Mechanistic Investigations of Uncatalysed and Osmium(VIII) Catalysed Oxidation of Chlorpheniramine an Antihistamine Drug by Diperiodatoargentate(III) Complex in Aqueous Alkaline Medium: A Comparative Kinetic Approach

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ABSTRACT

The oxidation of chlorpheniramine (CPM) an antihistamine agent by diperiodatoargentate(III) (DPA) has been investigated spectrophotometrically both in the absence and presence of osmium(VIII) catalyst in alkaline medium at a constant ionic strength of 0.10 mol dm^{-3}. The oxidation products were identified as (4-chloro-phenyl)-pyridin-2yl-methanol, dimethyl amino acetaldehyde and Ag(I). The stiochiometry was same in both the cases, i.e., [CPM]:[DPA] = 1:2. In both the uncatalysed and catalysed, the order with respect to DPA concentration was unity while the order with respect to CPM concentration was < 1 over the concentration range studied. The rate increased with an increase in OH$^-$ ion concentration and decreased with an increase in IO$_4^-$ ion concentration. As the concentration of the catalyst, osmium (VIII), increased the rate of reaction also increased. The order with respect to Os(VIII) concentration was found to be unity. The mechanisms proposed and derived rate laws are consistent with the observed experimental kinetics. Kinetic experiments suggest that Ag(H$_2$IO$_6$)(H$_2$O)$_2$ is the reactive species of oxidant and [OsO$_4$(OH)$_2$]$^{2-}$ is the reactive species of catalyst. The activation parameters were evaluated with respect to slow step of the mechanism.

Keywords: Chlorophenaramine(CPM), Diperiodatoargentate(III), Oxidation Kinetics Osmium(VIII) catalysis.
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INTRODUCTION

Chlorpheniramine (CPM) is an antihistamine drug used to relieve symptoms of allergy, hay fever, and the common cold. Chlorpheniramine has been shown to work as a serotoninnorepinephrine reuptake inhibitor or SNRI [1]. A similar antihistamine, brompheniramine, led to the discovery of the SSRI zimelidine. Limited clinical evidence shows that it is comparable to several antidepressant medications in its ability to inhibit the reuptake of serotonin and also norepinephrine (noradrenaline)[2]. However, extensive clinical trials of its psychiatric properties in humans have not been conducted. It inhibits serotonin reuptake less than norepinephrine reuptake [3]. Phenylephrine is sympathomimetic (descongestants) and chlorpheniramine maleate is an H1-receptor antagonist (antihistaminic)[4]. Quantitative analysis of chlorpheniramine maleate and phenylephrine hydrochloride in nasal drops by differential-derivative spectrophotometric, zero-crossing first derivative UV spectrophotometric and absorbance ratio methods is also reported [5]. It is evident from the literature survey that Isatin derivatives dialkylamino alkyl derivatives showing more promising antihistaminic activity(Resembles chloramphleniramine) [6] and Hydrophilic matrices of Chlorpheniramine maleate prepared using combination of different grades of hydroxypropylmethylcellulose (HPMC), viz, HPMCK4M, HPMCK15M and HPMCK100M[7].

In recent years the study of the highest oxidation state of transition metals has intrigued many researchers. Transition metals in their higher oxidation state can generally be stabilized by chelating with suitable polydentate ligands. These metal chelates such as diperiodatoargentate(III), diperiodatocuprate(III), and diperiodatonickelate(IV) are used as oxidation reagents in organic chemistry as well as analytical chemistry [8-10].

Diperiodatoargentate(III) (DPA) is a powerful oxidizing agent in alkaline medium with the reduction potential 1.74V [11] . It is widely used as a volumetric reagent for the determination of various organic and inorganic species [10-12]. Jayaprakash Rao and other researchers have studied DPA as an oxidizing agent for the kinetics of oxidation of some organic substrates [13]. They normally found that order with respect to both oxidant and substrate was unity and [OH⁻] was found to enhance the rate of reaction. It was also observed that they did not arrive at the possible active species of DPA in alkali and on the other hand they proposed mechanisms by generalizing the DPA as $[Ag(HL)L]^{(x+1)}$. However, Kumar *et al* [14-16] put an effort to give an evidence for the reactive form of DPA in large scale of alkaline pH. Ag(III) complexes can be stabilized in alkaline medium by periodate or tellurate ions [17,18]. When the Ag(III) species are involved, it would be interesting to know which of the species is the active oxidant. In the present investigation, we have obtained the evidence for the active species of DPA in alkaline medium.

Transition metals are known to catalyse many oxidation-reduction reactions since they involve multiple oxidation states. In recent years the use of transition metal ions such as osmium, ruthenium, palladium, manganese, chromium, iridium, either alone or as binary mixtures, as catalysts in various redox processes has attracted and also considerable interest [19]. Although the mechanism of catalysis depends on the nature of the substrate, the oxidant and experimental conditions, it has been shown that metal ions act as catalysts by one of these different paths such as the formation of complexes with reactants or oxidation of the substrate itself or through the

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formation of free radicals. The role of osmium(VIII) as a catalyst in some redox reactions has been reviewed [20]. Osmium(VIII) catalysis in redox reactions involves different degrees of complexity, due to the formation of different intermediate complexes and different oxidation states of osmium.

There is no report on the kinetics of oxidation of chlorpheniramine by any oxidant in presence and absence of any catalyst. The authors found that, in alkaline medium, the reaction between chlorpheniramine and DPA occurs in the presnce and absence of catalyst osmium(VIII). In view of potential pharmaceutical importance of chlorpheniramine, to know the active species of Ag(III) and catalyst Os(VIII) and traces the complexity of the reaction, a detailed study of the title reaction becomes important. Hence, the present investigation is aimed at checking the reactivity of chlorpheniramine towards DPA in both uncatalysed and osmium(VIII) catalysed reactions and to arrive at the possible mechanisms.

EXPERIMENTAL SECTION

All reagents were of analytical grade and double distilled water was used throughout the study. A stock solution of chlorpheniramine (CPM) was prepared by dissolving an appropriate amount of recrystallised sample in double distilled water. The purity of chlorpheniramine (CPM) was checked by its m.p.132 $^{\circ}$C (Lit.m.p.130-135°C). The IR spectrum agreed with literature. The required concentration of chlorpheniramine was used from its stock solution. A standard stock solution of Os(VIII) was prepared by dissolving OsO$_4$ (Johnson Matthey) in 0.50 mol dm^{-3} NaOH. The concentration of osmium(VIII) was ascertained[21] by determining the unreacted [Fe(CN)$_6$]$^{4-}$ with standard cerium(IV) solution in an acidic medium. The ionic strength in the reaction mixture was maintained by adding KNO$_3$ solution and the pH value was regulated with KOH (BDH) solution. An aqueous solution of AgNO$_3$ was used to study the product effect, Ag(I). A stock solution of IO$_4^-$ was prepared by dissolving a known weight of KIO$_4$ (Riedel-de-Hean) in hot water and used after 24h. Its concentration was ascertained iodometrically[22] at neutral pH maintained using phosphate buffer. The pH of the medium in the solution was measured by ELICO (LI120) pH meter. Solutions of chlorpheniramine and DPA were always freshly prepared before use.

Preparation of DPA
DPA was prepared by oxidizing Ag(I) in presence of KIO$_4$ as described elsewhere[23]. The complex was characterized from its UV spectrum, which exhibited three peaks at 216, 255 and 362 nm. These spectral features were identical to those reported earlier for DPA [23]. The magnetic moment study revealed that the complex was diamagnetic. The compound prepared was analyzed [24] for silver and periodate by acidifying a solution of the material with HCl, recovering and weighing the AgCl for Ag and titrating the iodine liberated when excess KI was added to the filtrate for IO$_4^-$. The aqueous solution of DPA was used for the required DPA concentration in the reaction mixture.

Instrument used
(a) For kinetic measurements, a CARY 50 Bio UV–Vis Spectrophotometer (Varian, Victoria-3170, Australia) connected to rapid kinetic accessory (HI-TECH SFA-12) were used.

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(b) For product analysis, Bruker 300 MH$_Z$ ^{1}HNMR, QP-2010S Shimadzu gas chromatograph mass spectrometer, Nicolet 5700-FT-IR spectrometer (Thermo, U.S.A.), CHN Data analyzer and for pH measurements (Elico pH meter model LI120) were used.

Kinetic measurements

The kinetics runs were performed under pseudo first-order condition by ensuring an excess of [CPM] > [DPA] atleast 10 times in both uncatalysed and catalysed reactions at 25.0 ± 0.1ºC, unless specified. In the absence of catalyst the reaction was initiated by mixing DPA with the chlorpheniramine solution which also contained required concentrations of KNO$_3$, KOH and KIO$_4$. In the presence of catalyst since the initial reaction was too fast to be monitored by usual methods, the course of reaction was fallowed by monitoring the decrease in absorbance of DPA in a 1-cm quartz cell placed in the thermostatted compartment of Varian Carry -50 –Bio UV-Vis Spectrophotometer connected to a rapid kinetic accessory (HI-TECH SFA -12) at its absorption maximum of 360 nm as a function of time. Application of Beer's law had been verified between 1.0 x 10^{-5} 1.0 x 10^{-4} of DPA at 360 nm and 'ε' was found to be 13900 ± 100 dm^3 mol^{-1} cm^{-1}. The spectral changes during the chemical reaction for the standard condition at 25 ^{0}C are given in (Fig. 1.). It was verified that there was no interference from other species in the reaction mixture at this wavelength.

In the kinetic studies it was observed that, under the present experimental conditions in the absence of Os(VIII), the oxidation of CPM by DPA occurs slowly, but in measurable quantities. Hence, during the calculation of pseudo-first order rate constants, k$_c$, the uncatalysed rate has also to be taken in to account. Due to this, in case of each catalysed, kinetic run, a parallel kinetic run under similar conditions in the absence of catalyst were also carried out. The kinetic runs were followed more then 90% completion of the reaction and good first order kinetics were observed. The pseudo-first order rate constants in absence (k$_u$) and in presence of catalyst (k$_c$), were calculated from the slopes of the plots of log (absorbance) versus time. The pseudo first order plots in almost all cases, were linear over 85% completion of the reaction.

$$\text{Thus,} \quad k_T = k_u + k_c$$

$$k_c = k_T - k_u$$

The (k$_u$ or k$_c$) values were reproducible within ± 5% and are the average of at least, three independent kinetic runs (Table 1 and 2).

In the kinetic studies a constant concentration, *viz.* 1.0 x 10^{-5} mol dm^{-3} of KIO$_4$ was used throughout, unless otherwise stated. Thus, the possibility of oxidation of chlorpheniramine (CPM) by periodate was verified and found that there was no significant reaction between chlorpheniramine (CPM) and KIO$_4$ under present experimental conditions. The total concentrations of periodate and OH$^-$ was calculated by considering the amount present in the DPA solution and that additionally added. Kinetic runs were also carried out in N$_2$ atmosphere in order to understand the effect of dissolved oxygen on the rate of the reaction. No significant difference in the results was obtained in the presence and absence of nitrogen. In view of the ubiquitous contamination of carbonate in the basic medium, the effect of carbonate was also studied. Added carbonate had no effect on the reaction rates.

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RESULTS AND DISSCUSSION

Stiochiometry and product analysis
Different sets of reaction mixtures containing varying ratios of DPA to chlorpheniramine in presence of constant amount of OH^-, KIO_4, and KNO_3 in uncatalysed reaction and a constant amount of Os(VIII) in catalysed reaction were kept for 3 hrs in a closed vessel under nitrogen atmosphere. The remaining concentration of DPA was assayed by measuring the absorbance at 360 nm. The reaction products were identified as (4-chloro-phenyl)-pyridin-2yl-methanol, dimethyl amino acetaldehyde and Ag(I). The results indicated 1:2 stoichiometry for both uncatalysed and catalysed reactions as given in Eq. (1).
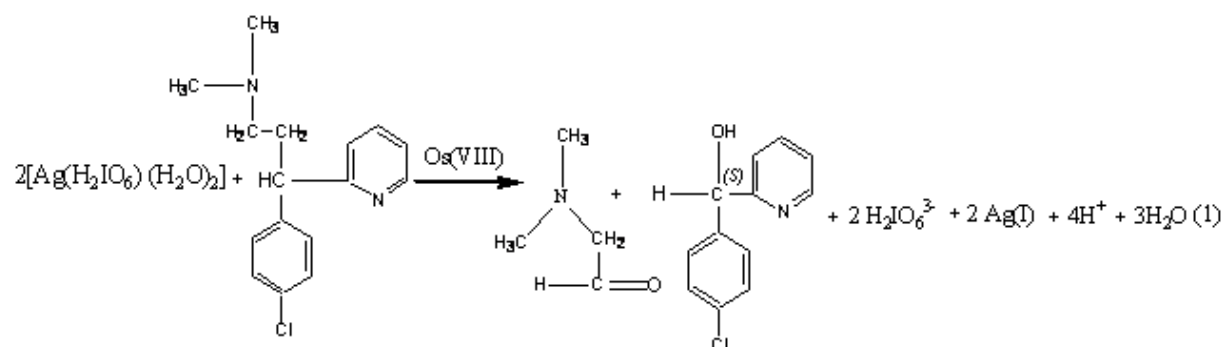
Characterization of products: The reaction mixture in the stiochiometric ratio was allowed to progress in the both absence and presence of osmium(VIII) catalyst for about 24 h at 298 K under stirred conditions. After completion of the reaction (monitored by thin layer chromatography), the reaction products were neutralized with dilute HCl and extracted with ether. The organic product was identified as (4-chloro-phenyl)-pyridin-2yl-methanol. The aqueous layer was made alkaline and extracted with ether, further it was dried over with anhydrous sodium sulphate to get dimethyl amino acetaldehyde. The products were initially confirmed by mass spectral analysis. The GC-MS data were obtained using electron impact ionization technique. The mass spectrum showed molecular ion peak at 218 m/z (Fig. 2.) which clearly matches with the molecular mass of (4-chloro-phenyl)-pyridin-2yl-methanol.). Futher for the aqueous layer the mass spectrum showed molecular ion peak at 87 m/z confirming dimethyl amino acetaldehyde (Fig. 3). All the other peaks observed in GC-MS were consistent with the structure of the products. Further these products were also confirmed by ^{1}HNMR.

^{1}HNMR for (4-Chloro-Phenyl)-Pyridin-2yl-Methanol.), δ^1 H / ppm (300 MHz, DMSO): 8.54-7.21 [m, 6H, Ar-H] and 4.18 [(s) CH-OH] (Fig 4).

^{1}HNMR for Dimethyl Amino Acetaldehyde, δ^1 H / ppm (300 MHz, DMSO): 8.17 [CHO], 2.09 [CH_3] and methylene protons merged with solvent peak (Fig. 5.).

Further dimethyl amino acid is also confirmed by the IR scanning which shows CHO stretching at 1764 cm^{-1}. The formation of Ag(I) in solution was detected by adding KCl solution to the reaction mixture, which produced white turbidity due to the formation of AgCl.

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Reaction order
The reaction orders have been determined form the slopes of $\log k_u$ versus log (concentration) plots in case of uncatalysed reaction and log k_c versus log (concentration) plots in case of catalysed reaction by varying concentration of oxidant, reductant, catalyst, alkali, inturn, while keeping the others constant in the variation of each reactant.

Effect of [DPA]
The oxidant, DPA concentration was varied in the range of 1.0×10^{-5} to 1.0×10^{-4} at fixed CPM, KOH and KIO_4 concentrations in both uncatalysed and catalysed reactions. The fairly constant pseudo first-order rate constants, k_u and k_c, indicate that the order with respect to DPA concentration was unity (Table 1 and Table 2). This was also confirmed by the linearity of the plots of log (absorbance) versus time upto 85% completion of the reaction.

Effect of [chlorpheniramine]
The effect of chlorpheniramine was studied for both the cases in the range of 1.0×10^{-4} to 1.0×10^{-3} mol dm^{-3} at constant concentrations of DPA, OH^-, IO_4^- and a constant ionic strength of 0.10 mol dm^{-3} in uncatalysed and at constant concentration of Os(VIII) in catalysed reaction. In the case of uncatalysed reaction as well as catalysed reaction, at constant temperature, the k_u and k_c values increased with increase in CPM concentration (Table 1 and Table 2). The order with respect to CPM concentration was less than unity. This was also confirmed by the plots of k_u versus $[CPM]^{0.35}$ and k_c versus $[CPM]^{0.60}$ which were linear rather than the direct plot of k_u versus [CPM] and k_c versus [CPM] (Fig. 6.).

Effect of [OH⁻]
The effect of alkali was studied, in absence and presence of catalyst, in the range of 0.01 to 0.10 mol dm^{-3} at constant concentrations of DPA, chlorpheniramine, IO_4^- and at constant ionic strength. The rate constants increased with increase in [alkali] and the order was found to be less than unity (Table 1 and Table 2). This was also confirmed by the plots of k_u versus $[OH^-]^{0.45}$ and k_c versus $[OH^-]^{0.58}$ which were linear rather than the direct plot of k_u versus $[OH^-]$ and k_c versus $[OH^-]$(Fig .7.).

Effect of [IO₄⁻]
The effect of periodate was studied for, both uncatlysed and catalysed cases, in the range of 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3} at constant concentrations of DPA, CPM, OH^- and at constant ionic strength. The experimental results indicated that the k_u and k_c values decreased with increase in the $[IO_4^-]$ (Table 1 and Table 2). The order with respect to IO_4^- was negative fractional.

Effect of [Os(VIII)]
The osmium(VIII) concentrations was varied from 1.0×10^{-7} to 10.0×10^{-7} mol dm^{-3} range, at constant concentration of diperiodatoargentate(III), chlorpheniramine, alkali and ionic strength. The order with respect to osmium(VIII) concentration was found to be unity. This was also confirmed from the linearity of the plot of k_c versus [Os(VIII)].

Effect of ionic strength and dielectric constant
The effect of ionic strength was studied by varying KNO_3 concentration. Dielectric constant of the medium was studied by varying the t-butyl alcohol and water percentage. It was found that

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there was no significant effect of ionic strength and dielectric constant of the medium on the rate of reaction in both uncatalysed and catalysed reactions.

Effect of initially added products
Initially added products, Ag(I), (4-chloro-phenyl)-pyridin-2yl-methanol, dimethyl amino acetaldehyde did not have any significant effect on the rate of reaction in both cases.

Polymerization study
For both uncatalysed and catalysed reactions, the involvement of free radicals in the reaction was verifed as follows: The reaction mixture, to which a known quantity of acrylonitrile (i.e., 2 ml scavenger) had been added initially, was kept for 2 hrs in an inert atmosphere. On diluting the reaction mixture with methanol, a white precipitate was formed, indicating the intervention of free radicals in the reactions.

Effect of temperature
The kinetics were studied at four different temperatures, 15, 20, 25 and 30 ^{0}C, for uncatalysed catalysed and reactions under varying concentrations of chlorpheniramine, alkali and periodate, keeping other conditions constant. It was observed that, as temperature increases the rate of reaction also increases. The rate constant, k_1, of the slow step of Scheme 1 was obtained from the slopes and the intercepts of the plots of $1/k_u$ versus $1/$ [CPM] at four different temperatures. The values are given in Table 3. The rate constant, k_2, of the slow step of Scheme 2 was obtained from the slopes and the intercepts of the plots of $[Os(VIII)]/k_c$ versus $1/[CPM]$ at four different temperatures. The values are given in Table 4. In both cases the energy of activation was obtained from the plot of logk versus $1/T$ and from which other activation parameters were calculated (Table 3 and Table 4).

Catalytic activity
It has been pointed out by Moelwyn-Hughes [25] that in the presence of catalyst, the uncatalysed and catalysed reactions proceed simultaneously, so that,
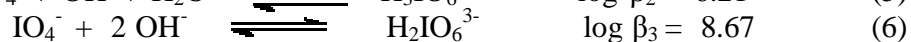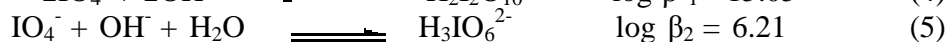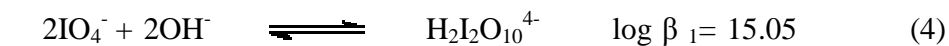
$$k_T = k_u + K_C[Os(VIII)]^x \tag{2}$$

Here k_T is the observed pseudo first-order rate constant in the presence of Os(VIII) catalyst, k_u is the pseudo first-order rate constant in the absence of catalyst K_C is the catalytic constant and '*x*' is the order with respect to osmium(VIII) concentration. In the present investigation the value of '*x*' was found to be unity.

$$K_C = \frac{k_T - k_u}{[Os(VIII)]^x} = \frac{k_c}{[Os(VIII)]} \quad (\text{where} \quad k_T - k_u = k_c) \tag{3}$$

The values of K_C were evaluated at different temperatures and are found to vary with temperature. Further, the plot of log K_C versus $1/T$ was linear and the values of energy of activation and other activation parameters with reference to catalyst were determined (Table 5).

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Due to strong versatile nature of two electron oxidant, the kinetics of oxidation of various organic and inorganic substrates has been studied by Ag(III) species. The literature survey [23] reveals that the water soluble diperiodatoargentate(III) (DPA) has a formula $[Ag(IO_6)_2]^{7-}$ with dsp^2 configuration of square planar structure, similar to diperiodatocopper(III) complex with two bidentate ligands, periodate to form a planar molecule. In the alkaline medium, the dissociative equilibria (4 - 6) of the IO_4^- were detected and the corresponding equilibrium constants were determined at 298.2 K by Aveston [26].
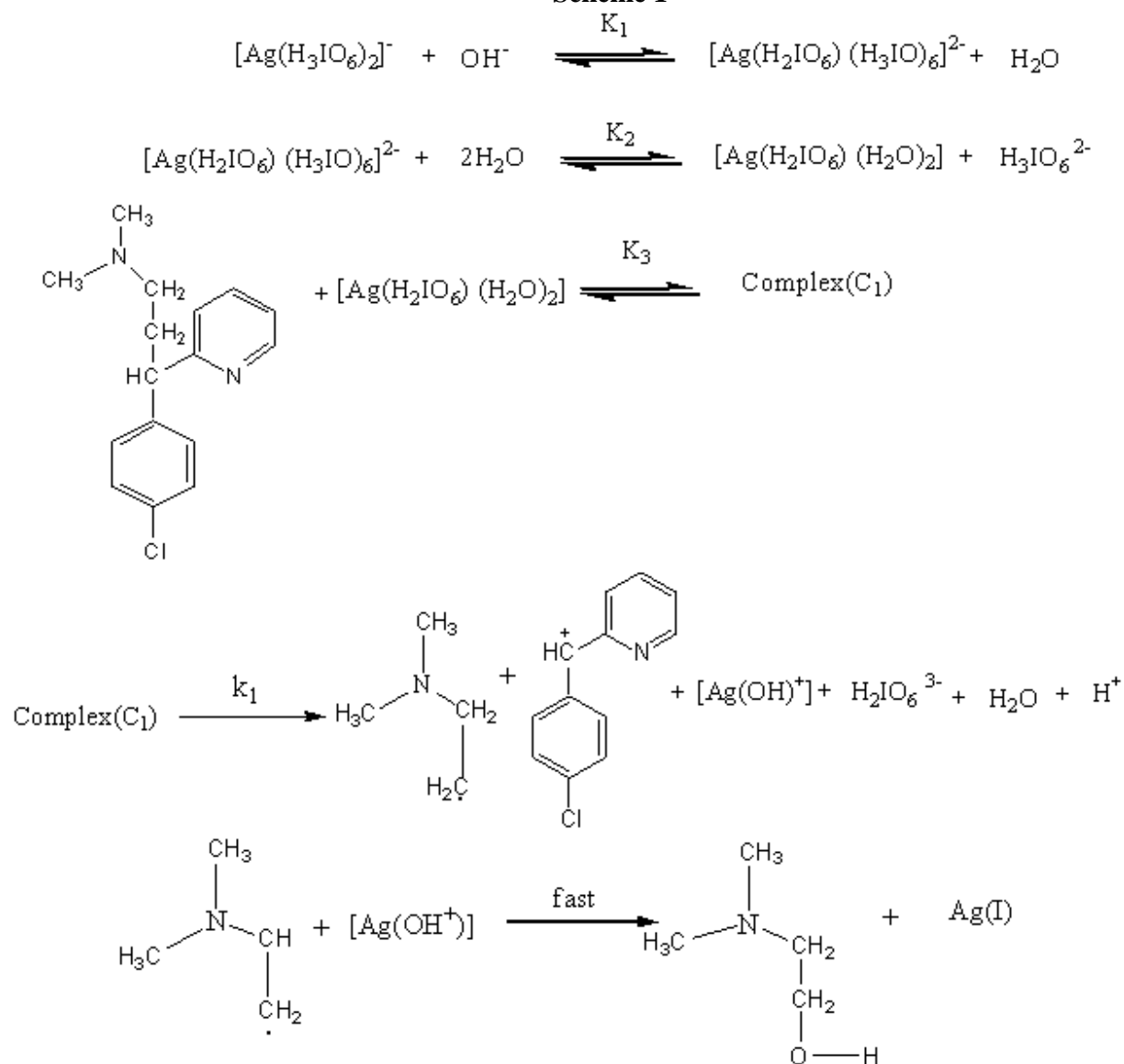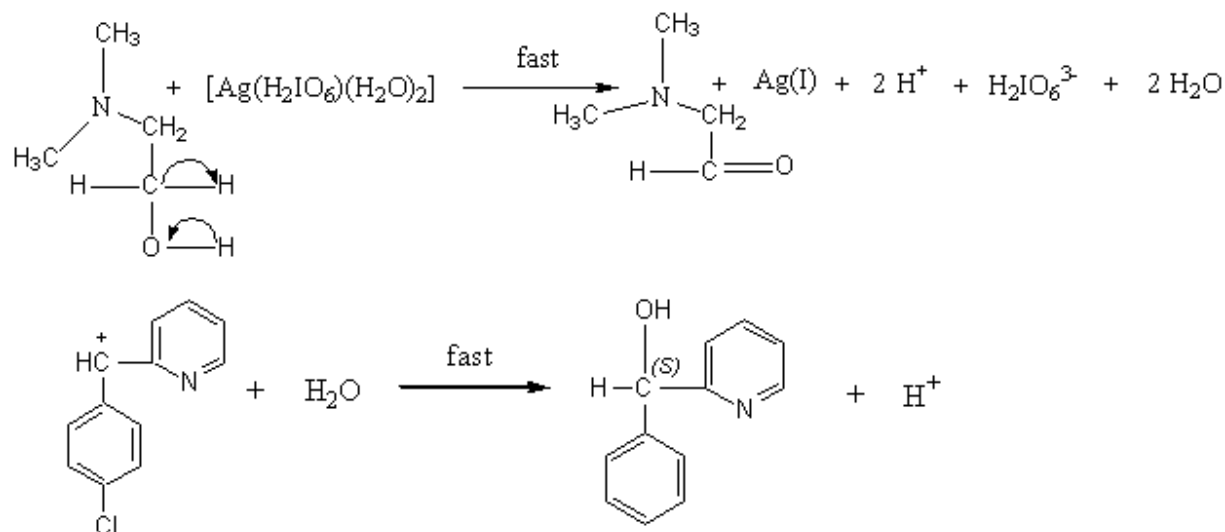
$$2IO_4^- + 2OH^- \rightleftharpoons H_2I_2O_{10}^{4-} \qquad \log \beta_1 = 15.05 \qquad (4)$$
$$IO_4^- + OH^- + H_2O \rightleftharpoons H_3IO_6^{2-} \qquad \log \beta_2 = 6.21 \qquad (5)$$
$$IO_4^- + 2OH^- \rightleftharpoons H_2IO_6^{3-} \qquad \log \beta_3 = 8.67 \qquad (6)$$

The distribution of all species of periodate in aqueous alkaline solution can be calculated from equilibria (4 - 6). In the $[OH^-]$ range used in this work the amount of dimer $(H_2I_2O_{10}^{4-})$ and IO_4^- species can be neglected. The main species of periodate are $H_2IO_6^{3-}$ and $H_3IO_6^{2-}$, which are consistent with the result calculated from Crouthamel's data [27]. Hence, DPA could be as $[Ag(H_3IO_6)_2]^-$ or $[Ag(H_2IO_6)_2]^{3-}$ in alkaline medium. Therefore, under the present experimental conditions, diperiodatoargentate(III), may be depicted as $[Ag(H_3IO_6)_2]^-$. The similar speciation of periodate in alkali was proposed for diperiodatonickelate(IV) [28].

The reaction between DPA and CPM in alkaline medium presents a 1:2 stoichiometry of oxidant to reductant. Since, the reaction was enhanced by OH^- ion concentration added periodate retarded the rate and first order dependency in DPA concentration and fractional order in CPM and OH^- concentrations, plausible reaction mechanism has been proposed which also explains all other experimental observations (Scheme 1).

Mechanism for uncatalysed reaction
In view of the observed experimental results, monoperiodatoargentate (III) (MPA) is considered to be the active species. The fractional order dependence of k_u on $[OH^-]$ suggests that OH^- takes part in the pre-equilibrium step 1 with DPA to give a deprotonated diperiodatoargentate(III). The plot of $1/k_u$ versus $[IO_4^-]$ is linear with a positive intercept indicating a dissociative equilibrium in which the DPA loses a periodate ligand from its coordination sphere, forming a reactive monoperiodatoargentate(III) complex (MPA) in the second step, which is evidenced by decrease in the rate with increase in $[IO_4^-]$. It may be expected that lower Ag(III) periodate species such as MPA will be more important in the reaction than DPA .The fractional order with respect to CPM presumably results from the complex formation between MPA and CPM prior to the slow step. Indeed it is to be noted that a plot of $1/k_u$ versus $1/[$ CPM] are linear and shows an intercept in agreement with the complex formation which slowly decomposes to form a free radical derived from chlorpheniramine, with formation of Ag(II) species. This free radical species further reacts with Ag(II) species in further fast steps to yield the products. All these results may be interpreted in the form of Scheme 1.

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Scheme 1

$$[Ag(H_3IO_6)_2]^- \ + \ OH^- \ \underset{}{\overset{K_1}{\rightleftharpoons}} \ [Ag(H_2IO_6)(H_3IO)_6]^{2-} + \ H_2O$$

$$[Ag(H_2IO_6)(H_3IO)_6]^{2-} \ + \ 2H_2O \ \underset{}{\overset{K_2}{\rightleftharpoons}} \ [Ag(H_2IO_6)(H_2O)_2] \ + \ H_3IO_6{}^{2-}$$

$$\text{Complex}(C_1) \ \xrightarrow{k_1} \ \cdots \ + [Ag(OH)^+] + \ H_2IO_6{}^{3-} + \ H_2O \ + \ H^+$$

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On the basis of square planar structure of DPA, the structure of MPA and complex may be proposed as shown below,
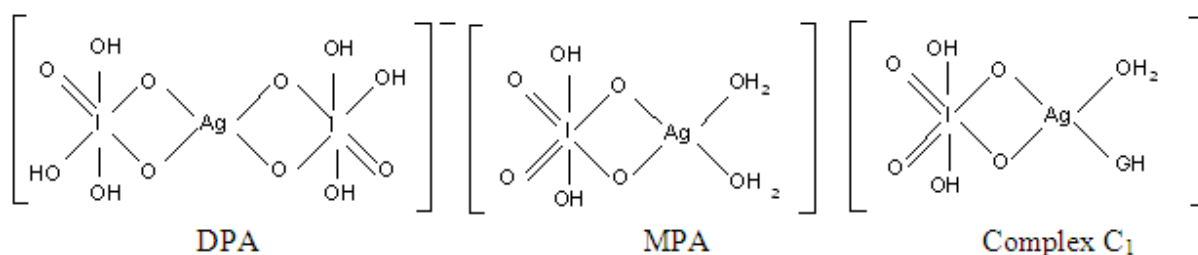
Spectroscopic evidence for the complex formation between DPA and CPM was obtained from UV-Vis spectra of CPM (5.0×10^{-4}), $[OH^-] = (0.05 \ mol \ dm^{-3})$ and a mixture of both. A bathochromic shift of about 10 nm from 360 to 370 nm in the spectra of the mixture of DPA and chlorpheniramine was observed (Fig. 8a.). The Michaelis-Menten plot proved the complex formation between oxidant and substrate, which explains less than unit order in CPM concentration. Such a complex between a oxidant and substrate has also been observed in other studies [29].

From Scheme 1, the rate law (7) can be derived, while explain all the observed.

$$\text{Rat} = -\frac{d[DPA]}{dt} = \frac{k_1 K_1 K_2 K_3 [DPA][CPM][OH^-]}{[H_3IO_6^{2-}] + K_1 [OH^-][H_3IO_6^{2-}] + K_1 K_2 [OH^-] + K_1 K_2 K_3 [OH^-][CPM]} \qquad (7)$$

Or

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$$k_u = \frac{\text{Rate}}{[\text{DPA}]} = \frac{k_1 K_1 K_2 K_3 [\text{CPM}][\text{OH}^-]}{[H_3IO_6{}^{2-}] + K_1[\text{OH}^-][H_3IO_6{}^{2-}] + K_1 K_2[\text{OH}^-] + K_1 K_2 K_3[\text{OH}^-][\text{CPM}]} \quad (7)$$

which explains all the observed kinetic orders of different species.

The rate law (7) can be rearranged into the following form which is suitable for verification.
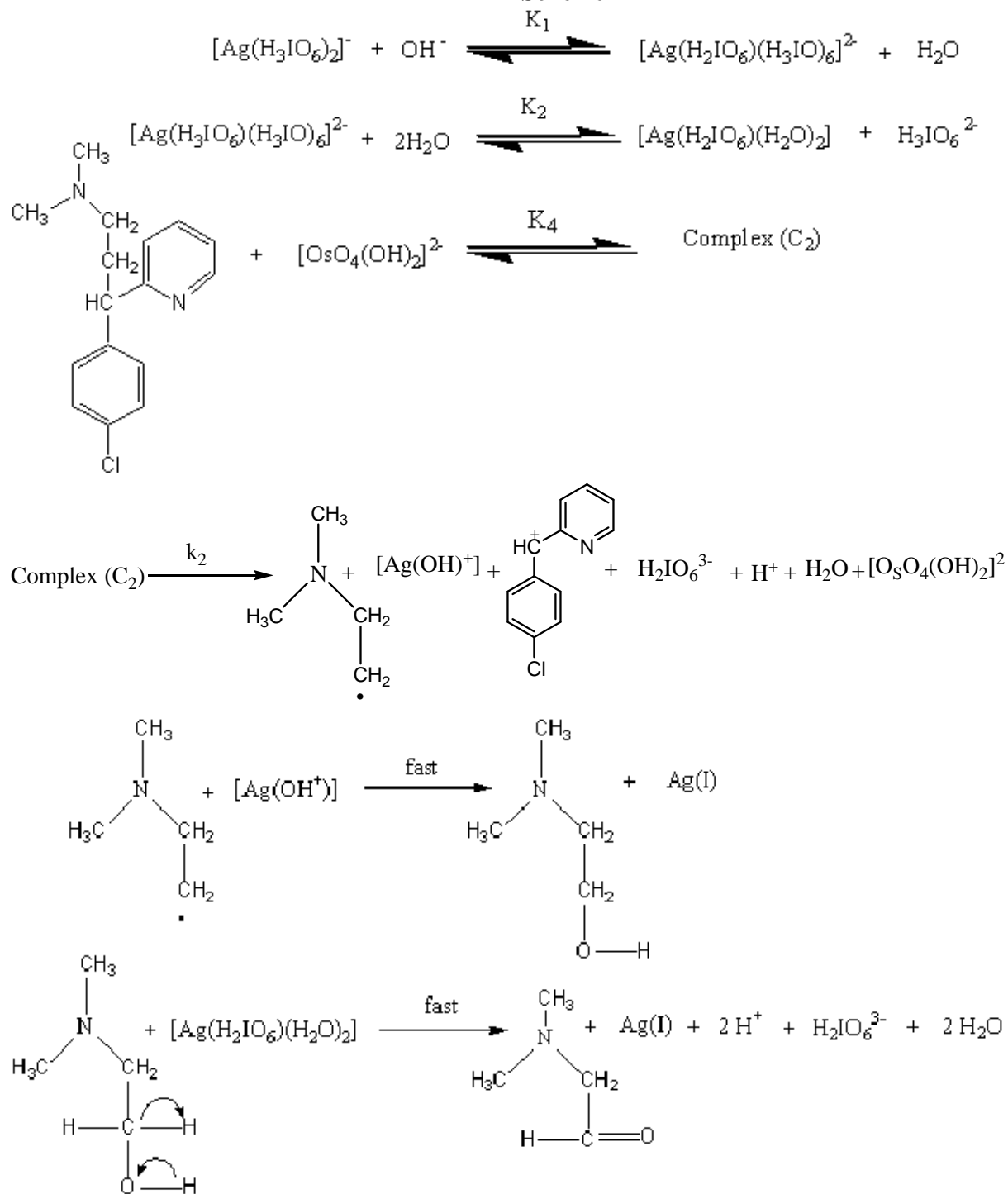
$$\frac{1}{k_u} = \frac{[H_3IO_6{}^{2-}]}{k1K1K2K3[\text{OH}^-][\text{CPM}]} + \frac{[H_3IO_6{}^{2-}]}{k_1 K_2 K_3[\text{CPM}]} + \frac{1}{k_1 K_3[\text{CPM}]} + \frac{1}{k_1} \quad (8)$$
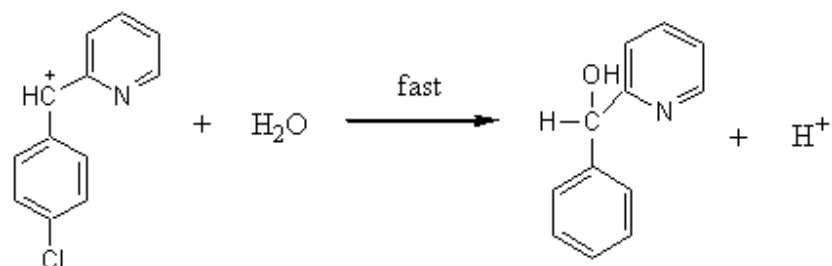
According to Eq. (8), other conditions being constant, plots of $1/k_u$ versus $1/[\text{CPM}]$, $1/k_u$ versus $1/[\text{OH}^-]$ and $1/k_u$ versus $[H_3IO_6{}^{2-}]$ should be linear and are found to be so (Fig 9a and 9b). The slopes and intercepts of such plots lead to the values of K_1, K_2, K_3 and k_1 (Table 3). The value of K_1 is in good agreement with the literature [30]. Using these constants, the rate constants were calculated over different experimental conditions by using Eq. (7) and there is a good agreement between the calculated and the experimental values (Table 1), which fortifies the proposed mechanism (Scheme 1). The equilibrium constant K_1 is far greater than K_2 which may be attributed to the greater tendency of DPA to undergo deprotonation compared to the formation of hydrolysed species in alkaline medium.

The thermodynamic quantities for the different equilibrium steps, in Scheme 1 can be evaluated as follows. The CPM, OH^- and $H_3IO_6{}^{2-}$ concentrations (Table 1) were varied at four different temperatures. The plots of $1/k_u$ versus $1[\text{CPM}]$, $1/k_u$ versus $1/[\text{OH}^-]$ and $1/k_u$ versus $[H_3IO_6{}^{2-}]$ should be linear and are found are to be so (Fig.10a. and 10b.). From the slopes and intercepts, the values of K_1, K_2 and K_3 were calculated at different temperatures (Table 3). A van't Hoff plot was made for the variation of K_1, K_2 and K_3 with temperature (log K_1 versus $1/T$, log K_2 versus $1/T$ and log K_3 versus $1/T$). The values of enthalpy of reaction ΔH, entropy of reaction ΔS and free energy of reaction ΔG were calculated for the first, second and third equilibrium steps. These values are given in Table 3. A comparison of the ΔH value (18.2 kJ mol^{-1}) from K_2 with that of $\Delta H^{\#}$ (56.9 kJ mol^{-1}) of rate limiting step supports that the reaction before the rate determining step is fairly fast as it involves low activation energy [31]. A negative value of $\Delta S^{\#}$ (-96.6 JK^{-1}mol^{-1}) suggests that intermediate complex is more ordered than the reactants [32].

Mechanis of Os(VIII) catalysed reaction
Osmium(VIII) is known to form different complexes [33] at different OH^- concentrations, $[OsO_4(OH)_2]^{2-}$ and $[OsO_5(OH)]^{3-}$. At higher concentration of OH^-, $[OsO_5(OH)]^{3-}$ is significant. At lower concentrations of OH^-, as employed in the present study and since the rate of oxidation increased with increase in $[\text{OH}^-]$, it is reasonable that $[OsO_4(OH)_2]^{2-}$ was operative and its formation is important in the reaction. Added periodate retards the rate of reaction. First order dependency in DPA and catalyst Os(VIII) concentrations and fractional order in CPM and OH^- concentrations was observed. To explain the observed orders the following Scheme 2 has been proposed for catalysed reaction.

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Scheme 2

$$[Ag(H_3IO_6)_2]^- \;+\; OH^- \;\underset{}{\overset{K_1}{\rightleftharpoons}}\; [Ag(H_2IO_6)(H_3IO)_6]^{2-} \;+\; H_2O$$

$$[Ag(H_3IO_6)(H_3IO)_6]^{2-} \;+\; 2H_2O \;\underset{}{\overset{K_2}{\rightleftharpoons}}\; [Ag(H_2IO_6)(H_2O)_2] \;+\; H_3IO_6{}^{2-}$$

$$+ \; [OsO_4(OH)_2]^{2-} \;\underset{}{\overset{K_4}{\rightleftharpoons}}\; \text{Complex (C}_2\text{)}$$

$$\text{Complex (C}_2\text{)} \xrightarrow{\;k_2\;} \quad + \; [Ag(OH)^+] \; + \quad + \; H_2IO_6{}^{3-} \; + H^+ + H_2O + [O_sO_4(OH)_2]^2$$

$$+ \; [Ag(OH^+)] \xrightarrow{\text{fast}} \quad + \; Ag(I)$$

$$+ \; [Ag(H_2IO_6)(H_2O)_2] \xrightarrow{\text{fast}} \quad + \; Ag(I) \; + \; 2\,H^+ \; + \; H_2IO_6{}^{3-} \; + \; 2\,H_2O$$

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In the prior equilibrium step 1, the OH⁻ deprotonates the DPA to give a deprotonated diperiodatoargentate(III); in the second step displacement of a ligand , periodate takes place to give free periodate which is evidenced by decrease in the rate with increase in IO_4^- ion concentration (Table 3). In view of this it may be expected that lower Ag(III) periodate species such as MPA is more important active species in the reaction than DPA. The inverse fractional order in $[H_3IO_6^{2-}]$ might also be due to this reason. In the pre-rate determining stage, the hydroxylated species of Os(VIII) combines with a molecule of CPM to give an intermediate complex (C_2), which further reacts with one mole of MPA in rate determining step to give a free radical derived from chlorpheniramine, with formation of Ag(II) species and regeneration of catalyst, Os(VIII). This free radical species further reacts with Ag(II) species in further fast steps to yield the products as given in Scheme 2.

The probable structure of the complex (C_2) is given below;
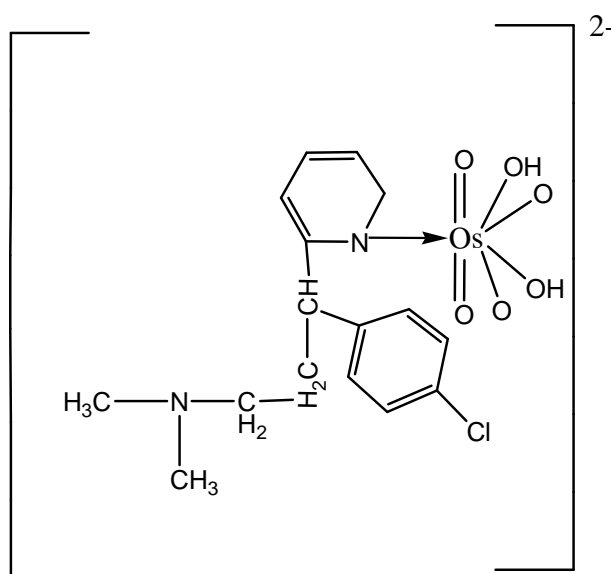
Spectroscopic evidence for the complex formation between Os(VIII) and CPM was obtained from UV-Vis spectra of CPM (5.0 x 10^{-4} mol dm⁻³), Os(VIII) (5.0 x 10^{-7} mol dm⁻³), [OH⁻] = (0.05 mol dm⁻³) and a mixture of both. A bathochromic shift of about 10 nm from 252 to 262 nm in the spectra of mixture of chlorpheniramine and osmium(VIII) was observed (Fig. 8b). The Michaelis-Menten plot proved the complex formation between catalyst and substrate, which explains less than unit order in [CPM]. Such a complex between a catalyst and substrate has also been observed in the literature [34].

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From Scheme 2, the rate law (9) can be derive

$$Rate = \frac{-d[DPA]}{dt} = \frac{k_2 \, K_1 \, K_2 \, K_4 \, [DPA] \, [CPM] \, [OH^-] \, [Os(VIII)]}{[H_3IO_6^{2-}] + K_1 [OH^-] \, H_3IO_6^{2-}] + K_1 K_2 [OH^-] + K_1 K_2 K_4 [OH^-] [CPM]} \tag{9}$$

or

$$\frac{Rate}{[DPA]} = k_c = k_T - k_u = \frac{k_2 K_1 K_2 K_4 [CPM][OH^-] \, [Os(VIII)]}{[H_3IO_6^{2-}] + K_1 [OH^-] [H_3IO_6^{2-}] + K_1 K_2 [OH^-] + K_1 K_2 K_4 [OH^-] [CPM]} \tag{9}$$

$$\frac{[Os(VIII)]}{k_c} = \frac{[H_3IO_6^{2-}]}{k_2 K_1 K_2 K_4 [OH^-][CPM]} + \frac{[H_3IO_6^{2-}]}{k_2 K_2 K_4 [CPM]} + \frac{1}{k_2 K_4 [CPM]} + \frac{1}{k_2} \tag{10}$$

According to Eq. (10), other conditions being constant, plots of $[Os(VIII)]/k_c$ versus $1/[CPM]$, $[Os(VIII)]/k_c$ versus $1/[OH^-]$ and $[Os(VIII)]/k_c$ versus $[H_3IO_6^{2-}]$ should be linear and are found to be so (Fig. 9a, 9b). The slopes and intercepts of such plots lead to the values of K_1, K_2, K_4 and k_2 (Table 4). The value of K_1 is in good agreement with the literature [29].Using these constants, the rate constants were calculated and compared with the experimental, k_c, values. There was a reasonable agreement with each other (Table 2), which fortifies the proposed mechanism (Scheme 2).

Table: 1   Effect of variation of DPA, CPM, OH$^-$ and IO$_4^-$ concentrations on the oxidation of chlorpheniramine, by diperiodatoargentate(III) in aqueous alkaline medium at 25 ^{0}C and I = 0.10 mol dm^{-3}

[DPA]x10^5 (mol dm^{-3})	[CPM]x 10^4 (mol dm^{-3})	[OH$^-$] x 10^2 (mol dm^{-3})	[IO$_4^-$] x 10^5 (mol dm^{-3})	k_u x 10^3(s^{-1})	
				Found	Calculated
1.0	5.0	5.0	1.0	3.81	3.90
3.0	5.0	5.0	1.0	3.81	3.90
5.0	5.0	5.0	1.0	3.82	3.91
8.0	5.0	5.0	1.0	3.82	3.91
10.0	5.0	5.0	1.0	3.81	3.91
5.0	1.0	5.0	1.0	1.60	1.60
5.0	3.0	5.0	1.0	3.33	3.31
5.0	5.0	5.0	1.0	3.81	3.90
5.0	8.0	5.0	1.0	4.50	4.50
5.0	10.0	5.0	1.0	4.71	4.80
5.0	5.0	1.0	1.0	2.01	2.02
5.0	5.0	3.0	1.0	3.60	3.60
5.0	5.0	5.0	1.0	3.80	3.81
5.0	5.0	8.0	1.0	3.46	3.47
5.0	5.0	10.0	1.0	4.80	4.80
5.0	5.0	5.0	1.0	4.16	4.17
5.0	5.0	5.0	3.0	4.04	4.03
5.0	5.0	5.0	5.0	3.80	3.81
5.0	5.0	5.0	8.0	3.41	3.42
5.0	5.0	5.0	10.0	3.08	3.03

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Table: 2 Effect of variation of DPA, CPM, OH⁻, IO₄⁻ and Os(VIII) concentrations on the osmium(VIII) catalysed oxidation of chlorpheniramine, by diperiodatoargentate(III) in aqueous alkaline medium at 25 ^{0}C and *I* = 0.10 mol dm^{-3}

[DPA] x10^5 (mol dm^{-3})	[CPM]x10^4 (mol dm^{-3})	[OH⁻] x10^2 (mol dm^{-3})	[IO₄⁻] x10^5 (mol dm^{-3})	[Os(VIII)]x10^7(mol dm^{-3})	k_Tx10^2 (s^{-1})	k_ux10^3 (s^{-1})	k_c x10^2 (s^{-1})	
							Found	Calcd.
1.0	5.0	5.0	1.0	5.0	2.08	3.81	1.69	1.69
2.0	5.0	5.0	1.0	5.0	2.08	3.81	1.69	1.68
5.0	5.0	5.0	1.0	5.0	2.08	3.82	1.68	1.69
8.0	5.0	5.0	1.0	5.0	2.08	3.82	1.68	1.67
10.0	5.0	5.0	1.0	5.0	2.08	3.81	1.69	1.68
5.0	1.0	5.0	1.0	5.0	0.81	1.60	0.65	6.49
5.0	3.0	5.0	1.0	5.0	1.51	3.33	1.18	11.5
5.0	5.0	5.0	1.0	5.0	2.08	3.81	1.70	17.7
5.0	8.0	5.0	1.0	5.0	2.69	4.50	2.20	22.3
5.0	10.0	5.0	1.0	5.0	4.71	4.71	2.62	26.0
5.0	5.0	1.0	1.0	5.0	0.87	2.01	0.69	2.80
5.0	5.0	3.0	1.0	5.0	1.62	3.60	1.26	4.10
5.0	5.0	5.0	1.0	5.0	2.08	3.80	1.70	5.60
5.0	5.0	8.0	1.0	5.0	2.75	3.46	2.40	6.40
5.0	5.0	10.0	1.0	5.0	3.23	4.80	2.78	6.67
5.0	5.0	5.0	1.0	5.0	7.55	4.16	7. 13	6.69
5.0	5.0	5.0	3.0	5.0	6.54	4.04	6.13	6.00
5.0	5.0	5.0	5.0	5.0	5.96	3.80	5.58	5.60
5.0	5.0	5.0	8.0	5.0	3.76	3.41	3.41	3.40
5.0	5.0	5.0	10.0	5.0	2.59	3.10	2.28	2.40
5.0	5.0	5.0	1.0	0.0	0.87	3.81	0.49	0.48
5.0	5.0	5.0	1.0	1.0	1.70	3.81	1.30	1.04
5.0	5.0	5.0	1.0	2.0	3.99	3.81	3.36	3.32
5.0	5.0	5.0	1.0	5.0	5.96	3.81	5.57	5.60
5.0	5.0	5.0	1.0	8.0	6.60	3.81	6.56	5.90
5.0	5.0	5.0	1.0	10.0	12.2	3.81	11.8	11.8

Table: 3 Activation parameters and thermodynamic quantities for the oxidation of CPM by diperiodatoargentate(III) in aqueousalkaline medium with respect to the slow step of Scheme1

(a) Effect of temperature and activation parameters

Temperature (K)	k_1 x 10^3 (s^{-1})	Parameters	Values
288	2.19	E_a (kJ mol^{-1})	59 ± 2
293	4.42	$\Delta H^{\#}$ (kJ mol^{-1})	56 ± 0.5
298	6.20	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	-96 ± 10
303	7.63	$\Delta G^{\#}$ (kJ mol^{-1})	85 ± 4
		log A	8.2 ± 0.2

(b) Effect of temperature on first, second and third equilibriumstep of Scheme 1

Temperature (K)	K_1 (dm^3 mol^{-1})	K_2 x10^5 (mol dm^{-3})	K_3 x10^{-3} (dm^3 mol^{-1})
288	12.4	6.8	1.94
293	10.8	7.6	2.40
298	8.4	8.8	4.28
303	4.8	9. 9	4.84

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(c) Thermodynamic quantities with respect to K_1, K_2 and K_3

Thermodynamic quantities	Values from K_1	Values from K_2	Values from K_3
ΔH (kJ mol^{-1})	-44.2	18.4	47.7
ΔS (JK^{-1} mol^{-1})	-128	-17	224
ΔG (kJ mol^{-1})	-5.40	23.6	-20.3

Table: 4 Activation parameters and thermodynamic quantities for the osmium(VIII) catalysed oxidation of CPM by diperiodatoargentate(III) in aqueous alkaline medium with respect to the slow step of Scheme 2

(a) Effect of temperature and activation parameters

Temperature (K)	k_2 x 10^{-4} (s^{-1})	Parameter	Value
288	3.0	E_a (kJ mol^{-1})	47.6 ± 1
293	4.6	$\Delta H^{\#}$ (kJ mol^{-1})	45.1 ± 1
298	6.1	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	-40.1 ± 0.2
303	8.3	$\Delta G^{\#}$ (kJ mol^{-1})	57.2 ± 0.1

(b) Effect of temperature on first, second and third equilibrium step of Scheme 2

Temperature (K)	K_1 (dm^3 mol^{-1})	K_2 x 10^5 (mol dm^{-3})	K_4 x 10^{-3} (dm^3 mol^{-1})
288	8.60	2. 47	2.1
293	6.60	3.63	2.5
298	3.56	4.06	3.2
303	2.34	6.54	3.8

(c) Thermodynamic quantities with respect K_1, K_2 and K_4

Thermodynamic quantities	Values from K_1	Values from K_2	Values from K_4
ΔH (kJ mol^{-1})	-66.9	43.7	27.3
ΔS (JK^{-1} mol^{-1})	-208.0	-60.0	156.7
ΔG (kJ mol^{-1})	-3.8	25.5	-20.0

Table: 5 Values of catalytic constant (K_C) at different temperatures and activation parameters calculated using K_C values

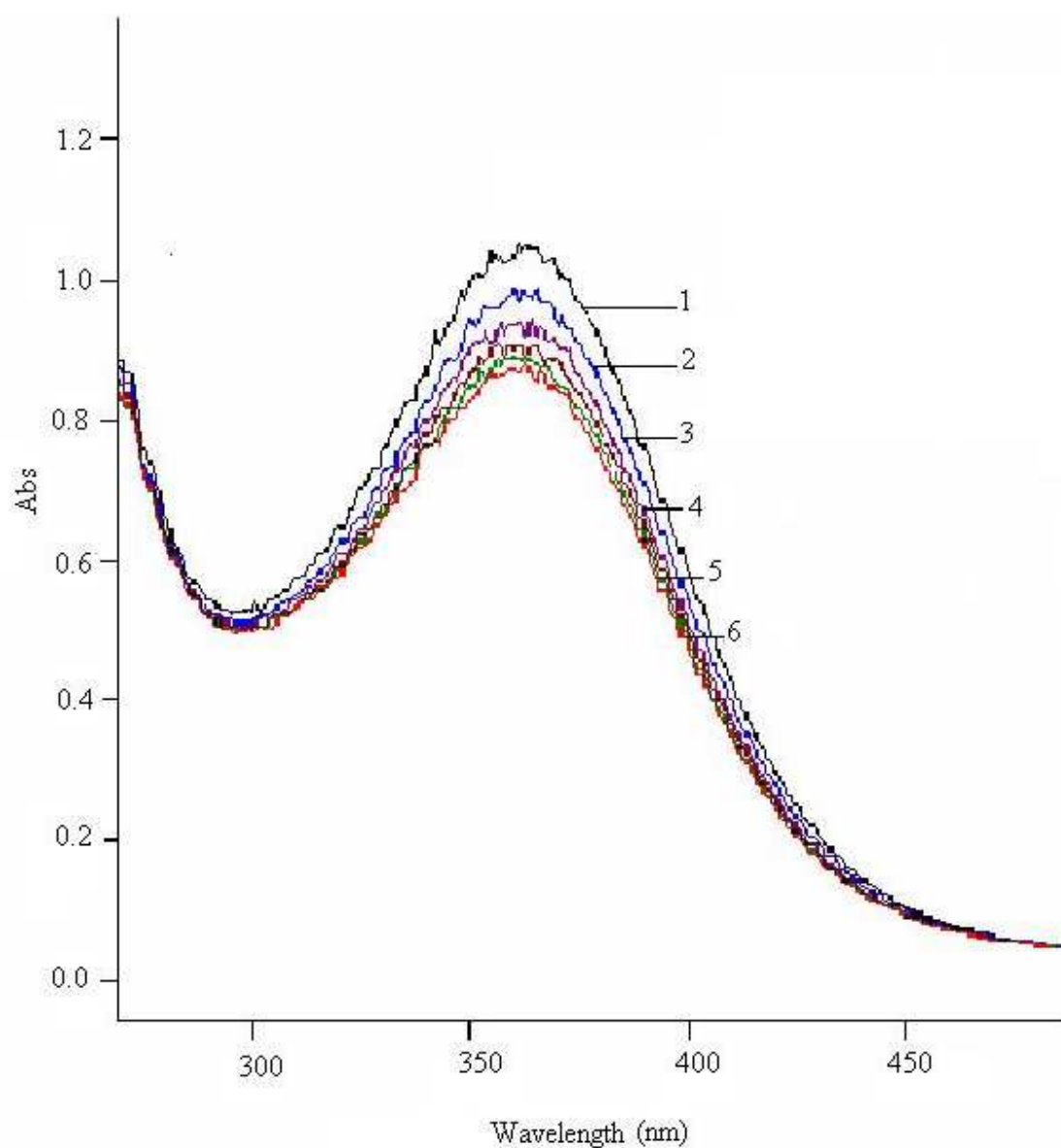| Temperature (K)	K_C x 10^{-4}	Activation parameters	values
288	1.4	E_a (kJ mol^{-1})	50.6
293	2.6	$\Delta H^{\#}$ (kJ mol^{-1})	48.1
298	3.4	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	-53.6
303	4.4	$\Delta G^{\#}$ (kJ mol^{-1})	64.1

Fig: 1 UV-vis. spectral changes during the oxidation of CPM by alkaline DPA at 25 ^{0}C, [DPA] = 5.0 X 10^{-5}, [CPM] = 5.0 X 10^{-4}, [OH$^-$] = 0.05 mol dm^{-3} and I = 0.10 mol dm^{-3} with scanning time interval of : (1) 1.0, (2) 2.0, (3) 3.0, (4) 4.0, (5) 5.0 and (6) 6.0 min
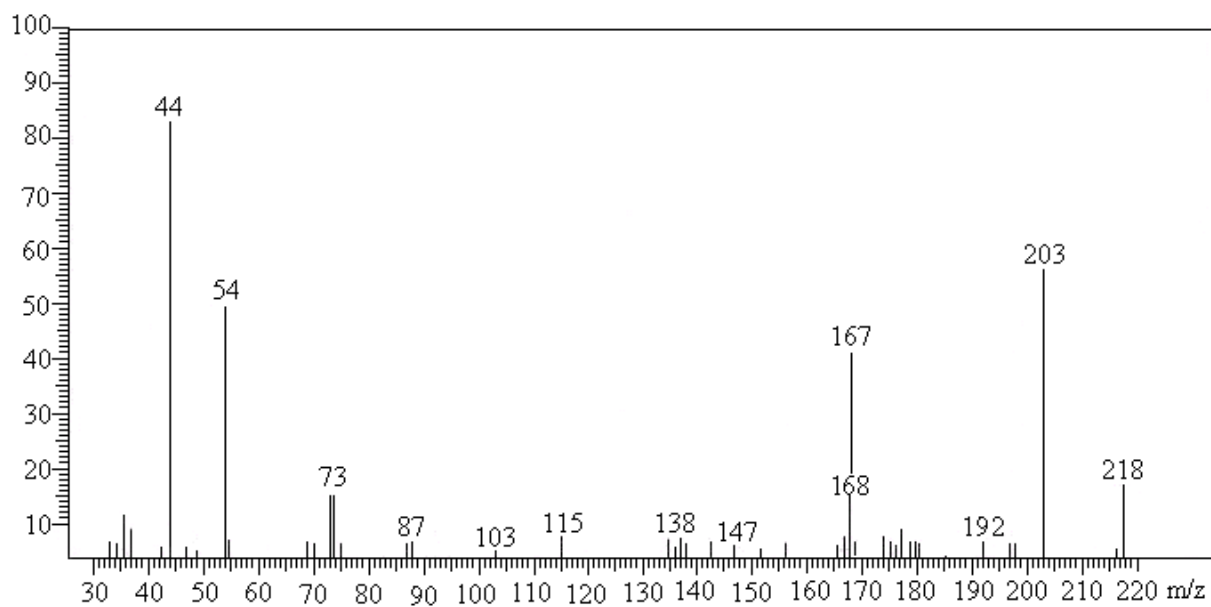
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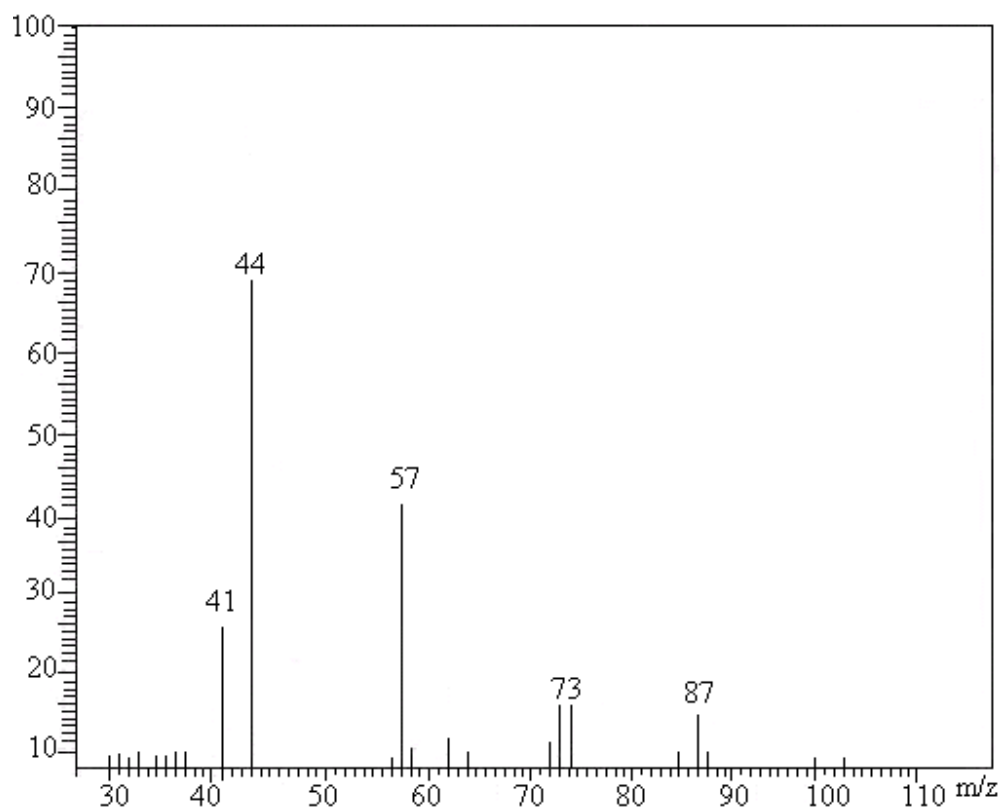**Fig: 2 Mass spectrum of (4-chloro-phenyl)-pyridine-2yl-methanol with base peak at 218 m/z**
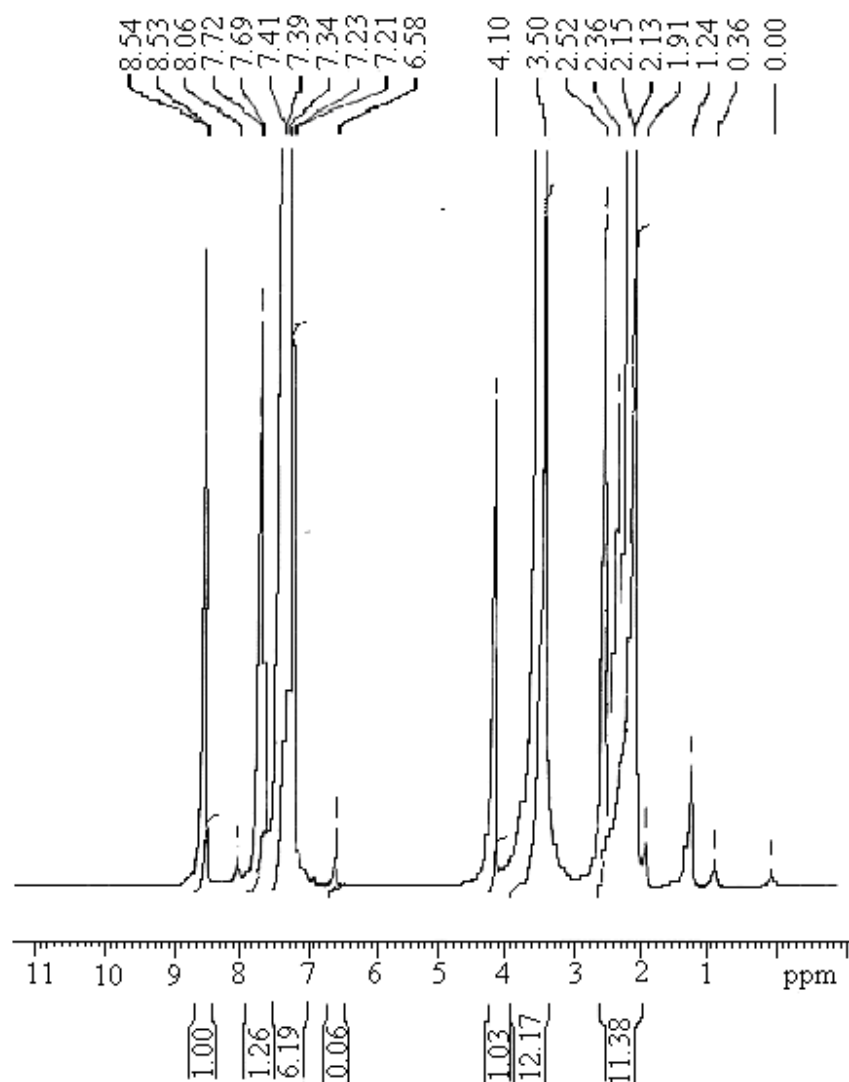
Fig: 3 Mass spectrum of dimethyl amino acid
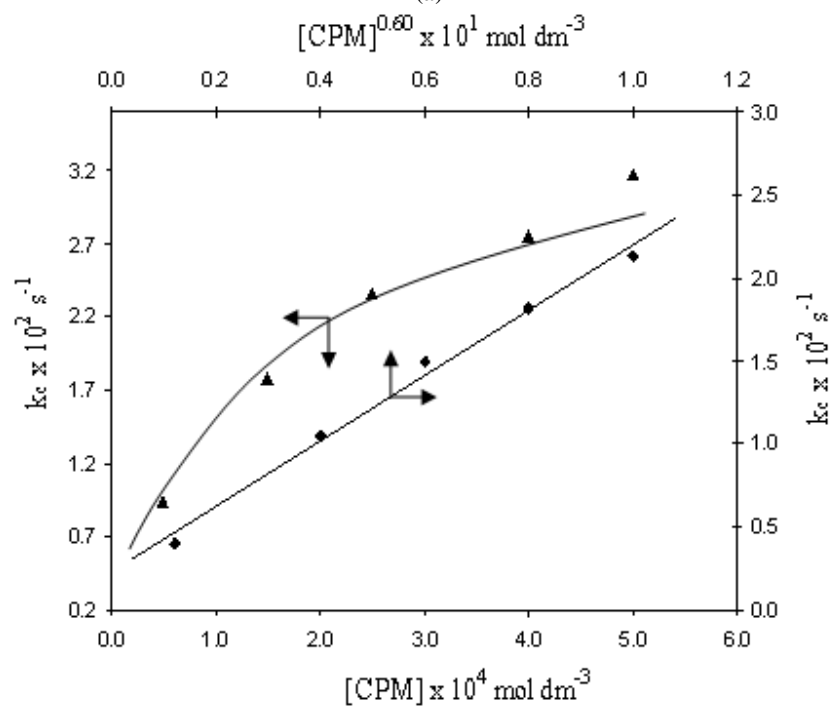
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Fig: 4   ¹H NMR spectrum of (4-chloro-phenyl)-pyridine-2yl-methanol

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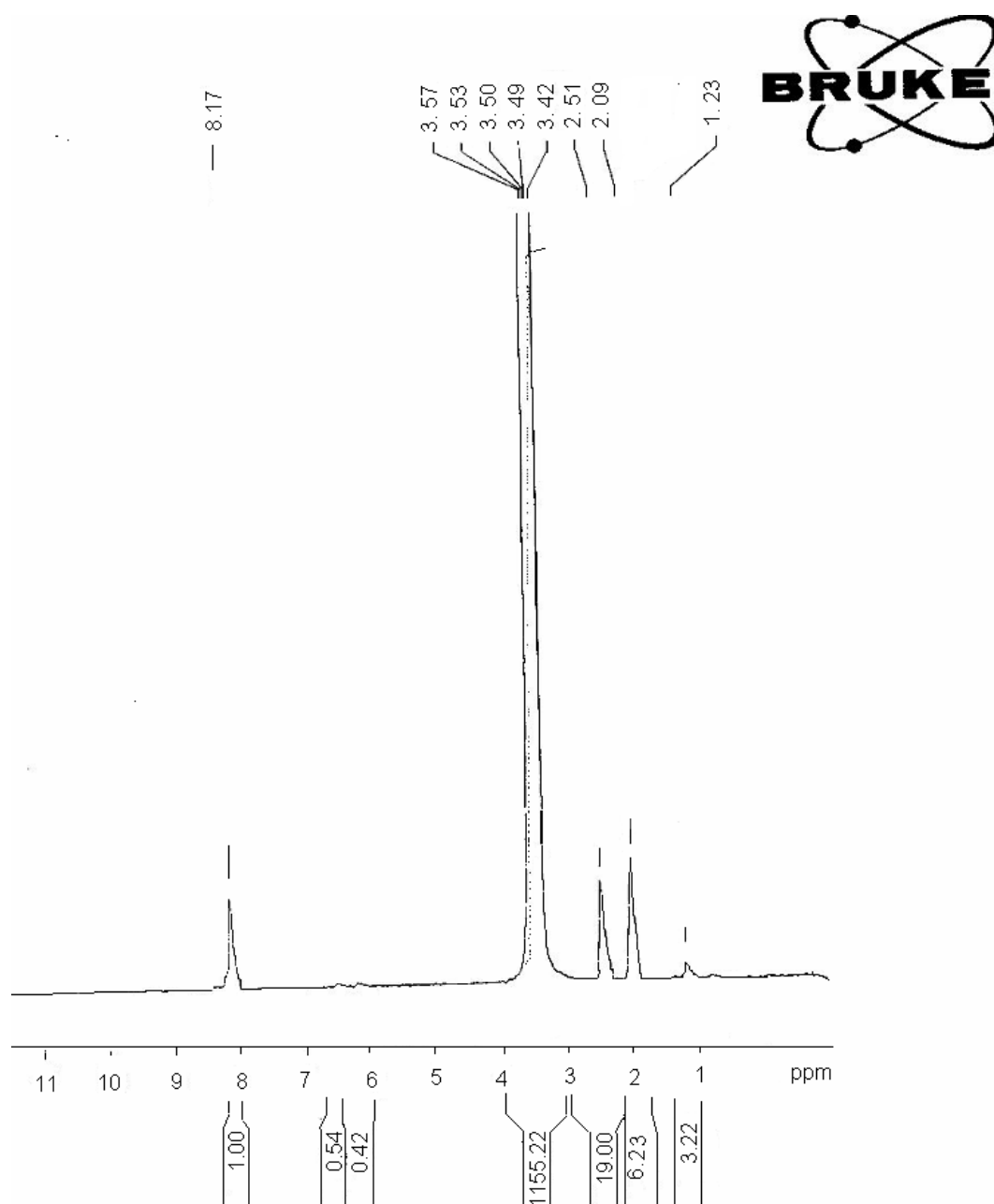
Fig: 5 H¹ NMR spectrum of dimethyl amino acetaldehyde

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(a)

(b)
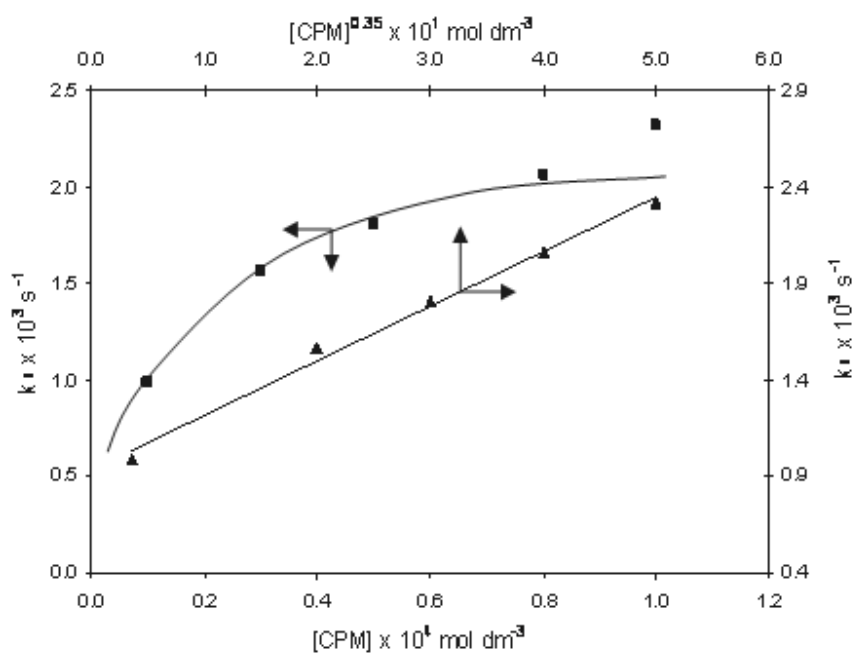
Fig: 6 Plots of (a) k_u versus $[CPM]^{0.35}$ and k_u versus [CPM] (conditions as in Table 1)
(b) k_c versus $[CPM]^{0.60}$ and k_c versus [CPM] (conditions as in Table 3)

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(a)

(b)
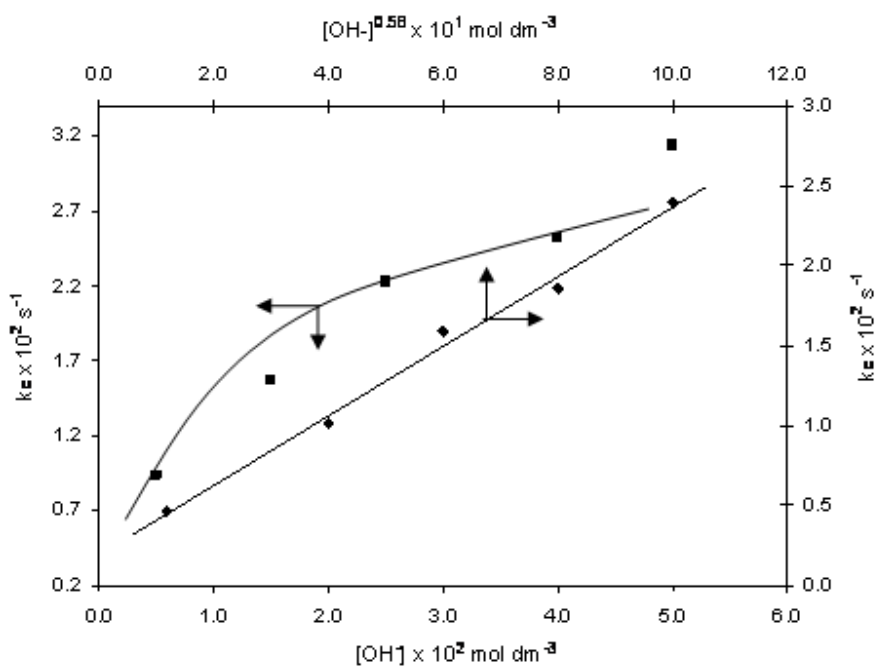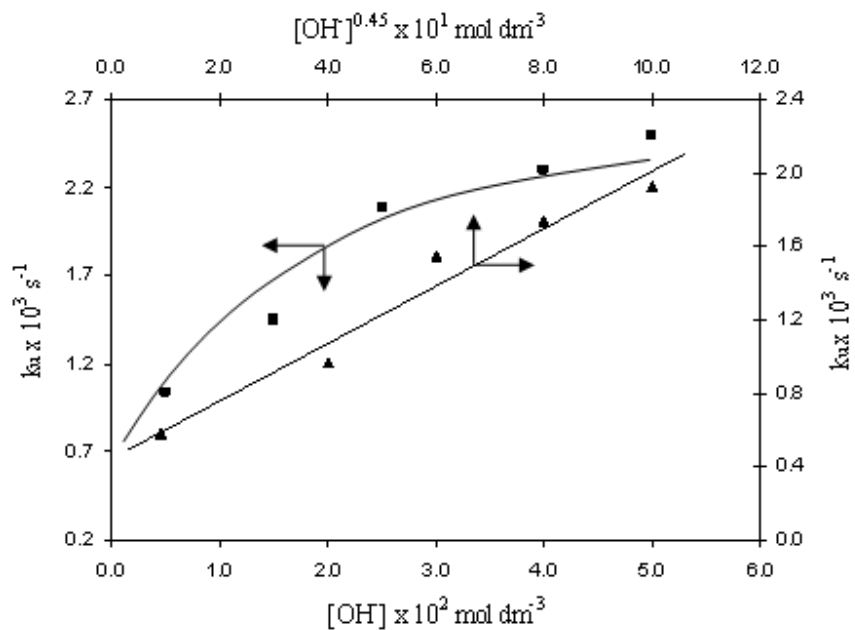
Fig: 7 Plots of (a) k_u versus $[OH^-]^{0.45}$ and k_u versus $[OH^-]$ (conditions as in Table 1)
(b) k_c versus $[OH^-]^{0.58}$ and k_c versus $[OH^-]$ (conditions as in Table 3)

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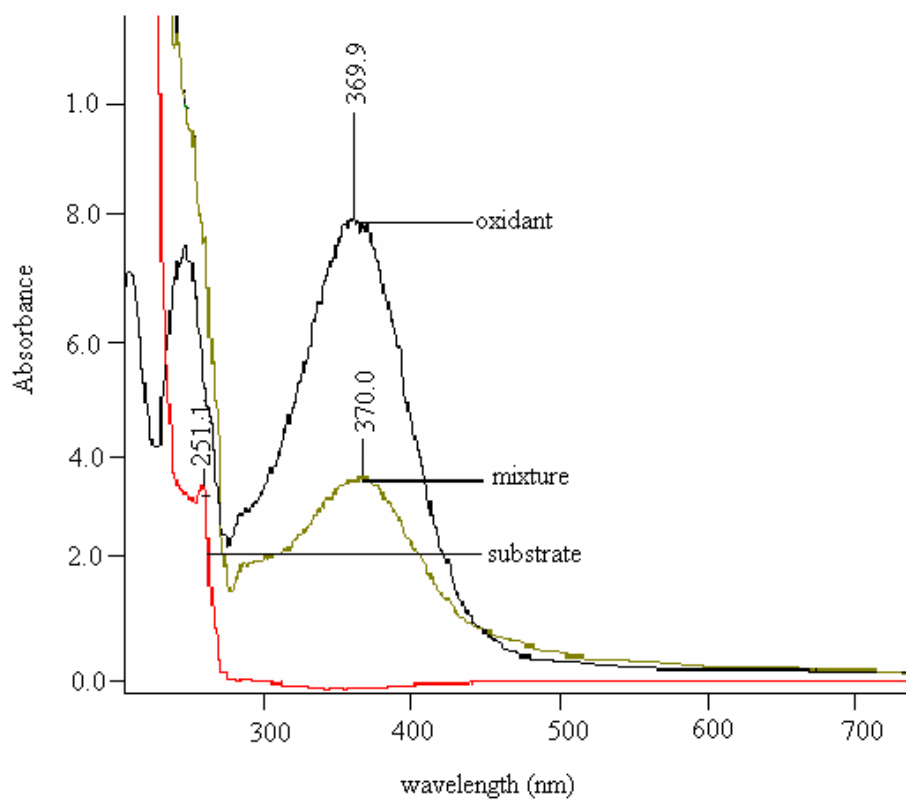
Fig: 8a Spectroscopic evidence for the complex formation between CPM and DPA
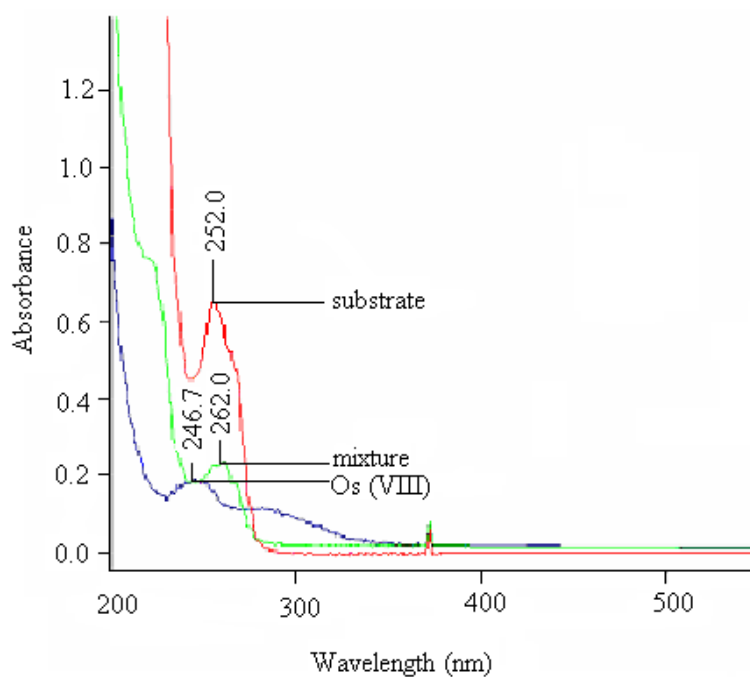
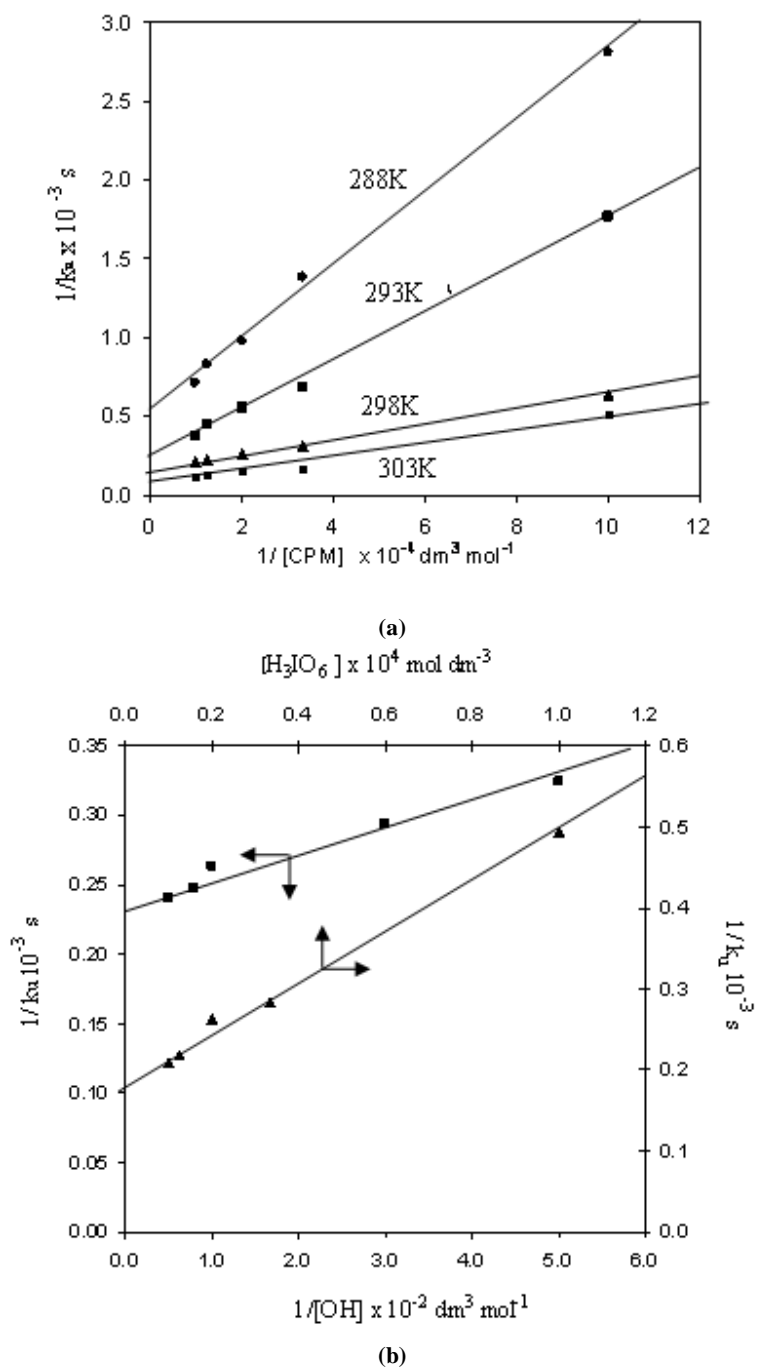**Fig: 8(b) Spectroscopic evidence for the complex formation between [Os(VIII)] and CPM**

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(a)

(b)

Fig: 9(a) Plots of $1/k_u$ versus $1/[CPM]$ at four different temperatures (conditions as in Table 1)
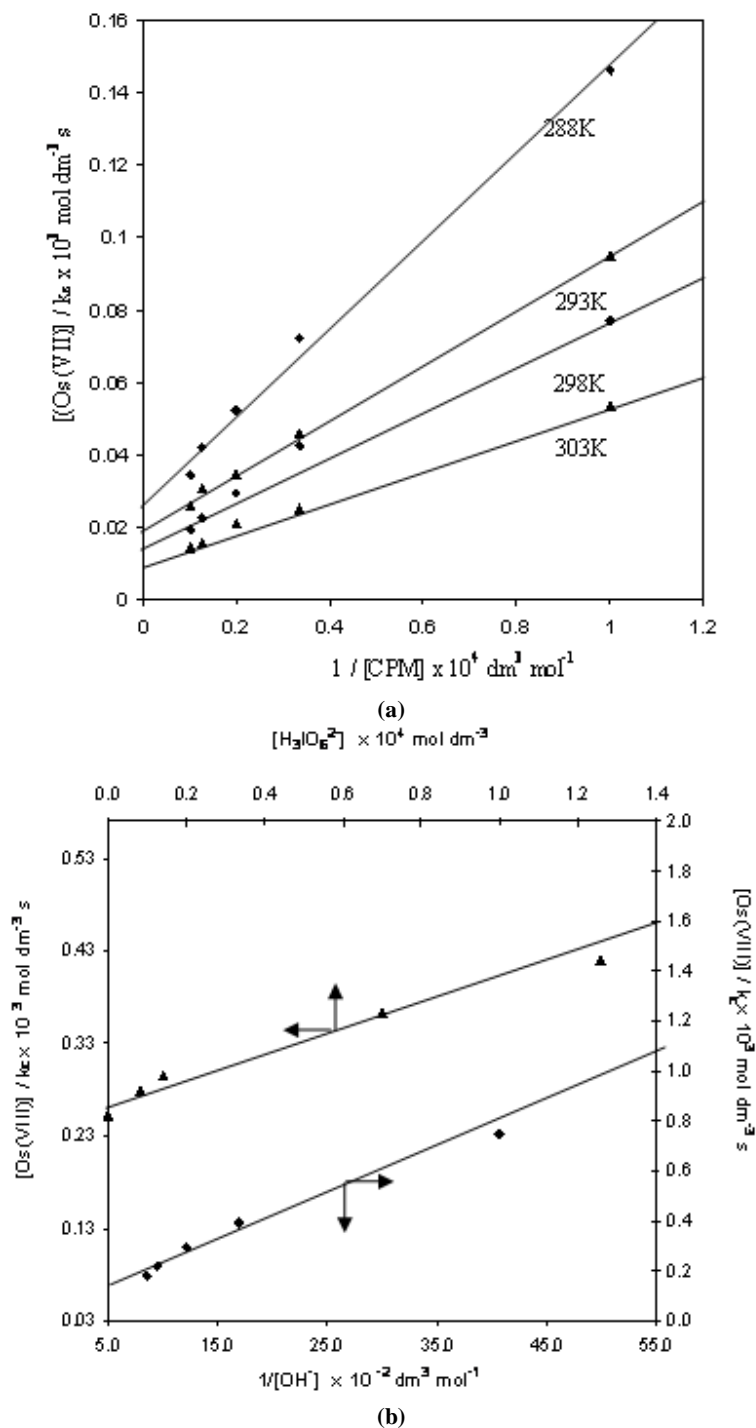**(b). Plots of $1/k_u$ versus $1/[OH^-]$ and $1/k_U$ versus$[H_3IO_6^{2-}]$ at 298 K (conditions as in Table 1)**

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(a)

(b)

Fig: 10 (a) Plots of [Os(VIII)] /k_c versus 1/[CPM] at four different temperatures (conditions as in Table3) (b) Plots of [Os(VIII)] /k_c versus 1/[OH⁻] and [Os(VIII)] /k_c versus [H$_3$IO$_6^{2-}$] at 298 K (conditions as in Table 3)

The thermodynamic quantities for the different equilibrium steps, in Scheme 2 can be evaluated as follows. The CPM and OH⁻ concentrations (Table 2) were varied at four different temperatures. The plots of [Os(VIII)]/k_c versus 1/[CPM], [Os(VIII)]/k_c versus 1/[OH⁻] and

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[Os(VIII)]/k_c versus [$H_3IO_6^{2-}$] should be linear and are found to be so (Fig. 10). From the slopes and intercepts, the values of K_1, K_2 and K_4 were calculated at different temperatures. A van't Hoff plot was made for the variation of K_1, K_2 and K_4 with temperature (log K_1 versus 1/T, log K_2 versus 1/T and log K_4 versus 1/T). The values of enthalpy of reaction ΔH, entropy of reaction ΔS and free energy of reaction ΔG, were calculated for the first, second and third equilibrium steps. These values are given in Table 4. A comparison of the ΔH value (43.7 kJ mol^{-1}) from K_2 with that of ΔH$^{\#}$ (45.1 kJ mol^{-1}) of rate limiting step supports that the reaction before the rate determining step is fairly fast as it involves low activation energy [35].

Negligible effect of ionic strength and dielectric constant in both uncatalysed and catalysed reaction might be due to involvement of *neutral* species *in* the reaction (Scheme 1 and 2). The negative value of ΔS$^{\#}$ (-40.8 JK^{-1}mol^{-1}) suggests that intermediate complex is more ordered than the reactants [36]. The observed higher rate constant for the slow step indicate that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by literature [37,38]. The activation parameters evaluated for the catalysed and uncatalysed reactions explain the catalytic effect on the reaction. Os(VIII) forms the complex (C_2) with substrate which enhances the reducing property of the substrate than that without catalyst. Further the catalyst Os(VIII) modifies the reaction path by lowering the energy of activation.

It is also interesting to note that the transient species involved in both the uncatalysed and Os(VIII) catalysed reaction is different but leads to the formation of same products. The uncatalysed reaction in alkaline medium has been shown to proceed via a MPA-CPM complex which decomposes slowly in a rate determining step to give the products, where as, in the catalysed reaction, it has been shown to proceed via Os(VIII) - CPM complex which further reacts with one mole of MPA in the rate determining step to give the products. Since in both the cases MPA and CPM were involved, the products obtained were same and the role of catalyst was to enhance the reducing property of the substrate and to provide an alternative path with low activation energy.

CONCLUSION

Through the kinetics study, we proposed the reaction mechanisms for both uncatalysed and Os(VIII) catalysed oxidation of chlorpheniramine by diperiodatoargentate(III). Among the various species of silver(III) in alkaline medium, [$Ag(H_2IO_6)(H_2O)_2$] is considered to be the active species for the title reaction. Active species of Os(VIII) is found to be [$OsO_4(OH)_2$]$^{2-}$. The reaction rates revealed that Os(VIII) catalysed reaction is about eight-fold faster than the uncatalysed reaction. It becomes apparent that in carrying out this reaction, the role of reaction medium is crucial. Activation parameters were evaluated for both catalysed and uncatalysed reactions. Catalytic constants and the activation parameters with reference to catalyst were also computed. The overall sequence described here is consistent with product, mechanistic, and kinetic studies.

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