IJPSR (2012), Vol. 3, Issue 12 **(Research Article)**

INTERNATIONAL JOURNAL
OF
PHARMACEUTICAL SCIENCES
AND
RESEARCH

Received on 20 August, 2012; received in revised form 26 October, 2012; accepted 25 November, 2012

OXIDATION OF TRICYCLIC ANTIDEPRESSANT AGENT, AMITRIPTYLINE, BY PERMANGANATE IN SULPHURIC ACID MEDIUM: KINETIC AND MECHANISTIC APPROACH

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Keywords:
Kinetics, Mechanism Oxidation,
Amitriptyline, Permanganate

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QUICK RESPONSE CODE

IJPSR:
ICV (2011)- 5.07

Website:
www.ijpsr.com

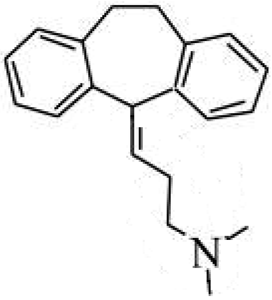
ABSTRACT

The kinetics of oxidation of amitriptyline by potassium permanganate in aqueous sulphuric acid medium at 298K and at a constant ionic strength of 0.20 mol dm^{-3} has been investigated spectrophotometrically. The reaction exhibits 5:4 stoichiometry (5 Amitriptyline:4 $KMnO_4$). The reaction was first order with respect to manganese(VII) concentration. The order with respect to amitriptyline was found to be less than unity (0.80). Increase in acid concentration increased the rate. The order with respect to acid concentration was also less than unity (0.40). The effect of added products, ionic strength and dielectric constant has been studied on the rate of reaction. The oxidation products were identified by using 2, 4 DNP derivative, IR, GCMS spectral studies. A suitable mechanism was proposed on the basis of experimental results. The reaction constants involved in the different steps of the reaction mechanism were calculated. The activation parameters with respect to slow step of the mechanism was determined and discussed.

INTRODUCTION: Potassium permanganate is widely used as an oxidizing agent as well as an analytical and also as disinfectant 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 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 ion finds extensive applications in organic syntheses [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 e.g. it is strong vividly coloured serving as its own indicator. In acidic medium it exists in different forms as $HMnO_4$, $H_2MnO_4^+$, $HMnO_3$, 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 reactions [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 to test such complexity.

Amitriptyline (3-(10,11-dihydro-5*H*-dibenzo[[*a*,*d*]] cyclo heptene-5-ylidene)-*N*, *N*-dimethyl-1-propanamine) (AMT) is a tricyclic antidepressant agent which has also analgesic properties. Whether its analgesic effects are linked to its mood- altering activity or attributable to discrete pharmacological action is unknown. Clinical trials demonstrate that oral amitriptyline achieves at least a good or moderate response in upto two-thirds of patients with post-herpetic neuralgia and threequarters of patients with painful diabetic neuropathy, neurogenic pain syndromes that are often unresponsive to narcotic analgesics. Amitriptyline is an effective drug in patients with diarrhea-dominant IBS. Some studies on the efficacy of this drug have been inconclusive because of the lack of control groups or failure to confirm the diagnosis of IBS by ruling out organic causes. In some cases, amitriptyline has been used in combination with other drugs, making it difficult to recognize the clinical contribution of amitriptyline [8]. The structure of amitriptyline is shown below.



AMITRIPTYLINE

In view of pharmaceutical importance of amitriptyline and lack of literature on the oxidation of this drug by any oxidant and the complexity of the reaction, a detailed study of the reaction becomes important. An understanding of the mechanism allows the chemistry to be intrepted, undestood and predicted. The biotransformation of this drug finds applications in pharmacuetical industry. To the best of our knowledge there are no reports on the oxidation of amitriptyline by permanganate in an acidic media.

The present investigation is aimed at checking the reactivity of amitriptyline towards permanganate, at determining the redox chemistry of the Mn(VII) in such media, and to arrive at plausible mechanism. For effective use and application of both the reductant and the oxidant in industries and laboratories, the kinetics and mechanism of their reaction is therefore reported in this paper.

EXPERIMENTAL:

Chemicals and reagents: All reagents were of analytical reagent grade and Millipore water was used throughout the work. A solution of amitriptyline (Aldrich Laboratories) was prepared by dissolving an appropriate amount of recrystallised sample in Millipore water.

The purity of amitriptyline (AMT) was checked by its m.p. 195 ^{0}C [Lit.m.p.196^{0}C]. The IR spectrum agreed with literature. The required concentration of AMT was used from its stock solution. The stock solution of permanganate was prepared by dissolving potassium permanganate (BDH AR) in water and concentrations were ascertained by titration against oxalic acid [9]. Always freshly prepared and standardized MnO^-_4, solutions were used in the kinetics. The manganese(II) solution was made by dissolving manganese sulphate (AR) in water. The acetic acid (CDH) solution was prepared by dissolving it in water. Na_2SO_4 (AR) and H_2SO_4 (AR) were used to provide the required ionic strength and acidity respectively. The pH of the medium in the solution was measured by ELICO (L1613) pH meter.

Instruments used:

(a) For kinetic measurements, a CARRY 50 Bio UV-vis spectrometer (Varian Victoria-3170, Australia) was used.

(b) For product analysis, a 17A Shimadzu gas chromatography with a QP-5050A shimadzu mass spectrometer using EI ionization technique, and Nicolet 5700-FT-IR spectrometer (Thermo, U.S.A.) were used. For pH measurements, ELICO pH meter model LI613 was used.

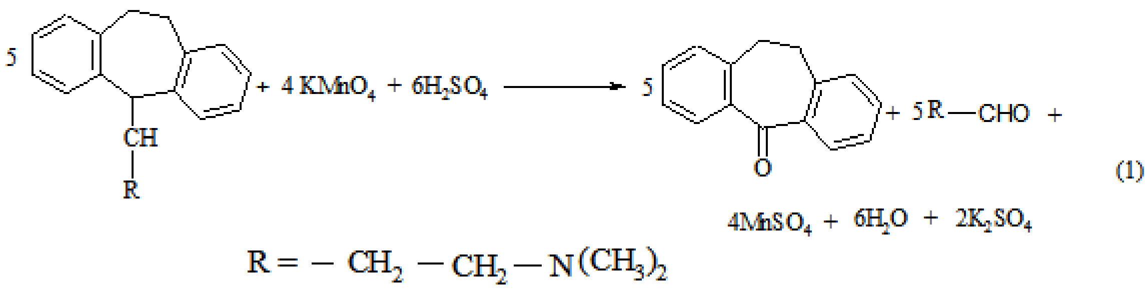
Kinetic measurements: All kinetic measurements were conducted under pseudo-first order conditions where the drug was maintained in excess over the permanganate ion concentration at constant temperature of 25 ± 0.1 ^{0}C unless otherwise stated. The reaction was initiated by mixing thermostatted solutions of permanganate and AMT which also contained the required amount of sulphuric acid and sodium sulphate. The course of reaction was followed by monitoring the decrease in absorbacne of permanganate ion at its absorption maximum, 525 nm.

The application of Beer's law for permanganate at 525 nm had earlier been verified, giving $\varepsilon = 2389 \pm 50$ dm^3 mol^{-1} cm^{-1} (Literature[10] $\varepsilon = 2400$ dm^3 mol^{-1} cm^{-1}) as a function of time. The kinetic runs were followed more than 85% completion of the reaction. The pseudo–first order rate constants, k_{obs} were calculated from the plots of log (absorbance) versus time plots which were linear.

The k_{obs} values were reproducible within ± 5% and are the average of at least three independent kinetic runs (Table 1).

RESULTS AND DISCUSSION:

Stoichiometry and product analysis: The reaction mixture containing varying ratios of the AMT to MnO_4^- were mixed in the presence of 2.7 x 10^{-2} mol dm^{-3} $[H^+]$ maintaining to a constant ionic strength of 0.20 mol dm^{-3}, then equilibrated for 24h at room temperature. Estimation of the unreacted $[MnO_4^-]$ showed that 5 moles of the amitriptyline consumed 4 moles of MnO_4^-. The results indicate 5:4 stoichiometry as given in equation (1).



(1)

$$R = -CH_2-CH_2-N(CH_3)_2$$

The main reaction products were eluted with heptane, which were identified as trans-4-aminocyclohexanal, and dibenzosuberone. Mn^{2+} was identified by UV-visible spectra and spot test [11]. The trans-4-aminocyclohexanal product was identified by its 2, 4-DNP derivative. To find the yield of aldehyde under these experimental conditions when [AMT] more than $[MnO_4^-]$, AMT (0.18 M) was mixed to permanganate 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 2,4-DNP solution was added and the mixture was stored overnight in the refrigerator.

The precipitated 2,4-DNP product was filtered onto a weighed crucible, dried, and weighed. A blank using aldehyde under the same experimental conditions was also run. It was found that the yield of 2,4-DNP derivative was 55% of the theoretical. The nature of trans-4-aminocyclohexanal was confirmed by its IR spectrum which showed a C=O stretching at 1715 cm^{-1} indicating the presence of C=O group and C-H stretching at 2100 cm^{-1}. It was further confirmed by its melting point 107 ^{0}C (lit. m.p. 108-113^{o}C) and trans-4-aminocycloxexanal was subjected to GC-MS on a 17A Shimadzu gas chromatography with a QP-5050A shimadzu mass spectrometer using EI ionization technique.

The mass spectrum (**Figure 1**) showed a molecular ion peak at 115 amu; hence trans-4-aminocyclohexanal was confirmed. Another product dibenzosuberone (5H-dibenzo-10,11dihydro [a,d] cyclohepten-5-one) was identified by IR spectrum contained a strong absorption at 1645 cm^{-1}.

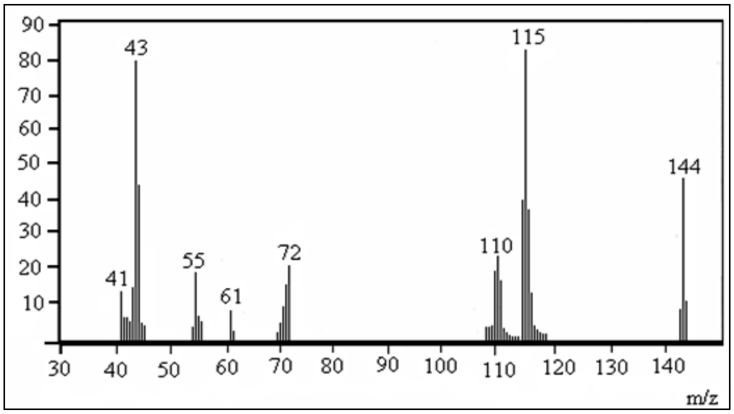


FIGURE 1: GC- MASS SPECTRUM OF *TRANS*-4-AMINO CYCLO-HEXANAL WITH ITS MOLECULAR ION PEAK AT 115 AMU

It was further confirmed by its melting point 31^{o}C (lit. m.p. 32-34^{o}C) and dibenzosuberone was subjected to GC-Mass spectral analysis (**Figure 2**) which showed molecular ion peak (M+1) at 208 amu confirming a dibenzosuberone.

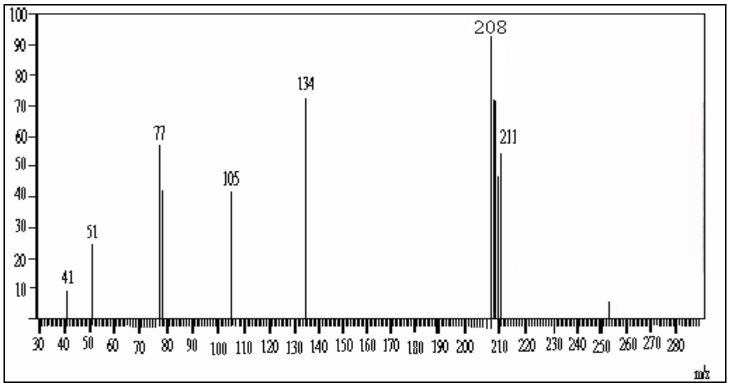


FIGURE 2: GC- MASS SPECTRUM OF DIBENZOSUBERONE WITH ITS MOLECULAR ION PEAK AT 208 AMU

This product was also in good agreement with earlier literature [12]. All other peaks observed in GC-MS can be interpreted in accordance with the observed structure of the product. It was observed that trans-4-aminocyclohexanal and dibenzosuberone do not undergo further oxidation under the present kinetic conditions.

Regression analysis of experimental data to obtain the regression coefficient r and standard deviation S, of points from the regression line was performed using Microsoft Excel-2003 programme.

Reaction Orders: The reaction orders were determined from slope of logk_{obs} versus log (concentration) plots by varying the concentrations of AMT and H^+ in turn while keeping all other concentrations constant.

The evaluation of pseudo-first order rate constants

The permanganate was varied in the range 2.0 X 10^{-5} to 2.0 X 10^{-4} mol dm^{-3} and the linearity plots of log(abs) versus time indicated a reaction order in $[MnO_4^-]$ as unity. This was also confirmed by varying the $[MnO_4^-]$, which did not show any change in pseudo-first order rate constant k_{obs} (**Table 1**).

TABLE 1: EFFECT OF $[MnO_4^-]$, [AMT], $[H^+]$ AND $[SO_4^{2-}]$ ON PERMANGANATE THE OXIDATION OF AMT IN ACIDIC MEDIUM AT 298K, I = 0.20 mol dm^{-3}.

$[MnO_4^-]$ x10^4 (mol dm^{-3})	[AMT] x10^3 (mol dm^{-3})	$[H^+]$ x10^2 (mol dm^{-3})	$[SO_4^{2-}]$ x10^2 (mol dm^{-3})	k_{obs} x 10^3 (s^{-1})	k_{Cal} x 10^3 (s^{-1})
0.2	2.0	2.7	5.4	1.9	2.0
0.5	2.0	2.7	5.4	2.0	2.0
0.8	2.0	2.7	5.4	1.9	2.0
1.0	2.0	2.7	5.4	1.8	2.0
2.0	2.0	2.7	5.4	1.9	2.0
0.5	0.4	2.7	5.4	0.3	0.4
0.5	0.6	2.7	5.4	0.5	0.6
0.5	0.8	2.7	5.4	0.7	0.8
0.5	2.0	2.7	5.4	2.0	2.1
0.5	4.0	2.7	5.4	2.6	2.5
0.5	2.0	0.7	5.4	1.0	1.0
0.5	2.0	1.0	5.4	1.2	1.2
0.5	2.0	2.7	5.4	2.0	2.1
0.5	2.0	5.8	5.4	2.8	2.7
0.5	2.0	11.7	5.4	3.1	3.1
0.5	2.0	2.7	2.5	1.9	2.0
0.5	2.0	2.7	5.4	2.0	2.0
0.5	2.0	2.7	10.8	2.2	2.0
0.5	2.0	2.7	17.8	2.1	2.0
0.5	2.0	2.7	25.5	2.0	2.0

The dependence of rate on the concentration of Amitriptyline: The effect of variation of AMT on the rate of reaction was studied in the concentration range, 4.0 x 10^{-4} to 4.0 x 10^{-3} mol dm^{-3}, at constant concentrations of MnO^-_4, H^+ and at constant ionic strength. It was observed that as the AMT concentration increased, rate of the reaction also increased (Table1). The value of the slope of the plot of logk_{obs} versus log[AMT] was found to be less than unity, which indicates less than unit order with respect to AMT concentration. The less than unit order in [AMT] was also noticed by the plot of k_{obs} versus $[AMT]^{0.80}$ which is linear rather than the direct plot of k_{obs} versus [AMT] (**Figure 3**).

The dependence of reaction rate on $[H^+]$ and $[SO_4^{2-}]$: The actual concentration of $[H^+]$ and $[SO_4^{2-}]$ i.e., $[H^+]_f$ and $[SO_4^{2-}]_f$ 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 $[H^+]$ on the reaction rate was studied by varying $[H^+]$ ion concentration in the range from 7.8 x 10^{-3} to 11.7 x 10^{-2} mol dm^{-3}. At fixed concentrations of $[MnO^-_4]$ = 5.0 x 10^{-5} mol dm^{-3}, AMT = 2.0 x 10^{-3} mol dm^{-3}, ionic strength 0.20 mol dm^{-3} and $[SO_4^{2-}]$ = 5.4 x 10^{-2} mol dm^{-3}, the apparent order in $[H^+]$ obtained was less than unity (Table 1). It was found that k_{obs} increased with increasing $[H^+]$ concentration.

This was also confirmed by the plots of k_{obs} versus $[H^+]^{0.40}$ which is linear rather than the direct plot of k_{obs} versus $[H^+]$ (**Figure 4**).

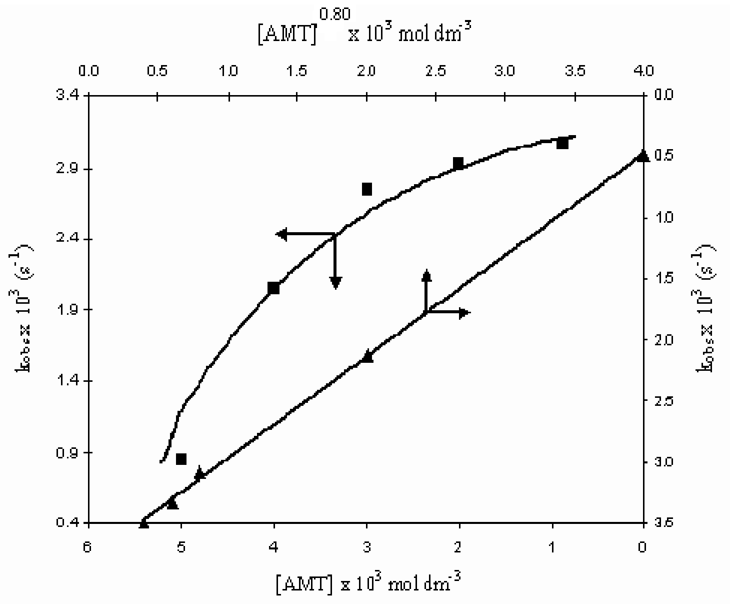


FIGURE 3: Plots of k_{obs} versus $[AMT]^{0.80}$ and k_{obs} versus [AMT] (conditions as given in Table 1)

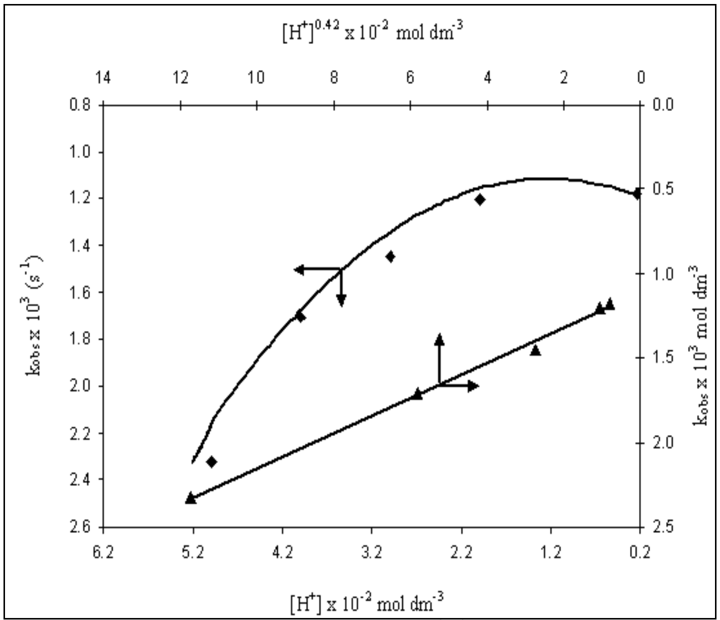


FIGURE 4. Plots of k_{obs} versus $[H^+]^{0.42}$ and k_{obs} versus $[H^+]$ (conditions as given in Table 1)

The effect of sulphate concentration on the reaction system was studied by varying it in the range of 2.5 x 10^{-2} to 2.5 x 10^{-1} mol dm^{-3}, all other reaction conditions being constant and $[H^+]$ at 2.7 x 10^{-2} mol dm^{-3} kept constant with the required concentration of H_2SO_4 concentrated from acid and sulfate equilibrium constant for various $[SO_4^{2-}]$ added extremely. It was observed that $[SO_4^{2-}]$ did not have significant effect on the reaction rate (Table 1).

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 from 0.1 to 1.0 mol dm^3 at constant concentrations of permanganate, amitriptyline 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. The plot of log k_{obs} versus 1/D was linear with negative slope (**Figure 5**).

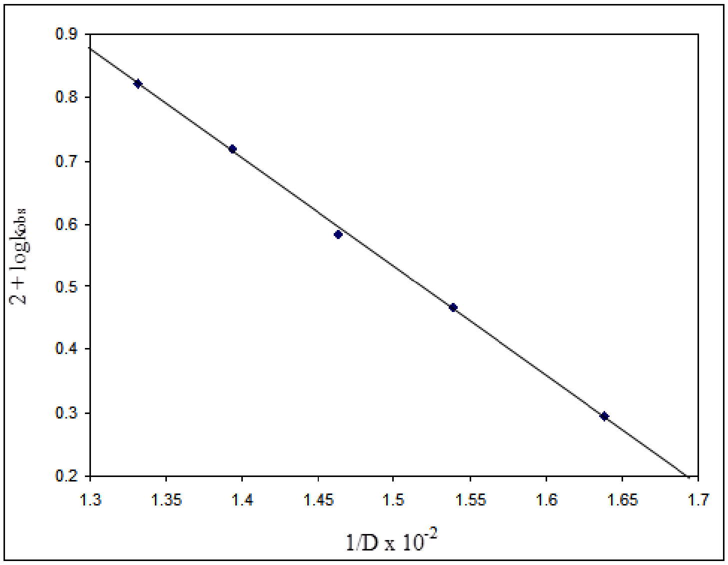


FIGURE 5: EFFECT OF DIELECTRIC CONSTANT ON THE OXIDATION OF AMITRIPTYLINE BY ACID MEDIUM AT 298K

Effect of initially added products: Initially added products, Mn(II), trans-4-aminocyclohexanal and dibenzosuberone did not have any significant effect on the rate of reaction.

Test for Free Radicals: The intervention of free radicals was examined as follows: The reaction mixture (10 cm^3), to which a known quantity (2 cm^3) 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.

The rate dependence on Temperature: The rate of reaction was calculated at different temperatures 15, 20, 25 and 30°C by varying [AMT] and $[H^+]$ concentrations. The rate of reaction increased with increase in temperature.

The rate constant, *k* of the slow step of Scheme 1 were obtained from the intercept of the plots of $1/k_{obs}$ versus 1/[AMT] and $1/k_{obs}$ versus $1/[H^+]$ 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.

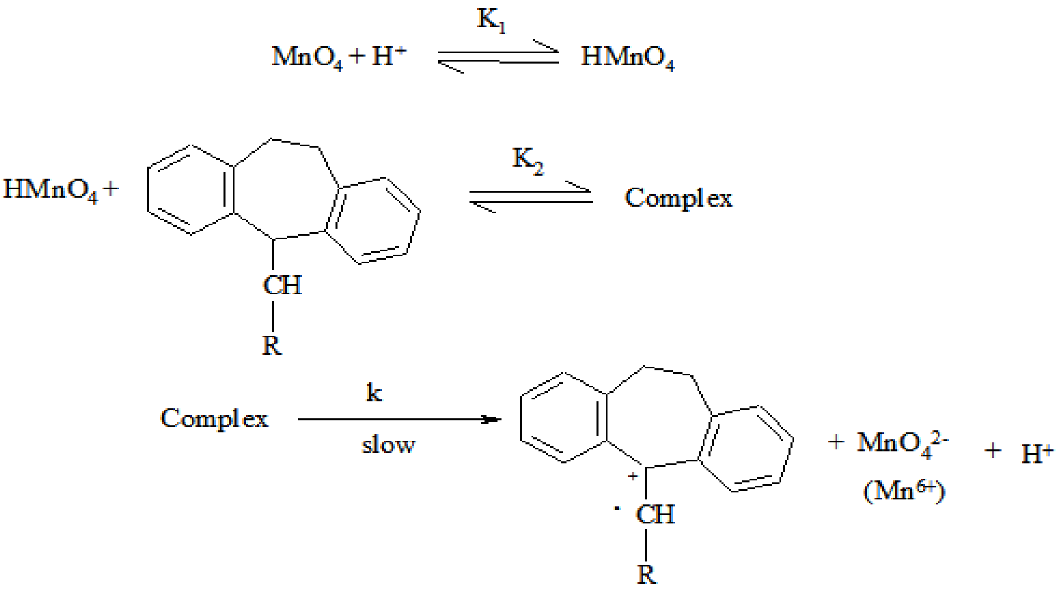
MECHANISM: The active species of permanganate in aqueous acid solution may be deduced from the dependence of the rate on $[H^+]_f$ in the reaction medium. The noticeable order of the reaction in $[H^+]_f$ is significantly less than unity, which may be an indication of the formation of permanganic acid from permanganate ion. In fact, permanganic acid, $HMnO_4$, is a more efficient oxidant species of manganese(VII) than permanganate ion [10]. In addition, it has been observed, that the reaction rate increased with increase in $[H^+]$ 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 Eqn (2).

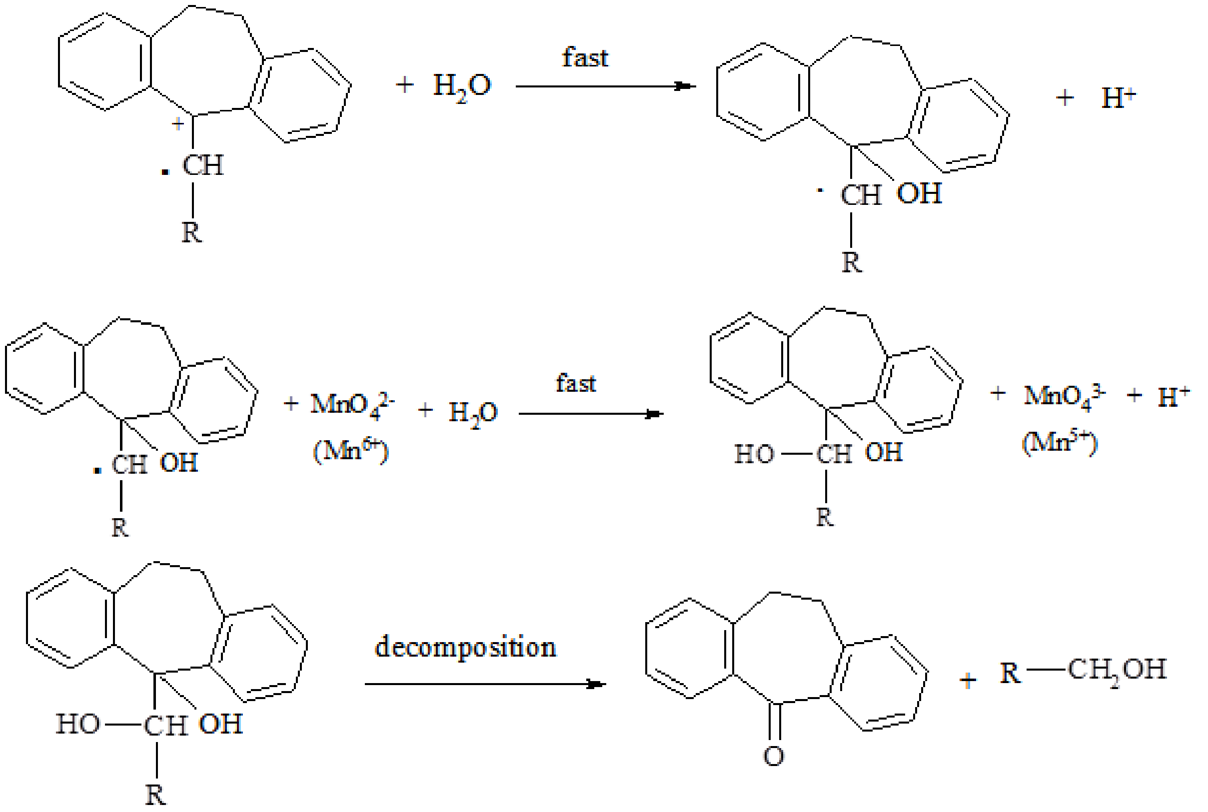
$$MnO_4^{-} + H^+ \overset{K_1}{\rightleftharpoons} HMnO_4 \qquad (2)$$

The reaction between permanganate and AMT in sulphuric acid has a stiochiometry 5:4 with first order in permanganate and less than unit order in AMT and H^+ concentrations. The oxidation products were manganese(II), trans-4-aminocyclohexanal and dibenzosuberone. Based on the experimental results, a mechanism can be proposed, in which all the observed orders in each constituent, such as [oxidant], [reductant] and $[H^+]_f$ may be well accommodated. In view of increasing the rate with increasing in $[H^+]$ ion, in the prior equilibrium step, H^+ reacts with MnO_4^- to form $HMnO_4$ species. Such type of $HMnO_4$ species is evidenced by literature [7].

In view of the apparent less than unit order with [AMT], in the second equilibrium step, $HMnO_4$ reacts with AMT to give the complex (I). Further in the rate determining step the complex decomposes to give the carbocation AMT radical, MnO_4^{2-} (Mn^{6+}) and H^+ species. Such type of carbocation is observed in literature [14]. In a fast step, carbocation AMT radical hydrolyses to give the intermediate compound and H^+. In a further fast step, the intermediate compound (III) reacts with MnO_4^{2-} to give vicinal diol, with generating MnO_4^{3-} and H^+ species.

In a further fast step the vicinal diol decomposes to give dibenzosuberone, 2-amino-3-methyl-1-butanol. In the subsequent last step, the 2-amino-3-methyl-1-butanol reacts with two Mn^{5+} species to give *trans*-4-aminocyclohexanal and Mn^{4+} species and another molecule 2-amino-3-methyl-1-butanol reacts with Mn^{4+} to give Mn^{2+} and give *trans*-4-aminocyclohexanal satisfying stoichiometric observations. The results are accommodated in the following mechanism;





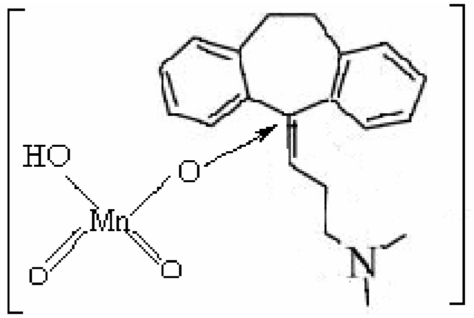
$$R—CH_2OH + 2MnO_4^{3-} + 6H^+ \xrightarrow{fast} R—CHO + 2MnO_2 + 4H_2O$$

$$R—CH_2OH + 2MnO_4^{3-} + 6H^+ \xrightarrow{fast} R—CHO + 2MnO_2 + 4H_2O$$

Where $R = -CH_2 - CH_2 - N(CH_3)_2$

SCHEME 1: DETAILED MECHANISM

The probable structure of complex (C) is given below;



The evidence for the complex formation was also obtained from UV-vis spectra of oxidant, substrate and reaction mixture, in which hypsochromic shift of 10 nm from 318.9 to 308.9 nm was observed at lower temperature (5.0 ^{0}C). A Lineweaver-Burk plot also proved the complex formation between oxidant and substrate, which explains less than unit order in [AMT]. Such type of complex formation between oxidant and substrate has been observed in other studies [14].

From Scheme 1, the following rate law can be derived as follows:

$$\text{Rate} = -\frac{d\,[MnO_4^-]}{dt} = k\,[\text{Complex}]$$

$$= k\,K_2\,[AMT]\,[HMnO_4^-]$$

$$= k\,K_1K_2[MnO_4^-]_f\,[AMT]_f + [H^+] \qquad (3)$$

The total permanganate ion concentration can be written as

$$[MnO_4^-]_T = [MnO_4]_f + [HMnO_4] + [\text{Complex}]$$

$$= [MnO_4^-]_f\,\{\,1 + K_1\,[H^+] + K_1\,K_2\,[AMT]\,[H^+]\,\}$$

$$= [MnO_4^-]_f + K_1\,[H^+]\,[MnO_4^-]_f + K_1\,K_2\,[AMT]\,[H^+]\,[MnO_4^-]_f$$

$$[MnO_4^-]_f = \frac{[MnO_4^-]_T}{\{1 + K_1\,[H^+] + K_1K_2\,[AMT]\,[H^+]\,\}} \qquad (4)$$

Similarly;

$$[H^+]_T = [H^+]_f + [HMnO_4]$$

$$= [H^+]_f + K_1 [H^+] [MnO_4^-]$$

In view of low concentration of $[H^+]$ ion is used, hence $K_1 [H^+] [MnO_4^-]$ are neglected

Therefore;

$$[H^+]_T = [H^+]_f \quad \text{......................5}$$

Similarly;

$$[AMT]_T = [AMT]_f \quad \text{..........................6}$$

where, t and f represents total and free concentration of $HMnO_4^-$.

Substituting the equations (4), (5) and (6), in eq (3) gives equation (7).

$$\text{Rate} = \frac{k\,K_1 K_2\,[MnO_4^-]_T [AMT]_T [H^+]}{1 + K_1 [H^+] + K_1 K_2 [H^+]\,[AMT]}$$

$$k_{obs} = \frac{\text{Rate}}{[MnO_4^-]} = \frac{k\,K_1 K_2 [AMT]\,[H^+]}{1 + K_1 [H^+] + K_1 K_2 [AMT]\,[H^+]} \qquad (7)$$

The rate law (7) may be rearranged to equation (8), which is suitable for verification.

$$\frac{1}{k_{obs}} = \frac{1}{k\,K_1 K_2 [AMT]\,[H^+]} + \frac{1}{k\,K_2 [AMT]} + \frac{1}{k} \qquad (8)$$

According to equation (8), other conditions being constant, plots of $1/k_{obs}$ versus $1/[AMT]$ ($r \geq 0.9918$, $S \geq 0.0047$) and $1/k_{obs}$ versus $1/[H^+]$ ($r \geq 0.9895$, $S \geq 0.0046$) should be linear and are found to be so at different temperatures (**Fig. 6**).

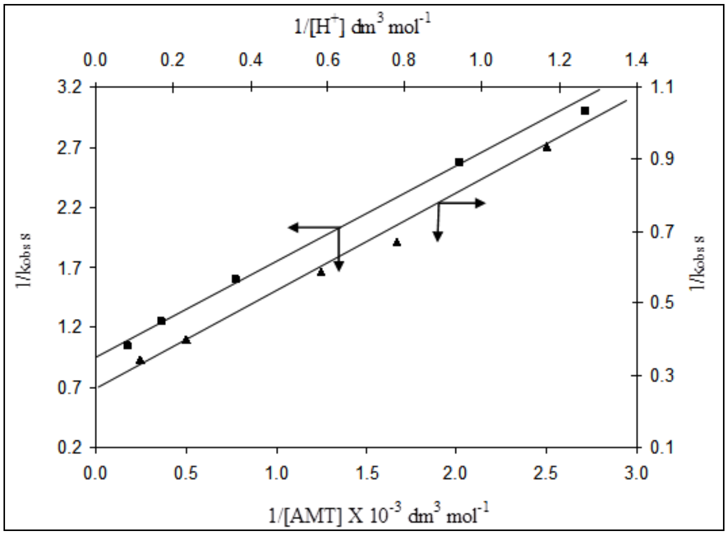


FIGURE 6: Plot of $1/k_{obs}$ versus $1/[AMT]$ and $1/k_{obs}$ versus $1/[H^+]$ at room temperature for verification rate law (7) in the form of equation (8) (Condition as in Table 1)

The slopes and intercept of such plots lead to the values of K_1, K_2 and k at 298K as 50.0 ± 1.3 $dm^3\,mol^{-1}$, 1.2 ± 0.05 $dm^3\,mol^{-1}$ and 1.4 ± 0.02 s^{-1} respectively. The K_1 value is in good agreement with the literature [10]. Using these values, the experimental rate constants can be computed. There is a reasonable agreement between the calculated and experimental rate constants (Table 1).

The thermodynamic quantities for the first and second equilibrium steps of Scheme 1 can be evaluated as follows. The [AMT] and $[H^+]$ as in Table 1 were varied at different temperatures. The plots of $1/k_{obs}$ versus $1/[AMT]$ and $1/k_{obs}$ versus $1/[H^+]$ 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 given in **table 2**. 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.

TABLE 2: THERMODYNAMIC ACTIVATION PARAMETERS FOR THE OXIDATION OF AMT BY PERMANGANATE IN ACIDIC MEDIUM WITH RESPECT TO THE SLOW STEP OF SCHEME 1

A. Effect of temperature

Temperture (K)	k (s^{-1})
288	0.5
293	0.8
298	1.4
303	2.2

B. Activation parameters with respect to slow step of scheme 1.

Activation parameters	Values
Ea (kJ mol^{-1})	72.5 ± 0.4
$\Delta H^{\#}$ (kJ mol^{-1})	70.0 ± 0.3
$\Delta S^{\#}$ (JK mol^{-1})	-6.7 ± 1.1
$\Delta G^{\#}$ (kJ mol^{-1})	72.0 ± 3.5
log A	12.8

C. Effect of temperature to calculate K_1 and K_2 for the oxidation of AMT by permanganate in acid medium.

Temperature (K)	K_1 ($dm^3 mol^{-1}$)	K_2 ($dm^3 mol^{-1}$)
288	119	0.86
293	79	1.0
298	50	1.2
303	33	1.5

D. Thermodynamic quantities using K_1 and K_2

Thermodynamic quantities	Values from K_1	Values from K_2
ΔH (kJ mol^{-1})	-62.3	26.8
ΔS (JK^{-1} mol^{-1})	-170	92.0
ΔG_{298} (kJ mol^{-1})	-9.8	-1.02

These values are given in Table 2. A comparison of the ΔH value of second step (26.8 kJ mol^{-1}) of Scheme 1 with that of $\Delta H^{\#}$ (70.0 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. Amis [15] has shown that a plot of log k_{obs} versus 1/D is linear with a negative slope for a reaction between a negative ion and a dipole or two dipoles, and with a positive slope for a positive ion-dipole interaction. 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 (the plot observed had a negative slope Figure 5), 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 [16]. The moderate values of $\Delta H^{\#}$ and $\Delta S^{\#}$ were both favorable for electron transfer processes. The negative value of $\Delta S^{\#}$ (-6.7 JK^{-1} mol^{-1}) suggests that intermediate complex is more ordered than the reactants [17]. 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 [18].

CONCLUSION: The kinetics of the permanganate oxidation of amitriptyline hydrochloride in a strong acid medium was investigated using the Spectrophotometric technique at different temperatures.

The main active species of permanganate is $HMnO_4$. The role of hydrogen ion is crucial to the reaction. The description of the mechanism is consistent with all the experimental evidences including kinetic, spectral and product studies. The transformation of this drug finds aplications in pharmacuetical industries.

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How to cite this article:

Pujeri KG, Lamani SD and Nandibewoor ST: Oxidation of Tricyclic Antidepressant agent, Amitriptyline, by Permanganate in Sulphuric acid Medium: Kinetic and Mechanistic Approach. *Int J Pharm Sci Res*. 3(12); 4856-4865.