Journal of Chemistry and Chemical Sciences, *Vol.12(5), 127-135, May 2022* *ISSN 2229-760X (Print)*
(An International Research Journal), *www.chemistry-journal.org IF 2020 = 7.36* *ISSN 2319-7625 (Online)*

Oxidative Removal Of Loperamide From Aquous System: A Kinetic And Mechanistic Approach

Syed Yousuf Hussain

Kohinoor Arts, Commerce & Science College Khuldabad,
Dist Aurangabad, M.S. 431101 INDIA
Department of Chemistry, Kohinoor Arts, Commerce & Science College Khuldabad,
Dist. Aurangabad 431101 INDIA
Email: sdyusufchem@gmail.com

(Received on: May 15, 2022)

ABSTRACT

The kinetic study of oxidation of loperamide withpotassium dichromate in acid medium using UV Visible Spectrophotometer was investigated in temperature range of 298K to 318K. The observed reaction rate was first order with respect to loperamide and potassium dichromate. The rate was found to be not depending on concentration of sulphuric acid. The reaction product is found to be loperamide N-oxide and stoichiometry was recorded as one mole of potassium dichromate is required for oxidizing three moles of loperamide. On the basis of results obtained appropriate mechanism was proposed and enthalpy, entropy and Gibbs free energy calculated.

Keywords:Aqueous, Kinetics, Mechanism, Oxidation, Pharmaceuticals

INTRODUCTION

In many countries including India, there is increased availability and affordability of medical treatment which led to an increased production and consumption of different classes of pharmaceuticals. Nowadays, a number of pharmaceuticals have been reported to be potentially toxic substances which are found in more concentrations in the environment and consumption of medical treatment.[1,2]

The pharmaceuticals are removed from the aqueous system through physical processes and biological processes. The efficiency of the removal of pharmaceuticals varies, depending upon the treatment process involved. A number of studies have confirmed conventional biological methods not being effective enough to provide for the complete

removal of residual pharmaceuticals in wastewaters.[3,4,5,6,7] The chemical oxidation using different oxidizing agents is another process which gives satisfactory removal of pharmaceuticals from aqueous systems.

In this study loperamideis oxidized using potassium dichromate in acid medium in the temperature range of 298K to 318K using UV Visible Spectrophotometerthrough kinetic and mechanistic approach. Loperamide is a pharmaceutical compound generally used to treat diarrhea. It slows intestinal motality and affects water and electrolyte movement through the bowel and inhibits peristaltic activity by a direct effect on circular and longitudinal muscles of the intestinal wall. It prolongs the transit time of intestinal contents, reduces fecal volume, increases fecal viscosity and bulk density, and diminishes loss of fluid and electrolytes. It is a medicine used to treat effectively number of types of diarrhea. It includes control of acute nonspecific diarrhea, mild traveller's diarrhea, irritable bowel syndrome, chronic diarrhea due to bowel resection and chronic diarrhea secondary to inflammatory bowel disease.

MATERIALS & METHODS

All the chemicals are 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 loperamide was freshly prepared with double distilled water. The oxidation of loperamide by potassium dichromate was followed under pseudo-first order conditions where concentration of loperamide was excess over concentration of dichromate at 298K.[8]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 loperamide with excess concentrations 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 potassium dichromate is consumed for oxidation of three moles of loperamide. Hence following equation is confirmed.

$$K_2Cr_2O_7 + 4H_2SO_4 + 3C_{29}H_{33}ClN_2O_2 \rightarrow 3\ C_{29}H_{33}ClN_2O_3 + K_2SO_4 + (Cr_2SO_4)_3 + 4H_2O$$

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}sulphuricacid. 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 loperamide N-oxide ($C_{29}H_{33}ClN_2O_3$). It is confirmed by spot tests.[9]

RESULTS & DISCUSSIONS

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

In this study the concentration of loperamide was varied from $1x10^{-2}$ to 6×10^{-2}mol dm^{-3} keeping all other conditions constant. Figure 1 represents plot of concentration of loperamide versus k_{obs}. The rate constant was found to be increasing with increase in concentration of loperamide with other conditions remaining constant indicating first order rate of the reaction.[10]

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

[LPM] mol dm^{-3}	0.01	0.02	0.03	0.04	0.05	0.06
k_{obs} x $10^{-4}s^{-1}$	5.0	5.5	6.1	6.6	6.9	7.3

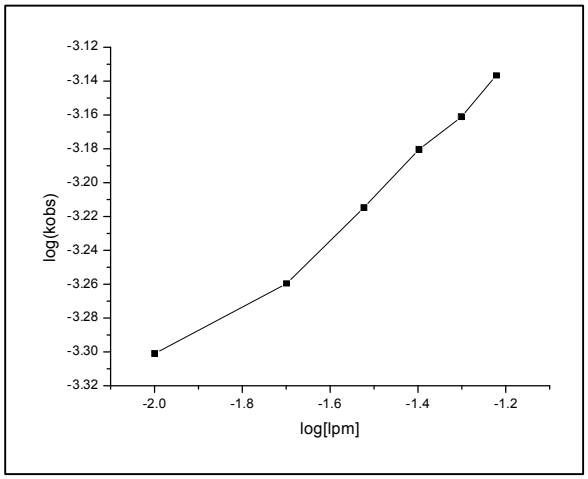

Figure 1: Plot of log(k_{obs}) vs log[lpm]

Effect of Oxidant concentration

Concentration of oxidant i.e. 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. The plot of log concentration of potassium dichromate versus log k_{obs} gives a straight line 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
k_{obs} x 10^{-4} s^{-1}	4.9	5.4	5.8	6.3	6.9	7.5

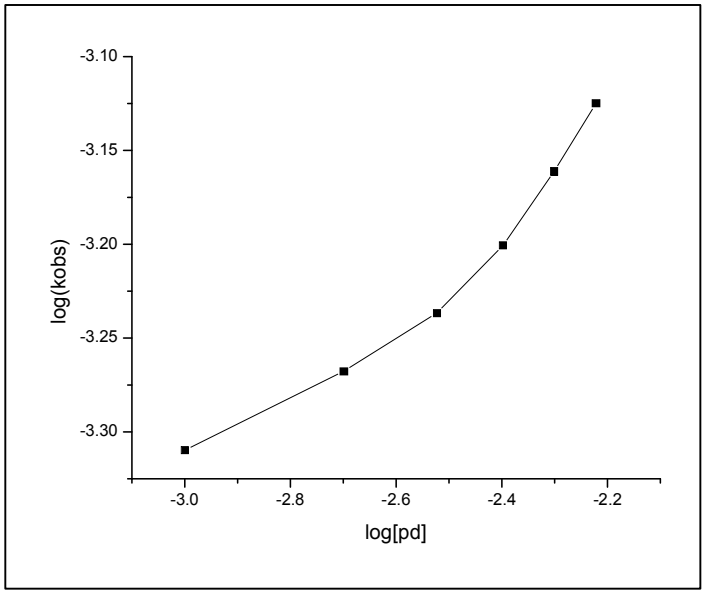

Figure 2: Plot of log(k_{obs}) vs log[pd]

Effect of temperature

Variation of temperature change on the rate of oxidation of loperamide 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. [LPM], [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
k_{obs} x 10^{-4} s^{-1}	5.1	5.6	6.2	6.8	7.3

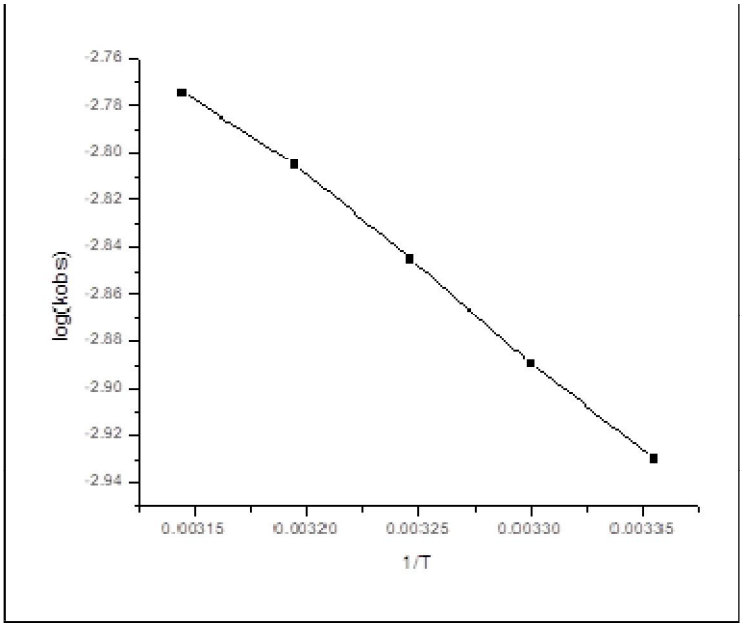

Figure 3: Plot of log(k_{obs}) vs 1/T

Table 4: Activation Parameters

Activation Parameters	**Ea**	**ΔH**	**ΔS**	**ΔG**
	14.106 kJmol^{-1}	**11.503 kJmol^{-1}**	**-270.81 JK^{-1}mol^{-1}**	**96.28 kJmol^{-1}**

Effect of acid concentration

The oxidation of loperamide with potassium dichromate was studied with different concentrations of sulphuricacid 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 on concentration of acid.

Free radical test

In the reaction mixture aqueous solution of acrylonitrile was added. It does not show initiation of polymerization reaction including non-involvement of free radical in the reaction sequences.[11,12]

Effect of salts added

Different salts were added to study the effect of salt on the rate of oxidation of lopermide 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 loperamide and so there is no interaction of charged species during the reaction.

Mechanism of the oxidation of Loperamide:

$K_2Cr_2O_7 + 4H_2SO_4 + 3C_{29}H_{33}ClN_2O_2 \rightarrow 3\ C_{29}H_{33}ClN_2O_3 + K_2SO_4 + (Cr_2SO_4)_3 + 4H_2O$

$K_2Cr_2O_7 + 4H_2SO_4 + 3LPMN \rightarrow 3LPMN{\rightarrow}O + K_2SO_4 + (Cr_2SO_4)_3 + 4H_2O$

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

$C_{29}H_{33}ClNO_2N + O{=}CrO_3^{-2} \rightarrow C_{29}H_{33}ClNO_2N{\rightarrow}O{—}CrO_3^{-2}$(Complex Intermediate) (StepII)
(Chromate Ester CE)

$C_{29}H_{33}ClNO_2N{\rightarrow}O{—}CrO_3^{-2} \rightarrow C_{29}H_{33}ClNO_2N{\rightarrow}O + CrO_3^{-2}$ (Cr IV) (Step-III)

(Loperamide N-Oxide)

Scheme- 1

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

$$-\frac{d}{dt}[Cr_2O_7^{-2}] = -\frac{d}{dt}[CrO_4^{-2}] = k_2[CE]$$

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

We can apply steady state approximation to CE

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

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

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

$$Rate = \frac{d[LPMN{\rightarrow}O]}{dtk_{-1} + k_2} = k_2\ [CE] = \frac{k_1\ k_2}{} [LPM]\ [PD]$$

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

$$Rate = k_1[LPM]\ [PD]$$

CONCLUSION

The most reasonable reaction mechanism which is suggested in scheme-1 has a fast intermediate formation between the substrate and the kinetically active chromate. It gets decomposed in the rate determining step to give rise to the final product. The kinetic study of oxidation of loperamide with potassium dichromate shows that loperamide undergoes oxidation in acid medium in which the nitrogen of piperidine part of the loperamidemolecule which is sterically less hindered undergoes oxidation to yield loperamideN-oxide as the main product. 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.[13,14] 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.

ACKNOWLEDGEMENT

The author is thankful to Principal Kohinoor Arts, Commerce & Science College Khuldabad, Dist Aurangabad for giving permission to carryout research work in the laboratory.

Conflict of Interest: The author does not have any conflict of interest

REFERENCES

1. Singh, P., Rani, B. and Maheshwari, R., 2011. Pharmaceutical pollution: A short communication. International Journal of Pharmacy and Biological Sciences (ISSN: 2230-7605) 1 (2), 26-30.
2. Albrecht, R.J., 2012. Pharmaceuticals in the environment: Looking to green governancefor a remedy. Journal of Energy and Environmental Law, 182-203.
3. Ternes, T.A. and Hirsch, R., 2000. Occurrence and behavior of x-ray contrast media insewage facilities and the aquatic environment. Environmental Science andTechnology 34, 2741-2748.
4. Kimura, K., Hara, H. and Watanabe, Y., 2005. Removal of pharmaceutical compounds bysubmerged membrane bioreactors (MBRs). Desalination 178, 135-140.
5. Vieno, N.M. Tuhkanen, T. and Kronberg, L., 2005. Seasonal variation in the occurrence ofpharmaceuticals in effluents from a sewage treatment plant and in the recipient water.Environmental Science and Technology 39, 8220-8226.
6. Suarez, S., Carballa, M., Omil, F. and Lema, J., 2008. How are pharmaceutical and personal care products (PPCPs) removed from urban wastewaters? Reviews in Environmental Science and Biotechnology 7, 125-138.
7. Hollender, J., Zimmermann, S.G., Koepke, S., Krauss, M., McArdell, C.S., Ort, C.,Singer,H., von Gunten, U. and Siegrist, H., 2009. Elimination of organic micropollutants ina municipal wastewater treatment plant upgraded with a full-scale post-ozonationfollowed by sand filtration. Environmental Science and Technology 43(20), 7862-7869.
8. Wiberg K.B., Oxidation in organic chemistry, Academic Press, London and New York, 1965.
9. F. Feigl, Spot tests in organic analysis, Elsevier, New York, NY, USA, 1957.

10. Joseph; Basheer K.M, Radhakrishnan Nair T.D., "Effects of substituents on the kinetics of the oxidation of benzyl chloride using acid dichromate, Asian J. Chem., 2007, 19(6): 4733-4738.
11. Vogel, Al, Text book of practical organic chemistry, Longman , London, 1967.
12. Laidler K. Chemical Kinetics, McGraw Hill, New York, USA, 1965.
13. Bailey N, Carrington A, Lott KAK, Symons MCR "Structure and reactivity of the oxyanions of transition metals". Part VIII. Acidities and spectra of protonated oxyanions. J ChemSoc,1960: 290-297.
14. Sasake Y Equilibrium studies on polyanions. 9. The first steps of acidification of chromate ion in 3M $Na(ClO_4)$ Medium at 25^oC. ActaChem Scand,1962;16: 719-734.