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A KINETIC STUDY OF OXIDATION OF DOMPERIDONE BY POTASSIUM DICHROMATE IN ACID MEDIUM

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ABSTRACT

Kinetics of oxidation of domperidone 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 domperidone where as it does not depend on the concentration of acid. The stoichiometry of the reaction was found that one mole of oxidant is consumed for oxidation of three moles of domperidone and the product found is domperidone N-oxide. 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, Domperidone, Potassium Dichromate.

INTRODUCTION

The domperidone 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 domperidone with potassium dichromate is studied kinetically. Chromium, permanganate ions in various forms are used as powerful oxidizing agent 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 in general and kineticists in particular are attracted to know more about such an interesting chemistry of this reagent. Literature survey reveals that no work is reported on oxidation of domperidone with any oxidizing agent.

MATERIALS AND METHODS

Potassium dichromate and domperidone 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 domperidone was freshly prepared with double distilled water. The oxidation of domperidone by potassium dichromate was followed under pseudo-first order conditions where concentration of domperidone was excess over concentration of dichromate at 298K.[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 domperidone with excess concentration of potassium dichromate in sulphuric acid were kept for 4-5 days for completion of reaction. The unreacted potassium dichromate was determined spectrophotometrically at 520nm. The stoichiometry of the reaction was found that one mole of oxidant is consumed for oxidation of three moles of domperidone. Hence following equation is confirmed.

$K_2Cr_2O_7 + 4H_2SO_{4(aq)} + 3C_{22}H_{24}ClN_5O_2 \rightarrow 3C_{22}H_{24}ClN_4O_2N \rightarrow O + K_2SO_4 + (Cr_2SO_4)_3 + 4H_2O$

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 4-5 days 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 domperidone N-oxide ($C_{22}H_{24}ClN_4O_2N \rightarrow O$). It is confirmed by spot tests.[8]

RESULT AND DISCUSSIONS

To study the effect of concentration change of domperidone, 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 domperidone concentration

In this study the concentration of domperidone was varied from $1x10^{-2}$ to $6x10^{-2}$ mol dm^{-3} keeping all other conditions constant. Figure 1 represents plot of concentration of domperidone versus $k_{obs.}$ The rate constant was found to be increasing with increase in concentration of domperidone with other conditions remaining constant indicating first order rate of the reaction.[9]

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

[DMP] mol dm^{-3}	0.01	0.02	0.03	0.04	0.05	0.06
k_{obs} x 10^{-4}	5.5	5.8	6.0	6.3	6.6	7.0

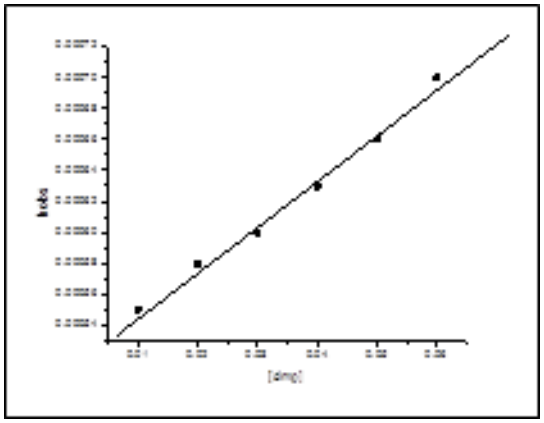

Figure 1: Graph of concentration versus k_{obs} of domperidone.

Effect of Potassium Dichromate concentration

Concentration of potassium dichromate was varied from $1x10^{-3}$ to $6x10^{-3}$ 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: [PDF] mol $dm^{-3}$and $k_{obs.}$

[PD] mol dm^{-3}	0.01	0.02	0.03	0.04	0.05	0.06
k_{obs} x 10^{-4}	6.3	6.6	6.8	7.0	7.3	7.6

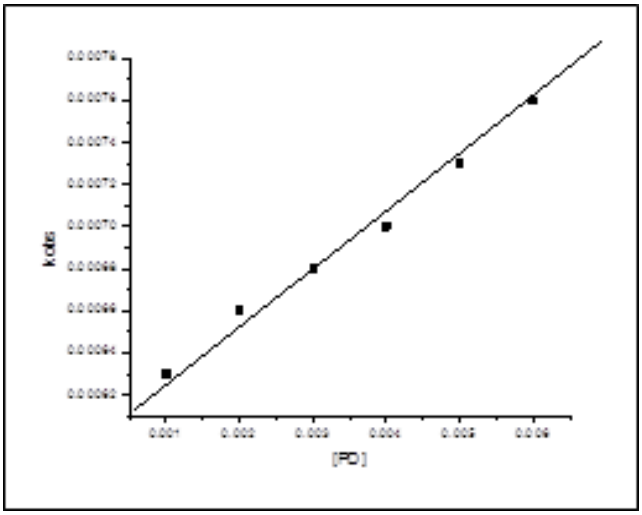

Figure 2: Graph of concentration versus k_{obs} of potassium dichromate.

Effect of Temperature

Variation of temperature change on the rate of oxidation of domperidone 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. [DMP], [PD] and $[H^+]$. The result shows increase in rate of reaction with the increase in temperature. From the linear Arrhenius plots of logk versus 1/T activation parameters were calculated and tabulated in table 4.

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

Temperature K	298	303	308	313	318
log k_{obs}	1.6710	1.8357	1.8975	1.9662	2.0044

Table 4: Activation Parameters.

Activation Parameters	**Ea**	**ΔH**	**ΔS**	**ΔG**
	11.166 kJmol^{-1}	**8.5635 kJmol^{-1}**	**-280.93 JK^{-1}mol^{-1}**	**96.466 kJmol^{-1}**

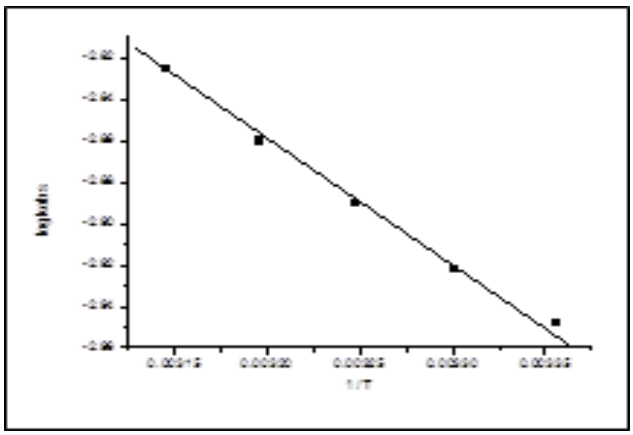

Figure 3: Graph of 1/T versus log k_{obs}.

Effect of acid concentration

The oxidation of domperidone with potassium dichromate was studied with different concentrations of sulphuric acid keeping all other conditions of the reaction constant. There is no significant change in the rate constant with increasing sulphuric acid concentrations i.e. rate of the reaction is not depending concentration of acid.

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]

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 domperidone and so there is no interaction of charged species during the reaction.

Mechanism of the oxidation of domperidone

$K_2Cr_2O_7 + 4H_2SO_{4(aq)} + 3C_{22}H_{24}ClN_4O_2 \rightarrow 3C_{22}H_{24}ClN_4O_2N \rightarrow O + K_2SO_4 + (Cr_2SO_4)_3 + 4H_2O$

$K_2Cr_2O_7 + 4H_2SO_{4(aq)} + 3DMPN \rightarrow 3DMPN \rightarrow O + K_2SO_4 + (Cr_2SO_4)_3 + 4H_2O$

$Cr_2O_7^{2-} + H_2O \rightarrow 2HCrO_4^-$ (Cr VI) (Step-I)

$C_{21}H_{25}ClNO_3N + O{=}CrO_3^{-2} \rightarrow C_{21}H_{25}ClNO_3N \rightarrow O—CrO_3^{-2}$ (Complex Intermediate) (Step-II)

(Chromate Ester CE)

$C_{21}H_{25}ClNO_3N \rightarrow O—CrO_3^{-2} \rightarrow C_{21}H_{25}ClNO_3N \rightarrow O + CrO_3^{-2}$ (Cr IV) (Step-III)

(Domperidone N-Oxide)

Scheme- 1

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

$$-\frac{d}{dt}[Cr_2O_7^{-2}] = -\frac{d}{dt}[HCrO_4^-] = k_2[CE]$$

$$DMP + PD \underset{k-1}{\overset{k1}{\leftrightarrows}} CE \xrightarrow{k2} DMPN \rightarrow O$$

$$-\frac{d}{dt}[Cr_2O_7^{-2}] = -\frac{d}{dt}[HCrO_4^{-}] = k_2[CE]$$

We can apply steady state approximation to CE

$$\frac{d[CE]}{dt} = 0 = k_1[DMP]\ [PD]\ - k_{-1}\ [CE] - k_2[CE]$$

$$[CE] = \frac{k_1}{k_{-1} + k_2}[DMP]\,[PD]$$

The overall rate is the rate of formation of DMPN→O

$$\text{Rate} = \frac{d[DMPN\rightarrow O]}{dt} = k_2[CE] = \frac{k_1 k_2}{k_{-1} + k_2}[DMP]\,[PD]$$

Since k_{-1} is much smaller than k_2, $k_{-1} << k_2$ neglecting k_{-1} in the above equation, rate equation is reduced to

Rate = k_1 [DMP] [PD]

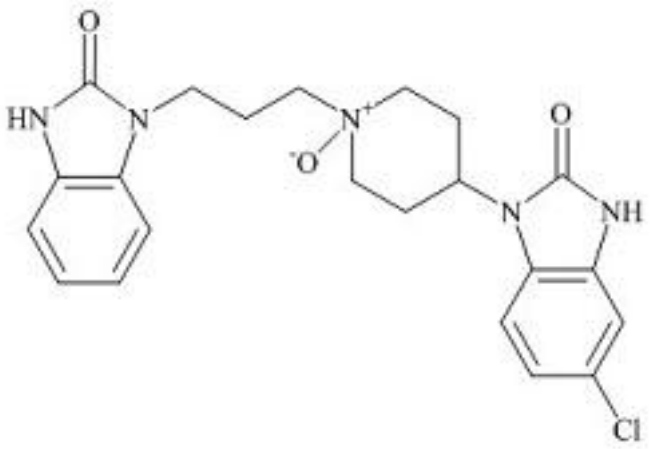

Fig. 4: Domperidone N-Oxide.

CONCLUSION

The most reasonable reaction mechanism which is suggested in scheme-1 has a fast intermediate formation between the substrate and the kinetically active chromic acid. It gets decomposed in the rate determining step to give rise to the final product. The kinetic study of oxidation of domperidone with potassium dichromate shows that domperidone undergoes oxidation in acid medium in which the nitrogen of piperidine moiety of the domperidone

molecule which is sterically less hindered undergoes oxidation to yield domperidone N-oxide as the main product fig. 4. The rate of the reaction is first order with respect to substrate and oxidant but it is not depending on the concentration of acid. In the reaction the chromium(VI) exists in acid media as chromic acid H_2CrO_4. It is indicated in the first step in scheme-1.[12], [13] The negative value of entropy of activation indicates formation of rigid transition state. It can be concluded from kinetic data the overall mechanistic sequence described is consistent with product and scheme-1.

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