

Kinetics And Mechanism Of Oxidation Of L-Histidine By Permanganate In Aqueous Alkaline, Aquo-Organic And Micellar Media

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Abstract

The kinetics of oxidation of L-Histidine by alkaline MnO_4^- have been investigated in the temperature range $298 \leq T/K \leq 318$ at $0.004 \leq [OH^-]/mol\ dm^{-3} \leq 0.03$ and $I = 0.5\ mol\ dm^{-3}$. The observed rate of oxidation is first order with respect to L-[Histidine] and $[OH^-]$. The main product of oxidation is β -keto acid identified by 1H NMR and FTIR. The ionic strength on the reaction rate has no significant effect. The effect of changing the dielectric constant of the medium on the rate indicates the reaction to be ion-dipole type. The electron transfer rate constant has been derived from the slow step of the mechanism of the reaction. The activation parameters with respect to slowest rate constants are computed. The moderate activation enthalpy and activation entropy favor the electron transfer reaction. An inner-sphere electron transfer mechanism is suggested. The proposed mechanism is consistent with the product, mechanistic and kinetic studies. Effect of micelles (SDS, CTAB) on such reaction have been studied. CTAB shows a marginal enhance rate whereas SDS produces no change in the rate of the electron transfer reaction. Effect of solvent on such reaction have been investigated with protic (methanol, acetic acid) and aprotic (acetonitrile) solvent. Higher rate acceleration effect is observed in acetonitrile whereas low rate of acceleration is observed in methanol and acetic acid.

Keywords: Kinetics, oxidation, L- Histidine, Permanganate ion, micelle effect, solvent effect.

Introduction

Mostly L-amino acids are blood plasma ligands form stable complexes with various essential metals in vivo^[1-3]. These L-amino acids are used in many biological processes in human body like transamination, decarboxylation, metabolism, intracellular mechanism and operate specific transport systems of the plasma membrane. L-Histidine is one of the twenty amino acids which is present in many proteins. It plays a significant role in growth and repair of tissues, ulcers, hyperacidity, digestion, production of red and white blood cells, maintenance of myelin sheaths that protects nerve cells, particularly the auditory nerve is used to treat some form of hearing disability. Research on L-Histidine shows that its deficiency leads to rheumatoid arthritis, eczema (for babies), cataracts, stomach and duodenal ulcer. There is limited research on the oxidation of L- Histidine.

This paper presents detail investigation of interaction of L-Histidine with Manganese (VII) as permanganate ion. Potassium permanganate is a powerful oxidant in aqueous alkaline medium. It is interesting because manganese exhibits variable oxidation state from +2 to +7. The permanganate oxidation of large biological molecule such as nucleic acid^[4], proteins^[5], thymine^[6], uracil^[7] and several amino acids^[8-16] have already been reported. This paper presents how manganese shows the change of various oxidation states during the course of the reaction. The product of the reaction have been isolated and characterised. Possible mechanism of the reaction has been suggested. Solvent and micellar effect on such reaction have been studied.

Experimental Materials

All chemicals used were analarR grade. L-Histidine (SRL, extra pure) and potassium permanganate (BDH) were used as such without purification. Ionic strength was maintained with freshly prepared sodium perchlorate (Merck). Potassium permanganate was standardized with oxalic acid^[17]. Solvents were purified by reported method^[18]. All solutions were prepared in freshly prepared double distilled water using an all glass distillation apparatus containing $KMnO_4$. SDS (Merck) and CTAB (Merck) micelles are used to study micellar effect on reaction mechanism. Fresh solutions of micelles are used for kinetic study.

Kinetic measurements

The kinetics of oxidation of L-Histidine was studied spectrophotometrically under pseudo-first order conditions with $[L-Histidine]:[KMnO_4] > 10:1$ at constant ionic strength ($I = 0.5\ mol\ dm^{-3}$). The $[L-Histidine]$ was varied from 1×10^{-3} to $5 \times 10^{-3}\ mol\ dm^{-3}$ and $[OH^-]$ was varied from 0.004 to 0.03 $mol\ dm^{-3}$.

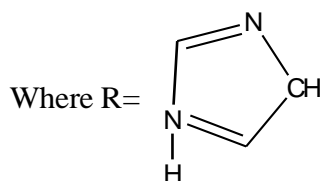
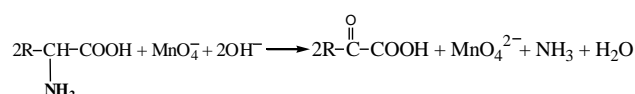
The Reaction Kinetics was followed by monitoring disappearance of Mn(VII) at $\lambda_{max} = 525\ nm$ using conventional mixing technique with CECIL – 7200 (UK) UV – VIS spectrophotometer equipped with a thermostatic bath for temperature control with an accuracy of $\pm 0.1^\circ C$. The pseudo-first order rate constant (k_{obs}) were evaluated from the slope of linear plots of $\ln(A_t - A_\infty)$ vs t(s) from the relationship.

$$\ln(A_t - A_\infty) = \ln(A_0 - A_\infty) - k_{obs}t$$

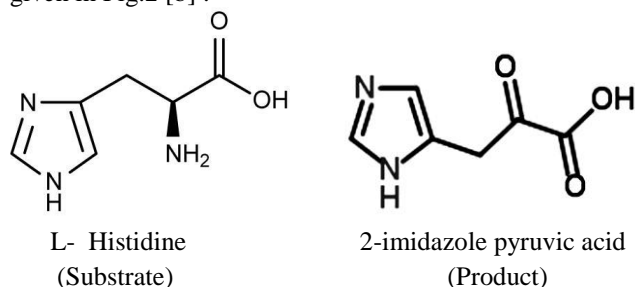
Where A_0 , A_t , A_∞ denote optical density of the reaction mixture at zero time, time t and infinite time respectively. A_∞ was measured after completion of the reaction. The correlation coefficients of plots used to determine k_{obs} were found to be 0.99 in most of the cases. All calculations were made on a PC using least square programme.

Stoichiometry and identification of Products

Different sets of the reaction mixture containing different amount of reactants $[MnO_4^-] > [L\text{-Histidine}]$ at constant $[OH^-] = 0.03 \text{ mol dm}^{-3}$ and constant ionic strength ($I = 0.5 \text{ mol dm}^{-3}$) were allowed to react for 3hr in an inert atmosphere. The remaining MnO_4^- was analyzed spectrophotometrically. The result showed that two moles of MnO_4^- reacted with one mole of L-Histidine. From the above stoichiometric study it is concluded that the stoichiometry of the reaction is



In order to get the reaction product 0.2 mol $KMnO_4$ and 0.02 mol of L-Histidine were mixed in a container and $[OH^-]$ was kept at 0.03 mol dm^{-3} . The reaction mixture was allowed to stand about 3h at 303K for completion of the reaction. The metal ion in the solution was removed by ion-exchange method and after neutralization with dilute $HClO_4$ it was treated with saturated 2,4, dinitro phenylhydrazine. The yellow precipitate 2,4, dinitrophenylhydrazone indicates the presence of Carbonyl group. One part of the solution was treated with Nessler's reagent which confirmed the presence of NH_3 . The solution after removal of metal ion was evaporated till it was reduced to one third of its original volume and kept overnight in refrigerator. The crystalline product formed was 60%. The product was identified by FT-IR as recorded in Perkin Elmer(UK) FTIR Spectrophotometer given in Fig. 1 as well as 1H NMR spectra recorded in 400 MHz FT NMR Spectrophotometer given in Fig.2 [b] .



FT-IR spectra of the product given in Fig.1 exhibits a broad peak at 3011 cm^{-1} which is a combination of C-H stretching, N-H stretching of imidazole ring as well as O-H stretching of carboxylic acid. A sharp peak at 1738 cm^{-1} corresponds to carbonyl stretching. The high value suggests intermolecular hydrogen bonding between C=O and O-H of carboxylic acid. Sharp peak at 1616 cm^{-1} , 1487 cm^{-1} , 1436 cm^{-1} corresponds to carboxylate group C-O stretching. The peaks of medium intensity from 1089 cm^{-1} to 1219 cm^{-1} also correspond to C-O stretching. The peak at 822 cm^{-1} corresponds to N-H outplane bending^[19]. All the above data predicts the product to be 2-imidazole pyruvic acid. The product was further confirmed by 1H NMR data given in Fig.2 and Table 1. Sharp peak at $\delta 12.56 \text{ ppm}$ corresponds to OH group of carboxylic acid. The peak at $\delta 13.4 \text{ ppm}$ corresponds to NH of imidazole. The peak at $\delta 6.86 \text{ ppm}$, $\delta 6.76 \text{ ppm}$ corresponds to CH of imidazole^[20]. The CH_2 peak at $\delta 3.17 \text{ ppm}$ in the substrate shifted to $\delta 4.78 \text{ ppm}$ in the product is a clear indication of formation of C=O group. The NH_2 peak at $\delta 8.81 \text{ ppm}$ in the substrate is absent in the product. The imidazole ring is not affected during oxidation is confirmed by the data given in Table 1. The product was confirmed to be 2-imidazole pyruvic acid, [3-(1-imidazole-2-yl)-2-oxopropanoic acid].

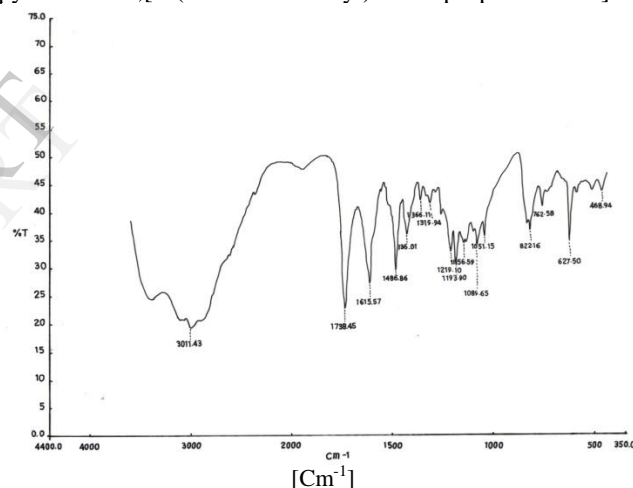


Figure 1. FTIR Spectra of the product

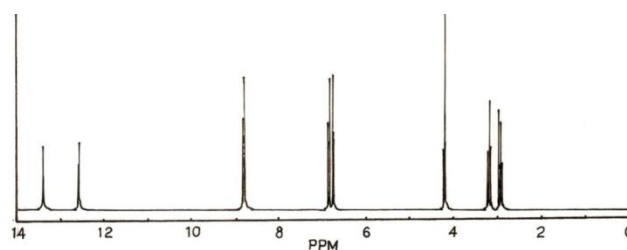


Figure 2[a]. 1H NMR Spectra of substrate, L-Histidine

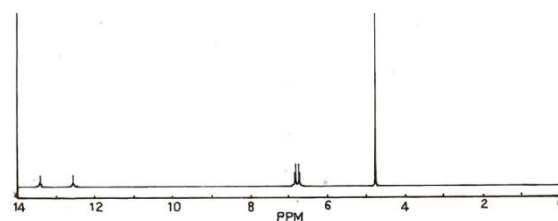


Figure 2[b]. 1H NMR Spectra of product

Table 1. ¹H NMR data of the substrate L-Histidine and product 2-Imidazole pyruvic acid

SL Component	Solvent	δ [ppm]						
		Imidazole NH	Imidazole CH	Imidazole CH	Amine NH ₂	Carboxylic acid OH	Methine CH	Methylene CH ₂
1. L-Histidine [Substrate]	D ₂ O	13.4	6.86	6.76	8.81	12.57	4.18	3.17
2. 2-Imidazole pyruvic acid [product]	D ₂ O	13.4	6.86	6.76	Absent	12.56	Absent	4.78

Results and Discussion

When L- Histidine was added to alkaline KMnO₄, the solution changes its colour from violet to blue then to green. The spectra of the green solution was identified as MnO²⁻₄. It is probable that the blue colour originates from violet of permanganate and green colour from manganate excluding the accumulation of hypomanganate. It is unmistakable from UV-VIS spectral scan shown in Fig. 3[a] of the reaction mixture that the concentration of permanganate [Mn(VII)] ion decreases at 525 nm where as the concentration of manganate [Mn(VI)] increases at 608 nm and 460nm during the reaction. After a long interval (after 5hr) the peak at 525 nm completely vanished in Fig. 3[b] indicating the complete reduction of Mn(VII)

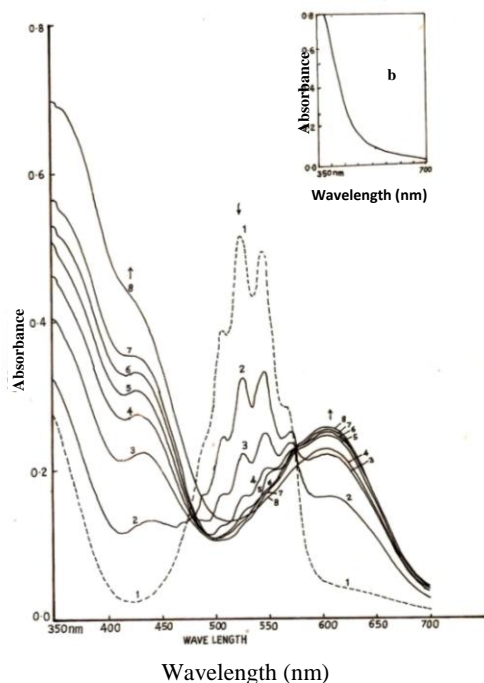


Figure 3. UV-VIS Spectral scan for oxidation of L-Histidine by MnO₄⁻ in aqueous alkaline medium [OH⁻] = 0.03 mol dm⁻³, I = 0.5 mol dm⁻³ at 303 K

[a] (1) [MnO₄⁻] = 2x10⁻⁴ mol dm⁻³ (2) Immediately after mixing, MnO₄⁻ with [L-Histidine] = 2 x 10⁻³ mol dm⁻³ curve (3-8), Δt = 1 min.

[b] Inset : Spectra of the above reaction mixture after 5h.

The Kinetics of the redox reaction (k_{obs}) were followed at different concentration of oxidant, substrate and alkali at λ_{max} =525nm. The effect of alkali was studied by varying [OH⁻] from (0.004 – 0.03) mol dm⁻³ at constant concentration of L-Histidine and potassium permanganate

and at constant ionic strength ($I = 0.5 \text{ mol dm}^{-3}$) at different temperature 298-318 K. The plot of k_{obs} versus [OH⁻] is linear at different substrate concentration given in Fig. 4 indicates first order dependence with respect to alkali. The reaction is also first order with respect to L-Histidine concentration in Fig. 5 at different [OH⁻] concentration. Increase in rate with increase in [OH⁻] indicates the presence of the hydroxylated species of Mn (VII) as a reaction species which is shown in the mechanism of the reaction. The results suggest the formation of a complex between the amino acid and hydroxylated Mn(VII) complex. The formation of the complex was also proved by non zero intercept of the plot of k_{obs}^{-1} versus [Hist]⁻¹ displayed in Fig. 6.

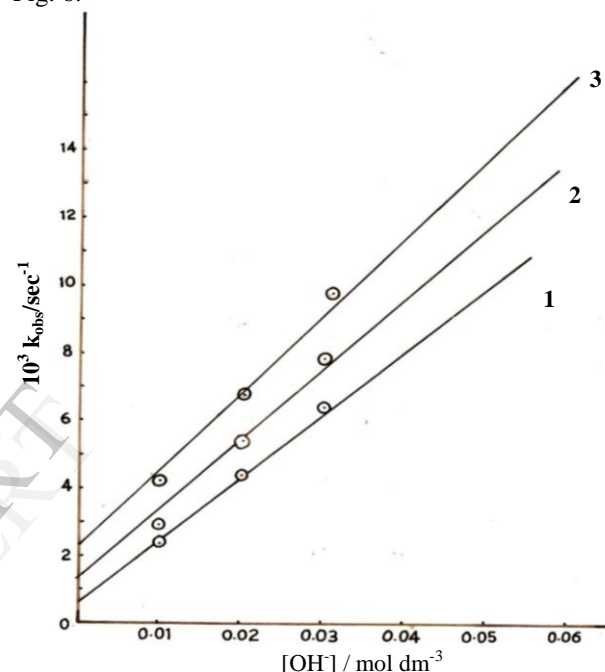


Figure 4. k_{obs} versus [OH⁻] at [L-Histidine] = 2 x 10⁻³ mol dm⁻³[1], 3 x 10⁻³ mol dm⁻³[2], 5 x 10⁻³ mol dm⁻³[3]

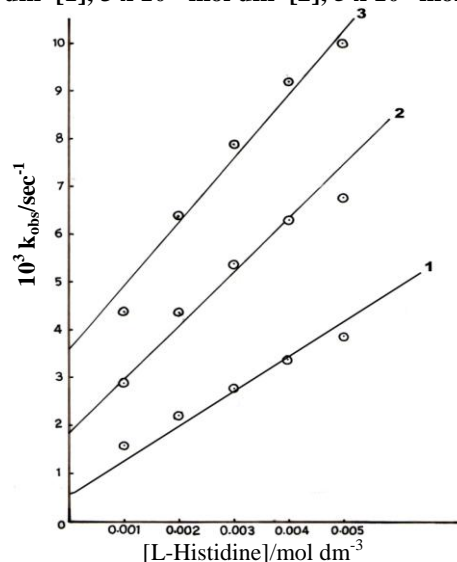


Figure 5. k_{obs} versus [L-Histidine] at [OH⁻] = 0.01 mol dm⁻³[1], 0.02 mol dm⁻³[2], 0.03 mol dm⁻³[3]

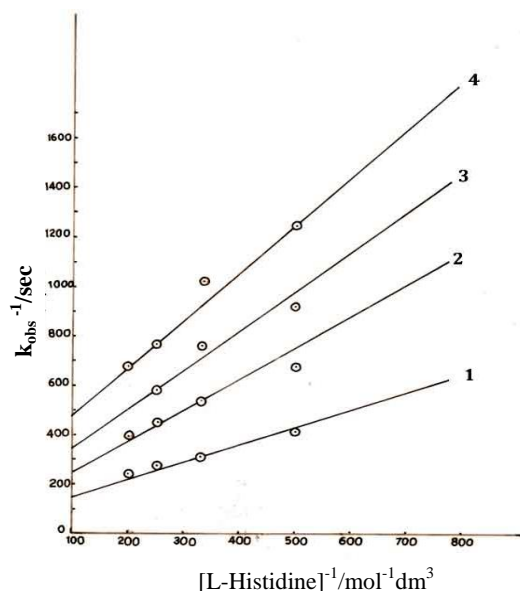


Figure 6. k_{obs}^{-1} versus $[L-Histidine]^{-1}$ at 313 K [1], 308K[2], 303K[3], 298K[4]

Table 2. Rate constants for the electron transfer reactions of $KMnO_4$ with L-Histidine in $I = 0.5 mol dm^{-3}$ ($NaClO_4$), $[MnO_4^-] = 2 \times 10^{-4} mol dm^{-3}$

Sl.	[OH ⁻] mol dm ⁻³	Amino Acid [L-Histidine] mol dm ⁻³	10 ³ k _{obs} (s ⁻¹)				
			298 K	303K	308K	313K	318K
1	0.004	0.001	0.70	0.90	1.18	1.60	1.85
		0.002	0.80	1.10	1.48	2.00	2.45
		0.003	0.95	1.30	1.85	2.40	3.26
		0.004	1.31	1.70	2.19	2.83	3.50
		0.005	1.48	1.82	2.50	3.20	3.95
2	0.008	0.001	1.03	1.50	2.20	3.30	4.30
		0.002	1.50	2.10	2.90	3.70	4.55
		0.003	1.80	2.40	3.30	4.20	5.56
		0.004	2.09	2.80	3.80	4.90	6.45
		0.005	2.23	3.00	4.07	5.60	7.00
3	0.01	0.001	1.23	1.80	2.75	3.80	5.52
		0.002	1.79	2.40	3.40	4.30	5.79
		0.003	2.10	2.80	3.85	4.90	6.48
		0.004	2.64	3.40	4.40	5.50	6.96
		0.005	2.66	3.60	5.00	6.50	8.71
4	0.02	0.001	1.58	2.20	3.20	4.20	5.80
		0.002	2.80	3.30	4.20	4.90	6.20
		0.003	4.00	4.50	5.10	5.60	6.60
		0.004	5.20	5.60	6.00	6.40	7.00
		0.005	6.50	6.80	7.00	7.10	7.50
5	0.03	0.001	3.73	4.40	5.00	5.70	6.45
		0.002	5.40	6.40	7.40	8.50	9.30
		0.003	7.09	7.90	8.80	9.70	10.72
		0.004	8.10	9.20	16.60	11.80	13.37
		0.005	8.27	10.00	12.20	14.30	16.90

Table 3. Second order rate constant, equilibrium constant and their activation parameters

Parameter	Temp (K)				
	298	303	308	313	318
$10^3 k dm^3 mol^{-1} s^{-1}$	5.10	6.10	7.45	8.42	10.46
$K_2 [dm^3 mol^{-1}]$	158.12	194.66	368.25	1099.33	1592.14
$\Delta H^\ddagger [kJ mol^{-1}]$	25.71±1.73				
$\Delta S^\ddagger [J K^{-1} mol^{-1}]$	-202.58±5.64				
$\Delta H [kJ mol^{-1}]$	99.99±0.010				
$\Delta S [J K^{-1} mol^{-1}]$	375.7 ± 43				

The effect of ionic strength was studied varying $I = 0.01$ to $0.05 mol dm^{-3}$ ($NaClO_4$) keeping all other conditions remaining constant. The rate of the reaction remains almost unchanged with increasing ($NaClO_4$). This indicates that the rate of the reaction is independent of ionic strength showing the involvement of neutral species at the rate determining step.

Addition of acrylonitrile (6% v/V) to the reaction mixture in an inert atmosphere, produced cloudiness due to formation of poly acrylonitrile, indicating the formation of free radicals during the reaction. A similar solution of acrylonitrile when added to blank solution of $KMnO_4$ or L-Histidine did not produce any cloudiness.

The effect of relative permittivity (D) was studied by varying aqueous acetic acid 20% to 70% (Fig.8) keeping all other conditions constant. The observed rate constant (k_{obs}) was increased with decrease in dielectric constant of the medium. A plot of $\log k_{obs}$ versus D^{-1} is linear with positive slope indicating ion-dipolar interaction^[21] in the rate determining step. Applying Born equation, Laidler and Eyring derived the equation^[22].

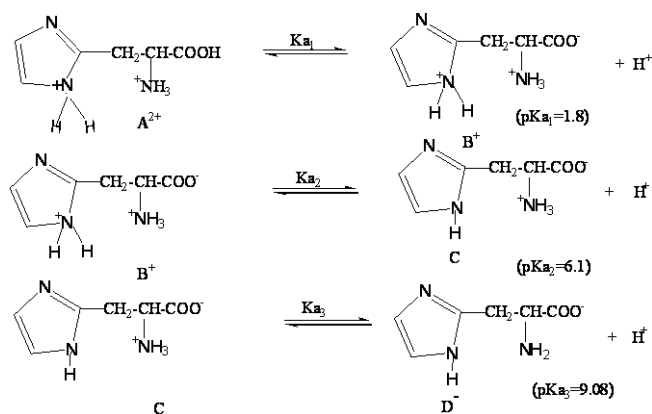
$$\ln k = \ln k_0 + \frac{NZ^2 e^2}{2DRT} \left(\frac{1}{r} - \frac{1}{r^*} \right) \quad [1]$$

Where k_0 is the rate constant in a medium of infinite dielectric constant and r and r^* refer to the radius of the reacting species and the activated complex respectively. It can be seen from the equation that the rate should be greater in medium of lower dielectric constant when $r^* > r$. The intra molecular hydrogen bonding that could stabilize the transition by increasing the size of activated complex by solvation is possible. It is likely that $r^* > r$ for L-Histidine thus explaining the experimental observation.

The energy of activation corresponding to the rate of the slowest step was evaluated from the plot of $\log (k/T)$ versus T^{-1} . The moderate values of activation parameters $\Delta H^\ddagger = 25.71 \pm 1.73 kJ mol^{-1}$ and $\Delta S^\ddagger = -202.58 \pm 5.64 J K^{-1} mol^{-1}$ favour outer sphere electron transfer processes. The ΔH^\ddagger values was due to release of energy of solution change in the transition state. The negative value of ΔS^\ddagger indicate the loss of degree of freedom and formation of rigid transition state (complex C_2). The shifting of peak of the reaction mixture shown in Fig. 3a indicates the formation of weak bridged complex between amino acid and Mn(VII) in complex C_2 suggesting inner electron transfer mechanism.

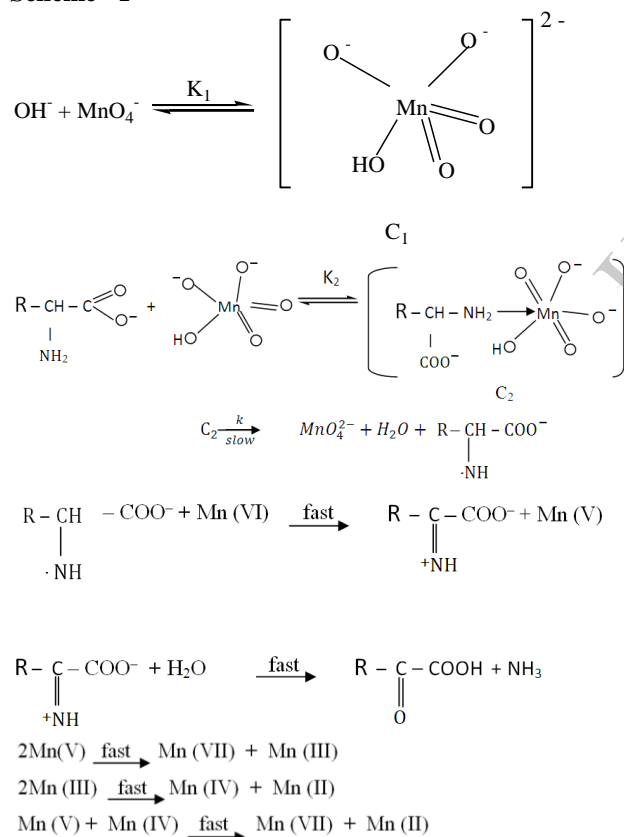
Mechanism of the reaction

L-Histidine exists in following equilibria between various L-Histidine species A^{2+} , B^+ , C , D^- with their equilibrium constants^[23]. In alkaline medium D^- is the predominant species.



The UV – VIS spectral scan in Fig. 3[a] shows the formation of a complex between MnO_4^- and amino acid in which bathochromic shift of 30nm of MnO_4^- from 315 nm to 345 nm and hyperchromicity at 430nm was observed. Such complex formation between substrate and oxidant was also observed in other studies^[24]. Based on the above experimental result the probable mechanism may be delineated as in scheme-I.

Scheme - I



HMnO_5^{2-} (C_1) forms a complex (C_2) with amino acid. The complex decomposed to form amino acid radical which is further oxidized to amino acid which in presence of water yields keto acid and ammonia. The keto acid was identified by FTIR and ^1H NMR as 2 imidazolpyruvic acid. It was supported by earlier report that the oxidation of amino acid

by tetrachloro aurate^[23] hydrazyl radical^[24] produced β -keto acid.

Basing on the above mechanism, rate law can be derived as

$$\begin{aligned} \text{Rate} &= k [\text{C}_2] = k K_2 [\text{Hist}]_T [\text{C}_1] \\ \text{Rate} &= k K_1 K_2 [\text{Hist}]_T [\text{MnO}_4^-]_e [\text{OH}^-]_e \end{aligned} \quad [2]$$

$$\begin{aligned} [\text{MnO}_4^-] &= [\text{MnO}_4^-]_e + \text{C}_1 + \text{C}_2 \\ &= [\text{MnO}_4^-]_e + K_1 [\text{MnO}_4^-]_e [\text{OH}^-]_e + \\ &\quad K_2 [\text{Hist}]_T [\text{C}_1] \\ &= [\text{MnO}_4^-]_e \{ 1 + K_1 [\text{OH}^-]_e + K_1 K_2 [\text{Hist}]_T [\text{OH}^-]_e \} \end{aligned}$$

$$[\text{MnO}_4^-]_e = \frac{[\text{MnO}_4^-]_T}{1 + K_1 [\text{OH}^-]_e + K_1 K_2 [\text{Hist}]_T [\text{OH}^-]_e} \quad [3]$$

Putting the value of (2) in equation (1)

$$\text{Rate} = \frac{k K_1 K_2 [\text{Hist}]_T [\text{MnO}_4^-]_T [\text{OH}^-]_e}{1 + K_1 [\text{OH}^-]_e + K_1 K_2 [\text{Hist}]_T [\text{OH}^-]_e} \quad [4]$$

$$\begin{aligned} \text{Rate} &= k_{\text{obs}} [\text{MnO}_4^-]_T \\ k_{\text{obs}} &= \frac{k K_1 K_2 [\text{Hist}]_T [\text{OH}^-]_e}{1 + K_1 [\text{OH}^-]_e + K_1 K_2 [\text{Hist}]_T [\text{OH}^-]_e} \end{aligned}$$

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k} + \frac{1}{k K_2 [\text{Hist}]} + \frac{1}{k K_1 K_2} \times \frac{1}{[\text{Hist}] [\text{OH}^-]} \quad [5]$$

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k} + \frac{1}{[\text{Hist}]} \left[\frac{1}{k K_2} + \frac{1}{k K_1 K_2} \frac{1}{[\text{OH}^-]} \right] \quad [6]$$

$\frac{1}{k_{\text{obs}}}$ is plotted against $\frac{1}{[\text{Hist}]}$ at different concentration of $[\text{OH}^-]$ (eqn.5).

A straight line is found with slope $\frac{1}{k K_2} + \frac{1}{k K_1 K_2} \frac{1}{[\text{OH}^-]}$ and intercept yields reciprocal of electron transfer rate constant (k). Again $\frac{1}{k_{\text{obs}}}$ is plotted against $\frac{1}{[\text{OH}^-]}$ at different concentration of $[\text{L-Histidine}]$ (eqn.4). The new intercepts are plotted against $\frac{1}{[\text{Hist}]}$ (eqn. 4). From slope and intercept K_2 is calculated. The value of k (electron transfer rate constant) & K_2 (formation constant of the complex) are computed at five different temperature 298-318K and tabulated in Table 3. Calculated K_1 value (eqn.5) at 298K is 8.41 which is comparable with the reported data 6.74 at 298K.^[22]

Micellar Effect

The kinetics of oxidation of L-Histidine with MnO_4^- was carried out in presence of SDS varying $[\text{SDS}] = 0.005$ to 0.07 mol dm^{-3} at 303K (Fig.7). The rate constant in presence of SDS is almost equivalent to rate constant in aqueous medium which indicates the reaction exclusively occur in aqueous –pseudo phase. The presence of Cationic surfactant CTAB enhanced the rate of oxidation reaction about three times that of the rate in aqueous medium. The rate acceleration in presence of CTAB is observed upto $[\text{CTAB}] = 0.005 \text{ mol dm}^{-3}$ and reaches a

limiting value in the range $[CTAB]=0.01$ to 0.07 mol dm^{-3} . The acceleration in the observed rate may be due to higher local concentration of both reactants and micelle as compared to their stoichiometric concentration in aqueous phase. The limiting value at higher concentration may be due to bimolecular micellar surface reaction. Similar results have been observed in several micellar catalysed reactions^[25-29].

Solvent effect

Solvent is a vital component for carrying out any reaction in solution. Many physico chemical process including reaction kinetics have also been investigated in non-aqueous and mixed aqueous solvent mixture in the present study. The oxidation of L-Histidine by MnO_4^- in alkaline medium was carried out with dipolar protic cosolvents (methanol, acetic acid) and dipolar aprotic cosolvent (acetonitrile). The rate constant against the volume percentage of solvent are displayed in (fig.8) which clearly indicate the rate acceleration effect in mixed solvent media. The effect is small in methanol and acetic acid but more pronounced in acetonitrile. In methanol and acetic acid rate slowly increases upto 70% but in acetonitrile the effect is maximum upto 20% but from 20% to 70% there is gradual retardation. The differential behavior is partly due to the solvation stabilisation of protic cosolvents (methanol, acetic acid) through Hydrogen bonding which is not possible for aprotic solvent (acetonitrile). The rate acceleration effect is linear in methanol-water medium where in acetonitrile the curve is non-linear which indicate the influence of preferential solvation and solvent structural effect on rate of the reaction. At high acetonitrile concentration there is solvent structural perturbation which affect the energy barrier of the reaction as a result activation entropy increases hence rate decreases. It explains the retardation of rate at higher acetonitrile concentration.

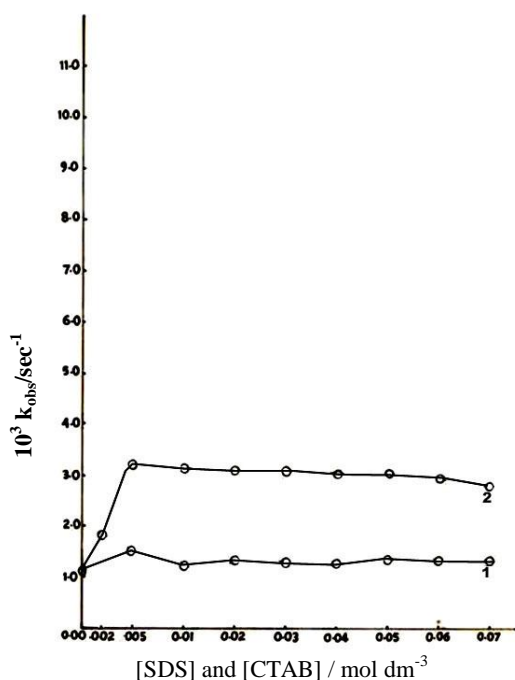


Figure 7. k_{obs} versus micelles, SDS[1], CTAB[2]

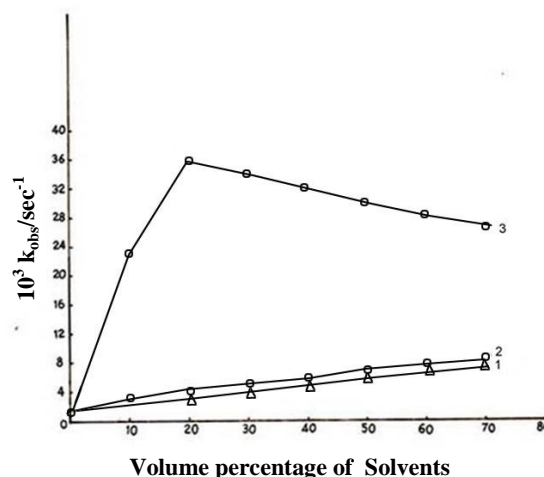


Figure 8. k_{obs} versus volume percentage of solvents Acetic Acid[1] Methanol[2] Acetonitrile [3]

Conclusion

In conclusion analysis of the results can supply information about the mode of action on reaction condition. The mechanistic pathways of Amino Acid Oxidation occur probably through an intermediate of Amino Acid Radical type which leads further to Keto Acid. The present study also give some importance in understanding natural ageing and Oxidative stress process mainly due to generation of free radicals in vivo. This experiment also provides method of synthesis of α -keto acid from amino acid (L-Histidine).

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