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Oxidative Degradation of Rasagiline By Dichromate In Acid Medium: A Kinetic Study

Sayyed Hussain^{1*} and Syed Yousuf Hussain²

¹Sir Sayyed College Aurangabad, Maharashtra, India 431001

², Kohinoor Arts, Commerce & Science College Khuldabad, Dist.Aurangabad, Maharashtra,
India 431101

ABSTRACT

Kinetics of oxidation of rasagiline using potassium dichromate as oxidizing agent in acid medium was studied spectrophotometrically at 520 nm. Rasagiline is used for the treatment of parkinson's disease. The result reveals that rate of oxidation is first order with respect to potassium dichromate and rasagiline 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 onemole of rasagilineand the product found is (2,3-dihydro-1*H*-inden-1-ylamino)acetic acid. From the results of kinetic studies, reaction stoichiometry and product analysis with suitable mechanism of the reaction was proposed. 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, Rasagiline, Potassium Dichromate

***Corresponding Author**

Dr. SayyedHussain

Associate Professor

Department of Chemistry

Sir Sayyed College Aurangabad

Maharashtra- 431001

Email ID- dshinorgchem@gmail.com Mob No. 9923320201

INTRODUCTION

The rasagiline is a selective dopamine receptor antagonist. It is an antiemetic and gastroprokinetic agent. It increases movement through the digestive system. It is used to treat symptoms of stomach disorders. It may also be used to prevent nausea and vomiting. Oxidation of rasagiline with potassium dichromate is studied kinetically. Chromium, permanganate ions in various forms are used as powerful oxidizing agents in organic and inorganic oxidation in polar media.¹ Chromium has frequently and extensively been employed as an oxidizing agent both for preparative as well as analytical methods in chemistry.^{2,3} 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.^{4,5,6} It is the reason for which the analytical chemists and kineticists are attracted to know more about such an interesting chemistry of this reagent. Literature survey reveals that no work is reported on oxidation of rasagiline with any oxidizing agent.

MATERIALS AND METHODS

Potassium dichromate and rasagiline 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 rasagiline was freshly prepared with double distilled water. The oxidation of rasagiline by potassium dichromate was followed under pseudo-first order conditions where concentration of rasagiline was excess over concentration of dichromate at 303K.⁷ 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 rasagiline 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 moles of oxidant is consumed for oxidation of one mole of rasagiline. Hence following equation is confirmed.



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 (2,3-dihydro-1*H*-inden-1-ylamino)acetic acid. It is confirmed by spot tests.⁸

RESULTS & DISCUSSIONS

To study the effect of concentration change of rasagiline, 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 Rasagiline concentration

In this study the concentration of rasagiline was varied from 1×10^{-2} to $6 \times 10^{-2} \text{ mol dm}^{-3}$ keeping all other conditions constant. Figure 1 represents plot of $\log[\text{RSG}]$ versus $\log k_{\text{obs}}$. The linear plot indicates first order rate of the reaction.⁹ The pseudo first order rate constants are tabulated in Table 1.

Table 1: [RSG] mol dm⁻³ and k_{obs}

[RSG] mol dm ⁻³	0.01	0.02	0.03	0.04	0.05	0.06
k _{obs} s ⁻¹	0.00035	0.00037	0.0004	0.00042	0.00045	0.00048

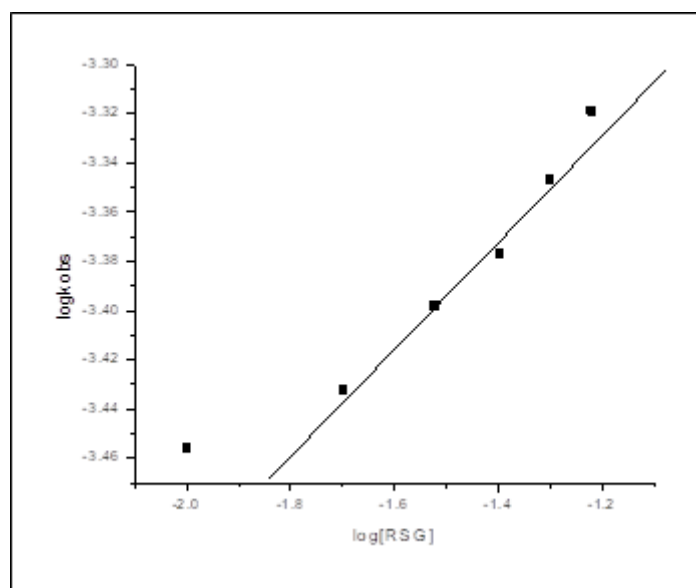


Figure 1: Graph of $\log[\text{RSG}]$ versus $\log k_{\text{obs}}$ of rasagiline

Effect of Potassium Dichromate concentration

Concentration of potassium dichromate was varied from 1×10^{-3} to $6 \times 10^{-3} \text{ mol dm}^{-3}$ keeping all other conditions constant. The k_{obs} values showed a sharp 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: [PD] mol dm⁻³ and k_{obs}

[PD] mol dm ⁻³	0.001	0.002	0.003	0.004	0.005	0.006
k _{obs} s ⁻¹	0.00036	0.00038	0.00041	0.00045	0.00048	0.00052

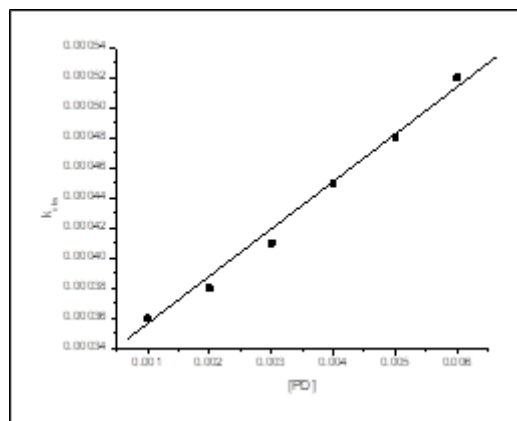


Figure 2: Graph of concentration versus k_{obs} of potassium dichromate

Effect of Temperature

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

Table 3: k_{obs} at different temperatures

Temperature K	298	303	308	313	318
$k_{obs} s^{-1}$	0.00034	0.00039	0.00045	0.00053	0.0006

Table 4: Activation Parameters

Activation Parameters	Ea	ΔH	ΔS	ΔG
		22.413 $kJmol^{-1}$	19.812 $kJmol^{-1}$	-247.26 $JK^{-1}mol^{-1}$

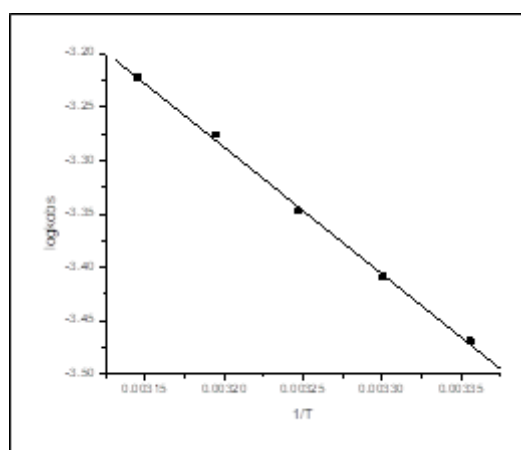


Figure 3: Graph of $1/T$ versus $\log k_{obs}$

Effect of acid concentration

The oxidation of rasagiline with potassium dichromate was studied with different concentrations of sulphuric acid keeping all other conditions of the reaction constant. There is no much variation in the rate constant with increasing sulphuric acid concentrations.

Table 5: k_{obs} at different acid concentration

$[H^+] \text{ mol dm}^{-3}$	0.01	0.02	0.03	0.04	0.05	0.06
$k_{obs} \text{ s}^{-1}$	0.00033	0.00035	0.00034	0.00033	0.00034	0.00035

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.^{10,11}

Effect of Salts added

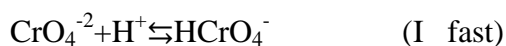
Different salts were added to study the effect of salt on the rate of oxidation of rasagiline with potassium dichromate. Sodium chloride (NaCl), potassium chloride (KCl), potassium bromide (KBr) and magnesium chloride ($MgCl_2$) these salts were added to the oxidation reaction at 298K. It is found that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

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

[PD]	[RS]	$[H^+]$	[Na]	[K]	[KB]	[Mg]	k_{obs}
0.00	0.01	0.1	0.1	-	-	-	3.4
0.00	0.01	0.1	0.2	-	-	-	3.4
0.00	0.01	0.1	0.3	-	-	-	3.3
0.00	0.01	0.1	0.4	-	-	-	3.4
0.00	0.01	0.1	-	0.1	-	-	3.4
0.00	0.01	0.1	-	0.2	-	-	3.3
0.00	0.01	0.1	-	0.3	-	-	3.3
0.00	0.01	0.1	-	0.4	-	-	3.3
0.00	0.01	0.1	-	-	0.1	-	3.5
0.00	0.01	0.1	-	-	0.2	-	3.5
0.00	0.01	0.1	-	-	0.3	-	3.4
0.00	0.01	0.1	-	-	0.4	-	3.5
0.00	0.01	0.1	-	-	-	0.1	3.4
0.00	0.01	0.1	-	-	-	0.2	3.4
0.00	0.01	0.1	-	-	-	0.3	3.5
0.00	0.01	0.1	-	-	-	0.4	3.5

Mechanism of the oxidation of Rasagiline

K1



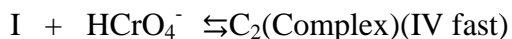
K₂



k

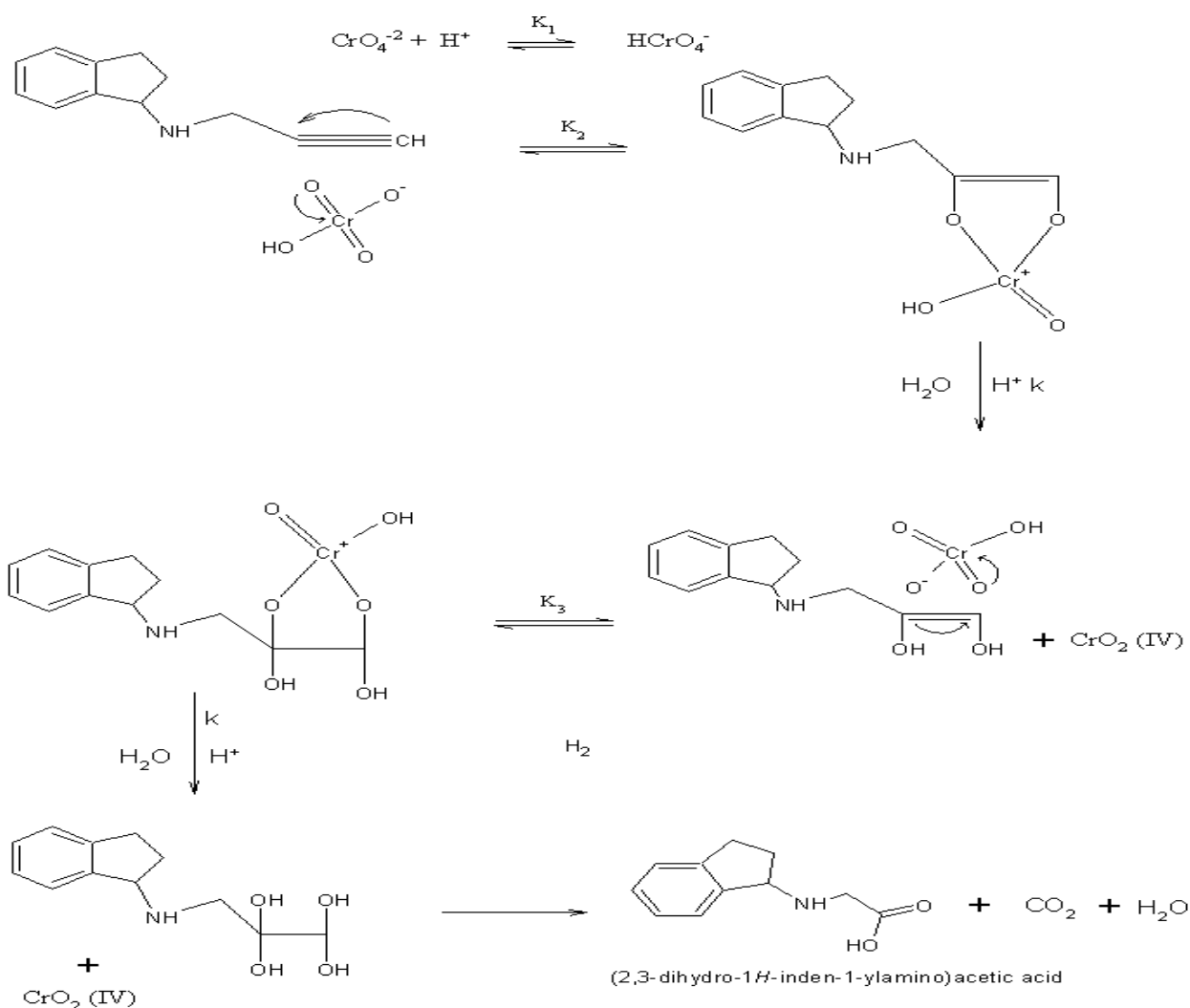


K₃



Scheme-1

In scheme-1 (C₁) and (C₂) are complexes formed with chromate ion and substrate in II and IV steps of the mechanism of the oxidation of rasagiline. In the first step chromate is protonated to in the presence of acid. In second step HCrO₄⁻ reacts with rasagiline to form a complex (C₁). The complex (C₁) gets converted to diol an intermediate (I). The diol reacts with second molecule of HCrO₄⁻ to give complex (C₂) which on hydrolysis is cleaved to give carboxylic acid, the final product and CO₂ is released. The structures of complex and intermediate are shown in scheme-2.



The probable rate equation for the above reaction can be expressed as follows

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

$$K_1 = \frac{[\text{HCrO}_4^-]}{[\text{CrO}_4^{2-}] [\text{H}^+]} \quad [\text{HCrO}_4^-] = K_1 [\text{CrO}_4^{2-}] [\text{H}^+] \quad (1)$$

$$K_2 = \frac{[\text{C}_1]}{[\text{RSG}] + [\text{HCrO}_4^-]} \quad [\text{C}_1] = K_2 [\text{RSG}] + [\text{HCrO}_4^-] \quad (2)$$

Substituting the value of equation (1) in equation (2) we get.

$$[\text{C}_1] = K_1 K_2 [\text{RSG}] [\text{CrO}_4^{2-}] [\text{H}^+] \quad (3)$$

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

$$-d[\text{CrO}_4^{2-}]$$

$$\text{Rate} = \frac{d[\text{C}_1]}{dt} = k[\text{C}_1] \quad (4)$$

Substituting equation (3) in equation (4) we get,

$$\text{Rate} = kK_1K_2[\text{RSG}] [\text{CrO}_4^{-2}] [\text{H}^+] \quad (5)$$

The total concentration of CrO_4^{-2} is given by

$$[\text{CrO}_4^{-2}]_T = [\text{CrO}_4^{-2}] + [\text{HCrO}_4^-] + [\text{C}_1] \quad (6)$$

(T- stands for total concentration of CrO_4^{-2})

Substituting the value of equation (1) & (3) in equation (6) we get

$$[\text{CrO}_4^{-2}]_T = [\text{CrO}_4^{-2}] + K_1 [\text{CrO}_4^{-2}] [\text{H}^+] + K_1K_2[\text{RSG}] [\text{CrO}_4^{-2}] [\text{H}^+] \quad (7)$$

Rearranging the equation (7)

$$[\text{CrO}_4^{-2}]_T = [\text{CrO}_4^{-2}] (1 + K_1 [\text{H}^+] + K_1K_2[\text{RSG}] [\text{H}^+]) \quad (8)$$

$$[\text{CrO}_4^{-2}] = \frac{[\text{CrO}_4^{-2}]_T}{1 + K_1 [\text{H}^+] + K_1K_2[\text{RSG}] [\text{H}^+]} \quad (9)$$

Substituting equation (9) in equation in equation (5) we get

$$\text{Rate} = \frac{kK_1K_2[\text{RSG}] [\text{CrO}_4^{-2}] [\text{H}^+]}{1 + K_1 [\text{H}^+] + K_1K_2[\text{RSG}] [\text{H}^+]} \quad (10)$$

Under pseudo-first order condition,

$$\text{Rate} = \frac{-d[\text{CrO}_4^{-2}]}{dt} = k_{\text{obs}} [\text{CrO}_4^{-2}] \quad (11)$$

On comparing equation (10) & (11) we get,

$$k_{\text{obs}} = \frac{kK_1K_2[\text{RSG}] [\text{H}^+]}{1 + K_1 [\text{H}^+] + K_1K_2[\text{RSG}] [\text{H}^+]} \quad (12)$$

Rearranging the terms in equation (11) we get,

$$\frac{1}{k_{\text{obs}}} = \frac{1 + K_1 [\text{H}^+] + K_1K_2[\text{RSG}] [\text{H}^+]}{kK_1K_2[\text{RSG}] [\text{H}^+]}$$

$$\frac{11}{k_{\text{obs}}} = \frac{1}{kK_1K_2[\text{RSG}][\text{H}^+]} + \frac{1}{kK_2[\text{RSG}]} + \frac{1}{k} \quad (13)$$

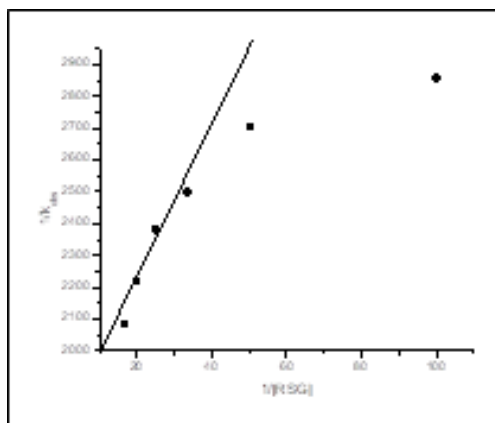


Figure 4: Graph of 1/[RSG] versus 1/k_{obs}

CONCLUSION

The kinetic study of oxidation of rasagiline with potassium dichromate shows that rasagiline undergoes oxidation in acid medium in which the terminal alkyne group is oxidized and cleaved to give carboxylic acid with one carbon less than the substrate as the main product and carbon dioxide gas is released during the reaction. The rate of the reaction is first order with respect to substrate, oxidant and acid. The added salts does not have any effect on the rate of the reaction indicating there is no ionic reaction. Free radical test does not show initiation of polymerization showing non-involvement of free radicals in the reaction. The chromium (VI) in acid media undergoes oxidation through two reaction mechanisms for electron transfer.¹² In the first suggested mechanism the one electron is transferred in successive two steps i.e. Cr(VI) to Cr(V), whereas two electron transfer takes place simultaneously in two steps in the second mechanism in a single step i.e. Cr(VI) to Cr(IV).¹³ The present investigation does not show free radical formation during the oxidation reaction the first mechanism is ruled out in which Cr(VI) is converted to Cr(V). Similarly chromium (VI) found to exist in aqueous acid media mainly as acid chromate shown in scheme 1[14]. The rate of reaction with respect to rasagiline is first order which is confirmed by the plot of 1/[RSG] versus 1/k_{obs} which gives straight line passing through origin figure 4.¹⁵

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