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Microamount of Pd(II) Catalyzed Oxidation of Nuroleptic Drug (Gabapentin) by Potassium Bromated (KBrO3) in Perchloric (HClO4) Acid Medium : A Kinetic Study

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ABSTRACT

Here we investigated the kinetics of Pd(II) catalyzed oxidation of gabapentin by potassium bromate in acidic medium and in temperature range 30-45^{0}C. Potassium bromate shows excellent oxidant properties and first order kinetics is observed with respect to it. Oxidation rate is also found to be first order with respect to catalyst, Pd(II).The reaction is carried out in the presence of mercuric acetate as a scavenger for chloride ion. The experimental results show first order kinetics with respect to the catalyst Pd(II)] while zero order with respect to substrate, i.e., gabapentin was observed. The reaction shows negligible effect of [$Hg(OAc)_2$], and ionic strength of the medium. [H^+] and Chloride ion positively influence the rate of reaction. The reaction between potassium bromate and gabapentin in acid medium shows 1:2 stoichiometry. To calculate activation parameters, the reactions have been studied at four different temperatures between 30 to 45ºC. A mechanism involving the complex formation between catalyst and oxidant has been proposed. [1-carboxy cyclohexane1-acetic acid] acid has been identified chromatographically and spectroscopically as the final product of oxidation of gabapentin. Based on the kinetic data, reaction stoichiometry and product analysis, a reaction mechanism has been proposed and rate law has been derived

Keywords: Kinetics, Potassium Bromated , Gabapentin, Pd(II)

I. INTRODUCTION

Potassium bromate [Br(V)] is known to be a powerfull oxidizing agent with redox potentials of 1.44 V in acid medium and 0.61V in alkaline medium. It has widely been used in the oxidation of many organic compound[1-5] . The bromate species has been reported as an oxidizing agents in acidic as well as alkaline medium[2-3] .Earlier it was reported that bromide ion, formed by the reduction of BrO_3^- give rise to molecular bromate which sets Parallel oxidation of gabapentin. In order to obviate molecular bromine oxidation and to ensure pure bromated oxidation oxidation mercuric acetate, which is used as bromide ion scavenger[6] .was added to the reaction mixture. The kinetics of redox reactions involving homogeneous catalyst such as platinum group metals particularly osmium (VIII), Rh(III), Palladium(II) and ruthenium(III) have extensively been investigated from the mechanistic point of view. The mechanism of the reaction depends upon the nature of the oxidant, nature of the substrate and ways in which trasition metal complex ion play their role in order to promote the reactant molecules to the activated state before changing into the final products under experimental conditions. Palladium(II) chloride is the most important salt in the catalytic chemistry of palladium the kinetics for the oxidation of ethylene aqueous Pd(II) is the example[7-8] .Recently palladium(II) chloride [9-14] has been reported by several workers to be an effective catalyst under both acidic and alkaline medium conditions with suitable oxidizing agents. Hence the choice of Pd(II) chloride as a suitable catalyst for the present work has been considerd on the basis of following facts :

- ✓ Cu(II) catalyzes the reactions and is to be used in higher concentrations. Since it is also an oxidant ad liberates iodine, it's use may present some complications in iodometric titration.
- ✓ Ag(I) may cause greater complications in iodometric estimation because of its precipitation as halides.
- ✓ Osmium tetraoxide being toxic was avoided.

Pd(II) chloride is comparatively less costly and has no toxic character. In addition it does not initiate further oxidation of products under controlled condition. Another advantage of this catalyst lies in the fact that it is used in low concentration as 1.0 x 10^{-6}M. In solution and give effective result. Gabapentin (GBP), 2-[1-(aminomethyl)cyclohexyl]acetic acid, is a neuroleptic drug and is important due to its biological significance and selectivity towards the oxidant. Gabapentin has been used as anti-convulsant agent that is useful in the treatment of epileptic seizures [15-17]. It has also been shown to be a potential drug for treatment of neurogenic pain [18-19]. GBP was designed as γ-aminobutyric acid, but has subsequently been shown not to interact with any of the enzymes on the GBP metabolic pathway [20]. Furthermore, GBP has been used for the treatment of some mood disorders, anxiety and tardive dyskinesia. (a neurological syndrome caused by the long term use the neuroleptic drugs)

II. MATERIAL AND PROCEDURE

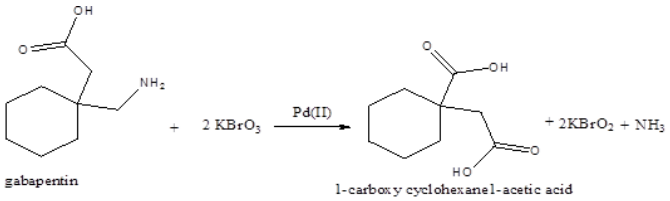
2.1. Materials:

Aqueous solution of palladium (II) chloride (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. Palladim di 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.

2.2. 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

III. DETMINATION OF STOICHIOMETRY AND PRODUCT ANALYSIS



The stoichiometry of the reaction was determined by equilibrating varying ratios of $KBrO_3$ and [GBP] at 35^0C 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 1760cm^{-1} and 1710cm^{-1} corresponds to two-C=O group and 3550 cm^{-1} corresponds to two –OH group clearly confirms 1-carboxy cyclohexane1-acetic acid.

IV. RESULT AND DISCUSSION

It was observed that the reaction do not proceed in the absence of Pd(II). For the determination of kinetics of the oxidation of paracetamol by $KBrO_3$ in an aqueous acidic medium in the presence of Pd(II) chloride was investigated at different initial concentration of all the reactants. It was observed that the reaction do not proceed in the absence of Pd(II). The initial rate (-dc/dt) in each kinetic run was calculated by the slope of tangent drawn at fixed time for the variation of [$KBrO_3$] while in the variation of other [reactants], tangents drawn at fixed [$KBrO_3$] which was written as [$KBrO_3^*$] (fig-1). The first order rate constant K_1 was calculated as

$$k_1 = \frac{-dc/dt}{[KBrO3]^*}$$

Each kinetic run was studied for two half lives of the reaction. The observed rates of reaction were reproducible with in ± 5% in replicate kinetic run. The order of reaction in each reactant was determined with the help of log-log plot of (-dc/dt) vs. Concentration of reactant. 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 substrate, indicating zero order in substrate i.e. gabapentin (Table-1). The rate of reaction increases as the concentration of Palladium (II) chloride is increased,(table-1). It was observed that values of (-dc/dt) were doubled when the concentration of Pd(II) was made two times, showing first order dependence on $PdCl_2$ indicating first order of catalyst i.e. Pd(II) chloride.(fig-2) 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 (fig-3). 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-4).

V. ROLE OF ENTROPY OF ACTIVATION AND OTHER ACTIVATION PARAMETERS

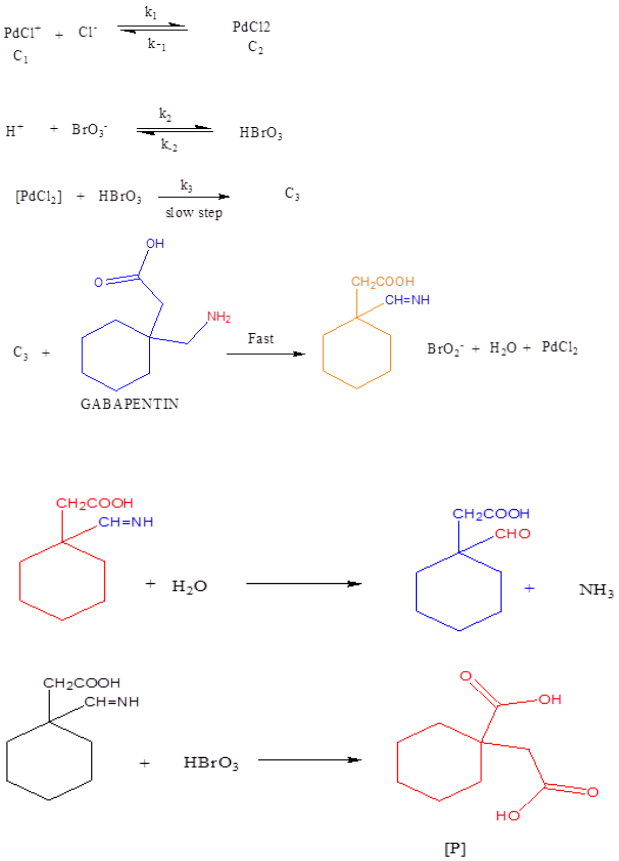
The value of energy of Activation (ΔE*) Arrhenius factor (A), entropy of activation (ΔS*) and free energy of activation (ΔG*) were calculated from rate measurement at 30^0, 35^0, 40^0, 45^0C and these values have been recorded in Table-3. Moderate ΔH* and ΔS* values are favourable for electron transfer 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. The observed modest enthalpy of activation and a higher rate constant for the slow step indicates that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by earlier observations [21]. 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 [22]. The activation parameters evaluated for the catalyzed and uncatalyzed reaction explain the catalytic effect on the reaction. Entropy of activation plays an important role in the case of reaction between ions or between an ion and a neutral molecule or a neutral molecule forming ions. When reaction takes place between two ions of opposite charges, their union will results in a lowering of net charge, and due to this some frozen solvent molecules will released with increase of entropy but on the other hand when reaction takes place between two similarly charged species, the transition state will be more highly charged ion and due to this, more solvent molecules will be required for seprate the ions, leading to decrease the entropy.

VI. MECHANISM AND RATE LAW

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 (Srivastava, S., (1999). 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 as well as in alkaline medium (Singh and Srivastava, 1991). Pd(II) chloride has been reported to give a number of possible chloro species dependent on pH of the solution. The kinetic results have been reported in Tables 1, 2 and 3.



Considering the above reaction steps and applying the steady state treatment, with reasonable approximation, the rate law may be written as equation.

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

$$[Pd(II)]_T = [C_1] + [C_2] \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (ii)$$

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

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

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

(*where* $K_1 = k_1/k_{-1}$)

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

$$[C_2] = \frac{[Pd(II)]_T\,K_1\,[Cl^-]}{1 + K_1\,[Cl^-]}$$

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

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

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

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

VII. CONCLUSION

Oxidation of Gabaentin by $KBrO_3$ does not proceed in the absence of catalyst, but it becomes facile in the presence of Pd(II) catalyst. The reactive species of oxidant and catalyst have been identified. Oxidation products were identified and activation parameters were evaluated. The observed results have been explained by a plausible mechanism and the related law has been deduced. Therefore, it can be concluded that Pd(II) acts as an efficient catalyst for the oxidation of Gabapentin. In the present study A kinetic and Mechanistic investigation on Pd(II) catalyzed oxidation of Gabapentin by potassium bromate ($KBrO_3$) in presence of $HClO_4$ acid medium : A kinetic study has been performed and following conclusions drawn:

- ✓ $[PdCl]^+$ is considered as the reactive species of Pd(II) 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.

VIII. REFERENCES

[1]. Singh, A.K.; Singh, A.K.; Singh, V.; Rahmani, S.; Ashish,; Singh, B. Ruthenium(III) catalyzed oxidation of diethanolamine and triethanolamine

by Br (V) in presence of perchloric acid: A kinetic and mechanistic study. J. Chem.Res., 2006, 8, 56-63.
[2]. Ashish,; Singh, S.P.; Singh, A.K.; Singh, B. Mechanistic study of osmium(VIII)promoted oxidation of crotonic acid by aqueous alkaline solution of potassium bromate. Transit. Metal Chem., 2005, 30, 610- 615
[3]. Singh, B.; Srivastava, S. Kinetics and mechanism of ruthenium tetroxide catalysed oxidation of cyclic alcohols by bromate in a base. Transit. Metal Chem., 1991, 16, 466-468.
[4]. Desai, S.M.; Halligudi, N.N.; Nandibewoor, S.T. Kinetics of osmium(VIII) catalyzed oxidation of allyl alcohol by potassium bromate in aqueous acidic medium-autocatalysis in catalysis. Int. J. Chem. Kinet., 1999, 31, 583-589.
[5]. Desai, S.M.; Halligudi, N.N.; Nandibewoor, S.T. Kinetics and mechanism of ruthenium(III)-catalysed oxidation of allyl alcohol by acid bromate-autocatalysis in catalysis. Transit. Metal Chem., 2002, 27, 207-212.
[6]. Bailar, J.C. The Chemistry of Coordination Compounds. Reinhold:New York, 1956, p. 4.
[7]. Jagadeesh, R. V. Puttaswamy. Ru(III), Os(VIII), Pd(II), and Pt(IV) catalysed oxidation of glycyl_glycine by sodium N-chloro ptoluenesulfonamide:Comparative mechanistic aspects and kinetic modeling. J. Phys. Org. Chem. 2008; 21(10): 844–858.
[8]. Henry, P. M. Palladium (II) Catalysed Oxidation of Hydrocarbons. D. Reidal Publishing Company: Dordrecht, The Netherlands. 1980; 2
[9]. Ashish, A.K. Singh, B. Singh; Ind. J. Chem., Vol. 43A, 1645-1653 (2004).
[10]. A. Shukla, S. Gupta, S.K. Upadhyay; Int. J. Chem. Kinet., 23, 279-288 (1991).
[11]. A.K. Singh, D. Chopra, S. Rahmani, V. Singh; Carbohydrate Res., Vol. 341, 397-409 (2006).
[12]. P.M. Henry, D. Reidal Publishers Company, Vol. 2, 11-12, (1980).
[13]. A.K. Singh, V. Singh, Ashish, J. Srivastava; Ind. J. Chem., Vol. 45A, 599-608 (2006).
[14]. A.K. Singh, T. Gupta, V.K. Singh, B. Singh; J. Mol. Cata.; Vol. 197, 91-100 (2003).
[15]. Taylor CP , New Trends in Epilepsy Management, edited by D Chadwick, Royal Society of Medicine Services,London,1993,13-40.
[16]. Jensen AA, Mosbacher J , Elg S. The Anticonvulsant Gabapentin (Neurontin) Does Not Act through γ-Aminobutyric Acid-B Receptors. Mol Pharmacol. 2002; 61:1377-
[17]. 1384.
[18]. Mahesh RT, Bellakki MB, Nandibewoor ST. Spectral and Mechanistic Study of the Ruthenium(III) Catalysed Oxidation of Gabapentin (Neurontin) by Heptavalent Manganese: A Free Radical Intervention. Catal Lett. 2004;97:91-98.
[19]. Singh L, Field MJ, Ferris P ,Hunter JC, Oles RJ, Williams RG, Woodruff GN. The antiepileptic agent gabapentin (Neurontin) possesses anxiolytic-like and antinociceptive actions that are reversed byd-serine. Psycopharmacol Berl. 1996;127:1-7.
[20]. Rosner H, Rubin L, Kestenbaum A. Gabapentin Adjunctive Therapy in Neuropathic Pain States Clin J Pain. 1996;12:56-58.
[21]. Taylor CP. Pharmacologic Intervention. Neurology. 1994;44:S10-S13.
[22]. Lewis, E. S. Investigation of Rates and Mechanism of Reactions in Techniques of Chemistry, A Weissberger, Ed.; Wiley: New York, 1974, p.421.
[23]. Onkar, A. S.; Naik, P. N.; Gunagi, S.D.; Nandibewoor S.T.; Chimatadar, A.S. Kinetics and mechanism of oxidation of tyrosine by vanadium (V) in aqueous hydrochloric and ethanoic acid medium . Ind. J. Chem. 2012, 51A, 1574-1579.

Table 1. Effect of variation of oxidant($KBrO_3$), substrate(Gabapentin), catalyst [Pd(II)] chloride at 35^{0}C

Oxidant x 10^3M (Potassium bromate)	[Substrate]x 10^2M (Gabapentin)	[Pd(II)Cl_2] x 10^5M Palladium chloride	(-dc/dt)x10^7ML^{-1}s^{-1}
0.80	1.00	11.20	1.03
1.00	1.00	11.20	1.27
1.25	1.00	11.20	1.60
1.69	1.00	11.20	2.15
2.50	1.00	11.20	3.20
5.00	1.00	11.20	6.30
1.00	0.40	11.20	1.22
1.00	0.50	11.20	1.10
1.00	0.66	11.20	1.32
1.00	1.00	11.20	1.27
1.00	2.00	11.20	1.13
1.00	4.00	11.20	1.00
1.00	1.00	5.60	0.62
1.00	1.00	11.20	1.27
1.00	1.00	16.80	1.82
1.00	1.00	22.40	2.45
1.00	1.00	33.60	3.66
1.00	1.00	44.80	4.95
1.00	1.25	1.00	1.35
1.00	1.69	1.00	1.66
1.00	2.50	1.00	2.45
1.00	5.00	1.00	3.92
1.00	1.00	0.80	2.00
1.00	1.00	1.00	1.27
1.00	1.00	1.25	1.80
1.00	1.00	1.67	1.88
1.00	1.00	2.50	1.00
1.00	1.00	5.00	1.22

Solution Condition: [$HClO_4$] = 1.00 X 10 $^{-3}$ M, [KCl] = 1.00 X 10 $^{-3}$ M , [$Hg(OAC)_2$] = 1.25 X 10 $^{-3}$ M

Solution Condition: [Oxidant ($KBrO_3$)] = 1.00 X 10^{-3} M, [Gabapentin(Gb)] = 1.00 X 10^{-2} M, [Pd (II) Chloride] = 11.2 X 10^{-5} M

Table 2. Effect of variation of reactant [$HClO_4$], [KCl], [$Hg(OAc)_2$] 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	1.00
1.00	1.00	1.00	1.27
1.25	1.00	1.00	1.62
1.67	1.00	1.00	2.10
2.50	1.00	1.00	3.05
5.00	1.00	1.00	6.15
1.00	0.80	1.00	1.15
1.00	1.00	1.00	1.27

Table 3. Activation parameters for Pd(II) chloride catalyzed oxidation of gabapentin by $KBrO_3$ at 35^{0}C

Parameter	Temperature (T^{0}C)	Gabapentin(-dc/dt)x 10^7
k_1 x 10^4s^{-1}	30^0	1.01
k_1 x 10^4s^{-1}	35^0	1.27
k_1 x 10^4s^{-1}	40^0	1.80
k_1 x 10^4s^{-1}	45^0	2.42
log A	...	9.51
Δ E* (k J mol^{-1})	35^0	55.25
Δ G* (k J mol^{-1})	35^0	76.12
Δ H * (k J mol^{-1})	35^0	55.52
Δ S* (JK^{-1}mol^{-1})	35^0	-66.82

Solution Condition: [Pd(II)] = 11.2 x 10-5 M, [KBrO3] = 1.00 x 10-3 M,
Gabapentin = 1.00 x 10-2 M, [Hg(OAc)2] = 1.25 x 10-3 M,[HClO4] = 1.00 x 10-3 M, [KCl] = 1.00 x 10-3 M

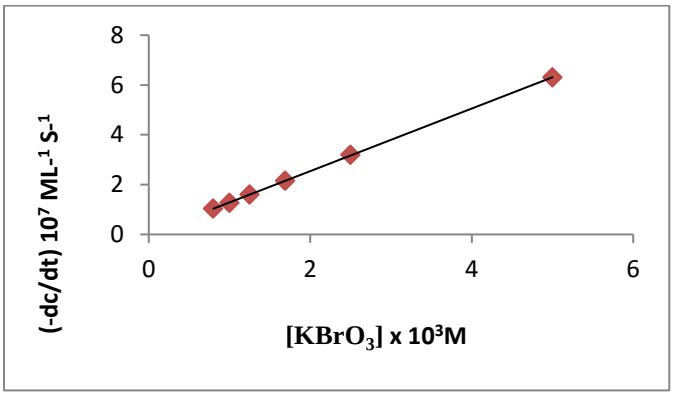


Figure 1. Plot between rate of reaction (dc/dt) vs [$KBrO_3$] for the oxidation of gabapentin at 35^{0}C. [$HClO_4$] = 1.00 X 10 ^{3} M, [KCl] = 1.00 X 10 ^{3} M, [$Hg(OAc)_2$] = 1.25 X 10 ^{3}M, Gabapentin [GB] = 1.00 x 10 ^{2} M, [Pd(II)CI_2] = 11.2 x 10 ^{5} M

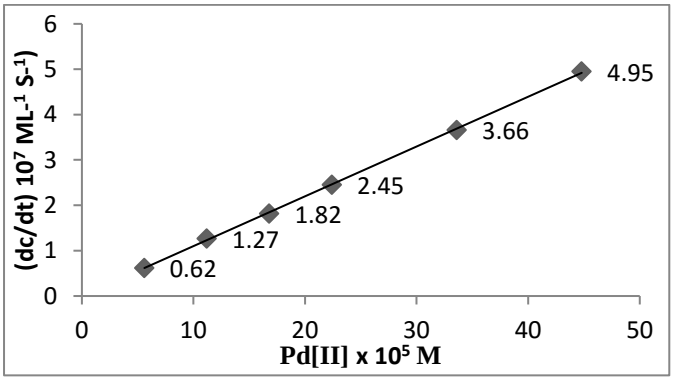


Figure 2. Plot between rate of reaction (-dc/dt) vs [Pd(II)] on the reaction rate at 35^{0}C. [$HClO_4$] = 1.00 X 10 ^{3}M, [KCl] = 1.00 X 10 ^{3} M, [$Hg(OAc)_2$] = 1.25 X 10 ^{3} M , [$KBrO_3$] = 1.00 X 10^3 M , [Gabapentin(GB)] = 1.00 X 10^2 M

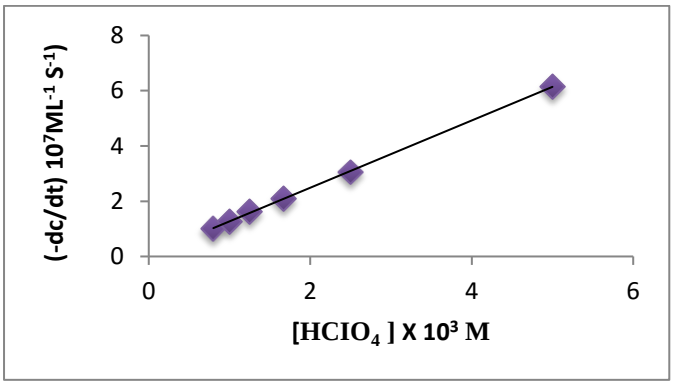


Figure 3. Plot between rate of reaction (-dc/dt) vs [$HClO_4$] for the oxidation of paracetamol at 35^{0}C. [Pd(II) Chloride] = 11.2 X 10^5 M, [KCl] = 1.00 X 10 ^{3} M, [$Hg(OAc)_2$] = 1.25 X 10 ^{3} M , [Oxidant ($KBrO_3$)] = 1.00 X 10^3 M, [Substrate(GB)] = 1.00 X 10^2 M

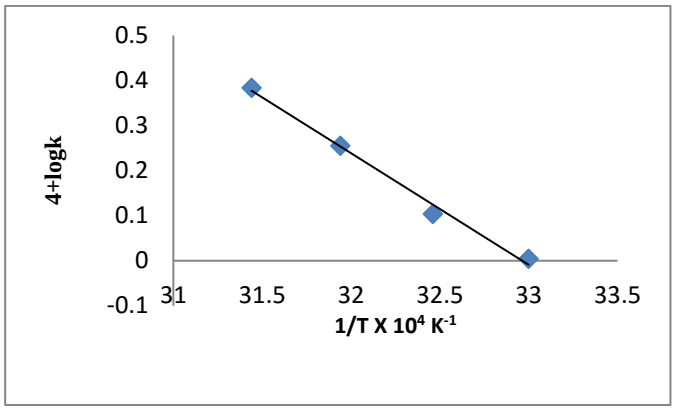


Figure 4. Arrhenius plot of the oxidation of paracetamol on the reaction rate at 35^{0}C .[Pd(II) Chloride] = 11.2 x 10^5 M, [KCl] = 1.00 x 10 ^{3} M, [$Hg(OAc)_2$] = 1.25 x 10 ^{3} M [Oxidant ($KBrO_3$)] = 1.00 x 10^3 M, [Gabapentin] = 1.00 X 10^2 M, [$HClO_4$] = 1.00 X 10 ^{3} M