Kinetic and Thermodynamic Studies of Oxidation of Naproxen by Permanganate in Alkaline Medium

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Abstract The kinetics and mechanism of oxidation of naproxen (NAP) by permanganate in alkaline medium have been studied. The stiochiometry has been observed to be 1:2 ratio of Mn(VII) and NAP consumed. The reaction shows first order with respect to oxidant. The reaction product was identified by LCMS. Activation parameters were calculated. The negative value of $S\Delta^{\#}$ (kJ mol^{-1}) indicates the oxidation occurs via inner sphere mechanism

Keywords Kinetic, Thermodynamic Studies, Oxidation, Naproxen

Introduction

Naproxen 2-(6-methoxynaphthalen-2-yl) propanoic acid (NAP) is a nonsteroidal anti-inflammatory drug used to treat pain, menstrual cramps, inflammatory diseases such as rheumatoid arthritis, and fever.
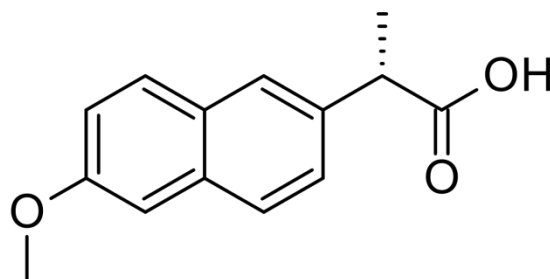

Figure 1: Structure of Naproxen

It works by blocking your body's production of certain natural substances that cause inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most prescribed drugs worldwide as antipyretic, analgesic, and anti-inflammatory agents. Naproxen acts by reducing the levels of prostaglandins, chemicals that are responsible for pain, fever and inflammation. It is also commonly used for the reduction of stiffness caused by conditions including kidney stones, rheumatoid arthritis and other inflammatory rheumatic diseases [1].

Potassium permanganate is widely used as an oxidizing agent in synthetic as well as in analytical chemistry. It is strong, brightly coloured serving as its own indicator. Mn(VII) in permanganate is reduced to various oxidation states in acid, alkaline and neutral media [2]. The oxidation by permanganate ion finds extensive applications in organic synthesis [3]. In this paper, the kinetics of oxidation of naproxen has been studied using potassium permanganate in alkaline media and thermodynamic parameters were calculated. Oxidation reactions by Potassium permanganate are of considerable academic and technological importance because of variable oxidation state of potassium [4].

Experimental

Materials

All chemicals used were of analytical reagent grade. Double distilled water was used throughout the work. The solution of naproxen was prepared by dissolving known amount of solid sample in double distilled water. The permanganate solution was prepared and standardised against oxalic acid [5]. Sodium hydroxide and potassium nitrate were used to maintain the required alkalinity and ionic strength respectively.

Kinetic Measurements

The kinetics of oxidation of naproxen was studied spectrophotometrically under pseudo-first order conditions where the naproxen was maintained in excess over the permanganate ion concentration at constant temperature and constant ionic strength. The reaction was initiated by mixing thermostated solutions of permanganate and NAP which also contained the required amount of sodium hydroxide. The Reaction Kinetics was followed by monitoring disappearance of Mn(VII) at λ_{max} = 525 nm using systronics UV – VIS spectrophotometer. The pseudo-first order rate constant (kobs) were evaluated from the slope of linear plots of ln $(A_t - A_\infty)$ v/s t(s) from the relationship [6].

ln $(A_t - A_\infty)$= ln $(A_o - A_\infty) - k_{obs}t$

Where A_o, A_t, A_∞ indicates optical density of the reaction mixture at zero time, time t and infinite time respectively. A_∞ was measured after completion of the reaction.

The kinetic runs were followed more than 95% completion of the reaction. The pseudo–first order rate constants (kobs) were calculated from the plots of log (absorbance) versus time which is linear. The kobs values were reproducible within ± 5%.
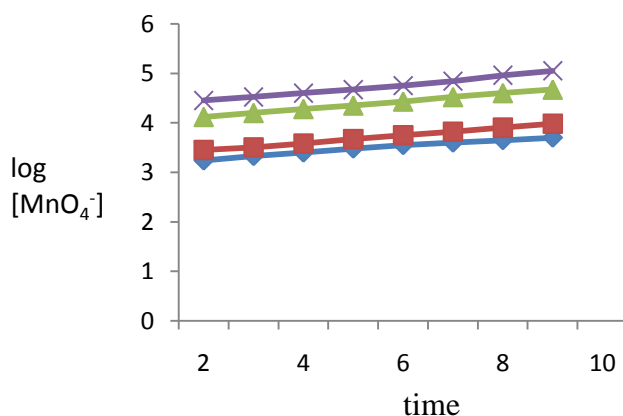

Figure 1

Stoichiometry

The reaction mixture containing excess permanganate concentration over naproxen were mixed in the presence of NaOH, adjusted to a constant ionic strength and allowed to react for about 24hours. The remaining permanganate ion was then analysed spectrophotometrically.

The results indicated that 2 mole of permanganate were consumed by 2 mole of naproxen.

The stoichiometry of the reaction was found to be 1:2. The product was identified by LC-MS spectra which give M^+H + peak at 178 mHz [Fig 2].The result indicated that 1 mole of NAP react with 1 mole permanganate. The product was found to be D-(-)-Tartaric acid dimethyl ester or (-)-Dimethyl D-tartrate shown in figure 3.
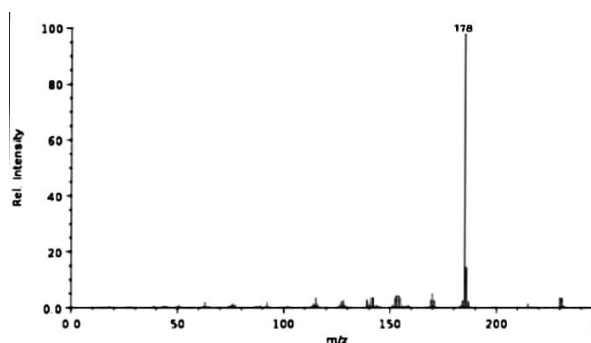
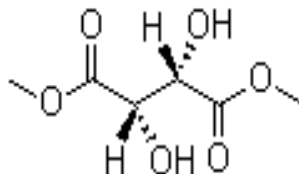*Figure 2: LCMS Spectra of oxidation of product of Naproxen*

Figure 3: Dimethyl D-tartrate

Reaction order

Effect of permanganate

The permanganate concentration varied from 1×10^{-4} to 7×10^{-4} mol dm^{-3}, and all other concentrations and conditions were constant. The plot of log absorbance versus time was linear indicating that the reaction is first order with respect to [KMnO$_4$]. The observed pseudo first order rate constant (kobs) were independent of the concentration of KMnO$_4$ shown in figure 4.

Effect of Naproxen

The effect of concentration variation of naproxen on the rate of reaction was studied in the range 2×10^{-3} to 10×10^{-3} mol dm^{-3} at constant concentration of permanganate, sodium hydroxide. The rate of reaction increases with increasing concentration of naproxen. A plot of log kobs versus log [NAP] was linear with a slope of 0.62, thus indicating a fractional-order dependence on naproxen concentration. This was confirmed by the plot of 1/kobs versus 1/ [NAP] which was also linear.

Effect of Concentration of Sodium hydroxide

The effect of concentration variation of sodium hydroxide on the rate of reaction was studied in the concentration range 2.0×10^{-1} to 7×10^{-1} mol dm^{-3} at fixed concentration of permanganate, naproxen and ionic strength. Pseudo first-order rate constant (kobs) was found to be increased with increase in [OH$^-$]. A plot of log kobs versus log [OH$^-$] was linear. This was confirmed by the plot of 1/kobs versus 1/ [OH$^-$] which was also linear.

Table 1: Effects of variation of [MnO4-], [NAP] and [OH$^-$] on the oxidation of naproxen by alkaline permanganate

10^4 [MnO$_4^-$] (mol dm^{-3})	10^3 [NAP] (moldm^3)	10^1 [OH$^-$] (mol dm^{-3})	10^3 kobs (s^{-1})
1	5	5	6.8
2	5	5	6.82
3	5	5	6.9
4	5	5	6.9
5	5	5	6.84
6	5	5	6.9
7	5	5	6.8
5	2	5	4.5
5	3	5	5.3

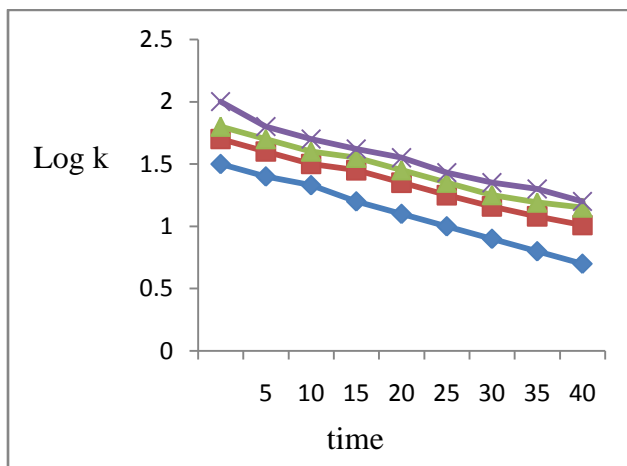| 5 | 4 | 5 | 6.0 |
5	5	5	6.9
5	7	5	7.8
5	10	5	8.5
2	2	2	4.1
2	2	3	5.0
2	2	4	6.2
2	2	5	6.9
2	2	7	7.8

Figure 4: First order plots of the variation of permanganate concentration

Effect of temperature

The effect of temperature was also studied at different temperature like 298, 302, 308, 312K at fixed concentration of naproxen, potassium permanganate, NaOH, KCl were at constant condition. Rate of reaction increased with increase in temperature. The rate constant 'k' is at different temperature. From Arrehnius plots of Log k v/s 1/T, the activation parameters $\Delta H^{\#}$, $\Delta S^{\#}$ were calculated and tabulated in Table 2. Rate k is calculated at different temperature and is given in the Table 3.
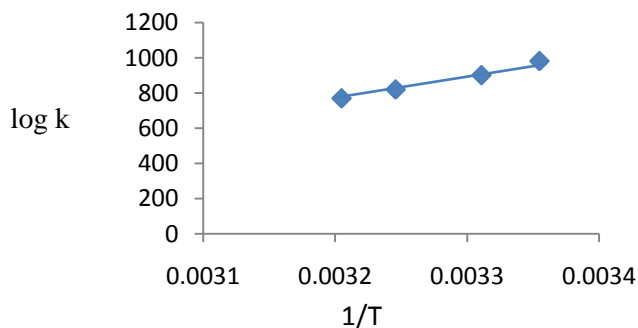

Figure 4

Table 2: Activation quantities

Parameters	Values
Ea (kJ mol^{-1})	11
$\Delta H^{\#}$(kJ mol^{-1})	7.8
$\Delta G^{\#}$(J K^{-1} mol^{-1})	-278
$\Delta S^{\#}$	84.1

Table 3: Rate constant with respect to temperature

| Temperature	K_{obs}
298	1.02
302	1.11
308	1.22
312	1.30

Effect of Ionic Strength

At constant concentration of reactants and other conditions constant, the ionic strength was varied by varying concentration of $[KCl] \times 10^{-1}$. Ionic strength had negligible effect on the rate of reaction.

Effect of halide ions

The addition of Halide ions that is NaCl had no effect on the rate of oxidation of Naproxen.

Effect of added product

Aldehyde, Ammonia was added, but did not alter on the rate of the reaction.
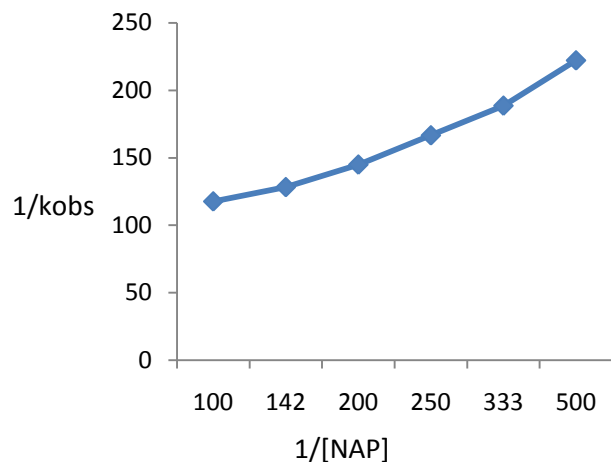
Figure 5: Plots of 1/kobs versus 1/ [NAP]
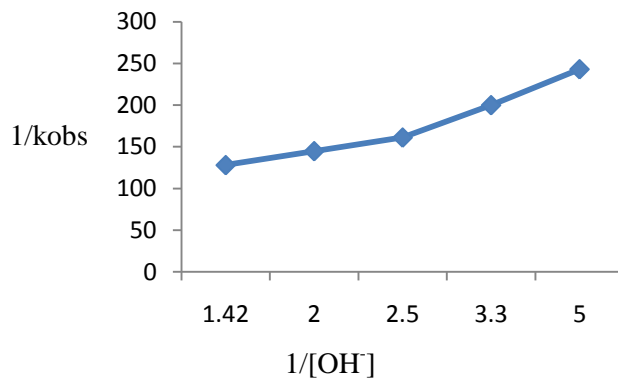
Figure 6: Plots of 1/kobs versus 1/ [OH⁻]

Discussion

Potassium Permanganate is a strong oxidant in an aqueous alkaline media. Since it shows various oxidation states, the stoichiometric results and the pH of reaction medium play a significant role [7].

Rate = -d[MnO_4^-]/dt = k [complex-C]

Rate = kK_2 [NAP] [$MnO_4.OH$]$^{2-}$ (1)

=kK_1K_2[NAP]$_f$ [MnO_4^-]$_f$[OH^-]$_f$

[NAP]$_T$ = [NAP]$_f$ (2)

[MnO_4^-]$_T$ = [MnO_4^-]$_f$ +[$MnO_4.OH$]$^{2-}$+[C]

[MnO_4^-]$_T$ = [MnO_4^-]$_f$ +K_1[MnO_4^-]$_f$ [OH^-] $_f$+K_1K_2[NAP] [MnO_4^-][OH^-]

[MnO_4^-]$_f$=[MnO_4^-]$_T$/ 1+K_1[OH^-]+K_1K_2[NAP] [OH^-] (3)

[TOR]$_T$ = [NAP]$_f$

[OH^-] $_T$ = [OH^-] $_f$

Rate=kK_1K_2[NAP][MnO_4^-][OH^-]/1+K_1[OH^-]+K_1K_2[NAP][OH^-] (4)

Kobs= Rate/[MnO_4^-] = kK_1K_2[NAP][OH^-] / 1+K_1[OH^-]+K_1K_2[NAP][OH^-] (5)

On rearranging equation (5), we will get

1/Kobs = $1/kK_1K_2$[NAP][OH^-] + $1/kK_2$[NAP] + 1/k (6)

According to equation (6), the plots of 1/kobs v/s 1/[NAP] and 1/kobs v/s 1/[OH^-] should be linear which is verified in figure 5 and figure 6. From slopes and intercepts k, K_1 and K_2 were calculated. k, K1, K2 were calculated in rate equation. Hence kobs and kexp values good conformity with each other.

Conclusion

The kinetic study of oxidation of naproxen with potassium permanganate in alkaline medium studied. The final oxidation product of vanillin was identified as Dimethyl D tartrate. The energy of activation was determined by the plot of log k versus 1/T. The moderate values of $\Delta H^{\#}$ and $\Delta S^{\#}$ are favourable for electron transfer reaction [8]. The negative value of $\Delta S^{\#}$ indicates the formation of complex in the reaction, and the complex is more ordered than the reactants

Reference

[1]. Stefano, J. S., Lima, A. P. D., Montes, R. H., Richter, E. M., & Muñoz, R. A. (2012). Fast determination of naproxen in pharmaceutical formulations by batch injection analysis with pulsed amperometric detection. *Journal of the Brazilian Chemical Society*, *23*(10), 1834-1838.

[2]. Hussain, S., Surendra, T., Ramdas, K., & Digambar, G. (2012). Permangnatic Oxidation of Ethyl-2-Cloroactotacetate: A Kinetic and Mechanistic Study. International Journal of Engineering Research and Applications (IJERA). 2(1), 558-561.

[3]. Pujeri, K. G., Lamani, S. D., & Nandibewoor, S. T. (2012). Oxidation of tricyclic antidepressant agent, amitriptyline, by permanganate in sulphuric acid medium: Kinetic and mechanistic approach. *International Journal of Pharmaceutical Sciences and Research*, *3*(12), 4856.

[4]. Hussain, S., & Surendra, T. (2012). Kinetics and mechanism of oxidation of 2, 5-Diamino-1, 3, 4-Thiadiazole metal complex in acid medium. *International J. Basic and Appl. Chem. Sci*, *2*(3), 90-96.

[5]. Vogel A. I. "Text book of Quantitative chemical Analysis." 5th edition, Longman group, UK, 1989, 371.

[6]. Senapati, S., Pattnaik, A. K., & Das, S. P. Kinetics And Mechanism Of Oxidation Of L-Histidine By Permanganate In Aqueous Alkaline, Aquo-Organic And Micellar Media. International Journal of Engineering Research & Technology, 1(10),

[7]. Jain, A., Tazwar, G., & Devra, V. (2017). Kinetics and mechanism of permanganate oxidation of nalidixic acid in aqueous alkaline medium. *Journal of Applied Pharmaceutical Science*, *7*(01), 135-143.

[8]. Sateesh, B., Shastry, V. A., Shashidhar, S., & Kumar, K. M. (2014). Kinetic and mechanism of ruthenium (III) catalyzed oxidation of 4-(3-hydroxy phenyl amino)-4-oxo butanoic acid by hexacyanoferrate (III) in aqueous alkaline medium. Int. J. Chem. Sci.: 12(4), 1109-1120.

[9]. Bilehal, D. C., Kulkarni, R. M., & Nandibewoor, S. T. (2003). Kinetics of oxidation of pyridylmethylsulphinylbenzimidazole by cerium (IV) in an aqueous perchloric acid medium. *Turkish Journal of Chemistry*, *27*(6), 695-702.