

MECHANISTIC OXIDATION OF CYANOCOBALAMIN (VIT-B₁₂) BY POTASSIUM PERMANGANATE IN ACIDIC MEDIUM

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Article Received on
01 June 2015,

Revised on 26 June 2015,
Accepted on 19 July 2015

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ABSTRACT

The kinetics of oxidation of [CCA] by permanganate in acidic medium at a constant ionic strength of 0.054 mol dm⁻³ has been studied spectrophotometrically. The reaction between permanganate and CCA in acidic medium exhibits 1:3 stoichiometry. The reaction shows first order in permanganate and has less than unit order dependence each in both [CCA] and [H⁺] and retarding effect of [MnO₄⁻] under the reaction conditions. The reaction is shown to proceed via a [CCA] complex, which decomposes in a rate-determining step to give intermediates followed by fast step to give the products. The reaction constants involved in the different steps of the mechanisms were calculated. The activation parameters with respect to slow step of the

mechanism were computed and discussed. The thermodynamic quantities were also determined for the reaction.

KEY WORDS: Cyanocobalamin, potassium permanganate, kinetic oxidation, double beam spectrophotometer.

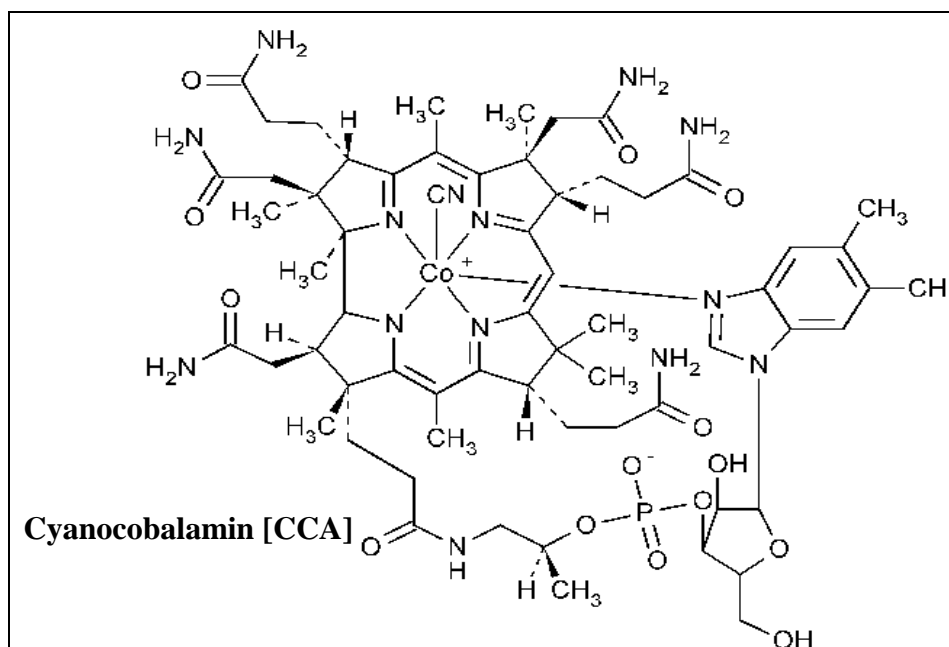
1. INTRODUCTION

Potassium permanganate is widely used as an oxidizing agent as well as an analytical reagent. These reactions are governed by the pH of the medium. Among six oxidation states of manganese from +2 to +7 permanganate, Mn (VII), is the most potent oxidation state in acid medium with reduction potential^[1] 1.69 V of Mn(VII)/ Mn(VI) couple and 1.51 V of Mn(VII)/Mn(II) couple. The oxidation by permanganate ions finds extensive application in organic synthesis.^[2] During oxidation by permanganate it is evident that permanganate is reduced to various oxidation states in acidic, alkaline and neutral media. According to insauti et al,^[3] it has several advantages as an analytical reagent.

The manganese chemistry involved in these multistep redox reactions is an important source of information as the manganese intermediate are relatively easy to identify when they have sufficiently long life times and oxidation states of the intermediate permit useful conclusions as to the possible reaction mechanisms including the nature of intermediates. In acidic medium it exists in the different forms HMnO_4 , H_2MnO_4^+ , HMnO_3 , and Mn_2O_7 and depending on the nature of the reductant, the oxidant has been assigned both inner sphere and outer sphere pathway in their redox reaction.^[4-5]

In earlier report on permanganate oxidation in acidic media, it has been observed that some investigators^[6] have observed the induction period and some have noticed^[7] autocatalytic nature either by Mn (II) or by one of the products and we have not observed such type complications. Hence it is worthwhile to study the permanganate oxidation in acid medium. Cyanocobalamin Vitamin B₁₂; CN-Cbl; anacobin; alpha(5,6Dimethylbenzimidazolyl), cyanocobamide, cyanocob(III)alamin, methylbenzimidazolylcobamide, Co(alpha)[(alpha)(5,6Dimethylbenzimidazolyl)]Co(beta)-cyanocobamide; cobalamin [Cobalt+(vit)amin] is a compound containing the substituted corrin ring (polyaromatic ring consisting of 4 pyrrole subunits which are joined by methylene links on opposite sides and the two of the pyrroles are joined directly) and 5,6-dimethylbenzimidazole as the aglycon attached by a glycosyllin. Vitamin B₁₂ is a cyanide ion substituted cobalamin derivative (cyanocobalamin) with the presence of cobalt mineral at 6 position and the structure of cyanocobalamin [CCA] shown in Scheme 1. Cyanocobalamin usually does not occur in living organisms, but animally can convert commercially produced cyanocobalamin into active (co-factor) forms of the vitamin, such as methylcobalamin. The amount of cyanide liberated in this process is so small that its toxicity is negligible.^[8]

Cyanocobalamin is active drug, we can not found any report in literature. Hence we studied kinetics on cyanocobalamin. Vitamin B₁₂ is the only vitamin which contains metal ion (trivalent cobalt). Cobalamin is some times defined as the synonym of vitamin B₁₂ although they are not same compound but closely related compounds to fulfill acid role. Cobalamin analogs prepared by this method include the naturally occurring coenzymes methylcobalamin and cobylamide and also other cobalamins which do not occur naturally, such as vinylcobalamin, carboxymethyl cobalamin and cyclohexyl cobalamin.



Scheme 1

Vitamin B₁₂ is needed in various body processes including the manufacture and the maintenance of red blood cells, synthesis of DNA, stimulate of nerves cells, growth protein and energy release. It is used to treat the absence of intrinsic factor which is responsible for the absorption of B₁₂ from the intestine. In case of cyanide poisoning the patient is given hydroxocobalamin, which is a precursor to cyanocobalamin. The hydroxocobalamin which the cyanide ion and forms cyanocobalamin which can then be secreted by the kidney. This has been used for many years in France and was approved by the FDA in Dec 2006, marked under the name cyanokit.^[9] It is used in particularly pernicious anemia and other megaloblastic anemia and associated neuropathy. Vitamin B₁₂ is administered subcutaneously, intramuscularly or orally. The oral use of cyanocobalamin may lead to several allergic reactions such as hives, difficult breathing, swelling of the face, lips, tongue or throat. Less serious side effects may include head ache, nausea, stomach upset, joint pain, itching or rash.^[10]

2. EXPERIMENTAL

2.1 Materials and Reagents

All reagents were of analytical reagent grade and Millipore water was used throughout the work. A solution of cyanocobalamin was prepared by dissolving an appropriate amount of solid sample in millipore water. The purity of cyanocobalamin [CCA] was checked by its m.p 298 °C (Lit. m.p. 290-300 °C).^[11] The required concentration of [CCA] was used from its

stock solution. The stock solution of permanganate was prepared by dissolving potassium permanganate in water and concentrations were ascertained by titration against oxalic acid.^[12] Always freshly prepared and standardized MnO_4^- solutions were used in the kinetics. The manganese (II) solution was made by dissolving manganese sulphate in water. Na_2SO_4 and H_2SO_4 were used to provide the required ionic strength and acidity respectively. The pH of the medium in the solution was measured by using pH meter.

2.2 Instruments used

For kinetics measurements, double beam spectrophotometer and pH meter was used.

2.3 Kinetic procedure

All kinetic measurements were conducted under pseudo-first order conditions where the drug was maintained in excess over the permanganate ion concentration at constant temperature of 25 °C, unless otherwise specified. The reaction was initiated by mixing solutions of permanganate and [CCA] which also contained the required amount of sulphuric acid and sodium sulphate. The course of reaction was followed by monitoring the decrease in absorbance of permanganate ion. The progress of reaction was followed spectrophotometrically at 525 nm by monitoring the decrease in absorbance due to KMnO_4 with the molar absorptivity index ' ϵ ' to be $2389 \pm 100 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$, (Fig. 1). The application of Beer's lamberts law for permanganate at 525 nm had earlier been verified, giving ϵ , was found to be $2389 \text{ dm}^3/\text{mol}/\text{cm}$ as a function of time. The kinetic runs were followed more than 85% completion of the reaction, (Table 1).

3. RESULT AND DISCUSSION

3.1 Stoichiometry and product analysis

The reaction mixture containing varying ratios of the [CCA] to $[\text{MnO}_4^-]$ were mixed in the presence of $2.7 \times 10^{-2} \text{ mol dm}^{-3} [\text{H}^+]$ maintaining to a constant ionic strength of $5.4 \times 10^{-2} \text{ mol dm}^{-3}$, and then equilibrated for 24h at room temperature. Estimation of the unreacted $[\text{MnO}_4^-]$ showed that 1 moles of the cyanocobalamin consumed 3 moles of MnO_4^- . The results indicate 1:3 stiochiometry as given in equation (1).



The main reaction products were observed when $[\text{MnO}_4^-]$ more than [CCA], MnO_4^- (0.20 M) was mixed to [CCA] solution (0.002-0.01M) and sulphuric acid (2 M). After an hour, the reaction mixture was cooled in ice bath to which the excess of xylene was added and the

mixture was stored overnight in the refrigerator. The precipitated xylene was filtered onto a weighed crucible, dried, weighed, blank using ether under the same experimental conditions was also run. The finally product were found that acid, nitrosyl hydride and manganese oxide.

3.2 Reaction orders

The reaction orders were determined from slope of $\log k_{\text{obs}}$ versus \log (concentration) plots by varying the concentrations of [CCA] and $[\text{H}^+]$ in turn while keeping all other concentrations constant.

3.3 The evaluation of pseudo-first order rate constants

The permanganate was varied in the range 2.0×10^{-5} to 2.0×10^{-4} mol dm⁻³ and the linearity plots of $\log(\text{abs})$ versus time indicated a reaction order in $[\text{MnO}_4^-]$ as unity. This was also confirmed by varying the $[\text{MnO}_4^-]$, which did not show any change in pseudo-first order rate constant k_{obs} .

3.4 The dependence of rate on the concentration of cyanocobalamin

The effect of variation of [CCA] on the rate of reaction was studied in the concentration range, 4.0×10^{-4} to 4.0×10^{-3} mol dm⁻³, at constant concentrations of MnO_4^- , H^+ and at constant ionic strength. It was observed that as the [CCA] concentration increased, rate of the reaction also increased shows in Table 2. The value of the slope of the plot of $\log k_{\text{obs}}$ versus \log [CCA] was found to be less than unity, which indicates less than unit order with respect to [CCA] concentration shown in Fig. 2.

3.5 The dependence of reaction rate on $[\text{H}^+]$ and $[\text{SO}_4^{2-}]$

The actual concentration of $[\text{H}^+]$ and $[\text{SO}_4^{2-}]$ i.e., $[\text{H}^+]_f$ and $[\text{SO}_4^{2-}]_f$ were calculated using acid-sulphate equilibrium constant^[13] for the various concentration of sulfuric acid. As the reaction was carried out in sulphuric acid, effect of $[\text{H}^+]$ on the reaction rate was studied by varying $[\text{H}^+]$ ion concentration in the range from 6.7×10^{-3} to 10.7×10^{-2} mol dm³. At fixed concentrations of $[\text{MnO}_4^-] = 5.0 \times 10^{-5}$ mol dm⁻³, $[\text{CCA}] = 2.0 \times 10^{-3}$ mol dm³, and $[\text{SO}_4^{2-}] = 5.4 \times 10^{-2}$ mol dm⁻³, the apparent order in $[\text{H}^+]$ obtained was less than unity (Table 3). It was found that k_{obs} increased with increasing $[\text{H}^+]$ concentration. The effect of sulphate concentration on the reaction system was studied by varying it in the range of 2.5×10^{-2} to 2.5×10^{-1} mol dm³, all other reaction conditions being constant and $[\text{H}^+]$ at 2.7×10^{-2} mol dm⁻³ kept constant with the required concentration of H_2SO_4 concentrated from acid and sulfate

equilibrium constant for various $[\text{SO}_4^{2-}]$ added extremely. It was found that the rate constants decreased by increasing $[\text{SO}_4^{2-}]$, (Fig. 3).

3.6 The dependence of rate on ionic strength (I) and dielectric constant (D)

The effect of ionic strength was studied by varying the sodium sulphate concentration 2.5×10^{-2} to $2.5 \times 10^{-1} \text{ mol dm}^{-3}$ at constant concentrations of permanganate, cyanocobalamin and H^+ . It was found that increasing ionic strength had no effect on the rate of reaction. The effect of dielectric constant of the medium was varied by varying acetic acid - water (v/v) content in the reaction mixture from 5 to 25% with all other conditions being maintained constant. As the acetic acid concentration increased in the reaction medium, the rate of reaction was decreased.

3.7 Test for free radicals

The intervention of free radicals was examined as follows, the reaction mixture to which a known quantity of acrylonitrile scavenger had been added initially was kept in an inert atmosphere for 5h. Upon diluting with methanol, white precipitate was formed, indicating the intervention of free radicals in the reaction.

3.8 The rate dependence on temperature

The rate of reaction was calculated at different temperatures 15, 20, 25 and 30 °C by varying $[\text{CCA}]$ and $[\text{H}^+]$ concentrations. The rate of reaction increased with increase in temperature. The rate constant, k of the slow step of Scheme was obtained from the intercept of the plots of $1/k_{\text{obs}}$ versus $1/[\text{CCA}]$ and $1/k_{\text{obs}}$ versus $1/[\text{H}^+]$ at different temperatures. The energy of activation was obtained by the plot of $\log k$ versus $1/T$, from which the other activation parameters were calculated.

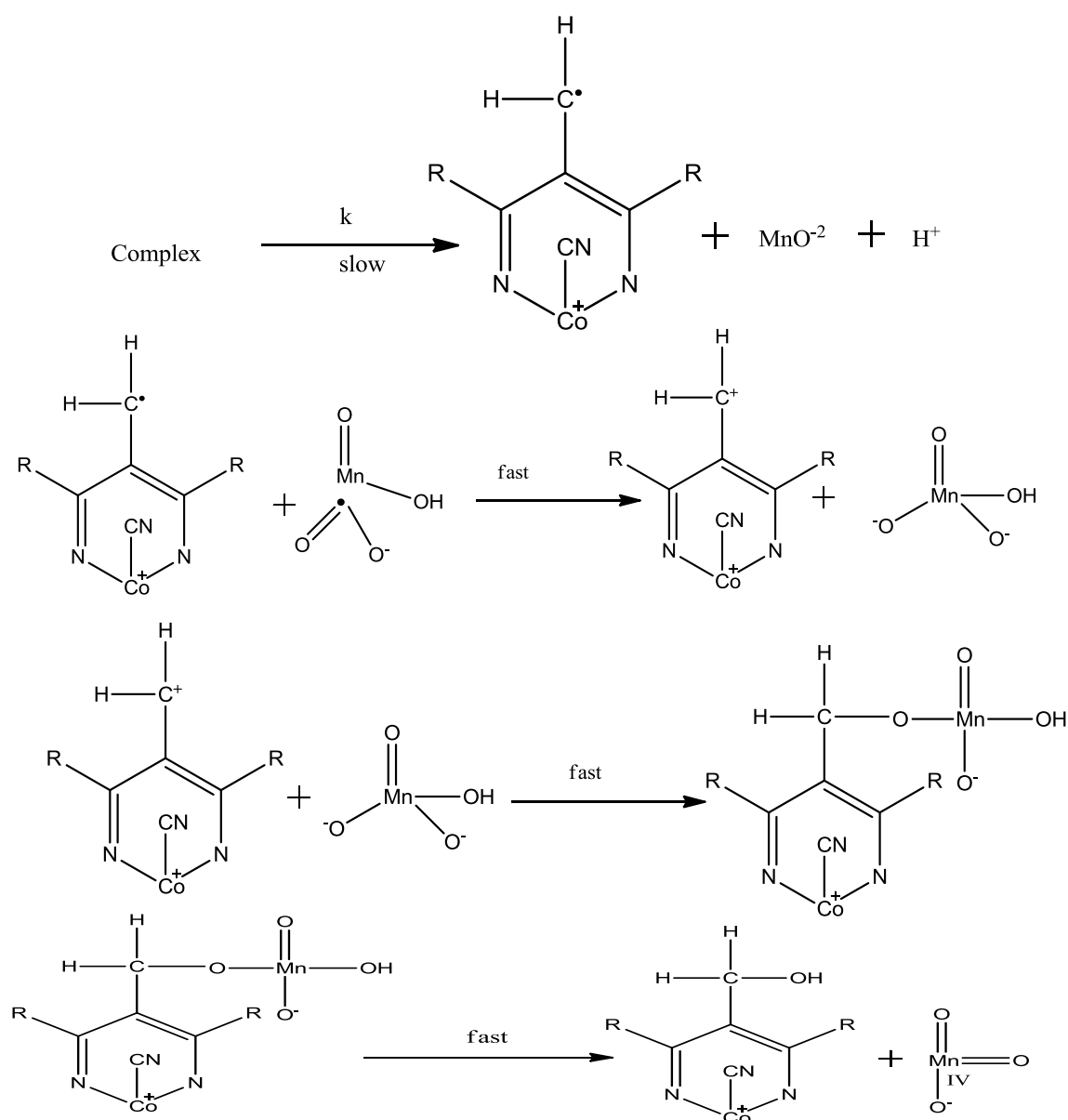
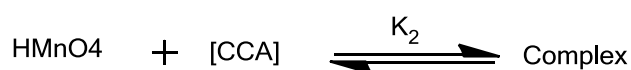
3.9 Uncatalysed mechanism

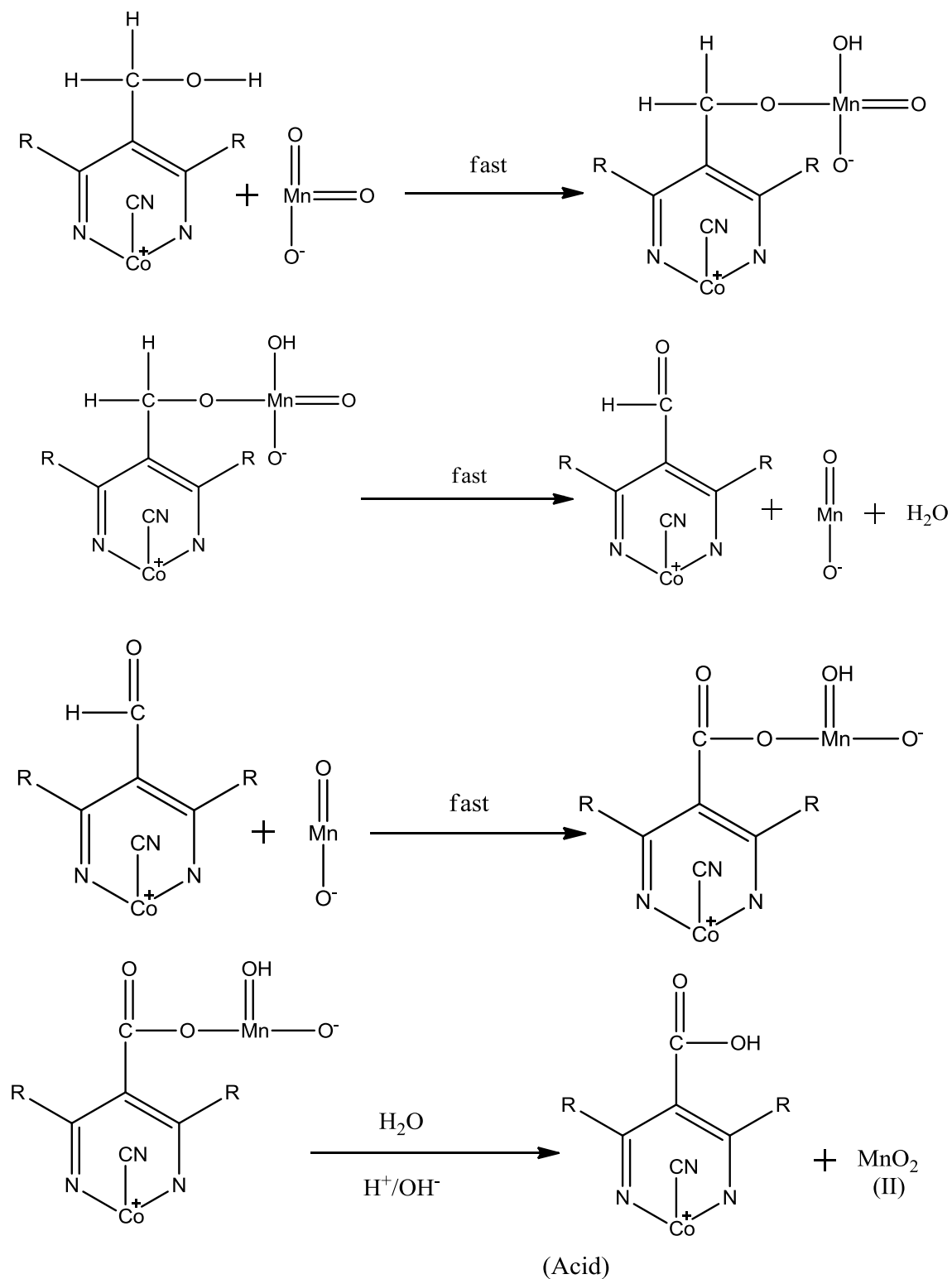
The active species of permanganate in aqueous acid solution may be deduced from the dependence of rate on $[\text{H}^+]_f$ in the reaction medium. The noticeable order of the reaction in $[\text{H}^+]_f$ is significantly less than unity, which may be an indication formation of permanganic acid from permanganate ion. In fact permanganic acid, HMnO_4 is more efficient oxidant species of manganese (VII) than permanganate ion. In addition, it has been observed that the reaction rate increased with increase in $[\text{H}^+]$ and was tending to attain a limiting value at high acidities. At higher acidities protonation is almost complete, leading to the limiting rate,

which indicates that only the protonated form is active thus the acid permanganate equilibrium can be represented by Equation (2).

The reaction between permanganate and [CCA] in sulphuric acid has stoichiometry 1:3 with first order in permanganate and less than unit order in [CCA] and $[H^+]$ concentration. The probable mechanism the oxidation products were identified as acid, nitrosyl hydride and manganese oxide are shown in different steps Schemes 2 and 3.

Scheme 2

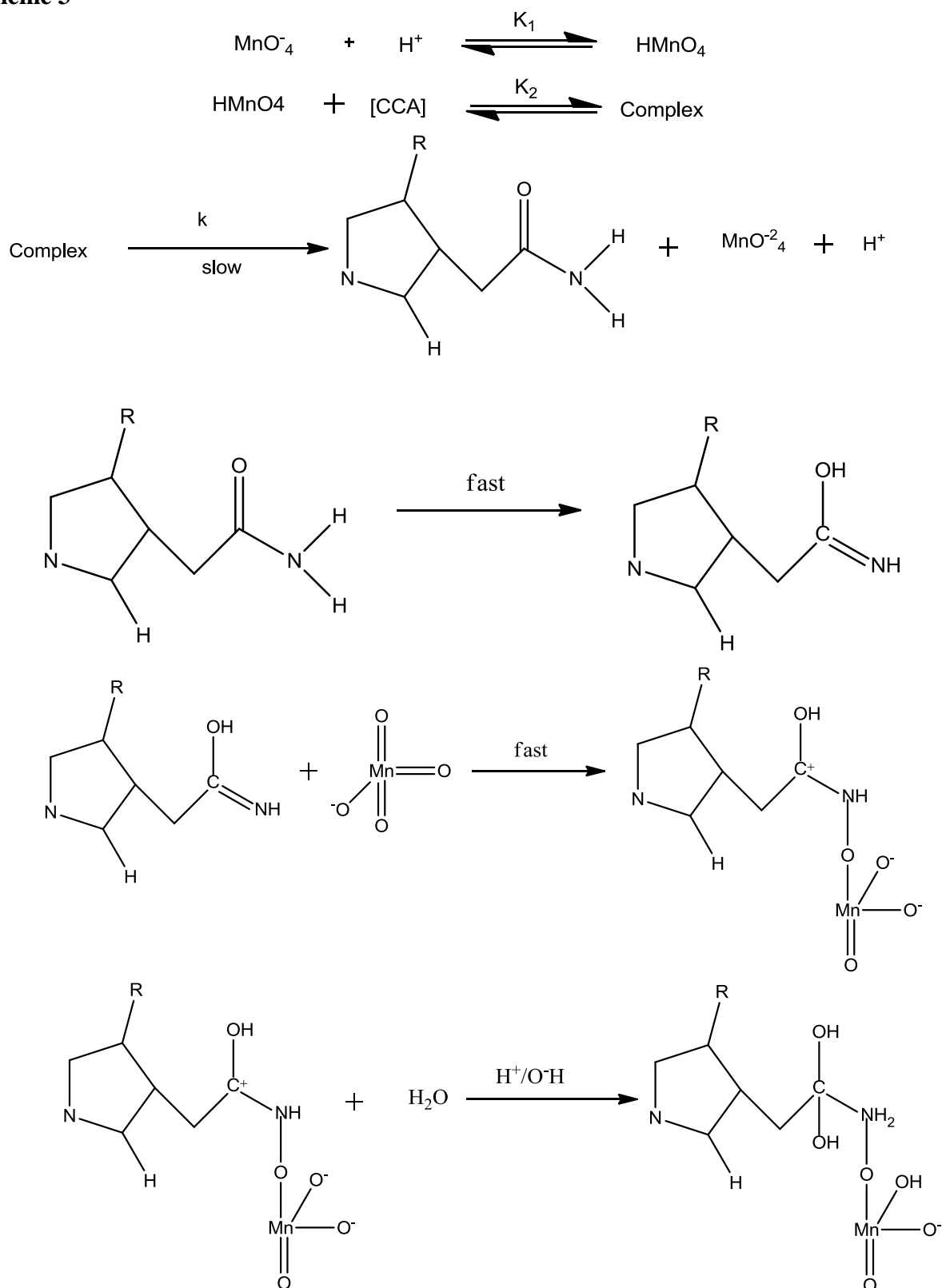


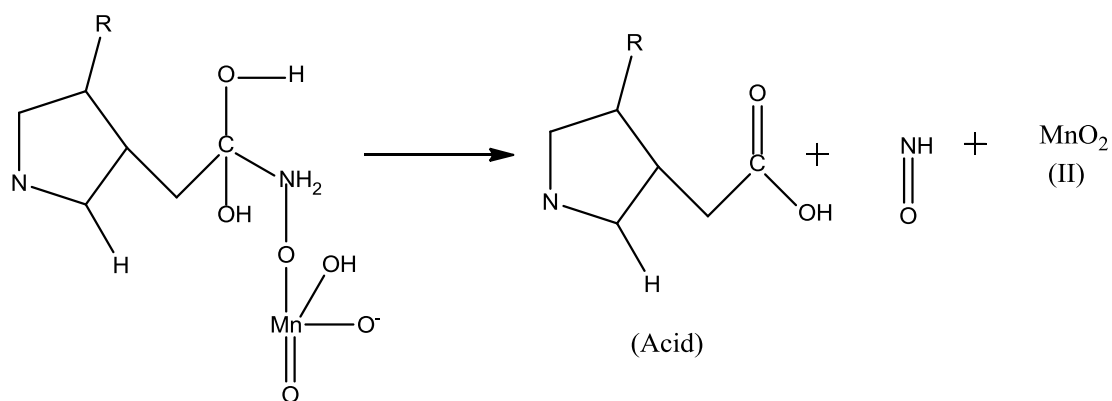


(R = alkyl group, heterocyclic group)

Scheme 2 shows possible mechanism

Scheme 3





(R = alkyl group, heterocyclic group)

Scheme 3 shows possible mechanism

The evidence for the complex formation was also obtained from UV-vis spectra of oxidant, substrate and reaction mixture, in which hypsochromic shift of 11 nm from 269.5 to 258.5 nm was observed at lower temperature (5.0 °C). A Lineweaver-Burk plot also proved the complex formation between oxidant and substrate, which explain less than unity order in [CCA].

From the scheme, the following rate law can be derived as follows

$$\text{Rate} = \frac{-d[\text{MnO}_4^-]}{dt} = k [\text{complex}] [\text{C}] \text{HMnO}_4$$

$$= k K_1 K_2 [\text{CCA}]_f [\text{MnO}_4^-]_f [\text{H}^+]_f \quad (\text{a})$$

The total concentration of $[\text{MnO}_4^-]_T$ is given as (where T and f refer to total and free concentration respectively)

$$[\text{MnO}_4^-]_T = [\text{MnO}_4^-]_f + [\text{HMnO}_4] + \text{Complex} [\text{C}] \quad (\text{b})$$

$$= [\text{MnO}_4^-]_f + k [\text{H}^+] [\text{MnO}_4^-] + K_1 K_2 [\text{CCA}] [\text{H}^+] [\text{MnO}_4^-]_f \quad (\text{c})$$

$$= [\text{MnO}_4^-]_f \{ 1 + K_1 [\text{H}^+] + K_1 K_2 [\text{CCA}] [\text{H}^+] \} \quad (\text{d})$$

I.e. T and f to total and free concentration

$$[\text{MnO}_4^-]_f = \frac{[\text{MnO}_4^-]_T}{1 + K_1 [\text{H}^+] + K_1 K_2 [\text{H}^+] [\text{CCA}]} \quad (\text{e})$$

$$\text{Similarly, } [\text{H}^+]_f + [\text{HMnO}_4] \quad (\text{f})$$

$$= [\text{H}^+]_f + K_1 [\text{H}^+] [\text{MnO}_4^-] \quad (\text{g})$$

The low concentration of $[\text{H}^+]_f$ used the second form can be neglected therefore

$$[\text{H}^+]_T = [\text{H}^+]_f \quad (\text{h})$$

$$[\text{CCA}] = [\text{CCA}] \quad (\text{i})$$

Substituting the values of $[\text{MnO}_4^-]_f$, $[\text{CCA}]_f$ and $[\text{H}^+]_f$ in equation (a)

$$\text{Rate} = \frac{kK_1K_2[\text{CCA}]_T[\text{MnO}_4^-]_T[\text{H}^+]}{1 + K_1[\text{H}^+] + K_1K_2[\text{H}^+][\text{CCA}]} \quad (\text{j})$$

$$K_{\text{obs}} = \frac{kK_1K_2[\text{CCA}][\text{H}^+]}{1 + K_1[\text{H}^+] + K_1K_2[\text{H}^+][\text{CCA}]} \quad (\text{k})$$

The rate equation (k) can be rearranged into the following form, which is suitable for verification

$$\frac{1}{K_{\text{obs}}} = \frac{1}{kK_1K_2[\text{CCA}][\text{H}^+]} + \frac{1}{kK_2[\text{CCA}]} + \frac{1}{k} \quad (\text{L})$$

According to equation (L), other conditions K_1 , K_2 , k being constant, plots of $1/k_{\text{obs}}$ versus $1/[\text{CCA}]$ and $1/k_{\text{obs}}$ versus $1/[\text{H}^+]$, should be linear and are found to be at different temperatures, (Fig. 4). The slopes and intercept of such plots lead to the values of K_1 , K_2 and k at 298K as $20 \pm 1.3 \text{ mol}^{-1} \text{ dm}^3$, $1.22 \pm 0.05 \text{ mol}^{-1} \text{ dm}^3$ and $0.56 \pm 0.02 \text{ S}^{-1}$ respectively. Using these values, the experimental rate constants can be computed. There is a reasonable agreement between the calculated and experimental rate constants. The thermodynamic quantities for the first and second equilibrium steps of Scheme can be evaluated as follows. The $[\text{CCA}]$ and $[\text{H}^+]$ as shown in Table 3 were varied at different temperatures. The plots of $1/k_{\text{obs}}$ versus $1/[\text{CCA}]$ and $1/k_{\text{obs}}$ versus $1/[\text{H}^+]$ should be linear. From the slopes and intercepts, the values of K_1 and K_2 were calculated at different temperatures, and these values are shown in Table 4. The Vant't Hoff plots were made for variation of K_1 and K_2 with temperature ($\log K_1$ versus $1/T$ and $\log K_2$ versus $1/T$). The values of enthalpy of reaction ΔH , entropy of reaction ΔS , and free energy of reaction ΔG were calculated at first and second equilibrium steps. A comparison of the ΔH value of second step of Scheme with that of ΔH^\ddagger ($15.9 \pm 0.7 \text{ kJ mol}^{-1}$) obtained for the slow step of the reaction shows that these values mainly refer to the rate limiting step, supporting the fact that the reaction before rate determining step is fairly fast and it involves low activation energy.^[14] The ionic strength had no effect on rate of reaction which is in the right direction of involvement of neutral species. However, in the present study, an increase in the content of acetic acid in the reaction medium leads to the decrease in the rate of reaction which is contrary to the Amis theory. Perhaps the effect is countered substantially by the formation of active reaction species to a greater extent in high relative permittivity media leading to the net increase in the rate.^[15] The moderate values of ΔH^\ddagger and ΔS^\ddagger were both favorable for electron transfer processes. The negative value of ΔS^\ddagger ($-195 \pm 10 \text{ JK}^{-1} \text{ mol}^{-1}$) suggests that intermediate complex is more ordered than the reactants.^[16] The observed modest enthalpy of activation and a relatively low

value of the entropy of activation as well as a higher rate constant of the slow step indicate that the oxidation presumably occurs via inner-sphere mechanism. This conclusion is supported by earlier observation.^[17]

Table 1: Example run for the oxidation of [CCA] by KMnO_4 in acidic medium at 25 °C.

Time (min)	Optical density (360nm)	$[\text{MnO}_4^-] \times 10^{-5}$ (mol dm^{-3})
0.5	0.4512	8.59
1.0	0.4123	7.85
1.5	0.3845	7.32
2.0	0.3498	6.66
2.5	0.3182	6.06
3.0	0.2846	5.42
3.5	0.2419	4.61
4.0	0.2062	3.93
4.5	0.1769	3.37
5.0	0.1539	2.93
5.5	0.1128	2.15
6.0	0.0923	1.76
6.5	0.0782	1.49

Table 2: Effect of variation of $[\text{KMnO}_4]$ and $[\text{CCA}]$ concentration on the oxidation of $[\text{CCA}]$ by permanganate in aqueous acidic medium at 25 °C.

$[\text{MnO}_4^-] \times 10^{-5}$	$[\text{CCA}] \times 10^{-3}$	$k_{\text{obs}} \times 10^{-3} (\text{s}^{-1})$
3.0	2.0	3.8
5.0	2.0	5.8
8.0	2.0	6.7
1.0	2.0	2.0
3.0	2.0	3.2
5.0	4.0	6.4
5.0	6.0	7.2
5.0	8.0	2.0
5.0	2.0	2.5
5.0	4.0	3.1

Table 3: Effect of variation of $[\text{H}^+]$ and $[\text{MnO}_4^-]$ concentrations on the oxidation of $[\text{CCA}]$ by KMnO_4 in aqueous acidic medium at 25 °C.

$[\text{H}^+] \text{ Mol dm}^{-3}$	$k_{\text{obs}} \times 10^{-3} (\text{s}^{-1})$
7.8	1.0
1.0	1.2
2.7	1.4
5.8	1.8
1.1	2.1

Table 4: (a) Effect of temperature.

Temperature (K)	k (s ⁻¹)
288	0.35
293	0.44
298	0.56
303	0.67

(b) Effect of temperature to calculate K_1 and K_2 for the oxidation of [CCA] by permanganate in acid medium.

Temperature (K)	K_1 (dm ³ mol ⁻¹)	K_2 (dm ³ mol ⁻¹)
288	36	0.45
293	28	0.86
298	20	1.22
303	12	1.64

(c) Activation parameters with respect to slow step.

Parameters	Value
E_a (KJ mol ⁻¹)	18.4 ± 0.8
ΔH^\ddagger (KJ mol ⁻¹)	15.9 ± 0.7
ΔS^\ddagger (JK ⁻¹ mol ⁻¹)	-195 ± 10
ΔG^\ddagger (KJmol ⁻¹)	74.1 ± 2.5

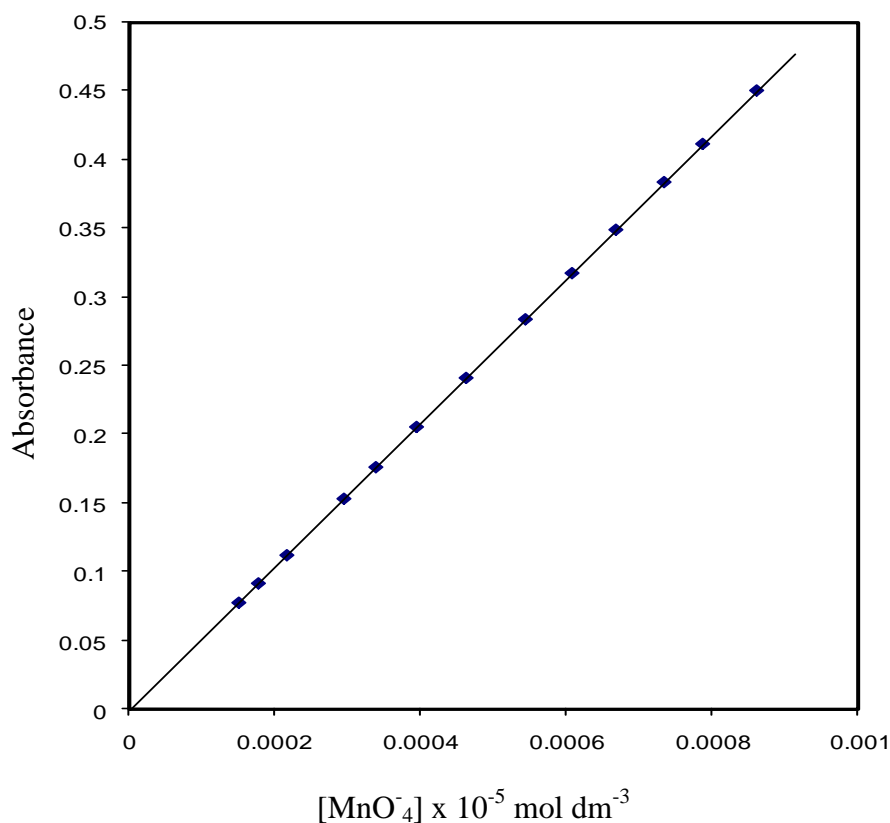


Figure I .Verification of Beer's Lamberts law for the potassium permanganate in acidic medium at 25 °C $[H^+] = 0.027 \text{ mol dm}^{-3}$; $[MnO_4^-] = 5.0 \times 10^{-5} \text{ mol}^{-1} \text{ dm}^{-3}$

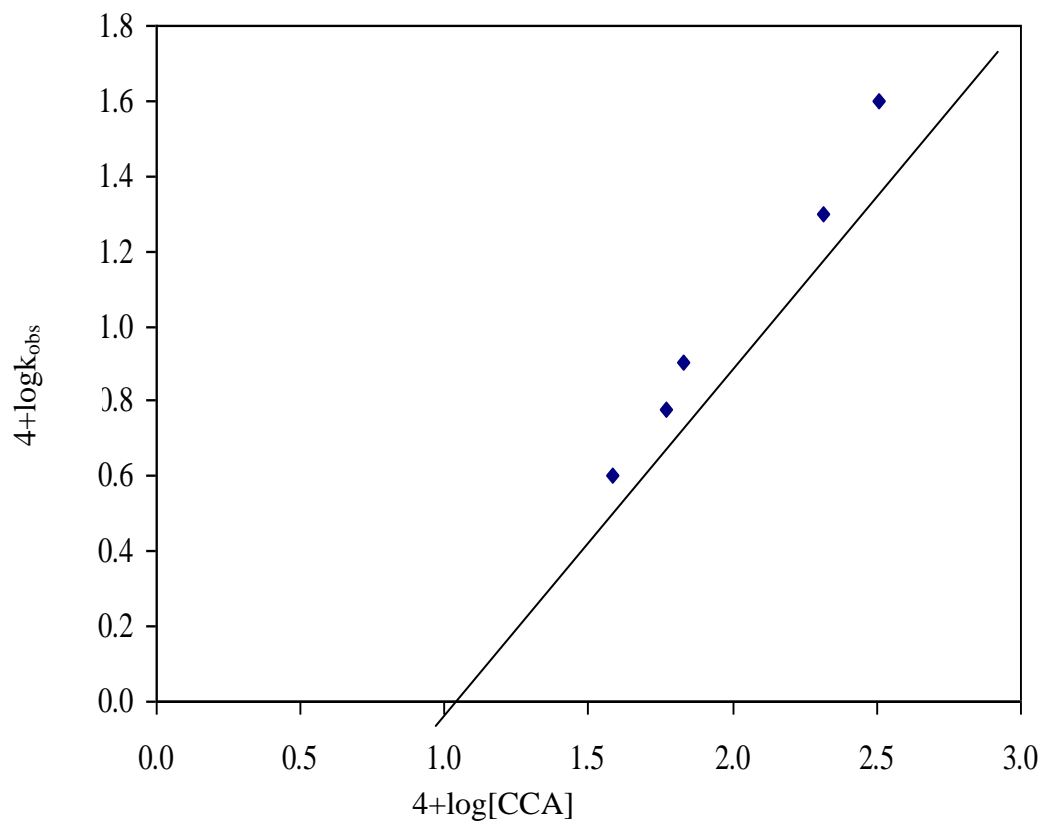
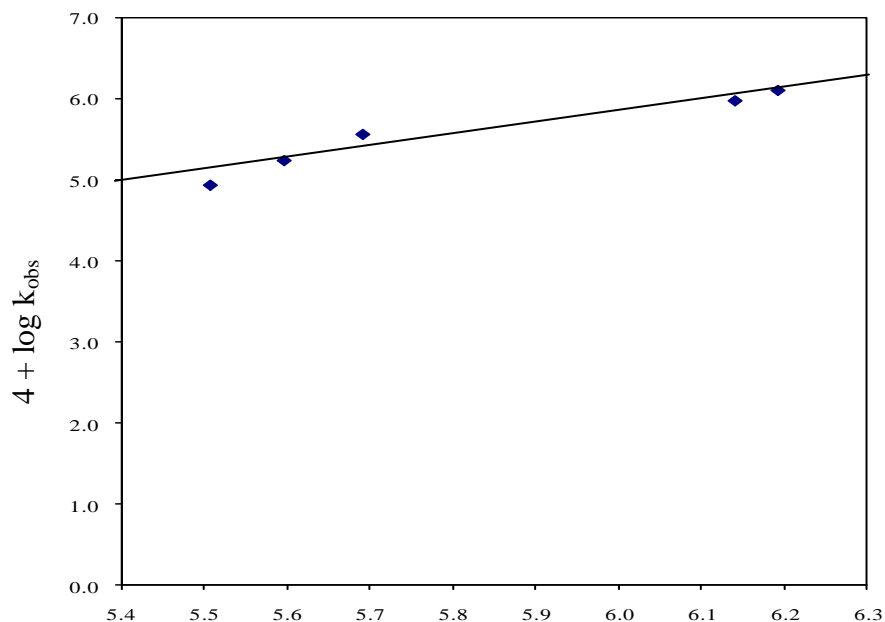


Figure II. Order with respect to [CCA] concentrations on the oxidation of [CCA] by KMnO_4 in aqueous acidic medium at 25 °C (Conditions as in (Table 2))



$4 + \log [H^+]$

Figure III. Order with respect to $[H^+]$ concentrations on the oxidation of [CCA] by $KMnO_4$ in aqueous acidic medium at 25 °C (Conditions as in Table 3)

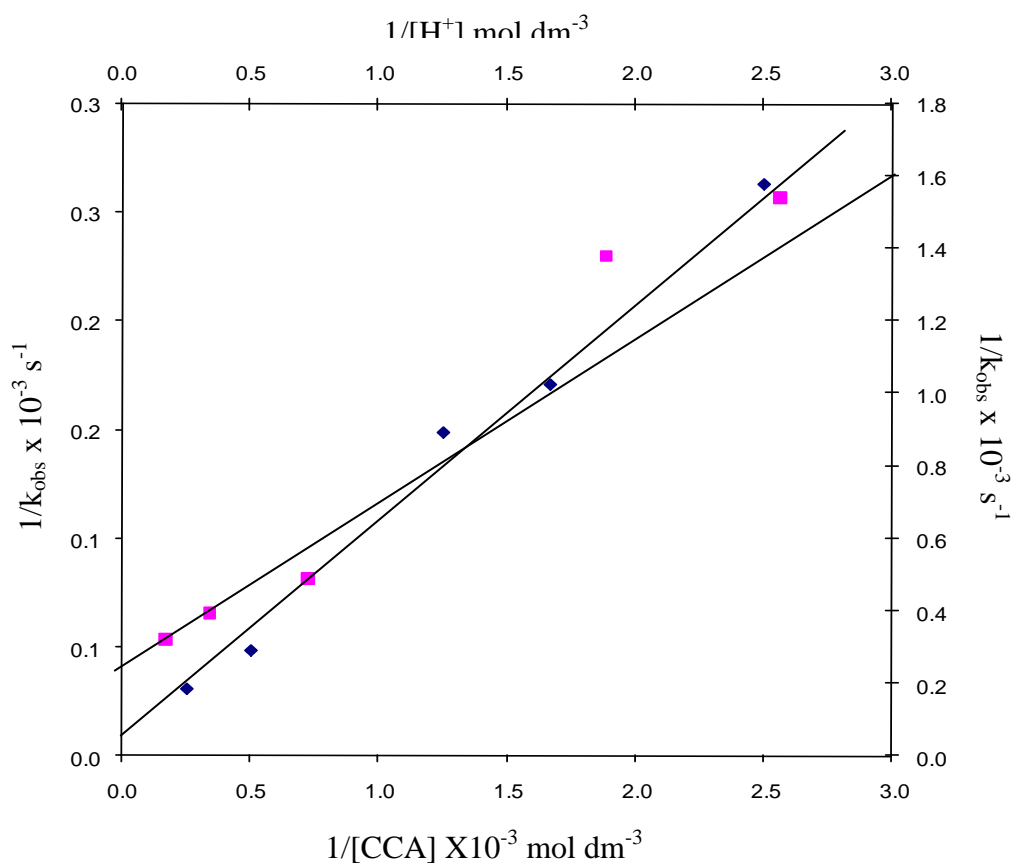


Figure IV. Verification of rate law (k) in the form of (b) for the oxidation of [CCA] by $[KMnO_4]$ at 25 °C. (Pink Dot shows $1/k_{obs}$ V/S $1/[CCA]$); (Blue Dot shows $1/k_{obs}$ V/S $1/[H^+]$)

4. CONCLUSION

The kinetics of the permanganate oxidation of cyanocobalamin in a strong acid medium was investigated using the spectrophotometric technique at five different temperatures. The main active species of permanganate is HMnO_4 . The role of hydrogen ion is crucial to the reaction. The proposed mechanism is dependable with all the experimental data.

ACKNOWLEDGEMENTS

The authors wish to thank the Principal of S.B. Arts and K.C.P. Science College, B.L.D.E. Association Bijapur for their support.

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