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OXIDATION OF PREGABALIN BY POTASSIUM DICHROMATE IN ACID MEDIUM: A KINETIC AND MECHANISTIC STUDY

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ABSTRACT

Kinetics of oxidation of pregabalin using potassium dichromate as oxidizing agent in acid medium was studied spectrophotometrically at 520 nm. The result interprets that rate of oxidation is first order with respect to potassium dichromate and fractional order with respect to pregabalin where as it does not depend on the concentration of acid. The stoichiometry of the reaction was found that two moles of oxidant is consumed for oxidation of three moles of pregabalin and the product found is 2(2-methyl propyl) butan-di-oic acid. From the results of kinetic studies, reaction stoichiometry and product analysis, the reaction is proposed with suitable mechanism. Based on results of the reaction at different temperatures, the activation parameters with respect to the slow step of the proposed mechanism was calculated.

KEYWORDS: Kinetics, Oxidation, Pregabalin, Potassium Dichromate, Mechanism.

INTRODUCTION

The pregabalin is used to treat epilepsy, neuropathic pain, fibromyalgia and anxiety disorder. It is a GABAergic anticonvulsant and depressant of the central nervous system. Epilepsy is a group of neurological diseases characterized by epileptic seizures. Pregabalin is an important anti-epileptic drug. Chemically it is (S)- 3-(aminomethyl)- 5- methyl haxanoic acid.[1] It binds with high affinity to the alpha 2-delta site in central nervous system tissues.[2] It is a potent anti-epileptic drug also called as 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 associated with spinal cord injury.[3] Literature survey indicates

that no one has studied kinetics of oxidation of pregabalin with potassium dichromate in acid medium. S Dakshayani and Puttaswamy studied the kinetics of oxidation of pregabalin with catalytic activity of ruthenium chloride and osmium tetraoxide and oxidant chloramine-T. Also N Suresha et al studied kinetics of oxidation of pregabalin with same oxidant and ruthenium chloride catalyzed and uncatalyzed reactions. Oxidation of pregabalin with potassium dichromate in acid medium is studied kinetically. Chromium, permanganate ions in various forms are used as powerful oxidizing agent in organic and inorganic oxidation in polar media.[4] Chromium has frequently and extensively been employed as an oxidizing agent both for preparative as well as analytical methods in chemistry. Chromic acid, aqueous dichromate, chromyl chloride, chromyl acetate and other substituted chromates have been employed in oxidation of organic as well as inorganic compounds in aqueous acid and alkaline media.[5-9] It is the reason for which the analytical chemists in general and kineticists in particular are attracted to know more about such an interesting chemistry of this reagent.

MATERIALS AND METHODS

Potassium dichromate and pregabalin is of analytical grade of purity supplied by local company. The stock solution of potassium dichromate was obtained by dissolving a known weight of it in double distilled water. The standard solution of pregabalin was freshly prepared with double distilled water. The oxidation of pregabalin by potassium dichromate was followed under pseudo-first order conditions where concentration of pregabalin was excess over concentration of dichromate at 30^{o}C. The reaction was initiated by mixing the required quantities of solutions of substrate and reagents with sulphuric acid. The unreacted dichromate was analyzed spectrophotometrically.

Stoichiometry and Product analysis: Different reaction mixtures containing different concentrations of pregabalin with excess concentration of potassium dichromate in sulphuric acid were kept for 48 hours for completion of reaction. The unreacted potassium dichromate was determined spectrophotometrically at 520nm. The stoichiometry of the reaction was found that two mole of oxidant is consumed for oxidation of three moles of pregabalin. Hence following equation is confirmed.

$$2K_2Cr_2O_7 + 8H_2SO_{4(aq)} + 3C_8H_{17}O_2N \rightarrow 3C_8H_{14}O_4 + 2K_2SO_4 + 2(Cr_2SO_4)_3 + 8H_2O + 3NH_3$$

The reaction product was confirmed by using reaction mixture containing 0.1 mol dm^{-3}, 0.2 mol dm^{-3} potassium dichromate and 0.1 mol dm^{-3} sulphuric acid. The reaction mixture was allowed to stand for 48 hours for completion of the reaction. The reaction mixture was

extracted with ether. The ether layer was neutralized using sodium bicarbonate and washed with distilled water. The ether layer was evaporated and dried to get product. The product was identified as 2(2-methyl propyl) butan-di-oic acid. It is confirmed by spot tests.[10]

RESULTS AND DISCUSSIONS

To study the effect of concentration change of pregabalin, potassium dichromate and sulphuric acid on oxidation at room temperature using UV-Visible spectrophotometer different concentrations of these substances were used and results were analyzed to calculate kinetic parameters.

Effect of substrate concentration

In this study the concentration of pregabalin was varied from $1x10^{-2}$ to $7x10^{-2}$ mol dm^{-3} keeping all other conditions constant. Figure 1 represents plot of 3+log [PGN] versus $5+logk_{obs}$ of pregabalin. The rate constant was found to be increasing with increase in concentration of pregabalin with slope less than unity with other conditions remaining constant indicating fractional order rate of the reaction with respect to pregabalin.

Table. 1: [PGN] mol $dm^{-3}$and $k_{obs.}$

[PGN] mol dm^{-3}	0.01	0.02	0.03	0.04	0.05	0.06	0.07
k_{obs} x 10^{-4} s^{1-}	3.9	4.3	4.9	5.3	5.6	6.1	6.8

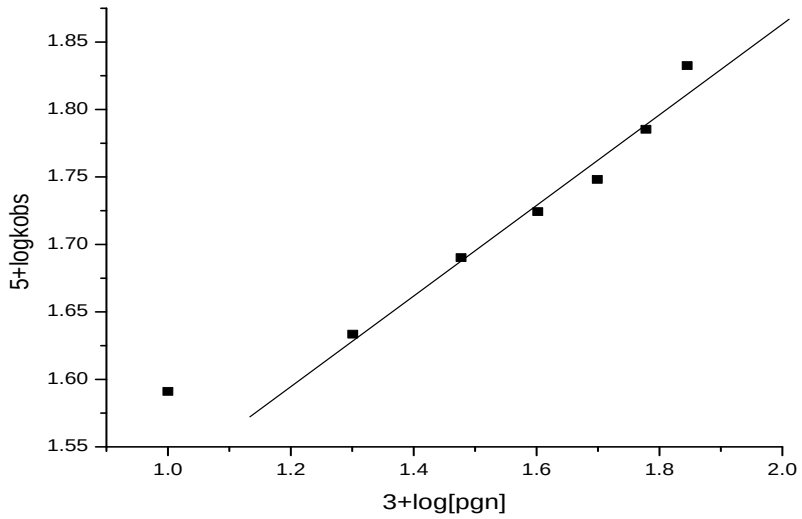

Fig. 1: Graph of 3+log [PGN] versus $5+logk_{obs}$ of Pregabalin.

Effect of Potassium Dichromate concentration: Concentration of potassium dichromate was varied from $1x10^{-3}$ to $7x10^{-3}$ mol dm^{-3} keeping all other conditions constant. The k_{obs} values showed an increase with the increase in concentration of potassium dichromate and

giving a linear graph with line passing nearly through origin indicating first order dependence of the rate of the reaction on concentration of potassium dichromate.

Table. 2: [PDF] mol $dm^{-3}$and $k_{obs.}$

[PD] mol dm^{-3}	0.001	0.002	0.003	0.004	0.005	0.006	0.007
k_{obs} x 10^{-4} s^{1-}	3.5	3.7	3.8	3.9	4.1	4.3	4.5

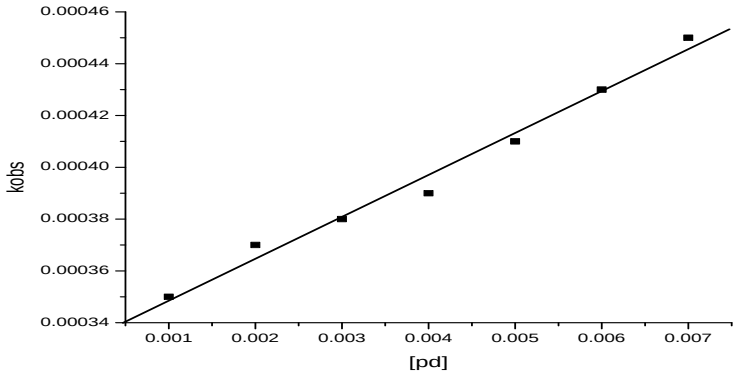

Fig. 2: Graph of concentration of potassium dichromate versus $k_{obs.}$

Effect of Temperature: Variation of temperature change on the rate of oxidation of pregabalin was studied by conducting kinetic runs at different temperatures ranging from 298, 303, 308, 313 and 318K keeping all other experimental conditions constant i.e. [PGN], [PD] and [H^+]. The result shows increase in rate of reaction with the increase in temperature table 3. From the linear Arrhenius plots of 5+logk versus 1/T activation parameters were calculated and tabulated in table 4.

Table. 3: 5+log k_{obs} at different temperatures.

Temperature K	298	303	308	313	318
5+log k_{obs} s^{1-}	1.724276	1.778151	1.819544	1.869232	1.903090

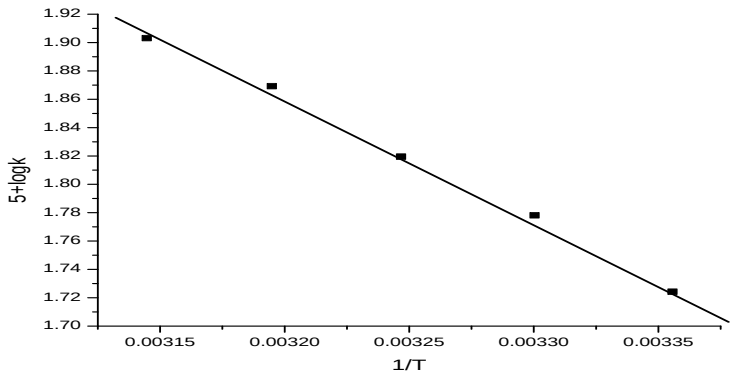

Fig. 3: Graph of 1/T versus 5+log k.

Table. 4: Activation Parameters.

Activation Parameters	Ea	ΔH	ΔS	ΔG
	16.459 $kJmol^{-1}$	13.8565 $kJmol^{-1}$	-262.96 $JK^{-1}mol^{-1}$	96.148 $kJmol^{-1}$

Effect of acid concentration: The oxidation of pregabalin with potassium dichromate was studied with different concentrations of sulphuric acid keeping all other conditions of the reaction constant. There is increase in the rate constant with increasing sulphuric acid concentrations. The plot of $log[H^+]$ versus log k_{obs} is linear with slope less than unity indicating fractional order rate of the reaction with respect to acid.

Table. 5: k_{obs} at different acid concentrations.

$[H^+]$ mol dm^{-3}	0.1	0.2	0.3	0.4	0.5	0.6	0.7
k_{obs} x 10^{-4} s^{1-}	3.5	3.6	3.8	4.0	4.1	4.3	4.4

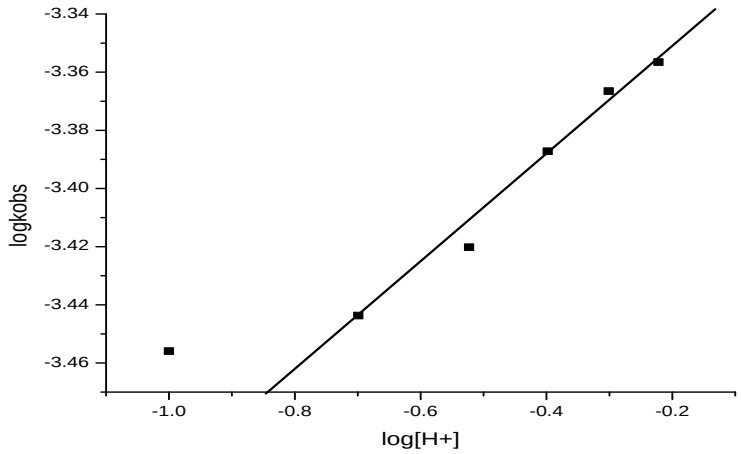

Fig. 4: $log[H^+]$ versus log k_{obs}.

Free radical test: In the reaction mixture aqueous solution of acrylonitrile was added. It does not show initiation of polymerization reaction indicating non-involvement of free radical in the reaction sequences.

Effect of Salts added

Different salts were added to study the effect of salt on the rate of oxidation of pregabalin with potassium dichromate. Sodium chloride (NaCl), potassium chloride (KCl), potassium bromide (KBr) and magnesium chloride ($MgCl_2$) these salts were added to the oxidation reaction at 298K. It is found that the added salt has no effect on the rate of oxidation of pregabalin and so there is no interaction of charged species during the reaction.

Table. 6: k_{obs} of different salts at various concentration.

[PD]	[PGN]	[H+]	[NaCl]	[KCl]	[KBr]	[MgCl2]	K_{obs} x 10^{-4} s^{-1}
0.001	0.01	0.1	0.1	-	-	-	3.6
0.001	0.01	0.1	0.2	-	-	-	3.6
0.001	0.01	0.1	0.3	-	-	-	3.7
.0.001	0.01	0.1	0.4	-	-	-	3.7
0.001	0.01	0.1	-	0.1	-	-	3.5
0.001	0.01	0.1	-	0.2	-	-	3.5
0.001	0.01	0.1	-	0.3	-	-	3.6
0.001	0.01	0.1	-	0.4	-	-	3.6
0.001	0.01	0.1	-	-	0.1	-	3.5
0.001	0.01	0.1	-	-	0.2	-	3.6
0.001	0.01	0.1	-	-	0.3	-	3.6
0.001	0.01	0.1	-	-	0.4	-	3.6
0.001	0.01	0.1	-	-	-	0.1	3.6
0.001	0.01	0.1	-	-	-	0.2	3.6
0.001	0.01	0.1	-	-	-	0.3	3.7
0.001	0.01	0.1	-	-	-	0.4	3.7

Mechanism of the oxidation of Pregabalin

$$Cr_2O_7^{-2} + 2H^+ \leftrightarrows 2HCrO_4$$

$$2HCrO_4^- \overset{K1}{\leftrightarrows} CrO_4^{2-} + 2H^+ \quad (I \text{ fast})$$

$$HCrO_4^- + PGN \overset{K2}{\leftrightarrows} C \quad (II \text{ fast})$$

$$C \overset{k}{\rightarrow} C' \quad (III \text{ slow \& r.d.s.})$$

$$C' \rightarrow \text{Products} \quad (IV \text{ fast})$$

Scheme-1.

In scheme-1 (C) and (C$^{/}$) are intermediates in II and III steps of the mechanism of the oxidation of pregabalin. In the first step chromic acid undergoes deprotonation in equibrilium to give CrO_4^{2-}. In second step CrO_4^{2-} reacts with pregabalin to form an intermediate chromate ester (C). The chromate ester (C) gets converted to an imine an intermediate (C$^{/}$). The imine on acid hydrolysis gives final product. The structures of these intermediates are shown in scheme-2.

$$HCrO_4^- + H^+ \overset{K1}{\leftrightarrows} H_2CrO_4$$

$$R—CH_2—NH_2 + O=CrO_3^{2-} \overset{K2}{\leftrightarrows} R—CH_2—NH_2—O—CrO_3^{2-} \quad (C)\ (Chromate\ Ester)$$

$$R—CH_2—NH_2—O—CrO_3^{2-}\ (C) \rightarrow R—CH_2—NH_2^+—O^- \rightarrow R—CH_2—NH—OH$$

$$R—CH_2—NH—OH \overset{k}{\rightarrow} R—CH=NH \quad (C') \quad (Intermediate)$$

$$R—CH=NH\ (C') + H—HSO_4^- \rightarrow R—CH=NH_2^+---HSO_4^- + H_2O$$

$$R—CH=NH_2^+---HSO_4^- + H_2O \rightarrow R—CH—(O^+H_2)--NH_2 + HSO_4^-$$

$$R—CH—(OH)—NH_3^+ \rightarrow R—CH=OH^+$$

$$R—CH=OH^+ + H_2O \rightarrow R—CH—(O^+H_2)—OH$$

$$R—CH—(O^+H_2)—OH \rightarrow R—CH—(OH)—OH + H^+$$

$$R—CH—(OH)—OH \rightarrow R—COOH \quad (P) \quad (Product)$$

$$[R = -CH_3—CH(CH_3)—CH_2—\underset{|}{CH}—CH_2COOH]$$

Scheme-2.

Rate law expression

As per the mechanism explained in scheme-2, we get

$$K_1 = \frac{[H_2CrO_4]}{[HCrO_4^-] + [H^+]} \quad [H_2CrO_4] = K_1\,[HCrO_4^-]\,[H^+] \qquad (1)$$

$$K_2 = \frac{[C]}{[PGN] + [H_2CrO_4]} \quad [C] = K_2\,[PGN] + [H_2CrO_4]$$

$$[C] = K_1\,K_2\,[PGN]\,[HCrO_4^-]\,[H^+] \qquad (2)$$

From step (III) of scheme-1 we can write

$$Rate = \frac{-d[HCrO_4^-]}{dt} = k[C] \qquad (3)$$

Substituting equation (2) in equation (3), we get,

$$Rate = kK_1\,K_2\,[PGN]\,[HCrO_4^-]\,[H^+] \qquad (4)$$

The total concentration of $HCrO_4^-$ is given by

$$[HCrO_4]_T = [HCrO_4^-] + [H_2CrO_4] + [C] \quad (5)$$

($_T$- stands for total concentration of $HCrO_4^-$)

Substituting the value of equation (2) in equation (5) we get

$$[HCrO_4^-]_T = [HCrO_4^-] + K_1 [HCrO_4^-] [H^+] + K_1 K_2 [PGN] [HCrO_4^-] [H^+] \quad (6)$$

Rearranging the equation (6)

$$[HCrO_4^-]_T = [HCrO_4^-] (1 + K_1 [H^+] + K_1 K_2 [PGN] [H^+]) \quad (7)$$

$$[HCrO_4^-] = \frac{[HCrO_4^-]_T}{1 + K_1 [H^+] + K_1 K_2 [PGN] [H^+]} \quad (8)$$

Substituting equation (8) in equation in equation (4) we get

$$\text{Rate} = \frac{kK_1 K_2 [PGN] [HCrO_4^-] [H^+]}{1 + K_1 [H^+] + K_1 K_2 [PGN] [H^+]} \quad (9)$$

Under pseudo-first order condition,

$$\text{Rate} = \frac{-d[HCrO_4^-]}{dt} = k_{obs} [HCrO_4^-] \quad (10)$$

On comparing equation (9) & (10) we get,

$$k_{obs} = \frac{kK_1 K_2 [PGN] [H^+]}{1 + K_1 [H^+] + K_1 K_2 [PGN] [H^+]} \quad (11)$$

Rearranging the terms in equation (11) we get,

$$\frac{1}{k_{obs}} = \frac{1 + K_1 [H^+] + K_1 K_2 [PGN] [H^+]}{kK_1 K_2 [PGN] [H^+]}$$

$$\frac{1}{k_{obs}} = \frac{1}{kK_1 K_2 [PGN] [H^+]} + \frac{1}{k K_2 [PGN]} + \frac{1}{k} \quad (12)$$

From equation (12) we can conclude that the graph of 1/[PGN] versus 1/ k_{obs} should give straight line with positive intercept and is confirmed from the figure 5.

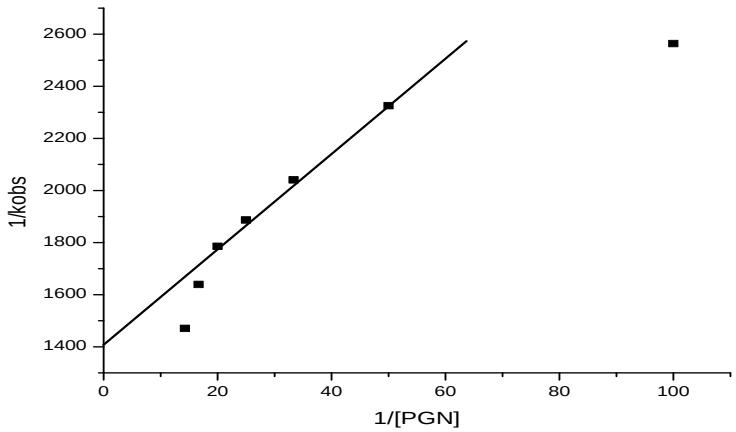

Figure. 5: 1/[PGN] versus $1/k_{obs.}$

CONCLUSION

The kinetic study of oxidation of pregabalin with potassium dichromate shows that pregabalin undergoes oxidation in acid medium to give 2(2-methyl propyl) butan-di-oic acid as the main product. The rate of the reaction is first order with respect to oxidant, fractional order with respect to substrate and acid. There is no effect of salts added means there is no reaction of the ions and there is no free radical formation during oxidation reaction. In redox reactions of chromium (VI) in acid media there are two suggested reaction mechanisms for electron transfer, the first one was proposed to involve a successive one-electron transfer in two steps.[11] The second suggested mechanism was a simultaneous two-electron transfer in a single step. During redox reaction both mechanisms can be considered i.e. Cr (VI) converted either to Cr (V) or Cr (IV).[12]

In this study as the free radical test is negative the formation of Cr (V) is neglected. Similarly chromium (VI) found to exist in aqueous acid media mainly as acid chromate shown in scheme 1.[13] The reaction between potassium dichromate and pregabalin takes place through the complex formation as order with respect to pregabalin is less than unity. It is also proved by the plot of 1/[PGN] versus $1/k_{obs}$ giving straight line with intercept on y-axis, figure 5.[14] The complex formation between chromium (VI) and different substrates was reported earlier.[15]

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