Spectral and mechanistic study of the ruthenium(III) catalysed oxidation of gabapentin (neurontin) by heptavalent manganese: a free radical intervention

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The kinetics of ruthenium(III) catalysed oxidation of Gabapentin by permanganate in alkaline medium at a constant ionic strength has been studied spectrophotometrically. The reaction between permanganate and gabapentin in alkaline medium exhibits 2:1 stoichiometry ($KMnO_4$: gabapentin). The reaction shows first order dependence on [permanganate] and [ruthenium(III)] and apparent less than unit order dependence each in gabapentin and alkali concentrations. Reaction rate decreases with increase in ionic strength and decrease in solvent polarity of the medium. Initial addition of reaction products did not affect the rate significantly. A mechanism involving the formation of a complex between catalyst and substrate has been proposed. The activation parameters were computed with respect to the slow step of the mechanism and discussed.

KEY WORDS: oxidation; gabapentin; catalysis; ruthenium(III); kinetics.

1. Introduction

Potassium permanganate is widely used as an oxidising agent in synthetic as well as in analytical chemistry and also as a disinfectant. The reactions with permanganate are governed by 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 as well as in alkaline medium.

The manganese chemistry involved in these multistep redox reactions is an important source of information as the manganese intermediates are relatively easy to identify when they have sufficiently long life times and oxidation states of the intermediates permit useful conclusions as to the possible reaction mechanism including the nature of intermediates.

The oxidation by permanganate ion finds extensive applications in organic syntheses [1–7] especially since the advent of phase transfer catalysis [3,4,6],which permits the use of solvents such as methylene chloride and benzene. Kinetic studies are important sources of mechanistic information on the reactions, as demonstrated by the results referring to unsaturated acids both in aqueous [1,3,7] and non-aqueous media [8].

During the oxidation by permanganate, it is evident that permanganate is reduced to various oxidation states in acidic, alkaline and neutral media. Furthermore, the mechanism by which the multivalent oxidant oxidises a substrate depends not only on the substrate but also on the medium [9] used for the study. In strongly alkaline medium, the stable reduction product [10,11] of permanganate ion is manganate ion, MnO_4^{2-}. No mechanistic information is available to distinguish between a direct one-electron reduction to Mn(VI) (scheme 1) and a mechanism, in which a hypomanganate is formed in a two-electron reduction followed by a rapid oxidation of the hypomanganate ion [12] (scheme 2).

$$\mathrm{Mn(VII)} + \mathrm{S} \xrightarrow{K_1'} \mathrm{Mn(VI)} + \mathrm{S^{\cdot}}$$

$$\mathrm{Mn(VII)} + \mathrm{S^{\cdot}} \xrightarrow{K_2'} \mathrm{Mn(VI)} + \mathrm{Products}$$

$$\text{where, S} = \text{substrate; } K_2' \gg K_1'$$

Scheme 1.

$$\mathrm{Mn(VII)} + \mathrm{S} \xrightarrow{K_3'} \mathrm{Mn(V)} + \mathrm{Products}$$

$$\mathrm{Mn(VII)} + \mathrm{Mn(V)} \xrightarrow{K_4'} 2\mathrm{Mn(VI)}$$

$$\text{where, S} = \text{substrate; } K_4' \gg K_3'$$

Scheme 2.

The study of neuroleptic drugs becomes important because of their biological significance and selectivity towards the oxidant to yield different products. Gabapentin is prescribed usually in combination with other medications for the prevention of seizure in people suffering from seizure disorders. It is sometimes prescribed for the management of neuralgia [13] (nerve pain). Its anticonvulsant mechanism of action is not known. Gabapentin has been prescribed off-label for the treatment of some mood disorders, anxiety, and tardive dyskinesia (a neurological syndrome caused by the long-term use of neuroleptic drugs).

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Ruthenium(III) is known to be an efficient catalyst in several redox reactions particularly in alkaline medium [14]. The mechanism of catalysis can be quite complicated due to the formation of different intermediate complexes, free radicals and different oxidation states of ruthenium. The kinetics of fast reactions between ruthenate(VII), RuO_4^-, and manganate(VI), i.e., MnO_4^{2-} have been studied [15] and the reaction is presumed to proceed via an outer-sphere mechanism. The rapid exchange between MnO_4^{2-} and MnO_4^- has been studied in detail by a variety of techniques [16]. The uncatalysed reaction between gabapentin and permanganate in alkaline medium has been studied [17]. A micro amount of ruthenium(III) is sufficient to catalyse the reaction in alkaline medium and a variety of mechanisms are possible. Thus, in order to explore the mechanism of oxidation by permanganate ion in aqueous alkaline medium and to check the selectivity of gabapentin towards permanganate in catalysed system, we have selected ruthenium(III) as a catalyst. The present study deals with the title reaction to investigate the redox chemistry of permanganate, ruthenium(III) and gabapentin in such media and to arrive at a plausible mechanism.

2. Experimental

2.1. Materials

Stock solution of gabapentin (sd-fine chemicals) was prepared by dissolving the appropriate amount of sample in double distilled water. The solution of potassium permanganate (BDH) was prepared and standardized against oxalic acid [18]. Potassium manganate solution was prepared as described by Carrington and Symons [19]. The solution was standardized by measuring the absorbance on a Hitachi 150-20 spectrophotometer with a 1 cm quartz cell at 608 nm ($\varepsilon = 1530 \pm 20$ dm^3 mol^{-1} cm^{-1}). The ruthenium(III) solution was prepared by dissolving a known weight of $RuCl_3$ (sd. fine-chem) in 0.20 mol dm^{-3} HCl. Mercury was added to the ruthenium(III) solution to reduce any ruthenium(IV) formed during the preparation of ruthenium(III) stock solution and was kept for a day. The ruthenium(III) concentration assayed [20] by EDTA titration.

All other reagents were of analytical grade and their solutions were prepared by dissolving the requisite amounts of the samples in double distilled water. NaOH and $NaClO_4$ were used to provide the required alkalinity and to maintain the ionic strength, respectively.

2.2. Kinetic procedure

All kinetic measurements were performed under pseudo-first order conditions with [Gabapentin] excess over [MnO_4^-] at a constant ionic strength of 2.0 mol dm^{-3}. The reaction was initiated by mixing previously thermostatted solutions of MnO_4^-, and gabapentin which also contained the necessary quantities of ruthenium(III), NaOH and $NaClO_4$ to maintain the required alkalinity and ionic strength, respectively. The temperature was uniformly maintained at 25 ± 0.1 °C. The course of reaction was followed by monitoring the decrease in the absorbance of MnO_4^- in a 1 cm quartz cell of a Hitachi model 150-20 spectrophotometer at its absorption maximum of 526 nm as a function of time. The application of Beer's law to permanganate at 526 nm had been verified, giving $\varepsilon = 2083 \pm 50$ dm^3 mol^{-1} cm^{-1} (Literature $\varepsilon = 2200$ dm^3 mol^{-1} cm^{-1}). The first-order rate constants (k_c) were evaluated by plots of $\log(A_t\text{-}A_\infty)$ versus time, where A_t and A_∞ refers to absorbancies at time t and ∞ respectively. The first order plots in almost all cases were linear to 80% completion of the reaction and k_c were reproducible within ±5%.

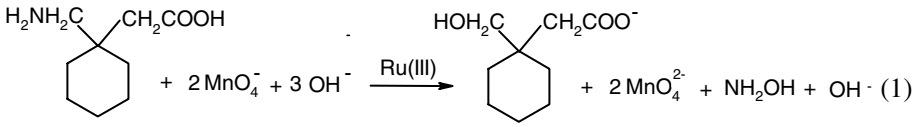
During the course of measurements, the solution changed from violet to blue and then to green. The spectrum of the green solution was identical to that of MnO_4^{2-}. It is probable that the blue colour originated from the violet of permanganate and the green from the manganate, excluding the accumulation of hypomanganate. It is also evident from the figure 1 that the absorbance of permanganate decreases at 526 nm whereas the absorbance of manganate increases at 608 nm. The effect of dissolved oxygen on the rate of reaction was checked by preparing the reaction mixture and following the reaction in an atmosphere of nitrogen. No significant difference between the results obtained under the nitrogen and in the presence of air was observed. In view of the ubiquitous contamination of basic solutions by carbonate, the effect of carbonate on the reaction was also studied. Added carbonate had no effect on the reaction rate. However, fresh solutions were used when conducting the experiments.

A regression analysis of experimental data in order to obtain the regression coefficient, r and standard deviation, s of plots from the regression line was performed with a Pentium-IV personal computer.

3. Results

3.1. Stoichiometry and product analysis

The reaction mixtures containing an excess permanganate concentration over gabapentin, and constant [Ru(III)], 1.0 mol dm^{-3} NaOH and adjusted ionic strength of 2.0 mol dm^{-3} was allowed to react for 2 h in an inert atmosphere at 25 ± 0.1 °C. After completion of the reaction, the remaining MnO_4^- was then determined by spectrophotometrically. The results indicated that two moles of MnO_4^- consumed by one mole of gabapentin as given by equation (1).



The products were eluted with solvent ether and organic product was submitted to spot tests. The main reaction product was identified as the 1-(Hydroxymethyl) cyclohexane acetic acid by spot test [21a] for free carboxyl group and —OH. The product was also confirmed IR spectra. In gabapentin, the IR spectra [22] shows that it exists as Zwitter ion indicating the absence of $-NH_2$ and —COOH groups; there is no absorption in the usual —NH stretching i.e., 3500–3300 cm^{-1} but instead the bands are observed in the region of 2800–3100 cm^{-1}, the band due to NH_3^+ stretching and also there is one characteristic band at 1541 cm^{-1} as assignable to NH_3^+ deformation vibration. In addition to this there is one more band at 1607 cm^{-1} which is assignable to ionic carboxyl absorption. At 1485 cm^{-1} a band is appeared which is assignable to NH_3^+ deformation vibration (second band). Whereas in the product, 1-(Hydroxymethyl) cyclohexane acetic acid, the presence of absorption band at 1681 cm^{-1} indicates the free $-COO^-$ group which was absent in gabapentin (due to Zwitter ion) and there is a broad valley in the region 3098–3500 cm^{-1} indicating the presence of —OH group as well as carboxylic —OH group. There is C—O stretching frequency of alcoholic —OH group (Hydroxy methyl group) at 1066 cm^{-1} indicating the formation of $-CH_2OH$ group which was absent in Gabapentin and two —OH deformation bands occur at 1329–1320 cm^{-1}.

The product was also confirmed by ^1H NMR spectra. From the spectra of Gabapentin, it is observed that the two $-CH_2$ peaks appeared at 2.24 and 2.82 δ ppm, respectively. The cyclohexyl proton appeared in the region of 1.18–1.31 δ ppm and as earlier suggested that $-NH_2$ and —COOH peaks are not observed because of Zwitter ion form. In 1-(Hydroxymethyl) cyclohexane acetic acid, the cyclohexyl protons appeared in the region of 1.27–1.65 δ ppm, and two $-CH_2$ bands appeared at down field to cyclohexyl protons i.e., 2.19–3.16 δ ppm, respectively. Another peak appeared at 4.60 δ ppm due to hydroxy methyl group. Another product, hydroxylamine was identified by spot test [21b]. It was further observed that the 1-(Hydroxymethyl) cyclohexane acetic acid does not undergo further oxidation under prevailing kinetic conditions.

3.2. Reaction orders

As the permanganate oxidation of Gabapentin in alkaline medium proceeds with a measurable rate in absence of ruthenium(III), the catalysed reaction is understood to occur in parallel paths with contributions from both the catalysed and uncatalysed paths. Thus, the total rate constants (k_T) is equal to the sum of the rate constants of the catalysed (k_C) and uncatalysed (k_u) reactions, so $k_C = k_T - k_u$. Hence the reaction orders have been determined from the slopes of log k_C versus

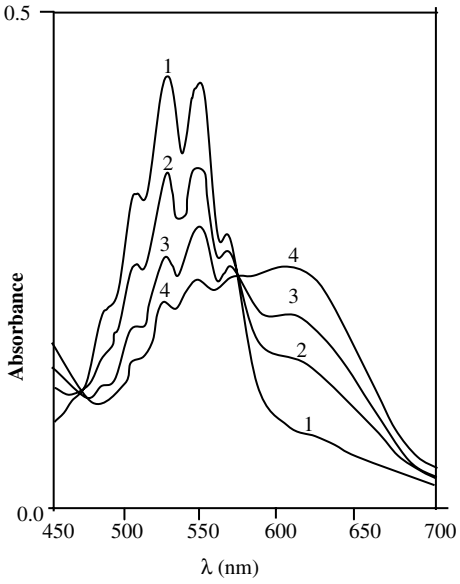


Figure 1. Spectroscopic changes occurring in the ruthenium(III) oxidation of gabapentin by alkaline permanganate at 25 °C, $[MnO_4^-] = 2.0 \times 10^{-4}$, $[GP] = 2 \times 10^{-3}$, $[OH^-] = 0.20$, $[Ru(III)] = 2.0 \times 10^{-7}$ mol dm^{-3} and I = 1.0 mol dm^{-3} (scanning time interval = 1 min).

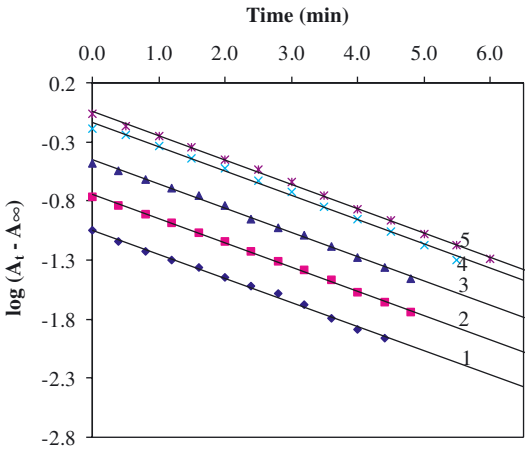


Figure 2. First order plot of aqueous alkaline permanganate ruthenium(III) catalysed oxidation of gabapentin at 25 °C $[MnO_4^-] \times 10^4 =$ (1) 0.5, (2) 1.0, (3) 2.0, (4) 4.0, (5) 5.0 /mol dm^{-3}. (Conditions as in Table 1)

Table 1
Effects of $[MnO_4^-]$, [GP], $[OH^-]$ and [Ru(III)] on ruthenium(III) catalyzed oxidation of gabapentin by $KMnO_4$ at 25° C; I = 1.0 mol dm^{-3}

$[MnO_4^-] \times 10^4$ (mol dm^{-3})	$[GP] \times 10^3$ (mol dm^{-3})	$[OH^-]$ (mol dm^{-3})	$[Ru(III)] \times 10^7$ (mol dm^{-3})	$k_T \times 10^3$ (s^{-1})	$k_u \times 10^3$(s^{-1})	$k_C \times 10^3$(s^{-1})	
						Found	Calculated
0.5	2.0	0.2	2.0	4.62	1.62	3.00	3.03
1.0	2.0	0.2	2.0	4.67	1.63	3.04	3.03
2.0	2.0	0.2	2.0	4.65	1.61	3.04	3.03
4.0	2.0	0.2	2.0	4.64	1.63	3.02	3.03
5.0	2.0	0.2	2.0	4.63	1.61	3.02	3.03
2.0	0.5	0.2	2.0	1.43	0.48	0.95	0.95
2.0	1.0	0.2	2.0	2.57	0.92	1.65	1.74
2.0	2.0	0.2	2.0	4.65	1.61	3.04	3.04
2.0	4.0	0.2	2.0	6.91	2.24	4.67	4.81
2.0	5.0	0.2	2.0	8.57	2.54	6.03	5.43
2.0	2.0	0.1	2.0	3.04	0.92	2.12	2.11
2.0	2.0	0.2	2.0	4.65	1.61	3.04	3.03
2.0	2.0	0.4	2.0	5.93	2.21	3.72	3.88
2.0	2.0	0.8	2.0	6.94	2.53	4.41	4.50
2.0	2.0	1.0	2.0	7.79	2.81	4.98	4.66
2.0	2.0	0.2	0.5	2.32	1.61	0.71	0.75
2.0	2.0	0.2	1.0	3.02	1.61	1.41	1.51
2.0	2.0	0.2	2.0	4.65	1.61	3.04	3.03
2.0	2.0	0.2	4.0	7.74	1.61	6.13	6.06
2.0	2.0	1.0	5.0	10.0	1.61	8.41	7.58

log concentration plots by varying the concentrations of reductant, Ru(III) and alkali concentration while keeping the others constant.

The potassium permanganate concentration was varied in the range of 5.0×10^{-5} to 5.0×10^{-4} mol dm^{-3} and the linearity of plots of $\log[A_t\text{-}A_\infty]$ versus time ($r > 0.9985$, $s \leq 0.027$) indicated a reaction order of unity in $[MnO_4^-]$ figure 2. This was also confirmed by variation of $[MnO_4^-]$, which did not result any change in the pseudo-first order rate constants, k_C (table 1). The substrate, gabapentin concentration was varied in the range of 5.0×10^{-4} to 5.0×10^{-3} mol dm^{-3} at 25 °C while keeping other reactants and conditions constant (table 1). The reaction order with respect to [Gabapentin] was found to be less than unity. The catalyst The Ru(III) concentration was varied in the range of 5.0×10^{-7} to 5.0×10^{-6} at constant concentration of potassium permanganate, gabapentin and a constant ionic strength of 1.0 mol dm^{-3}. The order in [Ru(III)] was found to be unity. The effect of alkali on the reaction has been studied at constant concentrations of gabapentin and potassium permanganate and a constant ionic strength of 1.0 mol dm^{-3}. The rate constants increased with increasing $[OH^-]$. The reaction order in $[OH^-]$ was found be less than unity table 1.

3.3. Effect of initially added products

The externally added products such as manganate, hydroxyl amine and 1-(Hydroxymethyl) cyclohexane acetic acid did not show any significant effect on the rate of the reaction.

3.4. Effect of ionic strength and relative permitivity

The effect of ionic strength was studied by varying the sodium perchlorate concentration from 0.5 to 2.5 mol dm^{-3} at constant concentrations of permanganate, gabapentin, ruthenium(III) and alkali. It was found that the rate constant increases with increase in concentration of $NaClO_4$ and the plot of log k_C versus $I^{1/2}$ was linear with positive slope, which is given figure 3.

The effect of relative permitivity($\in_T$) effect was studied by varying the *t*-butanol water content in the reaction mixture with all other conditions being maintain constant. Attempts to measure the dielectric constants were not successful. However, they were computed from the values of pure liquids [23]. The solvent did not react with the oxidant under the experimental conditions. The rate constants (k_c) increased with decrease in the dielectric constant of the medium. The plot of log k_c versus $1/\in_T$ was linear with positive slope as shown in figure 3. ($r > 0.9983$, $s \leq 0.036$).

3.5. Polymerisation study

The reaction mixture was mixed with acrylonitrile monomer and kept for 2 h in an inert atmosphere. On diluting with methanol a white precipitate was formed, indicating the intervention of free radicals in the reaction. The blank experiments of either MnO_4^- or Gabapentin alone with acrylonitrile did not induce polymerization under the same conditions as those induced with reaction mixtures. Initially added acrylonitrile decreases the rate indicating the free radical intervention which is the case in earlier work [24].

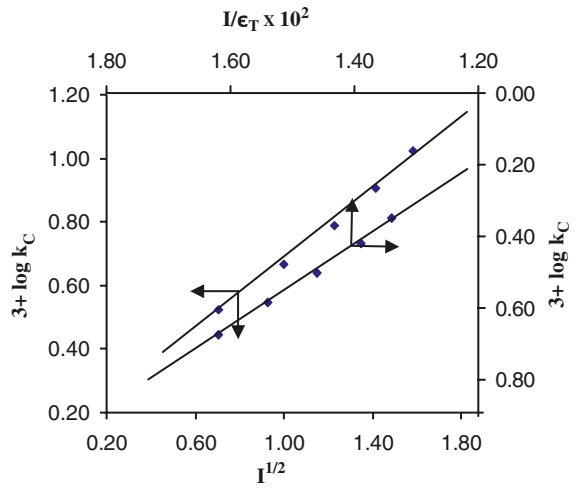


Figure 3. Plot of log k_c versus $I^{1/2}$ and log k_c versus $1/\epsilon_T$.

3.6. *Effect of temperature*

The rate of the reaction was measured at four different temperatures with varying [OH^-], keeping other conditions constant. The rate was found to increase with increase in temperature. The rate constants, k of the slow step of scheme 3 were obtained from the intercept of the plots of [Ru(III)]/k_C versus 1/[GP] ($r \geq 0.976$, $s < 0.0064$) for different temperatures. The values of k at different temperatures are tabulated in table 2. The energy of activation corresponding to these constants were evaluated from the Arrhenius plot of log k versus $1/T$ ($r \geq 0.948$, $s < 0.00592$) and other activation parameters with respective to slow step were calculated and are given in table 2. These values are comparable with the uncatalysed reaction.

4. Discussion

Permanganate ion, MnO_4^-, is a powerful oxidant in an aqueous alkaline medium. As it exhibits many oxidation states, the stoichiometric results and pH of the reaction media play an important role. Under the prevailing experimental conditions at pH > 12, the reduction product of Mn(VII) is stable and further reduction of Mn(VI) might be stopped [25]. The Diode Array Rapid Scan Spectrophotometric (DARSS) studies have shown that at pH > 12, the product of Mn(VII) is Mn(VI) and no further reduction was observed as reported [26] by Simandi *et al*. However, on prolonged standing, the green Mn(VI) is reduced to Mn(IV) under our experimental conditions.

The permanganate in alkaline medium exhibits various oxidation states, such as Mn(VII), Mn(V) and Mn(VI). The colour of the solution changed from violet to blue and further to green excluding the accumulation of hypomanganate. The violet colour originates from

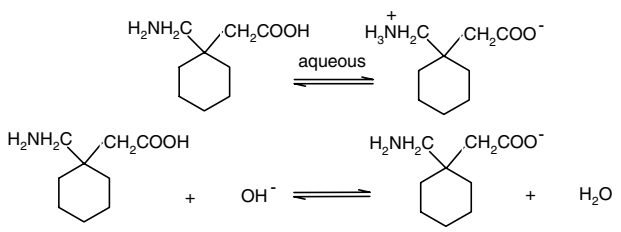
Table 2
Effect of temperature on the Ru(III) catalysed permanganate oxidation of Gabapentin in an aqueous alkaline medium at 25 °C. [L-proline] = 2.0×10^{-3}, [MnO_4^-] = 2.0×10^{-4}, [OH^-] = 0.20, [Ru(III)] = 2.0×10^{-7}, I = 1.0/mol dm^{-3}

Temperature (K)	$K \times 10^{-4}$ dm^3 mol^{-1} s^{-1}
298	5.75
303	6.05
308	6.69
313	7.36

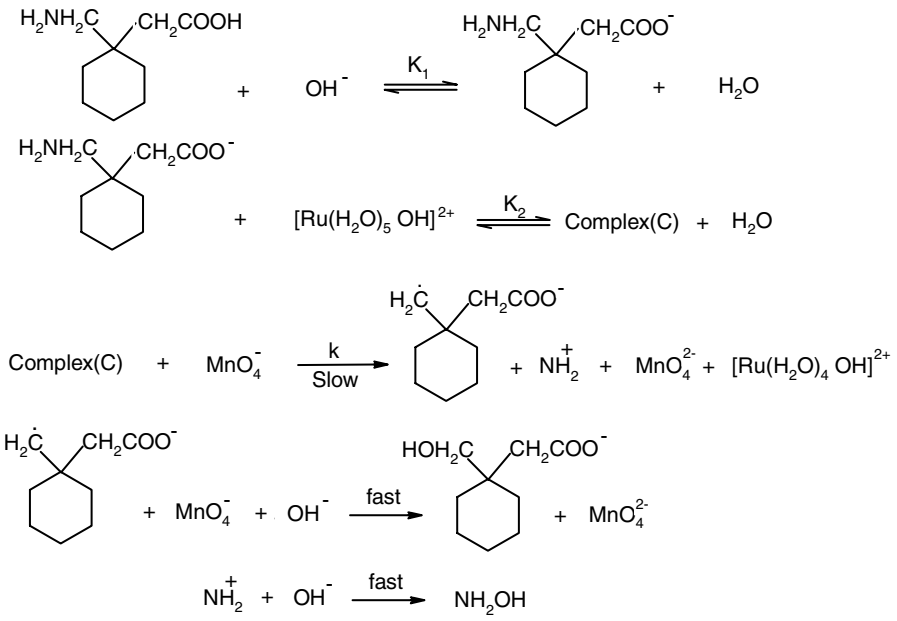
pink of permanganate and blue from hypomanganate is observed during the course of the reaction. The colour change of $KMnO_4$ solution from violet Mn(VII) ion to dark green Mn(VI) ion through blue Mn(V) ion has been observed.

It is interesting to identify the probable species of ruthenium(III) chloride in alkaline medium. Electronic spectral studies [27] have confirmed that ruthenium(III) chloride exists in hydrated form as $[Ru(H_2O)_6]^{3+}$. In the present study it is quite probable that the species $[Ru(H_2O)_5OH]^{2+}$ might assume the general form $[Ru(III)(OH)_x]^{3-x}$. The value of x would always be less than six because there are no definite reports of any hexahydroxy species of ruthenium. The remainder of the coordination sphere will be filled by water molecule. Hence under the experimental conditions $[OH^-] \gg [Ru^{III}]$, Ru^{III} is mostly present as the hydroxylated species $[Ru(H_2O)_5OH]^{2+}$.

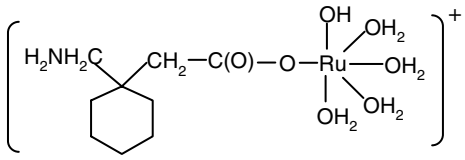
The reaction between permanganate and Gabapentin in alkaline medium has a stoichiometry of 2:1 with a first order dependence on the [MnO_4^-] and [Ru(III)] and less than unit order dependence on both the [alkali] and [gabapentin]. No effect of added products such as 1-(Hydroxymethyl) cyclohexane acetic acid and ammonium hydroxide was observed. It is known that gabapentin exists in the form of Zwitter ion [28] in aqueous medium. In acidic medium, it exists in the protonated form, whereas in basic medium, it is fully in the deprotonated form according to the following equilibria.



Gabapentin in the deprotonated form reacts with ruthenium(III) species to form a complex (C). This complex (C) reacts with permanganate species in a slow step to form a free radical derived from Gabapentin which further reacts with another permanganate species in a fast step to yield the products. The experimental results can be accommodated in scheme 3.



The probable structure of complex (C)



Scheme 3.

Spectral evidence for such a catalyst-substrate complex was obtained from the UV–Vis, spectra of both ruthenium(III) and ruthenium(III)–gabapentin mixtures, in which a bathochromic shift of ruthenium(III) from 219 to 225 nm and hyperchromicity was observed at 225 nm. This is also evident from the plot of $1/k_c$ versus 1/[GP] (Michaelis–Menten plot)($r \geq 0.8930$, $s \geq 0.0047$) which shows a straight line with non-zero intercept (figure 4). Such type of substrate-catalyst complex formation has also been observed in other studies [29]. The observed modest enthalpy of activation, relatively low value of the entropy of activation and higher rate constant for the slow step of the mechanism, indicate that oxidation presumably occurs by an inner-sphere mechanism. This conclusion is supported by earlier work [30]. Since scheme 3 is in accordance with generally well accepted principle of non-complementary oxidations taking place in a sequence of one-electron steps, the reaction would involve a radical intermediate. Since permanganate is a one electron oxidant in alkaline medium, the reaction between substrate and oxidant would give rise to a radical intermediate. Free radical scavenging experiment revealed such a possibility. This type of radical intervention in the oxidation of amino acids has also been observed earlier [31].

The thermodynamic quantities for the first equilibrium step in scheme 1 and activation parameters for the limiting step in scheme 1 can be evaluated as follows: The hydroxyl ion concentration as in table 1 was varied at four different temperatures and the K_1 value was determined at each temperature. The values of K_1 ($dm^3\ mol^{-1}$) were obtained as 3.43, 3.81, 4.34 and 4.95 at 25, 30, 35 and 40 °C, respectively. A vant Hoff's plot was made for the variation of K_1 with temperature (i.e.,

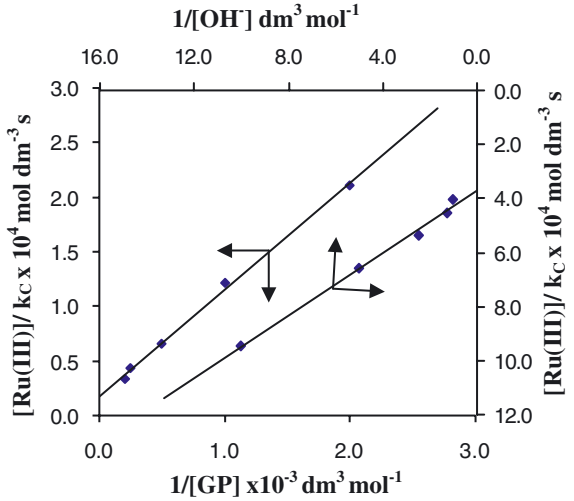


Figure 4. Verification of rate law (3) in the form of (4) on the Ru(III) catalysed oxidation of permanganate by Gabapentin in aqueous alkaline medium at 25 °C. (Conditions as in Table 1)

Table 3
Thermodynamic activation parameters with respect to slow step of scheme 3

Activation parameters	Values
E_a (kJ mol^{-1})	13.0 ± 0.5
$\Delta H\#$ (kJ mol^{-1})	11.0 ± 0.5
$\Delta S\#$ (J K−1mol^{-1})	−299 ± 10
$\Delta G\#$ (kJ mol^{-1})	102 ± 6

log K_1 versus $1/T$) ($r \leq 0.9835$, $s \leq 0.041$) and the values of the enthalpy of the reaction, ΔH, entropy of the reaction, ΔS, and free energy reaction, ΔG, were calculated as 19.08 kJ mol^{-1}, 17.7 JK^{-1} mol^{-1} and −13.8 kJ mol^{-1}, respectively. A comparison of these values with those 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 the rate determining step is slow and involves more activation energy [32].

Scheme 3 leads to the following rate law (2).

$$\text{rate}_{\text{cat}} = \text{rate}_{\text{total}} - \text{rate}_{\text{uncat}},$$

$$\text{Rate}_{\text{cat}} = \frac{k K_1 K_2 [\text{GP}]_t [\text{MnO}_4^-]_t [\text{Ru(III)}]_t [\text{OH}^-]_t}{(1 + K_1[\text{OH}^-] + K_1K_2[\text{OH}^-][\text{Ru(III)}])(1 + K_1[\text{GP}] + K_1K_2[\text{Ru(III)}][\text{GP}])(1 + K_1K_2[\text{OH}^-][\text{GP}])} \quad (2)$$

The terms $(1 + K_1\ K_2\ [\text{OH}^-][\text{Ru(III)}])$ and $(1 + K_1\ [\text{GP}] + K_1K_2\ [\text{Ru(III)}][\text{GP}])$ in the denominator of equation (6) approximate to unity in view of low concentration of gabapentin(GP) and ruthenium (III) used. (omitting the subscripts t and f), in terms of rate constants,

$$k_C = k_T - k_u = \frac{k K_1 K_2 [\text{GP}][\text{Ru(III)}][\text{OH}^-]}{(1 + K_1[\text{OH}^-])(1 + K_1K_2[\text{GP}][\text{OH}^-])}$$

$$k_C = \frac{k K_1 K_2 [\text{GP}][\text{Ru(III)}][\text{OH}^-]}{1 + K_1K_2[\text{GP}][\text{OH}^-] + K_1[\text{OH}^-] + K_1{}^2K_2[\text{OH}^-]^2[\text{GP}]}$$

Neglecting square term in view of low value compared to unity, we get

$$k_C = \frac{kK_1K_2[\text{GP}][\text{Ru(III)}][\text{OH}^-]}{1 + K_1K_2[\text{GP}][\text{OH}^-] + K_1[\text{OH}^-]} \quad (3)$$

The above equation (3) can be rearranged to the following form which is used for the verification of the rate law.

$$\frac{[\text{Ru(III)}]}{k_C} = \frac{1}{kK_1K_2[\text{GP}][\text{OH}^-]} + \frac{1}{kK_2[\text{GP}]} = \frac{1}{k} \quad (4)$$

According to equation (4), the plots of $[\text{Ru(III)}]/k_C$ versus $1/[\text{GP}]$ ($r > 0.9978$, $s \leq 0.048$) and $[\text{Ru(III)}]/k_C$ versus $1/[\text{OH}^-]$ ($r > 0.9823$, $s \leq 0.049$) should be linear with non-zero intercept, which is verified in figure 4. The slopes and intercepts of such plots lead to the values of k, K_1 and K_2 at 25 °C of 5.75 ± 0.2 × 10^4 dm^3 mol^{-1} s^{-1}, 3.43 ± 0.1 dm^3 mol^{-1} and 4.40 ± 0.06 × 10^2 dm^3 mol^{-1}, respectively. Using these values, the rate constants under different experimental conditions were calculated by equation (3) and compared with experimental data. There is a good agreement between them, which supports the scheme 3. The value of K_1 is in good agreement with earlier work [17].

The effect of ionic strength on the rate can be understood essentially on the basis of ionic species as in scheme 3. The effect of solvent on the reaction kinetics has been described in detail in the literature. In the present study the rate determining step involves the reaction between two ions and so equation (5) is applicable:

$$\ln k = \ln k_\infty - Z_A Z_B e^2 / k_B T r_{AB} \in_T, \quad (5)$$

where k_∞ is the rate constant in a medium of infinite dielectric constant, r_{AB} is the sum of the ionic radii and Z_A and Z_B are the charges on the two ions and $\in_T$ is the dielectric constant of the medium. The observed linear plot of log k_{obs} versus $1/\in_T$ with positive slope (Figure 3) is in accordance with equation (5) as Z_A and Z_B have opposite charges (scheme 3). The values of $\Delta H^\#$ and $\Delta S^\#$ were both favourable for electron transfer process. The less negative value of $\Delta S^\#$, suggests the complex is less ordered than the reactants.

4.1. Catalytic effect

The activation parameters are compared with the uncatalysed reaction [17]. The difference in the activation parameters for the catalysed and uncatalysed reactions, explains the catalytic effect on reaction. The catalyst, ruthenium(III) forms a complex with gabapentin which complex with gabapentin which shows more reducing property than gabapentin itself and hence the catalyst, Ru(III) lowers the energy of activation.

5. Conclusions

It is interesting that the oxidant species $[\text{MnO}_4^-]$ requires a pH > 12, below which the system becomes disturbed and the reaction will proceed further to give a reduced product of the oxidant as Mn(IV), which slowly develops yellow turbidity. Hence, it becomes apparent that in carrying out this reaction the role of pH in a reaction medium is crucial. It is also noteworthy that under the conditions studied the reaction occurs in two

successive one-electron reductions (scheme 3) rather than two-electron in a single step (scheme 2). A micro amount of Ru(III) is sufficient to catalyse the title reaction. The description of the mechanism is consistent with all the experimental evidence including both kinetic and product studies.

Appendix

According to scheme 3

$\text{rate}_{\text{cat}} = \text{rate}_{\text{total}} - \text{rate}_{\text{uncat}}$

$$\begin{aligned}\text{Rate}_{\text{cat}} &= k[\text{C}][\text{MnO}_4^-] \\ &= kK_1K_2[\text{GP}]_f[\text{MnO}_4^-]_f[\text{OH}^-]_f[\text{Ru(III)}]_f\end{aligned} \quad (A.1)$$

Total concentration of gabapentin, $[\text{GP}]_t$ is given by (Subscripts t and f stand for total and free, respectively)

$$\begin{aligned}[\text{GP}]_t &= [\text{GP}]_f + [\text{GP}^-]_f + [\text{C}] \\ &= [\text{GP}]_f + K_2[\text{Ru(III)}][\text{GP}] + K_1[\text{OH}^-][\text{GP}] + K_1 \\ &= [\text{GP}]_f + K_1[\text{OH}^-][\text{GP}] + K_1K_2[\text{Ru(III)}][\text{OH}^-][\text{GP}] \\ [\text{GP}]_t &= [\text{GP}]_f\{1 + K_1[\text{OH}^-] + K_1K_2[\text{OH}^-][\text{Ru(III)}]\}\end{aligned}$$

$$\text{Therefore,} \quad [\text{GP}]_f = \frac{[\text{GP}]_t}{1 + K_1[\text{OH}^-] + K_1K_2[\text{OH}^-][\text{Ru(III)}]} \quad (A.2)$$

Similarly,

$$[\text{OH}^-]_f = \frac{[\text{OH}^-]_t}{1 + K_1[\text{GP}] + K_1K_2[\text{Ru(III)}][\text{GP}]} \quad (A.3)$$

$$[\text{Ru(III)}]_f = \frac{[\text{Ru(III)}]_t}{1 + K_1K_2[\text{OH}^-][\text{GP}]} \quad (A.4)$$

Substituting equations A.2–A.4 in (A.1), we get

$$\begin{aligned}\text{Rate}_{\text{cat}} = [&kK_1K_2[\text{GP}]_t[\text{MnO}_4^-]_t[\text{Ru(III)}]_t[\text{OH}^-]_t] \\ &/[(1+K_1[\text{OH}^-]+K_1K_2[\text{OH}^-][\text{Ru(III)}]) \\ &\times (1+K_1[\text{GP}]+K_1K_2[\text{Ru(III)}][\text{GP}]) \\ &\times (1+K_1K_2[\text{OH}^-][\text{GP}])]\end{aligned} \quad (A.5)$$

$$[\text{GP}]_t = [\text{GP}]_f\{1 + K_1[\text{OH\_}] + K_1K_2[\text{OH\_}][\text{Ru(III)}]\}.$$

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