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Ruthenium(III) catalysed oxidation of gabapentin (neurontin) by diperiodatocuprate(III) in aqueous alkaline medium—A kinetic and mechanistic study

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Abstract

The oxidation of a neuroleptic drug gabapentin (GP) by a new oxidant diperiodatocuprate(III) (DPC) has been studied in an aqueous alkaline medium. A minute amount (10^{-7} mol dm^{-3}) of ruthenium(III) is sufficient to catalyse the reaction. The reaction is first order in [DPC] in the presence of ruthenium(III). The order in [GP] is less than unity, whereas that in [Ru(III)] is unity. Increase in [OH^-] accelerates the reaction rate. A plausible mechanism involving the active species of oxidant and catalyst is proposed. The reaction constants in the mechanism have been evaluated.

Keywords: Gabapentin; Diperiodatocuprate(III); Ruthenium(III); Oxidation; Kinetics; Catalysis; Reduction

1. Introduction

The periodate and tellurate complexes of copper in its trivalent state have been extensively used in the analysis of several organic compounds. Diperiodatocuprate(III) (DPC) is a versatile one electron oxidant for various organic compounds in the alkaline media and it is used in the estimation of amino acids [1]. Movius reported [2] the reactivity of some alcohols with diperiodatocuprate(III). It is shown that copper(III) is an intermediate in the copper(II) catalysed oxidation of amino acids by peroxydisulphate [3]. Use of diperiodatocuprate(III) as an oxidant in an alkaline medium is new and restricted to a few cases due to its limited solubility and stability in aqueous medium [4]. Moreover, when copper(III) periodate complex is an oxidant, it needs to be made clear which of the species is the active oxidant; multiple equilibria between the different copper(III) species are involved.

Gabapentin (GP) is prescribed in combination with other medicines for the prevention of seizure in people suffering from seizure disorders. It is sometimes prescribed for the management of neuralgia [5] (nerve pain). Its anticonvulsant mechanism of oxidation is not known.

Ruthenium(III) is known to be an efficient catalyst in several redox reactions particularly in the alkaline medium [6]. 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 rate of uncatalysed reaction under the identical conditions was found to be 5.44×10^{-4} s^{-1}. A minute amount of the ruthenium(III) is sufficient to catalyse the reaction in the alkaline medium and a variety of mechanisms are possible. In view of the various mechanistic possibilities and in order to identify the active species of diperiodatocuprate(III) and ruthenium(III), the title reaction has been studied.

2. Experimental

2.1. Materials

Reagent grade chemicals and double distilled water were used throughout. The diperiodatocuprate(III) was prepared by the known method [7]. The diperiodatocuprate(III) complex was characterised by a UV–vis spectrum, which showed a broad absorption band at 415 nm. The aqueous solution of diperioda-

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tocuprate(III) was standardised by the known method [7]. The stock solution of gabapentin was prepared by dissolving the appropriate amount of gabapentin in water. The ruthenium(III) solution was made by dissolving the ruthenium chloride (S.d.-fine chemicals) in 0.20 mol dm^{-3} hydrochloric acid and its concentration was ascertained by EDTA titration [8]. The copper(II) solution was made by dissolving the copper sulphate (BDH) in water. Periodate solution was prepared by weighing out the required amount of potassium periodate in hot water and kept for 24 h. Its concentration was determined iodometrically [9] at the neutral pH. Since the periodate is present in excess in diperiodatocuprate(III), the possibility of oxidation of gabapentin by periodate in the alkaline medium was checked. It was found that no significant reaction was observed under the experimental conditions. Sodium hydroxide and sodium perchlorate were used to maintain alkalinity and ionic strength, respectively, in reaction solutions. Fresh solutions were used for each kinetic run.

2.2. Kinetics

The oxidation of gabapentin by diperiodatocuprate(III) was followed under pseudo-first order conditions, where the gabapentin concentration was excess over diperiodatocuprate(III) concentration at $25 \pm 0.1\,^{\circ}C$ unless otherwise stated. The reaction was initiated by mixing the required quantities of previously thermostatted solutions of gabapentin and diperiodatocuprate(III), which also contained definite quantities of sodium hydroxide and sodium perchlorate to maintain the required alkalinity and ionic strength. The total alkalinity was calculated by considering the sodium hydroxide in diperiodatocuprate(III) as well as sodium hydroxide added. Similarly, the total periodate concentration was calculated by considering the periodate present in diperiodatocuprate(III) solution as well as periodate added. The progress of the reaction was followed by measuring the absorbance of unreacted diperiodatocuprate(III) in the mixture at 415 nm in a 1 cm cell placed in the thermostatted compartment of a Varian Cary-50 Bio UV–vis spectrophotometer. Beer's law was verified between 1.0×10^{-5} and 1.6×10^{-4} mol dm^{-3} of diperiodatocuprate(III) at 415 nm under the reaction conditions ($\varepsilon = 6213 \pm 250\ dm^3\ mol^{-1}\ cm^{-1}$). The rate constants, k_{obs}, were calculated from the plots of log(absorbance) versus time. The plots were linear over 75% completion of the reaction and the rate constants were reproducible within ±5%.

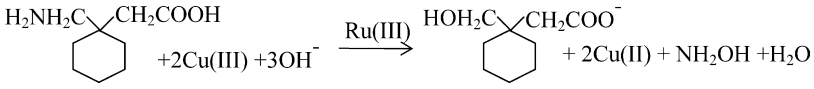
In view of the modest concentration of alkali used, attention was paid on the effect of the reaction vessel on the kinetics. Use of polythene/acrylic equipment and quartz or polyacrylate cells gave the same results, indicating that the surface did not play any significant role in the kinetic studies.

The effect of dissolved oxygen on the reaction mixture was studied by preparing the reaction mixture and following the reaction in an atmosphere of nitrogen. No significant differences between the results were observed. In view of ubiquitous contamination of carbonate in basic solutions, the effect of carbonate on the reaction was studied. Added carbonate showed no effect on the reaction rate. However, fresh solutions were always used while the experiment was performed.

3. Results and discussion

3.1. Stoichiometry and product analysis

The reaction mixtures containing an excess diperiodatocuprate(III) concentration over gabapentin at constant alkalinity, ruthenium(III) concentration and ionic strength were kept for 3 h in an inert atmosphere at 25 °C and then analysed. The remaining diperiodatocuprate(III) was assayed spectrophotometrically. The results indicate that 2 mol of diperiodatocuprate(III) consumed by 1 mol of gabapentin.



(1)

The products were eluted with solvent ether and the organic product was submitted to spot tests. The main reaction product was identified as the 1-(hydroxymethyl)cyclohexane acetic acid by spot test [10] for free carboxyl and –OH groups. The product was also confirmed by IR and ^1H NMR spectra [11]. The IR spectra of gabapentin 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 appeared which is assignable to NH_3^+ deformation vibration (second band). 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 $–CH_2–OH$ group, which was absent in gabapentin, and –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 2.244 and 2.819 δ ppm, respectively. The cyclohexyl proton appeared in the region of 1.185–1.310 δ ppm and as earlier suggested $–NH_2$ and –COOH peaks are not observed because of the 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 4.6 δ ppm due to the hydroxymethyl group. The product copper(II) was characterized by the UV–vis

Table 1
Effect of variation of diperiodatocuprate(III), gabapentin, ruthenium(III) and alkali concentrations on the ruthenium(III) catalysed oxidation of gabapentin by diperiodatocuprate(III) in an aqueous alkaline medium at $I = 0.50\,mol\,dm^{-3}$ and at 25 °C

$[DPC] \times 10^4$ ($mol\,dm^{-3}$)	$[GP] \times 10^3$ ($mol\,dm^{-3}$)	$[Ru(III)] \times 10^7$ ($mol\,dm^{-3}$)	$[OH^-] \times 10^2$ ($mol\,dm^{-3}$)	$[IO_4^-] \times 10^5$ ($mol\,dm^{-3}$)	$k_{obs} \times 10^3\,s^{-1}$	
					Expt.	Calc.
0.1	1.0	2.0	5.0	1.0	2.81	2.80
0.3	1.0	2.0	5.0	1.0	2.79	2.80
0.5	1.0	2.0	5.0	1.0	2.87	2.80
0.7	1.0	2.0	5.0	1.0	2.92	2.80
1.0	1.0	2.0	5.0	1.0	2.84	2.80
1.0	0.5	2.0	5.0	1.0	1.51	1.45
1.0	1.0	2.0	5.0	1.0	2.84	2.80
1.0	2.0	2.0	5.0	1.0	5.32	5.28
1.0	3.0	2.0	5.0	1.0	7.36	7.47
1.0	5.0	2.0	5.0	1.0	11.4	11.2
1.0	1.0	0.5	5.0	1.0	0.70	0.70
1.0	1.0	1.0	5.0	1.0	1.42	1.40
1.0	1.0	2.0	5.0	1.0	2.84	2.80
1.0	1.0	3.0	5.0	1.0	4.35	4.21
1.0	1.0	5.0	5.0	1.0	7.30	7.01
1.0	1.0	2.0	1.0	1.0	0.73	6.70
1.0	1.0	2.0	2.0	1.0	1.35	1.29
1.0	1.0	2.0	5.0	1.0	2.84	2.80
1.0	1.0	2.0	8.0	1.0	3.85	3.99
1.0	1.0	2.0	10.0	1.0	4.50	4.66
1.0	1.0	2.0	5.0	0.5	2.91	2.80
1.0	1.0	2.0	5.0	1.0	2.84	2.80
1.0	1.0	2.0	5.0	2.0	2.89	2.80
1.0	1.0	2.0	5.0	3.0	2.80	2.80
1.0	1.0	2.0	5.0	5.0	2.79	2.80

spectra [12] and hydroxylamine was identified by the spot test [10]. It was observed that the hydroxylamine and 1-(hydroxymethyl)cyclohexane acetic acid did not undergo further oxidation under the present kinetic conditions.

3.2. Reaction order

The reaction orders with respect to gabapentin, ruthenium(III), alkali and periodate were determined from the slopes of $\log k_{obs}$ versus log(concn.) plots by varying the concentrations of reductant, alkali and periodate, in turn while the others were kept constant.

The diperiodatocuprate(III) concentrations were varied from 1.0×10^{-5} to $1.0 \times 10^{-4}\,mol\,dm^{-3}$ at constant concentrations of gabapentin, ruthenium(III), alkali, periodate and at constant ionic strength of $0.50\,mol\,dm^{-3}$. The parallel and linearity of the plots of log[DPC] versus time indicates first order in diperiodatocuprate(III) concentration. This was also confirmed by varying the concentration of diperiodatocuprate(III), which did not show any change in the pseudo-first order rate constants, k_{obs} (Table 1).

The substrate gabapentin concentration was varied in the range 5.0×10^{-4} to $5.0 \times 10^{-3}\,mol\,dm^{-3}$ with all other reactant concentrations and conditions kept constant The reaction order was determined from the slopes of $\log k_{obs}$ versus log(concn.) plot. The order with respect to gabapentin concentration was found to be less than unity, ca. 0.78 (Table 1).

At constant oxidant, reductant and alkali concentrations of 1.0×10^{-4}, 1.0×10^{-3} and $0.05\,mol\,dm^{-3}$, respectively, and at constant ionic strength of $0.50\,mol\,dm^{-3}$, the ruthenium(III) concentration was varied between 5.0×10^{-8} and $5.0 \times 10^{-7}\,mol\,dm^{-3}$. The order in the ruthenium(III) concentration was found to be unity (Table 1).

The effect of alkali on the reaction was studied in the range of 0.01–0.1 $mol\,dm^{-3}$, at constant diperiodatocuprate(III), gabapentin and ruthenium(III) concentrations and at a constant ionic strength of $0.50\,mol\,dm^{-3}$ at 25 °C. The rate constants progressively increased with increase in the concentrations of alkali. The order with respect to alkali concentration was found to be less than unity, ca. 0.71 (Table 1).

The concentration of periodate was varied in the range of 5.0×10^{-6} to $5.0 \times 10^{-5}\,mol\,dm^{-3}$ with all other reactant concentration and conditions kept constant. It was found that the added periodate did not show any significant effect on the rate of the reaction.

3.3. Effect of added products

The externally added products such as 1-(hydroxymethyl) cyclohexane acetic acid, hydroxylamine and copper(II) sulphate did not show any significant effect on the rate of the reaction.

3.4. Effect of dielectric constant and ionic strength

The relative permittivity (D) effect was studied by varying the t-butanol–water content in the reaction mixture with all other conditions being maintained constant. With increase in the percentage of t-butanol, the rate of reaction also increased. There

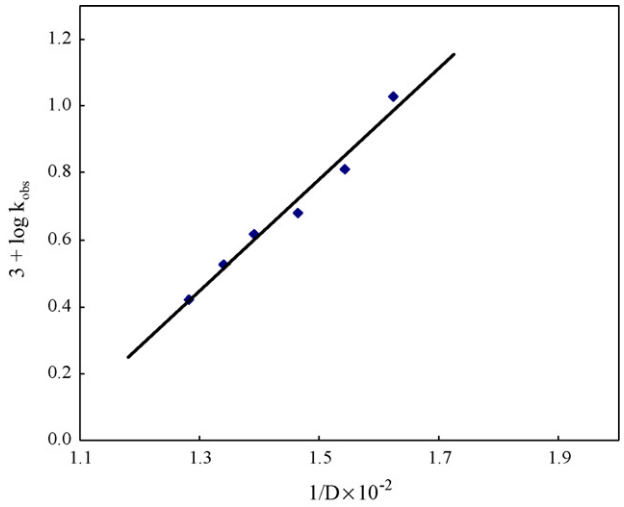


Fig. 1. Effect of variation of dielectric constant (D) on the ruthenium(III) catalysed oxidation of the gabapentin by diperiodatocuprate(III) in an aqueous alkaline medium.

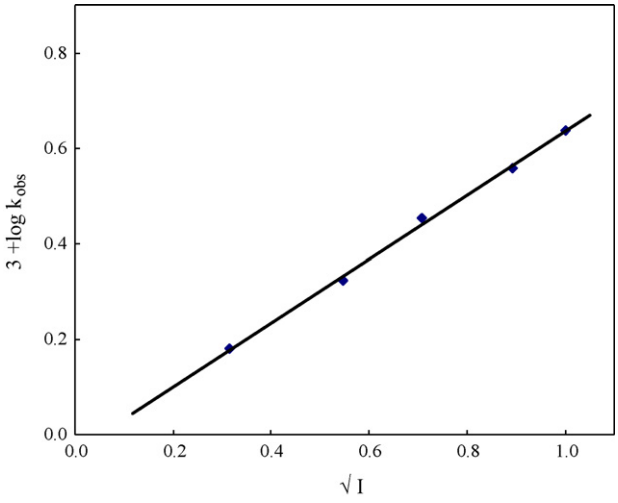


Fig. 2. Effect of variation of ionic strength (I) on the ruthenium(III) catalysed oxidation of the gabapentin by diperiodatocuprate(III) in an aqueous alkaline medium.

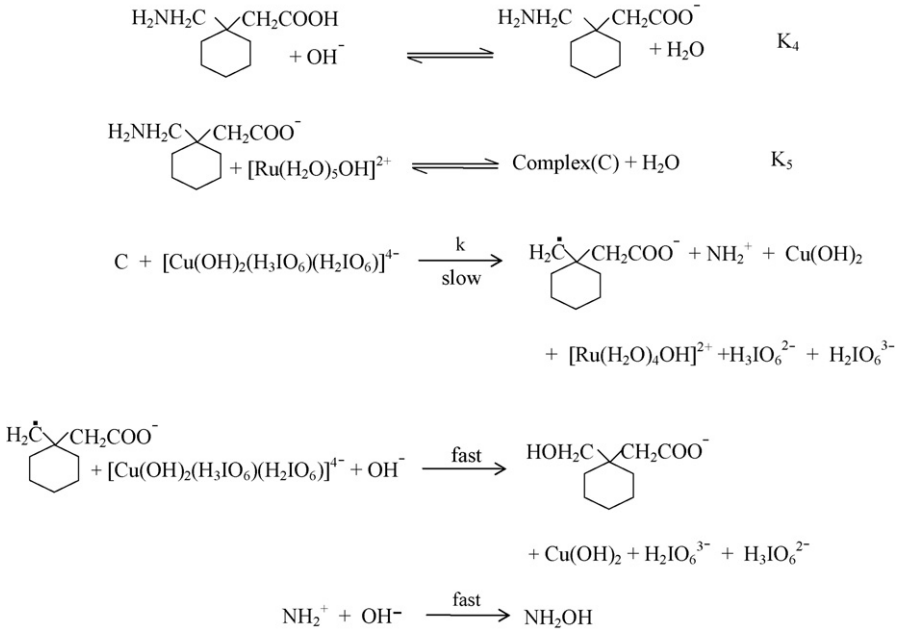
was no reaction of the solvent with the oxidant under the experimental conditions used. The plot of $\log k_{obs}$ versus $1/D$ was linear with a positive slope (Fig. 1). The addition of $NaClO_4$ to increase the ionic strength of the reaction, increased the rate of reaction and the plot of $\log k_{obs}$ versus $I^{1/2}$ was linear with a positive slope (Fig. 2).

3.5. Test for free radicals

To test for free radical, the reaction mixture containing acrylonitrile scavenger was kept in an inert atmosphere for 24 h. When the reaction mixture was diluted with methanol, a white precipitate was formed, indicating the intervention of free radicals in the reaction. The blank experiments of either diperiodatocuprate(III) or gabapentin alone with acrylonitrile did not induce any polymerisation under similar reaction conditions. The decrease in the rate of reaction with addition of acrylonitrile also indicates free radical intervention.

3.6. Effect of temperature

The rate of the reaction was measured at four different temperatures with varying gabapentin concentrations with other conditions kept constant. The rate was found to increase with increase in temperature. The rate constants k of the slow step of Scheme 1 were obtained from the intercepts of the plots of $1/k_{obs}$ versus 1/[GP] at four different temperatures. The data were subjected to least square analysis. The energy of activation



Scheme 1.

Table 2a
Effect of variation of temperature with respect to slow step of Scheme 1 on the ruthenium(III) catalysed oxidation of gabapentin by diperiodatocuprate(III) in an aqueous alkaline medium

Temperature (K)	$1/T \times 10^3$ (K^{-1})	$k \times 10^{-5}$ ($dm^3\ mol^{-1}\ s^{-1}$)
298	3.3560	2.2
303	3.3000	2.4
308	3.2470	2.6
313	3.1950	2.9

$[DPC] = 1.0 \times 10^{-4}$; $[GP] = 1.0 \times 10^{-3}$; $[Ru(III)] = 2.0 \times 10^{-7}$; $[OH^-] = 0.05$; $[IO_4^-] = 1.0 \times 10^{-5}$; $I = 0.50\ mol\ dm^{-3}$.

was evaluated from the plot of log k versus $1/T$ and other activation parameters of the reaction were calculated and are given in Tables 2a and 2b.

The water soluble Cu(III) periodate complex is reported [13] to be $[Cu(HIO_6)_2(OH)_2]^{3-}$. However, in an aqueous alkaline medium and at a high pH range as employed in the study, periodate is unlikely to exist as HIO_6^{4-} (as present in the complex) as is evident from its involvement in the following multiple equilibria [14] (2)–(4) depending on the pH of the solution.

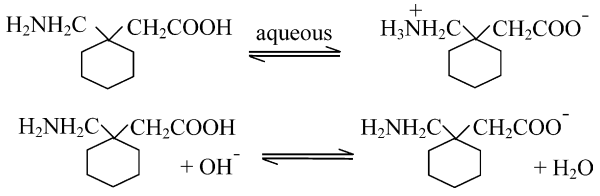
$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+ \quad K_1 = 5.1 \times 10^{-4} \tag{2}$$

$$H_4IO_6^- \rightleftharpoons H_3IO_6^{2-} + H^+ \quad K_2 = 4.9 \times 10^{-9} \tag{3}$$

$$H_3IO_6^{2-} \rightleftharpoons H_2IO_6^{3-} + H^+ \quad K_3 = 2.5 \times 10^{-12} \tag{4}$$

Periodic acid exists as H_5IO_6 in an acid medium and as $H_4IO_6^-$ at pH 7. Thus, under alkaline conditions, the main species are expected to be $H_3IO_6^{2-}$and $H_2IO_6^{3-}$. At higher concentrations, periodate also tends to dimerise. Hence, at pH employed in this study, the soluble copper(III) periodate complex exists as diperiodatocuprate(III), $[Cu(OH)_2(H_3IO_6)_2]^{3-}$ in the aqueous alkaline medium, a conclusion also supported by the literature [4].

It is known that gabapentin exists in the form of zwitter ion [12] in aqueous media. In the acidic medium, it exists in the protonated form, whereas in basic media, it is fully in the deprotonated form according to the following equilibria.



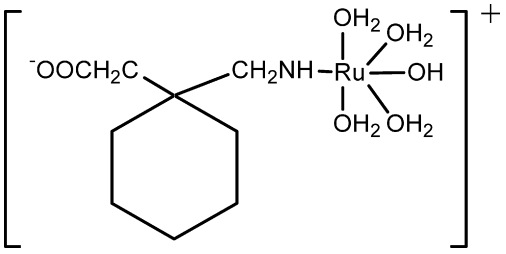
In alkaline media, ruthenium(III) is known to exist as hydroxylated species [15] ($[Ru(OH)_x(H_2O)_{6-x}]^{(3-x)}$ where $x < 6$). The value of 'x' would always be less than six because there are no definite reports of any hexahydroxy species of ruthenium. Under present experimental conditions $[Ru(H_2O)_5OH]^{2+}$ is considered as the probable active species of ruthenium(III).

Table 2b
Activation parameters with respect to the slow step of Scheme 1

Parameters	Values
E_a ($kJ\ mol^{-1}$)	13 ± 1
ΔH ($kJ\ mol^{-1}$)	11 ± 1
ΔS ($J\ K^{-1}\ mol^{-1}$)	−258 ± 15
$\Delta G^{\#}$ ($kJ\ mol^{-1}$)	90 ± 6

The reaction between the gabapentin and diperiodatocuprate(III) complex in alkaline media has the stoichiometry of 1:2 with first order dependence on the diperiodatocuprate(III) and ruthenium(III) concentrations and apparently less than first order dependence on the gabapentin and alkali concentrations. In most of the reports [4] on diperiodatocuprate(III) oxidation, periodate had retarding effect and order in the $[OH^-]$ was found to be less than unity and monoperiodatocuprate(III) is considered to be the active species. However, in the present kinetic study, different observations have been obtained; i.e., periodate has totally no effect on the rate of reaction. Accordingly, the diperiodatocuprate(III) is considered to be the active species. The observed less than unity order with respect to hydroxyl ion concentration suggests that gabapentin reacts with hydroxyl ion to liberate the deprotonated form of gabapentin, which in tern reacts with hydroxylated ruthenium(III) species to form a complex (C). This complex (C) further reacts with 1 mol of diperiodatocuprate(III) species in a slow step to give a free radical of gabapentin, NH_2^+, $Cu(OH)_2$ with regeneration of catalyst. Further this free radical reacts with another mole of diperiodatocuprate(III) species in a fast step to give the products, copper(II) ion in the form of $Cu(OH)_2$, 1-(hydroxymethyl)cyclohexane acetic acid and periodate. In a further fast step, NH_2^+ reacts with hydroxyl ion to give hydroxylamine. All these experimental results can be accommodated in Scheme 1.

The probable structure of the complex (C) is



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 obtained at 225 nm. This is also evident from the plot of $1/k_{obs}$ versus 1/[GP], which shows straight line with non-zero intercept. Such type of catalyst–substrate complex formation was also observed in other studies [16].

The rate constant, k of the slow step of Scheme 1 was obtained by plotting $[Ru(III)]/k_{obs}$ versus 1/[GP] at 25, 30, 35 and 40 °C. 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 the oxidation presumably occurs by an inner-sphere mechanism. This conclusion is supported by earlier work [17]. Since Scheme 1 is in accordance with generally well accepted principle of non-complementary oxidations taking place in a sequence of one electron steps, the reaction between the substrate and oxidant would afford a radi-

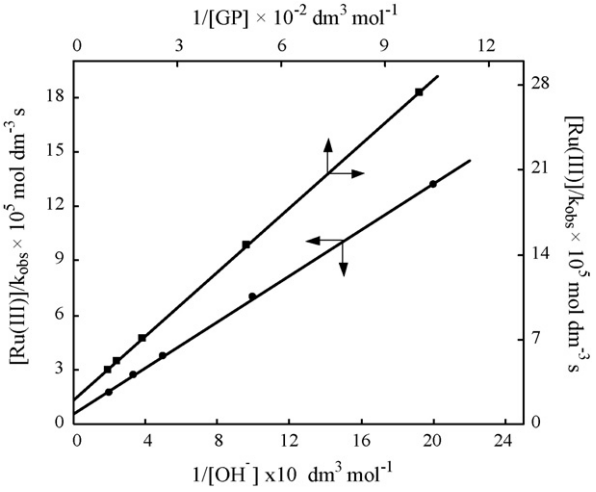


Fig. 3. Verification of rate law (5) in the form of (6).

cal intermediate. A free radical scavenging experiment revealed such possibility as given in Experimental section. This type of radical intermediate has been observed in amino acids [18]. From Scheme 1, including the observed orders in gabapentin, diperiodatocuprate(III), ruthenium(III), alkali and periodate the following rate law (5) can be obtained.

$$\text{Rate} = \frac{-\text{d[DPC]}}{\text{d}t} = \frac{kK_4K_5[\text{DPC}][\text{GP}][\text{Ru(III)}][\text{OH}^-]}{1 + K_4[\text{OH}^-] + K_4K_5[\text{GP}][\text{OH}^-]} \quad \text{or}$$

$$\frac{\text{Rate}}{[\text{DPC}]} = k_{\text{obs}} = \frac{kK_4K_5[\text{GP}][\text{Ru(III)}][\text{OH}^-]}{1 + K_4[\text{OH}^-] + K_4K_5[\text{GP}][\text{OH}^-]} \quad (5)$$

The rate law (5) may be rearranged to Eq. (6) which is suitable for verification.

$$\frac{[\text{Ru(III)}]}{k_{\text{obs}}} = \frac{1}{kK_4K_5[\text{GP}][\text{OH}^-]} + \frac{1}{kK_5[\text{GP}]} + \frac{1}{k} \quad (6)$$

According to Eq. (6), the plots of $[\text{Ru(III)}]/k_{\text{obs}}$ versus $1/[\text{GP}]$ and $[\text{Ru(III)}]/k_{\text{obs}}$ versus $1/[\text{OH}^-]$ should be linear with non-zero intercept, which is found to be so (Fig. 3). The slopes and intercepts of such plots lead to the values of k, K_4 and K_5 at 25 °C are $(2.2 \pm 0.2) \times 10^5$ dm^3 mol^{-1} s^{-1}, 3.5 ± 0.1 dm^3 mol^{-1} and $(4.50 \pm 0.06) \times 10^2$ dm^3 mol^{-1}, respectively. Using these values, rates under different experimental conditions were calculated by Eq. (5) and found to agree well with experimental values. The value of K_4 is in good agreement with literature value [19]. The effect of ionic strength and dielectric constant on the rate of reaction supports the proposed mechanism. The highly negative value of $\Delta S^{\#}$ indicates the intermediate complex is more ordered than the reactants (Scheme 1).

3.7. Catalytic activity and catalytic coefficient

It has been pointed out by Moelwyn-Hughes [20] that in presence of the catalyst, the uncatalysed and catalysed reactions proceeds simultaneously, so that

$$k_1 = k_0 + K_C[\text{catalyst}]^x$$

Here k_1 is the observed pesudo-first order rate constant in the presence of Ru(III) catalyst, k_0 the pseudo-first order rate constant for the uncatalyzed reaction, K_C the catalytic constant and x the order of the reaction with respect to [Ru(III)]. In the present investigation, x value for the standard run was found to be unity. The value of K_C is calculated by using the equation

$$K_C = \frac{k_1 - k_0}{[\text{Ru(III)}]^x}$$

The value of K_C was evaluated as 1.15×10^4. The high value of K_C as compared with earlier work [21] shows the greater efficiency of the catalyst in the present study.

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

4. Conclusion

The oxidation of gabapentin (GP) by diperiodatocuprate(III) (DPC) has been studied in an aqueous alkaline medium. A minute amount (10^{-7} mol dm^{-3}) of ruthenium(III) is sufficient to catalyse the reaction. Among the various species of Cu(III) in the alkaline medium, diperiodatocuprate(III), $[\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^{4-}$, is considered to the active species for the title reaction. Active species of Ru(III) is found to be $[\text{Ru(H}_2\text{O)}_5\text{OH}]^{2+}$. Activation parameters were evaluated for both catalysed and uncatalysed reactions. The overall sequence is consistent with the product, and mechanistic and kinetic studies.

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