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Kinetic and thermodynamic properties of pharmaceutical drug (Gabapentin) by potassium bromate ($KBrO_3$) in presence of micro amount of Ir(III) chloride as catalyst in acidic medium

Reena Patel[1], Shailesh Kumar[1], Abhishek Verma[1] and Sheila Srivastava[2,*]

[1]Department of Applied Chemistry B. B. A. U. Lucknow U.P., India
[2]Department of Chemistry Feroze Gandhi College, Raebareli U.P., India
*Corresponding author's E. mail: she_ila72@yahoo.com, patel.reena14@gmail.com

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The kinetic and thermodynamic properties of pharmaceutical drug (gabapentine) by potassium bromate ($KBrO_3$) in presence of Micro amount of Ir(III) chloride as catalyst in acidic medium was studied in the temperature range 30 to 45 ^{0}C. The reaction is carried out in the presence of mercuric acetate as a scavenger for chloride ion. 1-carboxy cyclohexane l-acetic acid was obtained as the oxidation product and identified chromatographically. The rate law followed a first order and zero order dependence with respect to $KBrO_3$ and GBP respectively. The reaction followed first order with respect to Ir(III) chloride and [H^+]. Negligible effect of [$Hg(OAc)_2$] and ionic strength of the medium was observed. Chloride ion positively influenced the rate of reaction. The values of rate constants observed at different temperatures (30 to 45 ^{0}C) were utilized to calculate the activation parameters. Feasible mechanism is proposed which are composed with the kinetics, stochiometry and product of the reaction. The rate law has been derived from obtained kinetic data.

Capsule Summary: Effect of Ir(III) chloride and temperature on kinetic and thermodynamic properties of gabapentine was studied and study revealed that both catalyst and temperature affected both kinetic and thermodynamic properties considerably.

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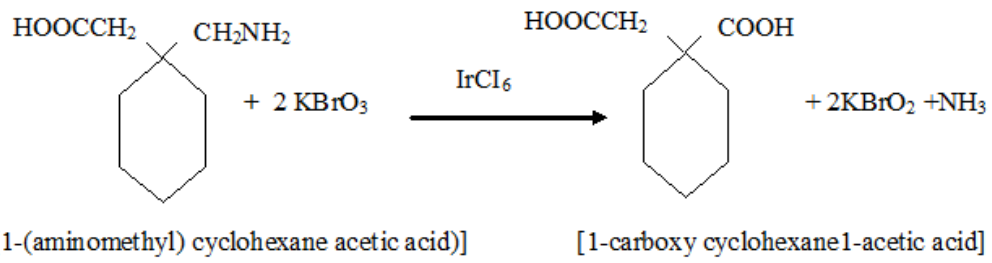
INTRODUCTION

The transition metal catalysed reactions are important for the chemical industry from both practical and economic point of view. Transition metal ions are found to be good catalysts and their complexes are also able to catalyze a wide variety of reactions like hydrogenation, oxidation and polymerization. The applications of transition metal catalyst such as Ru(III)(Singh et al., 2007; Hosahalli et al., 2012), Rh(III) (Singh et al., 2009 and 2010), Cu(II) (Li et al., 2009; Olusanya and Odebunmi, 2011) and Pd(II) (Koli and Nandibewoor, 2000; Singh et al., 2010) in kinetic studies of redox reaction involving organic substrate are reported in literature. It was found that these catalysts work efficiently in both acidic and alkaline media. The use of Ir(III) chloride as a non-toxic and homogenious catalyst has been reported (Bai et al., 2008; Munavalli et al., 2008; Singh et al., 2004; Wen-yu



Scheme 1: Stoichiometry of Ir(III) catalyzed oxidation of gabapentin by potassium bromate [$KBrO_3$]

et al., 2005). The reaction path depends not only upon the nature of the oxidant and the nature of the substrates but also upon the ways in which reactive species of transition metal ion forms complex with the reactant molecules before changing into final products under experimental conditions. Oxidant such as NBS (Goel and Sharma, 2012; Mohana K N & Ramya, 2009), NBA (Singh et al., 2007), Periodate (Kaushik et al., 2010; Chaturvedi and Mishra, 2010), and iodate (Chanakira et al., 2006; Singh et al., 2011), have been successfully utilized in kinetic and mechanistic investigations of various organic substrate. Amongst various inorganic oxidants, iodate has been used as an oxidant in the uncatalyzed oxidation of oxalic acid (Ramana and Rao, 1991), acetophenone (Munikyamba et al., 1983), benzeldehyde (Munikyamba et al., 1981). Others introduced various reports in the literature regarding the oxidation of reducing sugars involving Ir(III) as homogenious catalyst (Brahmaiah and Manikyamba , 1995; Muthakia and Jonnalagadda, 1989; Mambo and Simoyi, 1993; Radhakrishamurti and Tripathy, 1986).

Potassium bromate is known to be a powerfull oxidizing agent with redox potential 1.44 volts and has been used widely in the oxidation of several organic substrates (Radhakrishnamurthy and Sarangi, 1981). However, till date no report is available in which bromate as an oxidant and Ir(III) as homogeneous catalyst have been used in the oxidation of gabapentine in acidic medium. Gabapentin (GBP) is most potent drug prescribed usually in combination with other medications for the prevention of seizure. It is sometimes prescribed for the management of neuralgia (nerve pain) (Jensen et al., 2002). Gabapentin has been prescribed for the treatment of some mood disorders, anxiety etc. The study of neuroleptic drug is more important due to biological significance of these drugs and their selectivity towards the oxidation to yield different products.

MATERIAL AND METHODS

Chemical and reagents

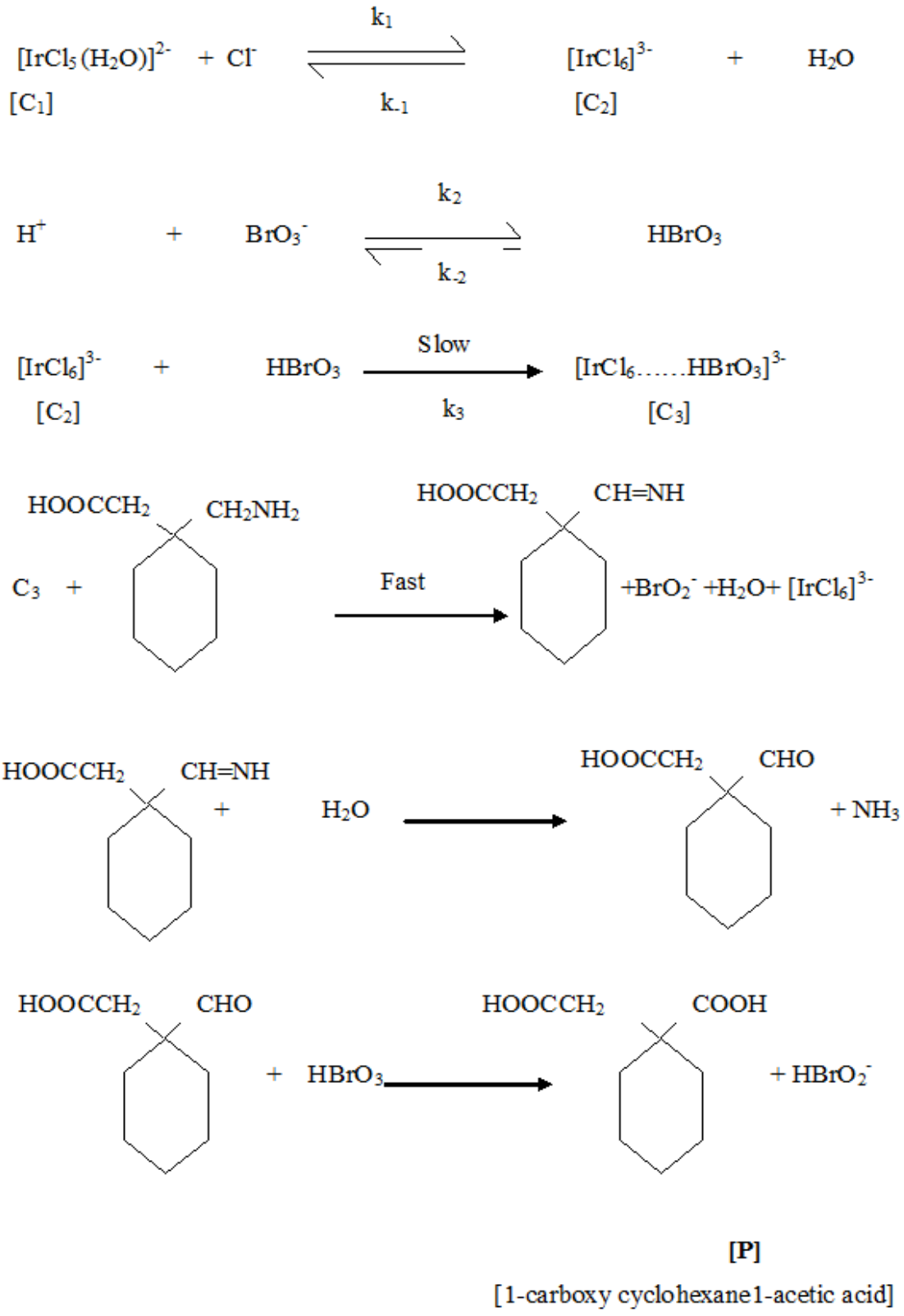
Aqueous solution of Gabapentin (CDH), potassium bromate (S.D. Fine A.R.) and mercuric acetate (E. Merck) were prepared by dissolving the weighed amount of sample in triple distilled water. Perchloric acid (60% E. Merck) was used as a source of hydrogen ions. Iridium tri chloride (Johnson Matthey) was prepared by dissolving the sample in hydrochloric acid of known strength. All other reagents of analytical grade were available. Sodium perchlorate (E. Merck) was used to maintain the ionic strength of the medium. The reaction stills were blackened from outside to prevent photochemical effect.

Kinetic procedure

Aliquots (5ml) of the reaction mixture were pipetted out at regular intervals of time and poured in to a conical flask containing 5 ml of 4 % KI solution and 5 ml of dilute sulfuric acid. The liberated bromine equivalent to consumed oxidant was estimated with standard sodium thiosulphate solution using starch as an indicator. The initial rates were obtained from slopes of concentration vs. time graph in the initial stages of the reaction by plane mirror method.

Stoichiometry of Ir(III) catalyzed oxidation of gabapentin by potassium bromate [$KBrO_3$]

The stoichiometry of the reaction was determined by equilibrating varying ratios of $KBrO_3$ and [GBP] at 35^{0}C for 48 hours under kinetic condition. Estimation of unconsumed $KBrO_3$ revealed that, one mole of gabapentin consumes 2 moles of potassium bromate. This result confirms 1:2 stoichiometry. According to the above reaction the oxidation product of gabapentin is 1-carboxycyclohexane1-acetic acid, which was identified and confirmed by paper chromatography. 1-carboxy cyclohexane1-acetic acid was identified and confirmed by IR spectral analysis. The bands at 1760 cm^{-1} and 1710 cm^{-1} corresponds to two-C=O group and 3550 cm^{-1} corresponds to two –OH group clearly confirms 1-carboxy cyclohexane1-acetic acid (Scheme 1).



Scheme 2: Proposed reaction mechanism

Table 1: Effect of variation of oxidant, substrate and catalyst at 35 ^{0}C

Oxidant x 10^3M (Potassium bromate)	[Substrate]x 10^2M (Gabapentin)	Ir(III) x 10^5M	(-dc/dt)x10^7ML^{-1}s^{-1}
0.80	1.00	1.00	1.30
1.00	1.00	1.00	2.00
1.25	1.00	1.00	2.10
1.69	1.00	1.00	3.20
2.50	1.00	1.00	6.20
5.00	1.00	1.00	13.00
1.00	0.33	1.00	2.21
1.00	0.44	1.00	2.00
1.00	0.55	1.00	2.10
1.00	0.66	1.00	2.31
1.00	1.00	1.00	2.11
1.00	2.00	1.00	2.22
1.00	1.00	0.66	1.00
1.00	1.00	1.33	2.00
1.00	1.00	2.67	2.62
1.00	1.00	4.01	3.50
1.00	1.00	5.34	6.00
1.00	1.00	6.67	11.3

Table 2: Effect of variation of reactant ($HClO_4$ and KCl, $NaClO_4$) at 35^{0}C

$HClO_4$ x 10^3M	[KCl] x 10^3M	$Hg(OAc)_2$ x 10^3M	(-dc/dt)x10^7ML^{-1}s^{-1}
0.80	1.00	1.00	1.20
1.00	1.00	1.00	2.00
1.25	1.00	1.00	2.30
1.69	1.00	1.00	4.20
2.50	1.00	1.00	6.20
5.00	1.00	1.00	12.00
1.00	0.80	1.00	1.10
1.00	1.00	1.00	2.00
1.00	1.25	1.00	2.80
1.00	1.69	1.00	3.70
1.00	2.50	1.00	5.20
1.00	5.00	1.00	9.31
1.00	1.00	0.80	2.00
1.00	1.00	1.00	2.50
1.00	1.00	1.25	2.22
1.00	1.00	1.69	3.00
1.00	1.00	2.50	2.00
1.00	1.00	5.00	2.13

RESULTS AND DISCUSSION

The kinetic results were collected at several initial concentrations of reactants (Table 1). First order rate constant k_1 i.e. (-dc/dt/$KBrO_3$*) were calculated from the plots of unconsumed potassium bromate vs. time. The plots of log(-dc/dt) versus log (oxidant) were linear indicating first order dependence on $KBrO_3$ (Fig-1).Insignificant effect on the rate was observed on increasing the concentration of

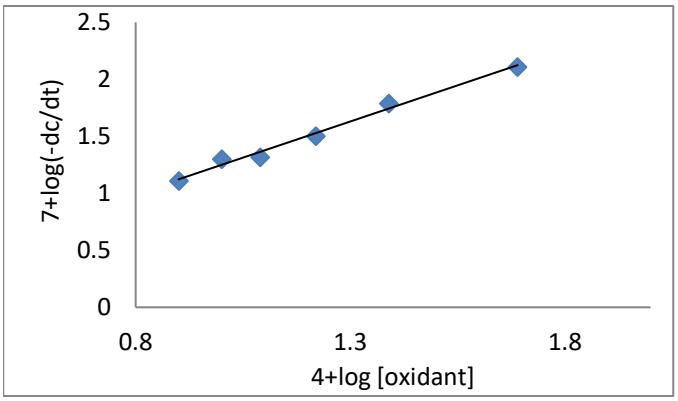


Fig. 1: Plot of log (-dc/dt) and log [$KBrO_3$] in oxidation of gabapentin

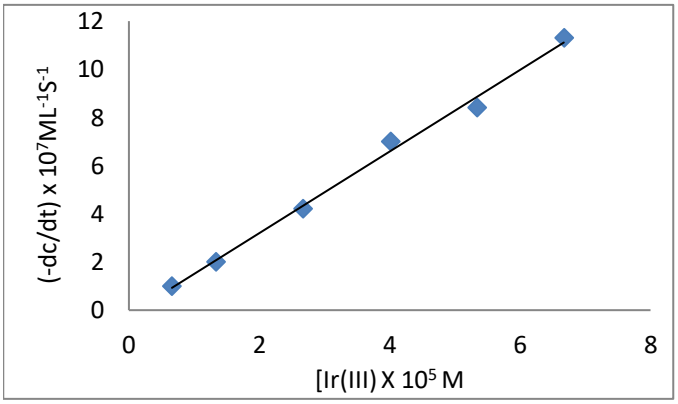


Fig. 2: Plot of (-dc/dt) and [Ir(III)] in oxidation of gabapentin

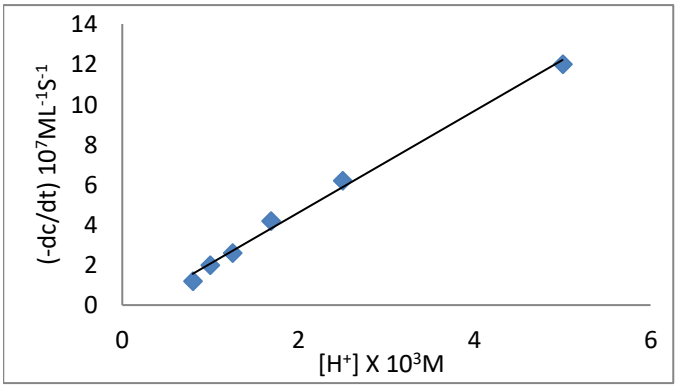


Fig. 3: Plot of (-dc/dt) and [H^+] in oxidation of gabapentin

substrate, indicating zero order in substrate i.e. gabapentin (Table-1). The rate of reaction increases as the concentration of Iridium (III) chloride is increased, It was observed that values of (-dc/dt) were doubled when the concentration of iridium(III) was made two times, showing first order dependence on $IrCl_3$ indicating first order of catalyst i.e. Ir(III) chloride (table-1). Kinetic result obtained on varying concentrations of chloride ions indicates fractional positive order of chloride ion, which implies that rate of reaction increases when the concentration of Cl^- is increased (Table 2). With increasing the concentration of [H^+], the value of reaction rate also increases (Table-2). This showed first order dependence of [H^+] on the rate of oxidation of gabapentin. The rate measurements were taken at 30^0-45^0C and specific rate constants were used to draw a plot of log k vs. 1/T which was linear (Fig-2). The value of energy of Activation (ΔE^*) Arrhenius factor (A), entropy of activation (ΔS^*) and free energy of activation (ΔG^*) were calculated from rate measurement at 30^0, 35^0, 40^0, 45^0C and these values have been recorded in Table-3. Moderate ΔH^* and ΔS^* values are favourable for electron transfer reaction. The value of ΔH^* was due to energy of solution changes in the transition state. The high positive values of change in free energy of activation (ΔG^*) indicates highly solvated transition state, while fairly high negative values of change in entropy of activation(ΔS^*) suggest the formation of an activated complex with reduction in the degree of freedom of molecule. Negligible effect of mercuric acetate excludes the possibility of its involvement either as a catalyst or as an oxidant because it does not help the reaction proceed without potassium bromate. Hence the function of mercuric acetate is to act as a scavenger for any [Br^-] ion formed in the reaction. It helps to eliminate the parallel oxidation by Br_2 which would have been formed as a result of interaction between Br^- and bromate ion. Potassium bromate has been used as an oxidant for a variety of compounds in acidic media (Natarajan and Venkatasubramaniam, 1969) sometimes in the presence of a catalyst. In alkaline and acidic medium, potassium bromate is ionised:

$$KBrO_3 \longrightarrow K^+ + BrO_3^-$$

The BrO_3^- species has been reported to act as an oxidising agent in acidic (Anandan and Gopalan, 1985) as well as in alkaline medium (Singh and Srivastava, 1991). Ir(III) chloride has been reported to give a number of possible chloro species dependent on pH of the solution. Under the experimental pH range in the present investigation $[Ir(Cl)_5(H_2O)]^{2-}$ has been proposed and confirmed as the reactive species dominant in the pH range 1.0 to 3.0. The kinetic results have been reported in Tables 1, 2 and 3.

Mechanism

Considering the reaction steps shown in **scheme 2** and applying the steady state treatment, with reasonable approximation, the rate law may be written as shown in equations below.

$$Rate = k_3[C_2][HBrO_3] \qquad (i)$$

$$[Ir(III)]_T = [C_1] + [C_2] \qquad (ii)$$

$$\frac{d[C_1]}{dt} = k_{-1}[C_2] - k_1[C_1][Cl^-] \qquad (iii)$$

$$[C_1] = \frac{k_{-1}[C_2]}{k_1[Cl^-]} \qquad (iv)$$

$$[C_1] = \frac{[C_2]}{K_1[Cl^-]} \qquad (v)$$

Where, $K_1 = k_1/k_{-1}$)

$$[Ir(III)]_T = [C_2]\left[\frac{1 + K_1[Cl^-]}{K_1[Cl^-]}\right]$$

$$[C_2] = \frac{[Ir(III)]_T K_1[Cl^-]}{1 + K_1[Cl^-]}$$

$$\frac{d[HBrO_3]}{dt} = \frac{k_2[H^+][BrO_3^-]}{k_{-2}[HBrO_3]}$$

$$[HBrO_3] = K_2[H^+][BrO_3^-]$$

Putting the values of [C_2] and [$HBrO_3$] in equation (i), we get :

$$Rate = \frac{K_1 K_2 k_3[Ir(III)]_T[Cl^-][H^+][BrO_3^-]}{1 + K_1[Cl^-]}$$

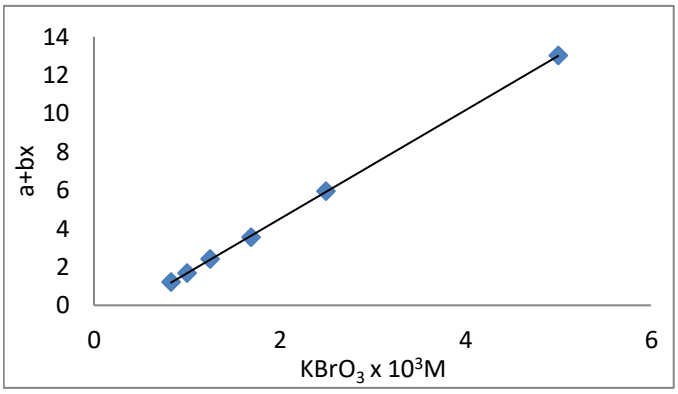


Fig. 4: Plot of (a+bx) and [$KBrO_3$] x 10^3 M in oxidation of gabapentin

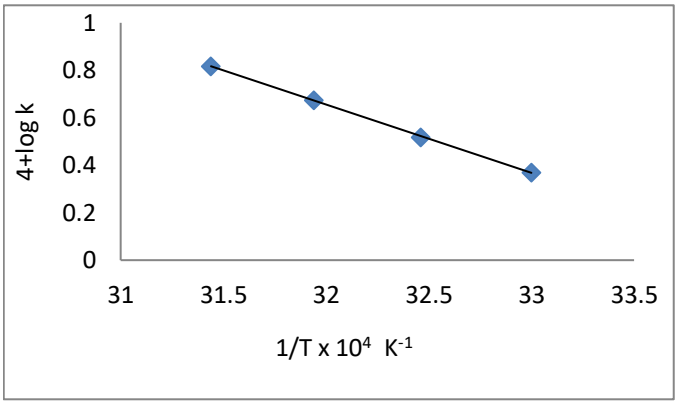


Fig. 5: Arrhenius plot for the oxidation of gabapentin

CONCLUSIONS

In the present study of kinetic and thermodynamic properties pharmaceutical drug (gabapentin) by potassium bromate ($KBrO_3$) in presence of Micro amount of Ir(III) chloride as catalyst in acidic medium. The following

Table 3: Activation parameters for Ir(III) chloride catalyzed oxidation of gabapentin by $KBrO_3$ at 35 ^{0}C

Parameters	Temperature(T^{0}C)	Gabapentine(-dc/dt)x 10^7
k_1 x 10^4s^{-1}	30^0	1.65
k_1 x 10^4s^{-1}	35^0	2.00
k_1 x 10^4s^{-1}	40^0	3.21
k_1 x 10^4s^{-1}	45^0	4.80
log A	...	12.02
Δ E* (k J mol^{-1})	35^0	69.13
Δ G* (k J mol^{-1})	35^0	74.83
Δ H * (k J mol^{-1})	35^0	73.47
Δ S* (JK^{-1}mol^{-1})	35^0	-18.392

conclusions can be drawn:

$[IrCl_6]^{3-}$ is considered as the reactive species of Ir(III) in acidic medium. $HBrO_3$ is the reactive species of potassium bromate in acidic medium. The stoichiometry of the reaction was found to be 2:1 and the oxidation products of gabapentin were identified. Activation parameters were computed from the Arrhenius plot. The observed results have been explained by a plausible mechanism and the related rate law has been derived.

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