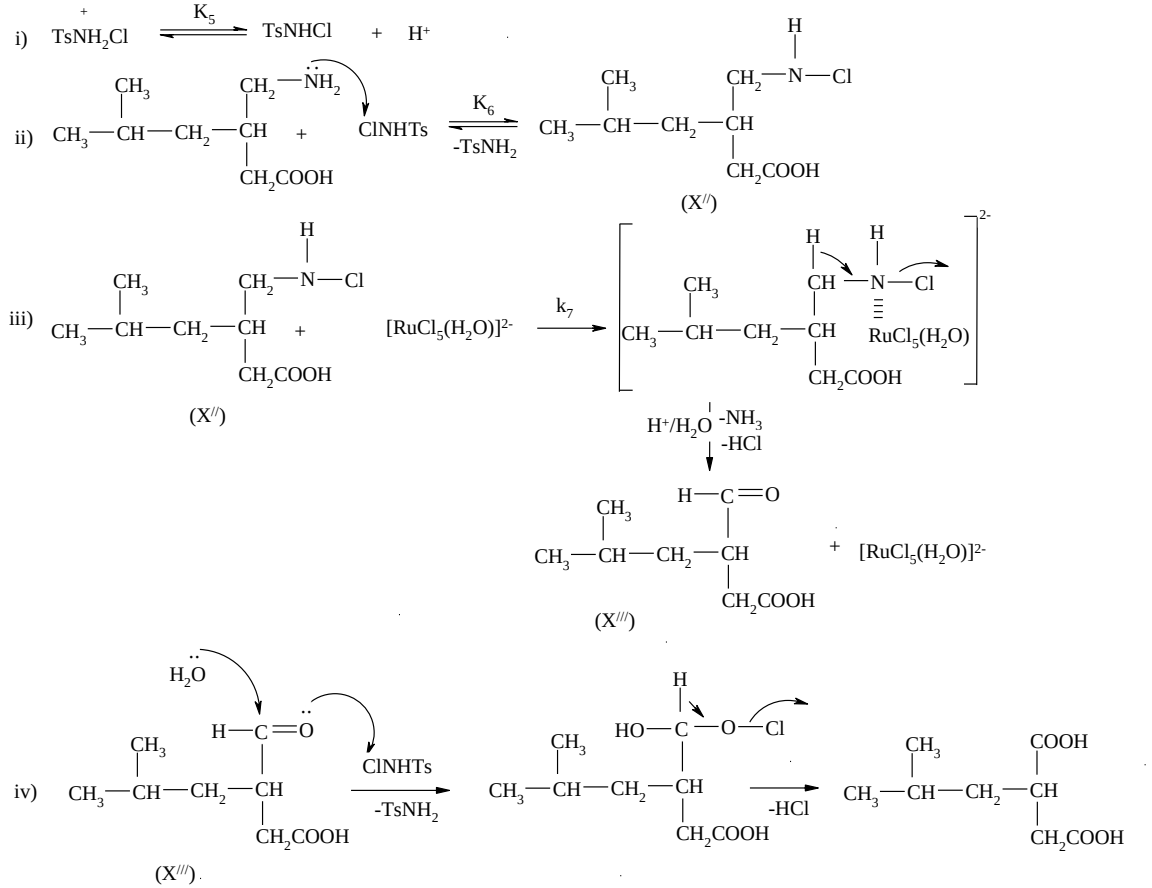
TABLE 3: EFFECT OF VARYING TEMPERATURE ON REACTION RATE AND ACTIVATION PARAMETERS

Temperature (K)	10^4 k' (s^{-1})		Activation parameters	Values	
	catalyzed	uncatalyzed		catalyzed	uncatalyzed
293	1.52	0.35	Ea(kJ mol^{-1})	59.28	76.61
298	2.32	0.58	$\Delta H^{\#}$(kJ mol^{-1})	56.76	74.12
303	3.36	1.03	$\Delta S^{\#}$(J $K^{-1}mol^{-1}$)	-124.22	-77.19
308	5.36	1.72	$\Delta G^{\#}$ (kJ mol^{-1})	94.39	97.51
313	7.45	2.69			

$[CAT]_o$ = 1.0 x 10^{-4} mol dm^{-3}; $[PG]_o$ = 1.0 x 10^{-3} mol dm^{-3}; $[HClO_4]$ = 0.6 x 10^{-3} mol dm^{-3}; [Ru(III)] = 1.93 x 10^{-6} mol dm^{-3}. Similar experimental conditions as above were employed for uncatalyzed reactions without Ru(III).

TABLE 4: VALUES OF CATALYTIC CONSTANT (KC) AT DIFFERENT TEMPERATURES AND ACTIVATION PARAMETERS CALCULATED USING Kc VALUES

Temperature (K)	Kc	Activation parameters	Values
293	60.62	Ea(kJ mol^{-1})	52.19
298	91.57	$\Delta H^{\#}$(kJ mol^{-1})	49.67
303	120.7	$\Delta S^{\#}$(J $K^{-1}mol^{-1}$)	-41.01
308	188.6	$\Delta G^{\#}$ (kJ mol^{-1})	62.11
313	246.6		



Scheme 4, Detailed mechanistic interpretation of pregabalin by CAT in presence of Ru(III) catalyst

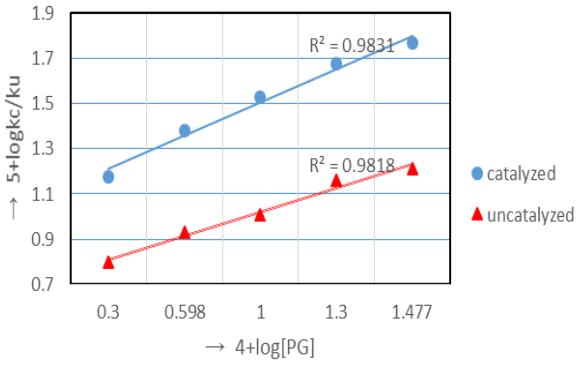


Figure 1: Effect of varying [PG]

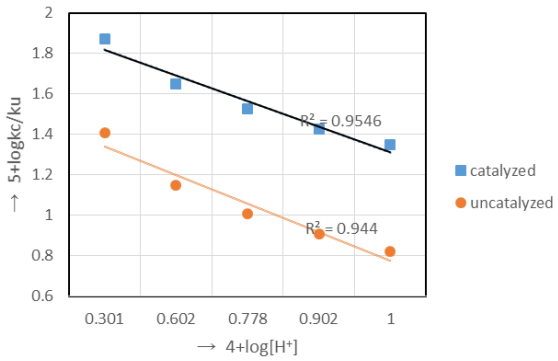


Figure 2: Effect of varying [H$^+$]

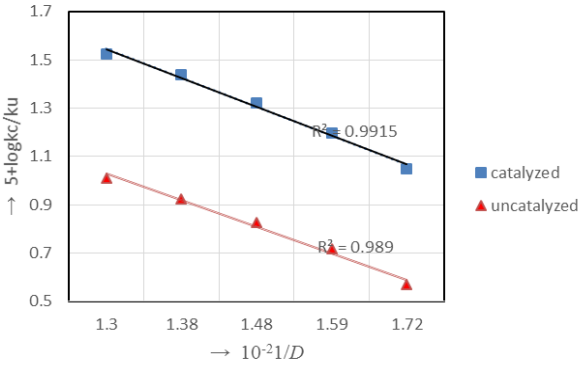


Figure 3: Effect of varying dielectric constant of medium

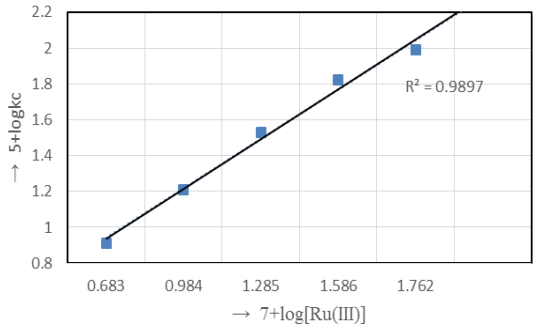


Figure 4: Effect of varying [Ru(III)]

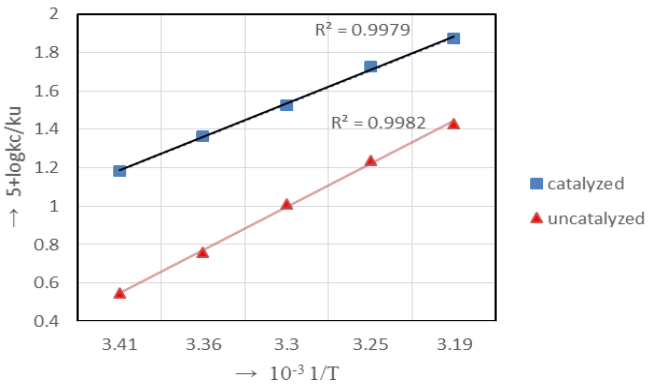


Figure 5: Effect of varying temperature

Catalytic Coefficient

According to Moelwyn-Hughes[29], the catalyzed and uncatalyzed reactions proceed simultaneously in presence of catalyst, so that

$k_c = k_u + Kc[Ru(III)]^x$ (15)

Here kc and ku are rate constants for catalyzed and uncatalyzed reactions respectively, x is the order of reaction with respect to [Ru(III)] and Kc, the catalytic constant. The values of Kc were calculated using equation (15) at different temperatures and tabulated in Table 4. Activation parameters were computed for Kc values by plotting a graph of log Kc versus 1/T. The difference in activation parameters for catalyzed and uncatalyzed reactions clearly explains the catalytic effect of Ru(III) in the present study. Ru(III) forms complex with pregabalin, which shows more reducing property than pregabalin itself and hence catalyst alters the reaction path by lowering the activation energy.

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REFERENCES

1. Frampton J E. Pregabalin: A review of its use in adults with generalized anxiety disorder. CNS Drugs 2014; 28(9): 835-854.
2. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nurmikko T. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. European Journal of Neurology 2010; 17(9): 1113-1123.
3. Sweetman SC, Blake PS, Mc Glashan JM, Persons AV. Martindale – the complete drug reference. 33rd ed. Pharmaceutical Press, London, 2002; p 149-150.
4. Umemeto T, Fukami S, Tomigava G, Harasava K, Kavada K, Tomita K. Formal electrophile reactions of fluorine presumably involve alternative mechanisms. Journal of American Chemical Society 1990; 112: 8563-8575.
5. Kolvari E, Choghamarini AG, Salehi P, Shirini F, Zolfigol MA. Application of N-halo reagents in organic synthesis. Journal Iranian Chemical Society 2007; 4(2): 126-174.
6. Camphell MM, Johnson G. Chloramine-T and related N-halogeno-Nmetallo reagents. Chemical Reviews 1978; 78: 65-79.
7. Geethanjali A. Chloramine-T (Sodium N-Chloro-ptoluenesulfonamide). Synlet 2005; 18: 2857-2858.
8. Banerji KK, Jayaram B, Mahadevappa DS. Mechanistic aspects of oxidations by N-metallo-N-halorylsulfonamides. Journal of Scientific and Industrial Research 1987; 46: 65-76.
9. Bremner DH. Synthesis of α-aminoaldehydes from Enamines Review. Synthesis Reagents 1986; 6: 9.
10. Puttaswamy, Dakshayani S. Mechanistic chemistry of oxidation of balsalazide with acidic chloramine-T and bromamine-T: A comparative spectrophotometric kinetic study. Journal of chemical Sciences 2014; 126: 1655-1664.
11. Mohan K, Jagadeesh MB. Kinetics of oxidation of gabapentin (neurontin) by chloramine-T in perchloric acid medium. Indian Journal of Chemistry-Section A 2008; 47:1226-1229.
12. Jayadevappa HP, Nagendrappa. Kinetics, mechanistic and thermodynamic aspects of lidocaine oxidation by chloramine-T in perchloric acid medium. Research Journal of Chemical Sciences 2013; 3(7): 3-8.
13. Singh P, Roli R, Rishi R. Comparative study on Pd(II) and Ru(III) catalyzed oxidation of α-amino-β-hydroxypropionic acid (dl-series) by acid bromate: A kinetic study. Oriental Journal of Chemistry 2009; 25(4): 1047-1052.
14. Hosamani RR, Nandibevoor ST. Mechanistic study of ruthenium (III) catalyzed oxidation of L-lysine by diperiodatoargentate (III) in aqueous alkaline medium. Journal of Chemical Sciences 2009; 121(3): 275-281.
15. Chanabasayya V, Hiremath TS, Kiran, Nandibewoor ST. Os(VIII)/Ru(III) catalyzed oxidation of aspirin drug by a new oxidant, diperiodatoargentate(III) in aqueous alkaline medium: A comparative kinetic study. Journal of Molecular Catalysis A: Chemical 2006; 248(1):163-174.
16. Kamble DL, Chougale RB, Nandibewoor ST. Kinetic and mechanism of uncatalyzed and Ru (III) catalyzed oxidation of allyl alcohol by N-bromosuccinimide in aqueous alkaline medium. Indian Journal of Chemistry-Section A. 1996; 35: 865–869.
17. Reddy CS, Vijay Kumar T. Kinetic and mechanistic study of ruthenium(III) catalyzed and uncatalyzed oxidation of oxalic acid by acid bromate. Indian Journal of Chemistry-Section A 1995; 34: 615-620.
18. Puttaswamy, Suresha N, Jagadeesh RV. Mechanistic investigation of oxidation of atenolol by N-chloro-p-toluenesulfonamide in alkaline medium: A kinetic approach. Journal of Indian Chemical Society 2005; 82: 903-908.
19. Feigl F. Spot tests in organic analysis. 7th ed. Elsevier, Amsterdam; 1966. p 332-335.
20. Morris JC, Salazar JA, Winemann MA. Equilibrium studies on chloro compounds: The ionization constant of N-chloro-p-toluenesulfonamide. Journal of American Chemical Society 1948; 70: 2036-2041.
21. Bishop E, Jennings VJ. Titrimetric analysis with chloramine-T: The status of chloramine-T as a titrimetric reagent. Talanta 1958; 1: 197-199.
22. Hardy FF, Johnston JP. The interaction of N-bromo-N-sodiobenzene-sulphonamide (bromamine-B) with p-nitrophenoxide ion. Journal of the Chemical Society 1973; 2: 742-746.
23. Narayan SS, Rao VRS. Chlorine isotopic exchange reaction between chloramine-T and chloride ion. Radiochem Acta 1983; 32(4): 211-214.
24. Subhashini M, Subramanian M, Rao VRS. Determination of the protonation Constants of Chloramine – B. Talanta 1985; 32: 1082-1085.
25. Khan AAP, Khan A, Asiri AM, Singh AK. Homogeneous catalysis of Ru(III) for the oxidation of thiamine by chloramine T in acidic medium. International Journal of Electrochemical Science 2015; 10: 759-774.
26. Divya, Pushpa I, Ramachandrappa R. Oxidation of tranexamic acid by bromamnie-T in HCl medium catalyzed by $RuCl_3$: A kinetic and mechanistic approach. Research Journal of Chemical Sciences 2012; 2(7): 7-15.
27. Chimatadar SA, Basavaraj T, Thabaj TA, Nandibewoor ST. Ruthenium(III) catalyzed oxidation of gabapentin by diperiodatocuprate in aqueous alkaline medium-A kinetic and mechanistic study. Journal of Molecular Catalysis A: Chemical 2007; 267: 65-71.
28. Singh AK, Reena N, Bhawana J, Yokraj K, Singh SP, Sharma VK. Kinetics and mechanism of Ru(III) catalyzed oxidation of paracetamol by chloramine-T in aqueous acidic medium. Catalysis Letters 2009; 132: 285-291.
29. Molelwyn EA, Hughes J. Kinetics of reactions in solutions; Oxford University Press: London, 1947; p 297–299.

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