

Scientific paper

Catalytic Activity of Ruthenium(III) on the Oxidation of an Anticholinergic Drug-Atropine Sulfate Monohydrate by Copper(III) Periodate Complex in Aqueous Alkaline Medium – Decarboxylation and Free Radical Mechanism

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Received: 05-12-2012

Abstract

Atropine sulfate monohydrate (ASM) is an anticholinergic drug, having a wide spectrum of activity. Hence, the kinetics of oxidation of ASM by diperiodatocuprate (DPC) in the presence of micro (10^{-6}) amounts of Ru(III) catalyst has been investigated spectrophotometrically in aqueous alkaline medium at $I = 0.50 \text{ mol dm}^{-3}$. The reaction between DPC and ASM exhibits 1:2 stoichiometry (ASM:DPC) i. e., one mole of ASM require two moles of DPC to give products. The main oxidation products were confirmed by spectral studies. The reaction is first order with respect to [DPC] and [Ru(III)], while the order with respect to [ASM] and $[\text{OH}^-]$ was less than unity. The rates decreased with increase in periodate concentration. The reaction rates revealed that Ru(III) catalyzed reaction was about seven-fold faster than the uncatalyzed reaction. The catalytic constant (K_c) was also determined at different temperatures. A plausible mechanism is proposed. The activation parameters with respect to slow step of the mechanism were calculated and the thermodynamic quantities were also determined. Kinetic experiments suggest that $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$ is the reactive Cu(III) species and $[\text{Ru}(\text{H}_2\text{O})_5\text{OH}]^{2+}$ is the reactive Ru(III) species.

Keywords: Atropine sulfate, Diperiodatocuprate(III), Oxidation, Ru(III) Catalysis, Kinetics, Active species

1. Introduction

The most common atropine compound used in medicine is atropine sulfate monohydrate (ASM) ($\text{C}_{17}\text{H}_{23}\text{NO}_3$)₂ · H_2SO_4 · H_2O , and its full chemical name is 1 α H, 5 α H-Tropan-3- α -ol (\pm)-tropate(ester), sulfate monohydrate (Fig. 1).

Atropine sulfate is a core medicine in the World Health Organization's »Essential drug list«, which is a list of minimum medical needs for a basic health care system.¹ Although atropine, earlier enjoyed a widespread use in the treatment of peptic ulcer, today it is mostly used in resuscitation², anaesthesia³, and ophthalmology, usually as the more soluble sulfate salt. It is a specific antidote for the treatment of poisoning with organophosphorus and carbamate insecticides and organophosphorus nerve agents. Its degradation by microorganisms has been reported by several groups.^{4,5}

Transition metals in their higher oxidation states can generally be stabilized by chelation with suitable polyden-

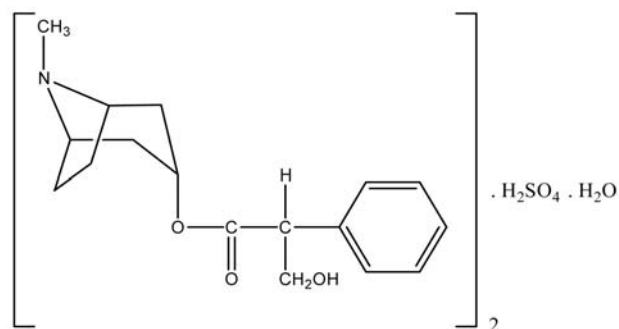


Figure 1. Chemical structure of atropine sulfate monohydrate

tate ligands. Metal chelates such as diperiodatocuprate(III),⁶ diperiodatoargentate(III)⁷ and diperiodatonickelate(IV)⁸ are good oxidants in a medium with an appropriate pH value. Diperiodatocuprate(III) (DPC) is a versatile one-electron oxidant and the oxidation study of DPC is

scanty in view of its limited solubility and stability in aqueous medium. Its use as an analytical reagent is now well recognized.⁹ The kinetics of self-decomposition of these complexes was studied in detail. Copper(III) is shown to be an intermediate in the copper(II) catalysed oxidation of aminoacids by peoxydisulphate. The oxidation reaction usually involves the copper(II)–copper(I) couple and such aspects are dealt in different reviews.^{10,11} When copper(III) periodate complex is the oxidant and multiple equilibria between different copper(III) species are involved, it would be interesting to know which of the species is the active oxidant.

Ruthenium(III) acts as a catalyst in the oxidation of many organic and inorganic substrates.^{12,13} Although the mechanism of catalysis depends on the nature of the substrate, oxidant and experimental conditions, it has been shown¹⁴ 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 formation of free radicals. Ruthenium(III) catalysis in redox reactions involves different degrees of complexity, due to the formation of different intermediate complexes and different oxidation states of ruthenium.

Literature survey revealed that no attention has been paid towards the oxidation of atropine sulfate monohydrate (ASM) with any oxidant and its catalysis by any metal ions from the kinetic and mechanistic point of view. We have observed that Ru(III) in micro amounts catalyses the oxidation of ASM by DPC in alkaline medium. Such studies are of much significance in understanding the mechanistic profile of ASM in redox reactions and provide an insight into the interaction of metal ions with the substrate and its mode of action in biological systems. Such types of catalyzed reactions are helpful to design rigorous kinetic models, to deduce the thermodynamic parameters and ascertain various reactive species and to characterize the oxidation products. Hence, the present investigation is aimed at checking the reactivity of ASM towards DPC in the presence of micro amounts of Ru(III) catalyst and to arrive at the plausible mechanisms.

2. Experimental

2.1. Materials and Methods

All reagents were of analytical grade and millipore water was used throughout the work. A solution of ASM (sd fine chem. Ltd) was prepared by dissolving an appropriate amount in millipore water. The purity of ASM was checked by comparing it with its m.p. 192 °C (Literature: 190–194 °C). The required concentration of ASM was obtained from its stock solution. The DPC was prepared^{15,16} and standardized by a standard procedure¹⁷. The UV-vis spectrum with maximum absorption at 415 nm verified the existence of copper(III) complex. A standard stock solution of ruthenium(III) was prepared by dissolving RuCl₃

(sd fine chem. Ltd) in 0.20 mol dm⁻³ HCl. The concentration was determined^{18,19} by EDTA titration. The ionic strength was maintained by adding KNO₃ (Himedia) solution and the pH value was regulated with KOH (Himedia) solution. A stock solution of IO₄⁻ was prepared by dissolving a known weight of KIO₄ (Himedia) in hot water and used after 24 hrs to attain the equilibrium. Its concentration was ascertained iodometrically²⁰ at neutral pH maintained using phosphate buffer. Solutions of ASM and DPC were always freshly prepared before use. Instruments used for (i) Kinetics measurements: A CARY 50 Bio UV-vis Spectrophotometer (Varian, Victoria-3170, Australia) was used. (ii) Product analysis: A QP-2010S Shimadzu gas chromatograph mass spectrometer, Nicolet 5700-FT-IR spectrometer (Thermo, U.S.A.), 300 MHz ¹H NMR spectrophotometer (Bruker, Switzerland) were used to obtain GC-MS, IR and ¹H NMR spectra respectively. Elico pH meter model LI120 was used for pH measurements.

2.2. Kinetic Measurements

The oxidation of ASM by DPC was followed under pseudo first-order condition where [ASM] > [DPC] at 25.0 ± 0.1 °C, unless otherwise specified. The reaction was initiated by mixing DPC with the ASM solution which also contained required concentrations of KNO₃, KOH, KIO₄ and Ru(III) catalyst. The progress of the reaction was monitored spectrophotometrically at 415 nm i.e., decrease in absorbance of DPC with the molar absorptivity, $\epsilon = 6231 \pm 100 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$. The spectral changes during the chemical reaction for the standard condition at 298 K are shown in SI Fig. 1. It is evident from the figure that the concentration of DPC decreases at 415 nm. It was verified that there was almost no interference from other species in the reaction mixture at this wavelength.

The pseudo-first order rate constants, ' k_c ', were determined from slopes of plots of log(absorbance) versus time plots (SI Fig. 2). The plots were linear up to 80% completion of the reaction. The rate constants were reproducible to within ± 5% and are the average of three independent kinetic runs (Table 1). During kinetics a constant concentration *viz.* $1.0 \times 10^{-5} \text{ mol dm}^{-3}$ of KIO₄ was used throughout the study unless otherwise stated. Since excess of periodate is present in DPC, the possibility of oxidation of ASM by periodate in alkaline medium at 25 °C was verified and found that there was no significant interference due to IO₄⁻ under experimental conditions. The total concentrations of periodate and OH⁻ was calculated by considering the amount present in DPC solution and that additionally added. Kinetic runs were also carried out in N₂ 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 the added car-

bonate was also studied and it had no effect on the reaction rates.

Regression analysis of experimental data to obtain regression coefficient r and the standard deviation S , of points from the regression line, was performed with the Microsoft office excel 2003 program.

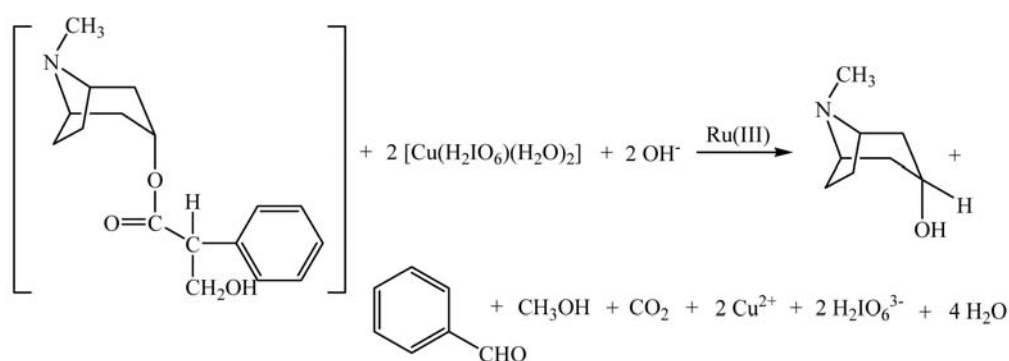
3. Results and Discussions

3.1. Stoichiometry and Product Analysis

Different sets of reaction mixture containing varying ratios of DPC to ASM in the presence of constant amount of OH^- , KIO_4 , KNO_3 and Ru(III) were kept for 5 h in a

closed vessel under nitrogen atmosphere. The remaining concentration of DPC was assayed by measuring the absorbance at 415 nm. The results indicated 1:2 stoichiometry i.e., one mole of ASM required two moles of DPC as shown in Scheme 1.

After completion of reaction, the reaction mixture was acidified, concentrated and extracted with ether. The ethereal layer was subjected to column chromatography using hexane and ethyl acetate in 8:2 (v/v) and the fractions were subjected to spectral investigations. The main reaction products were identified as tropine and benzaldehyde. The products were characterized and confirmed by FT-IR, GC-MS and ^1H NMR spectral studies.



Scheme 1. Stoichiometry of Ru(III) catalyzed oxidation of ASM by DPC in aqueous alkaline medium

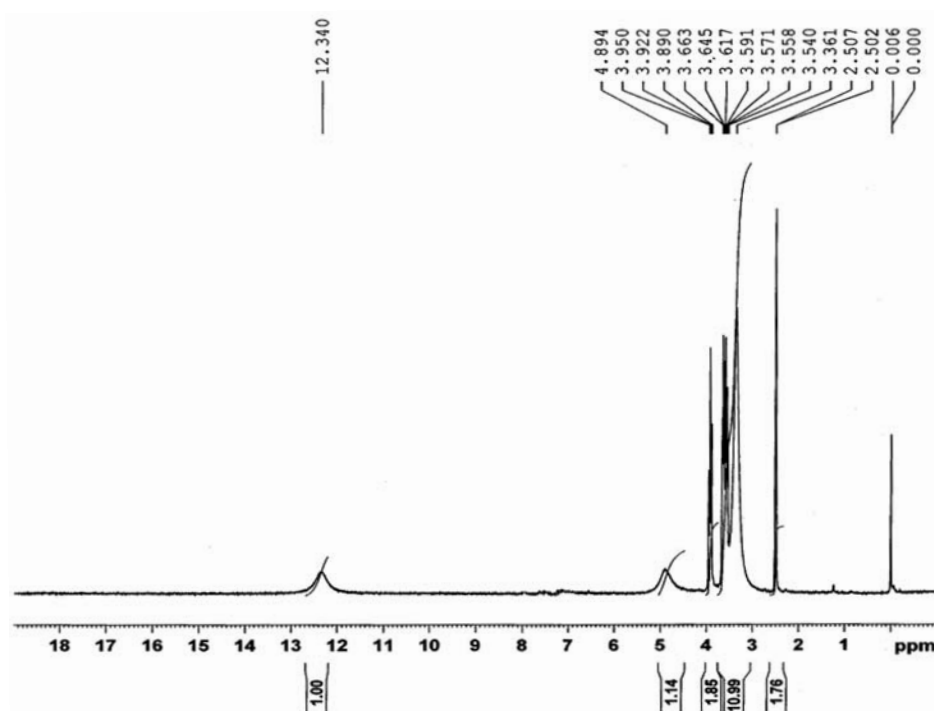


Figure 2. ^1H NMR spectrum of tropine, the oxidation product of atropine sulfate by alkaline dipiperidocuprate(III) in the presence of Ru(III) catalyst

The ^1H NMR spectral analysis of tropine showed a broad singlet for $-\text{OH}$ at δ 12.36 ppm (D_2O exchangeable), singlet for proton adjacent to $-\text{OH}$ group at δ 3.89 ppm, multiplets for the protons of $-\text{CH}_2$ are observed in the range δ 2.50 – 3.57 ppm. Methyl protons attached to nitrogen appear at δ 3.64 ppm and a singlet for the proton on the carbon attached to $-\text{OH}$ group appeared at δ 3.92 ppm (Fig. 2). The IR spectrum of tropine showed a broad band at 3245 cm^{-1} assigned to $-\text{OH}$ stretching. The GC-MS mass spectrum of tropine showed the base peak at 124 amu and molecular ion peak at 141 amu (Fig. 3). Thus confirming the product tropine. Another product benzaldehyde was confirmed by its GC-MS spectrum which showed a molecular ion peak at 106 amu and also confirmed by its hydrazone derivative²¹. The byproducts were identified as methyl alcohol, which was confirmed by sodium test²¹ and CO_2 was qualitatively detected by bubbling nitrogen gas through the acidified reaction mixture and passing the liberated gas through tube containing limewater. The presence of Cu(II) was confirmed by UV-visible spectra.

3. 2. Reaction Orders

As the DPC oxidation of ASM in alkaline medium proceeds with a measurable rate in the absence of Ru(III) , the catalyzed reaction is understood to occur in parallel paths with contributions from both the catalyzed and uncatalyzed paths. Thus the total rate constant (k_T) is equal to the sum of the rate constants of the catalyzed (k_C) and uncatalyzed (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 \log (concentration) plots by varying the concentrations of ASM, IO_4^- , OH^- , and catalyst Ru(III) , in turn while keeping others constant. The uncatalyzed reaction was follo-

wed under the condition, $[\text{DPC}] = 5.0 \times 10^{-5}$, $[\text{ASM}] = 3.0 \times 10^{-3}$, $[\text{OH}^-] = 0.3$, $[\text{IO}_4^-] = 1.0 \times 10^{-5}$, $I = 0.50 / \text{mol dm}^{-3}$. The rate constant of uncatalyzed reaction (k_U) was obtained by the plot of \log (absorbance) versus time by following the progress of the reaction spectrophotometrically at 415 nm.

3. 3. Effect of Diperioatocuprate(III)

The oxidant diperioatocuprate(III) (DPC) concentration was varied in the range of 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3} at constant concentrations of ASM, OH^- , IO_4^- and Ru(III) catalyst. The fairly constant k_C values indicate that order with respect to DPC concentration was unity (Table 1). This was also confirmed by the linearity of the plots of \log (absorbance) versus time plots up to 80% completion of reaction ($r \geq 0.9955$, $S \leq 0.006$).

3. 4. Effect of Atropine Sulfate

The effect of ASM was studied in the range of 5.0×10^{-4} to 5.0×10^{-3} mol dm^{-3} at constant concentrations of DPC, OH^- and IO_4^- at constant ionic strength of 0.50 mol dm^{-3} in the presence of Ru(III) catalyst at $25\text{ }^\circ\text{C}$. The rate constants (k_C) increased with increase in the concentration of ASM (Table 1). The order with respect to ASM concentration was found to be less than unity (0.65) ($r \geq 0.9882$, $S \leq 0.013$). This was also confirmed by the plots of k_C versus $[\text{ASM}]^{0.65}$ which was linear rather than the direct plot of k_C versus $[\text{ASM}]$ (SI Fig. 3).

3. 5. Effect of Alkali and Periodate

The effect of alkali concentration was studied in the range of 0.050 to 0.50 mol dm^{-3} at constant concen-

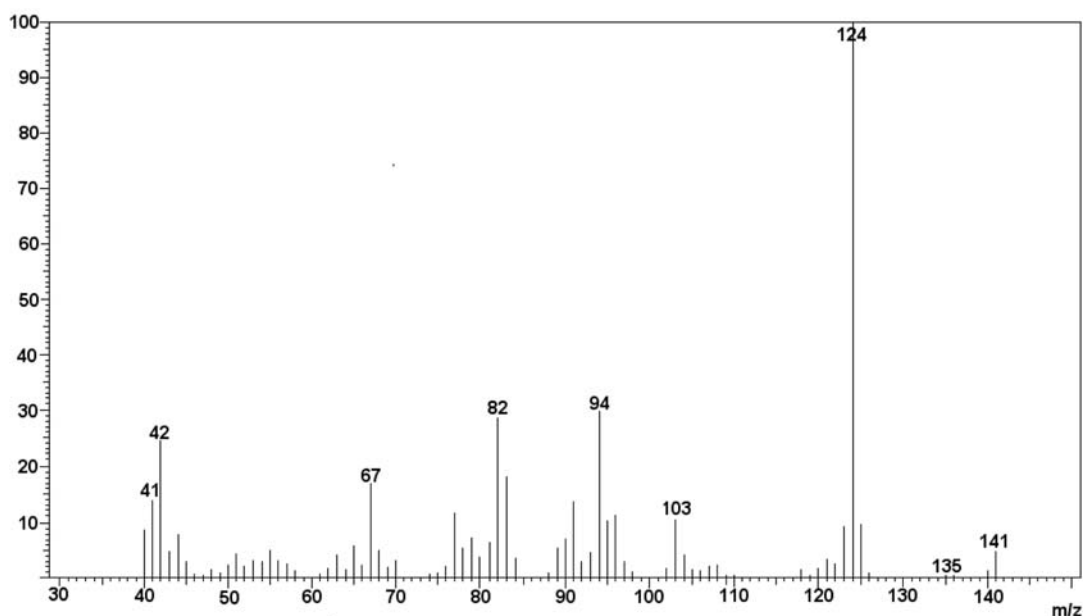


Figure 3. GC-MS spectra of tropine showed molecular ion peak at m/z 141 amu and base peak at m/z 124 amu

trations of DPC, ASM, IO_4^- and at constant ionic strength in the presence of Ru(III) catalyst. The rate constants (k_c) increased with increase in alkali concentration (Table 1). The order with respect to OH^- concentration was found to be less than unity (0.50) ($r \geq 0.9305$, $S \leq 0.019$).

The effect of periodate concentration was studied in the range of 1.0×10^{-5} to 1.0×10^{-4} mol dm $^{-3}$ at constant concentrations of DPC, ASM, OH^- and at constant ionic strength in the presence of Ru(III) catalyst. The experimental results indicated that the added periodate had a retarding effect on the rate of reaction (Table 1). The order with respect to IO_4^- concentration was found to be negative fractional (-0.62) ($r \geq 0.9784$, $S \leq 0.014$).

3. 6. Effect of Ruthenium(III)

The Ru(III) concentrations were varied from 4.0×10^{-7} to 4.0×10^{-6} mol dm $^{-3}$ range, at constant concentration of DPC, ASM, OH^- and ionic strength. As the catalyst concentration increases the rate of reaction also increases.

The order in [Ru(III)] was found to be unity from the linearity of the plot of k_c versus [Ru(III)] (Table 1).

3. 7. Effect of Ionic Strength and Dielectric Constant

The effect of ionic strength (I) was studied by varying KNO_3 concentration. Ionic strength was varied in the range of 0.3 to 1.0 mol dm $^{-3}$ at constant concentration of reactants. Dielectric constant of the medium (D) was studied by varying t-butyl alcohol and water percentage. It was experimentally observed that, both ionic strength and dielectric constant of the medium, did not have any significant effect on the rate of reaction.

3. 8. Effect of Added Products

The added products, copper(II) (CuSO_4), tropine and benzaldehyde did not have any significant effect on the rate of reaction.

Table 1. Effect of variation of DPC, ASM, OH^- , IO_4^- and Ru(III) concentrations on the ruthenium(III) catalyzed oxidation of atropine sulfate by alkaline copper(III) periodate complex at 25 °C and $I = 0.50$ / mol dm $^{-3}$

| 10^5 [DPC] (mol dm $^{-3}$) | 10^3 [ASM] (mol dm $^{-3}$) | [OH^-] (mol dm $^{-3}$) | 10^5 [IO_4^-] (mol dm $^{-3}$) | 10^6 [Ru(III)] (mol dm $^{-3}$) | $10^2 k_T$ (s $^{-1}$) | $10^3 k_U$ (s $^{-1}$) | $10^2 k_c$ (s $^{-1}$) | |
|-----------------------------------|-----------------------------------|--|---|---------------------------------------|----------------------------|----------------------------|-------------------------|-------|
| | | | | | | | Found | Calc. |
| 1.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.60 | 2.22 | 1.37 | 1.47 |
| 3.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.58 | 2.32 | 1.35 | 1.47 |
| 5.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.63 | 2.21 | 1.41 | 1.47 |
| 7.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.54 | 2.30 | 1.31 | 1.47 |
| 10.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.67 | 2.34 | 1.43 | 1.47 |
| 5.0 | 0.5 | 0.3 | 1.0 | 1.0 | 0.44 | 0.53 | 0.38 | 0.39 |
| 5.0 | 0.7 | 0.3 | 1.0 | 1.0 | 0.62 | 0.72 | 0.55 | 0.53 |
| 5.0 | 1.0 | 0.3 | 1.0 | 1.0 | 0.84 | 1.09 | 0.74 | 0.70 |
| 5.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.63 | 2.21 | 1.41 | 1.47 |
| 5.0 | 5.0 | 0.3 | 1.0 | 1.0 | 2.17 | 3.47 | 1.82 | 1.89 |
| 5.0 | 3.0 | 0.05 | 1.0 | 1.0 | 0.59 | 0.80 | 0.52 | 0.52 |
| 5.0 | 3.0 | 0.07 | 1.0 | 1.0 | 0.76 | 1.00 | 0.67 | 0.67 |
| 5.0 | 3.0 | 0.1 | 1.0 | 1.0 | 1.03 | 1.37 | 0.89 | 0.85 |
| 5.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.63 | 2.21 | 1.41 | 1.47 |
| 5.0 | 3.0 | 0.5 | 1.0 | 1.0 | 2.03 | 2.94 | 1.73 | 1.73 |
| 5.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.63 | 2.21 | 1.41 | 1.47 |
| 5.0 | 3.0 | 0.3 | 3.0 | 1.0 | 0.97 | 1.07 | 0.87 | 0.83 |
| 5.0 | 3.0 | 0.3 | 5.0 | 1.0 | 0.66 | 0.72 | 0.59 | 0.58 |
| 5.0 | 3.0 | 0.3 | 7.0 | 1.0 | 0.49 | 0.51 | 0.44 | 0.44 |
| 5.0 | 3.0 | 0.3 | 10.0 | 1.0 | 0.37 | 0.37 | 0.33 | 0.32 |
| 5.0 | 3.0 | 0.3 | 1.0 | 0.4 | 0.79 | 2.21 | 0.57 | 0.59 |
| 5.0 | 3.0 | 0.3 | 1.0 | 0.6 | 1.07 | 2.21 | 0.85 | 0.88 |
| 5.0 | 3.0 | 0.3 | 1.0 | 0.8 | 1.38 | 2.21 | 1.16 | 1.18 |
| 5.0 | 3.0 | 0.3 | 1.0 | 1.0 | 1.63 | 2.21 | 1.41 | 1.47 |
| 5.0 | 3.0 | 0.3 | 1.0 | 2.0 | 3.10 | 2.21 | 2.88 | 2.95 |
| 5.0 | 3.0 | 0.3 | 1.0 | 4.0 | 5.87 | 2.21 | 5.65 | 5.89 |

3. 9. Experimental Rate

Thus, from the observed results, the experimental rate law for the Ru(III) catalyzed reaction is $\text{Rate} = k_C [\text{DPC}]^{1.0} [\text{ASM}]^{0.65} [\text{OH}^-]^{0.50} [\text{Ru(III)}]^{1.0} [\text{IO}_4^-]^{-0.62}$

3. 10. Polymerization Study

The intervention of free radicals was detected as follows: the reaction mixture, to which a known quantity of acrylonitrile (scavenger) had been added initially, was kept for 2 h in an inert atmosphere. On diluting the reaction mixture with methanol, a white precipitate was formed, indicating the intervention of free radicals in the reaction. The blank experiments of either DPC or ASM alone with acrylonitrile did not induce any polymerization under the same condition as those induced for the reaction mixture. Initially added acrylonitrile decreases the rate of reaction indicating free radical intervention in the reaction, which is the case in earlier work.^{22,23}

3. 10. Effect of Temperature

The kinetics was studied at four different temperatures 15, 25, 35, 45 °C under varying concentrations of

ASM, alkali, periodate and Ru(III), keeping other conditions constant. The rate of reaction increased with increase in temperature. The rate constants (k) of the slow step of Scheme 3 were obtained from the slopes and the intercepts of the plots of $[\text{Ru(III)}]/k_C$ versus $1/[\text{ASM}]$, $[\text{Ru(III)}]/k_C$ versus $1/[\text{OH}^-]$ and $[\text{Ru(III)}]/k_C$ versus $[\text{H}_3\text{IO}_6^{2-}]$ at four different temperatures. The activation parameters were calculated from standard equations²⁴ and are given in Table 2.

3. 11. Catalytic Activity

It has been pointed out by Moelwyn-Hughes²⁵ that in the presence of catalyst, the uncatalyzed and catalyzed reactions proceed simultaneously, so that,

$$k_T = k_U + K_C[\text{Ru(III)}]^x \quad (1)$$

Here k_T is the observed pseudo first-order rate constant in the presence of Ru(III) catalyst; k_U , the pseudo first-order rate constant for uncatalyzed; K_C , the catalytic constant and x the order of the reaction with respect to Ru(III). In the present investigations, x values for the standard run were found to be unity.

Then the value of K_C is calculated using the equation,

Table 2. Effect of temperature on the ruthenium(III) catalyzed oxidation of atropine sulfate by alkaline copper(III) periodate complex.

a) Rate constants with respect to slow step of Scheme 3

| Temperature (K) | $10^{-5} k$ (s ⁻¹) |
|-----------------|--------------------------------|
| 288 | 0.17 |
| 298 | 0.33 |
| 308 | 0.57 |
| 318 | 1.18 |

(b) Activation parameters

| Parameters | Value |
|---------------------|--|
| ΔH^\ddagger | 45.4 ± 2 k J mol ⁻¹ |
| ΔS^\ddagger | -6.0 ± 1 J K ⁻¹ mol ⁻¹ |
| ΔG^\ddagger | 47.2 ± 4 k J mol ⁻¹ |
| log A | 12.9 ± 0.2 |

(c) Effect of temperature on first, second and third equilibrium step of Scheme 3

| Temperature (K) | $10^1 K_1$ (dm ³ mol ⁻¹) | $10^4 K_2$ (dm ³ mol ⁻¹) | $10^{-3} K_3$ (dm ³ mol ⁻¹) |
|-----------------|---|---|--|
| 288 | 4.47 | 0.47 | 0.68 |
| 298 | 2.14 | 0.68 | 0.94 |
| 308 | 0.65 | 1.49 | 1.33 |
| 318 | 0.31 | 2.06 | 1.96 |

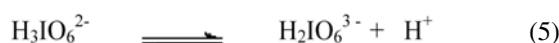
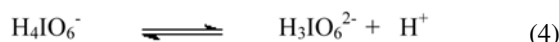
(d) Thermodynamic quantities with respect to first, second and third step of Scheme 3

| Thermodynamic quantities | Values from K_1 | Values from K_2 | Values from K_3 |
|--|-------------------|-------------------|-------------------|
| ΔH k J mol ⁻¹ | -70 ± 3 | 39.2 ± 2 | 27 ± 1 |
| ΔS J K ⁻¹ mol ⁻¹ | -249 ± 4 | 54 ± 2 | 148 ± 4 |
| ΔG_{298} k J mol ⁻¹ | 3.80 ± 0.05 | 23.7 ± 1 | -17 ± 0.8 |

$$K_C = \frac{k_T - k_U}{[\text{Ru(III)}]^x} = \frac{k_C}{[\text{Ru(III)}]} \quad (\text{where, } k_T - k_U = k_C) \quad (2)$$

The values of K_C were evaluated for Ru(III) catalyst at four different temperatures 15, 25, 35, 45 °C and were found to be 0.74×10^4 , 1.41×10^4 , 2.56×10^4 and 5.05×10^4 respectively.

The water soluble copper(III) periodate complex is reported²⁶ to be $[\text{Cu}(\text{HIO}_6)_2(\text{OH})_2]^{7-}$. However, in an aqueous alkaline medium and at a high pH range as employed in this study, periodate is unlikely to exist as HIO_6^{4-} (as present in the complex) as is evident from its involvement in the multiple equilibria²⁷ equation (3–5) depending on the pH of the solution.



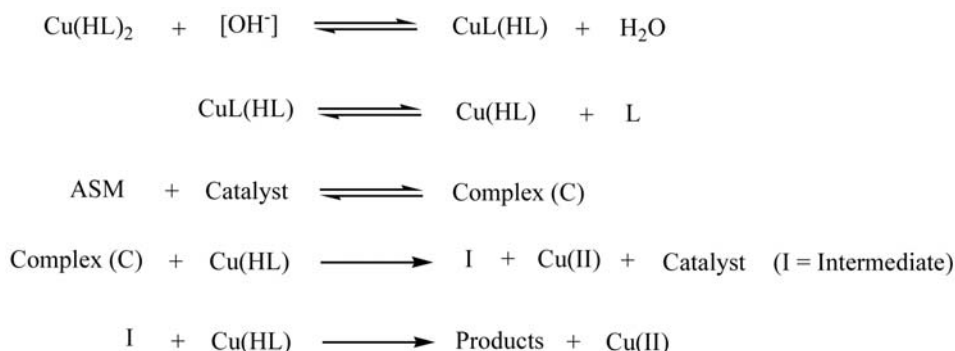
Periodic acid exists as H_5IO_6 in an acid medium and as H_4IO_6^- around pH 7. Thus, under the conditions employed in alkaline medium, the main species are expected to be $\text{H}_3\text{IO}_6^{2-}$ and $\text{H}_2\text{IO}_6^{3-}$. At higher concentrations, periodate also tends to dimerise. However, formation of this dimer species is negligible under conditions employed for kinetic study. Hence, at the pH employed in this study, the soluble copper(III) periodate complex exists as diperiodatocuprate(III), $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)]^{2-}$, a conclusion also supported by earlier work.^{6,16}

Ru(III) chloride acts as an efficient catalyst in many redox reactions, particularly in an alkaline medium.^{22,28} In the present study it is quite probable that the $[\text{Ru}(\text{H}_2\text{O})_5\text{OH}]^{2+}$ species might assume the general form $[\text{Ru(III)}(\text{OH})_x]^{3-x}$. The x value would always be less than six because there are no definite reports of any hexahydroxy ruthenium species. The remainder of the coordina-

tion sphere would be filled by water molecules. Hence, under the conditions employed, e.g., $[\text{OH}^-] \gg [\text{Ru(III)}]$, ruthenium(III) is mostly present in the form of hydroxylated species, $[\text{Ru}(\text{H}_2\text{O})_5\text{OH}]^{2+}$.²⁹ Based on the experimental rate law the kinetic model has been presented in Scheme 2.

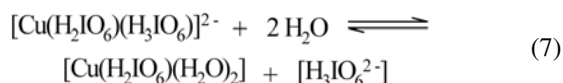
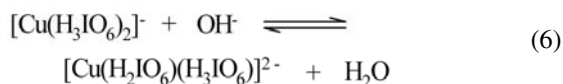
In the earlier reports of Ru(III) catalyzed oxidation, it was observed that,³⁰ if there exists a fractional order dependence with respect to [substrate] and [Ru(III)], and unit order with respect to [oxidant], it leads to the formation of Ru(III)–substrate complex. This complex is further oxidized by the oxidant to Ru(IV)–substrate complex followed by the rapid redox decomposition with regeneration of Ru(III) catalyst. In case,³¹ if the process involves a zeroth order dependence with respect to [oxidant], first order with respect to [Ru(III)] and a fractional order with respect to [substrate], it leads to the formation of Ru(III)–substrate complex and further cleaves to Ru(I) species which is rapidly oxidized by the oxidant to regenerate Ru(III) catalyst.

The reaction between DPC and ASM in alkaline medium presents $[\text{DPC}]/[\text{ASM}] = 2:1$ stoichiometry with first order dependency in [DPC] and catalyst [Ru(III)] and fractional order in [ASM] and $[\text{OH}^-]$, added periodate retarded the rate and no effect of added products were observed. On the basis of experimental results, a plausible reaction mechanism has been proposed for which all the observed orders in each constituent may be well accommodated. Lister³² proposed the copper(III) periodate in alkaline medium into three forms as diperiodatocuprate(III) (DPC), monoperiodatocuprate(III) (MPC) and tetrahydroxocuprate(III). The latter is ruled out as its equilibrium constant is 8.0×10^{-11} at 40 °C. Hence, in the present study, in view of the negative less than unit order in periodate concentration on rate of reaction, monoperiodatocuprate(III) MPC is considered to be the active species of copper(III) periodate complex. The results of increase in the rate with increase in alkali concentration and decrease in the rate with increase in periodate concentration suggest that equilibria of different copper(III) periodate complexes are possible as in equation (6) and



Scheme 2. Kinetic model for Ru(III) catalyzed oxidation of ASM by alkaline DPC.

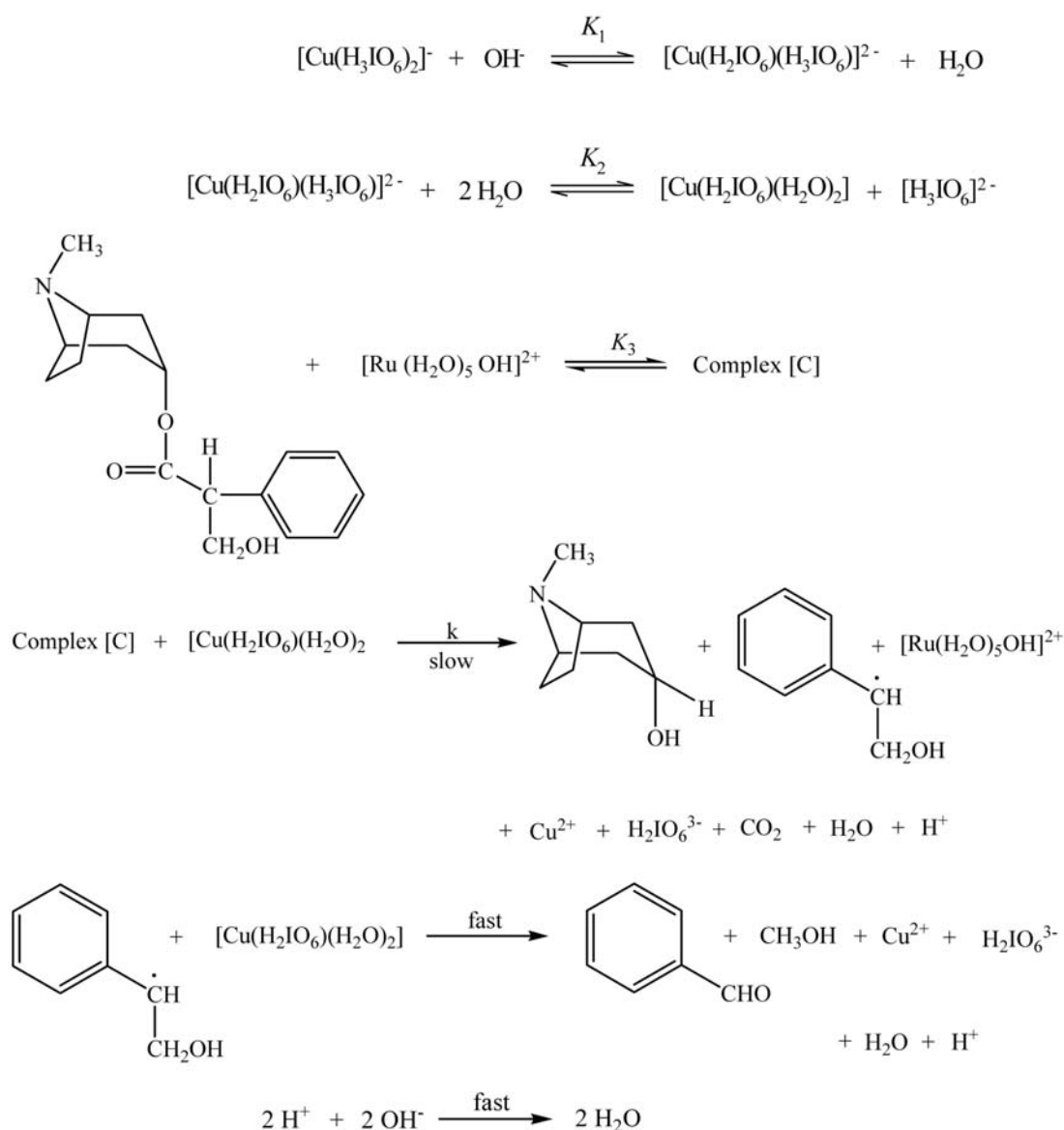
(7). The inverse fractional order in $[\text{IO}_4^-]$ might also be due to this reason.



In the present investigation, the reaction was enhanced by $[\text{OH}^-]$, added periodate retards the rate, first order dependency in $[\text{DPC}]$ and catalyst $[\text{Ru}(\text{III})]$ and fractional order in $[\text{ASM}]$ and $[\text{OH}^-]$ was observed. To explain the observed orders the Scheme 3 has been proposed for rut-

henium(III) catalyzed reaction between ASM and DPC in alkaline medium.

Less than unit order in $[\text{ASM}]$ presumably results from formation of a complex (C) between the ruthenium(III) and atropine sulfate prior to the formation of the products. K_3 is the composite equilibrium constant comprising the equilibrium to bind ASM to ruthenium(III) active species to form a complex (C) which further reacts with one mole of MPC in a slow step to form an intermediate free radical species and one of the final product tropine derived from atropine sulfate and byproduct $\text{Cu}(\text{II})$ and CO_2 with regeneration of catalyst, ruthenium(III). Further this intermediate free radical species reacts with another mole of MPC species in a fast step to form the products such as benzaldehyde, methyl alcohol, $\text{Cu}(\text{II})$



Scheme 3. Detailed Scheme of Ru(III) catalyzed oxidation of ASM by alkaline DPC.

and periodate. All these results may be interpreted in a detailed mechanistic scheme as shown in Scheme 3. Similar type of key step, in the mechanism, has been proposed for the catalyzed reaction in the earlier studies.³³

Spectroscopic evidence for the complex formation between Ru(III) and ASM was obtained from UV – vis spectra of ASM (3.0×10^{-3} mol dm⁻³), Ru(III) (1.0×10^{-6} mol dm⁻³), [OH⁻] (0.3 mol dm⁻³) and a mixture of both. A hypsochromic shift of about 6 nm from 246 to 240 nm in the spectra of ASM to mixture of Ru(III) and ASM was observed. The Michaelis-Menten plot (Fig. 6) proved the complex formation between catalyst and substrate, which explains less than unit order in [ASM]. Such a complex formation between catalyst and substrate was also observed in other studies.²³ The probable structure of complex is as shown in Fig. 5.

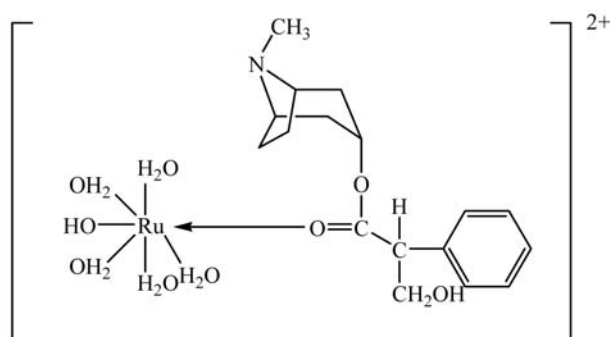


Figure 5. The probable structure of complex.

Scheme 3 leads to the rate law (8),

$$\frac{\text{Rate}}{[\text{DPC}]} = k_C = k_T - k_U \quad (8)$$

$$= \frac{k K_1 K_2 K_3 [\text{ASM}] [\text{OH}^-] [\text{Ru(III)}]}{[\text{H}_3\text{IO}_6^{2-}] + K_1 [\text{OH}^-] [\text{H}_3\text{IO}_6^{2-}] + K_1 K_2 [\text{OH}^-] + K_1 K_2 K_3 [\text{ASM}] [\text{OH}^-]}$$

which explains all the observed kinetic orders of different species. The rate law (8) can be rearranged into the following form, which is suitable for verification.

$$\frac{[\text{Ru(III)}]}{k_C} = \frac{[\text{H}_3\text{IO}_6^{2-}]}{k K_1 K_2 K_3 [\text{ASM}] [\text{OH}^-]} \quad (9)$$

$$+ \frac{[\text{H}_3\text{IO}_6^{2-}]}{k K_2 K_3 [\text{ASM}]} + \frac{1}{k K_3 [\text{ASM}]} + \frac{1}{k}$$

According to equation 9, other conditions being constant, plots of [Ru(III)]/ k_C versus 1/[ASM], [Ru(III)]/ k_C versus 1/[OH⁻] and [Ru(III)]/ k_C versus [H₃IO₆²⁻] should be linear and are found to be so (Fig. 6 A – C). The slopes and intercepts of such plots lead to the values of K_1 , K_2 , K_3 and k (Table 2). The value of K_1 is in agreement with earlier literature.²³ Using these con-

stants, the rate constants were calculated and compared with the experimental k_C values. There is a reasonable agreement with each other (Table 2), which fortifies the proposed mechanism (Scheme 3). The equilibrium constant K_1 is far greater than K_2 which may be attributed to the greater tendency of DPC to undergo hydrolysis compared to the dissociation of hydrolyzed species in alkaline medium.

The negligible effect of ionic strength and dielectric constant of medium on the rate explains qualitatively the reaction between neutral and positively charged ions, as seen in Scheme 3. The thermodynamic quantities for the different equilibrium steps, in Scheme 3 can be evaluated as follows. The vant 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 2. A comparison of the ΔH value (39 k J mol⁻¹) from K_2 with that of ΔH^\ddagger (45 k J mol⁻¹) of rate-limiting step is fairly fast as it involves low activation energy.²³ The negative value of ΔS^\ddagger (-6.1 JK⁻¹ mol⁻¹) suggests that intermediate complex is more ordered than the reactants.³⁴ The observed modest enthalpy of activation and higher rate constant for the slow step indicate that the oxidation presumably occurs *via* an inner-sphere mechanism. This conclusion is supported by earlier observation.^{35,36}

The activation parameters evaluated for the catalyzed and uncatalyzed reactions explain the catalytic effect on the reaction. The catalyst Ru(III) forms the complex (C) with substrate, which enhances the reducing property of substrate than that without catalyst. Further, the catalyst Ru(III) modifies the reaction path by lowering the energy of activation.

It is also interesting to note that the transient species involved in both the uncatalyzed³⁷ and Ru(III) catalyzed reactions is different but leads to the formation of the same products. The uncatalyzed reaction in alkaline medium has been shown to proceed via a MPC-ASM complex which decomposes slowly in a rate determining step to give the products via free radical in the further fast steps,³⁷ whereas, in the catalyzed reaction, it has been shown to proceed *via* Ru(III)-ASM complex which further reacts with one mole of MPC in the rate determining step to give the products via free radical in the further fast steps. Since in both the cases MPC and ASM were involved, the products obtained were the same. The catalyst Ru(III) forms the complex with ASM, which shows a greater reducing property than ASM itself. Hence, the catalyst, Ru(III), lowers the energy, i.e., it provides an alternative pathway with lower activation parameters for the reaction. The difference in the activation parameters evaluated for the catalyzed ($E_a = 47.8$ kJ mol⁻¹) and uncatalyzed ($E_a = 58$ kJ mol⁻¹) reaction explains the catalytic effect on the reaction.

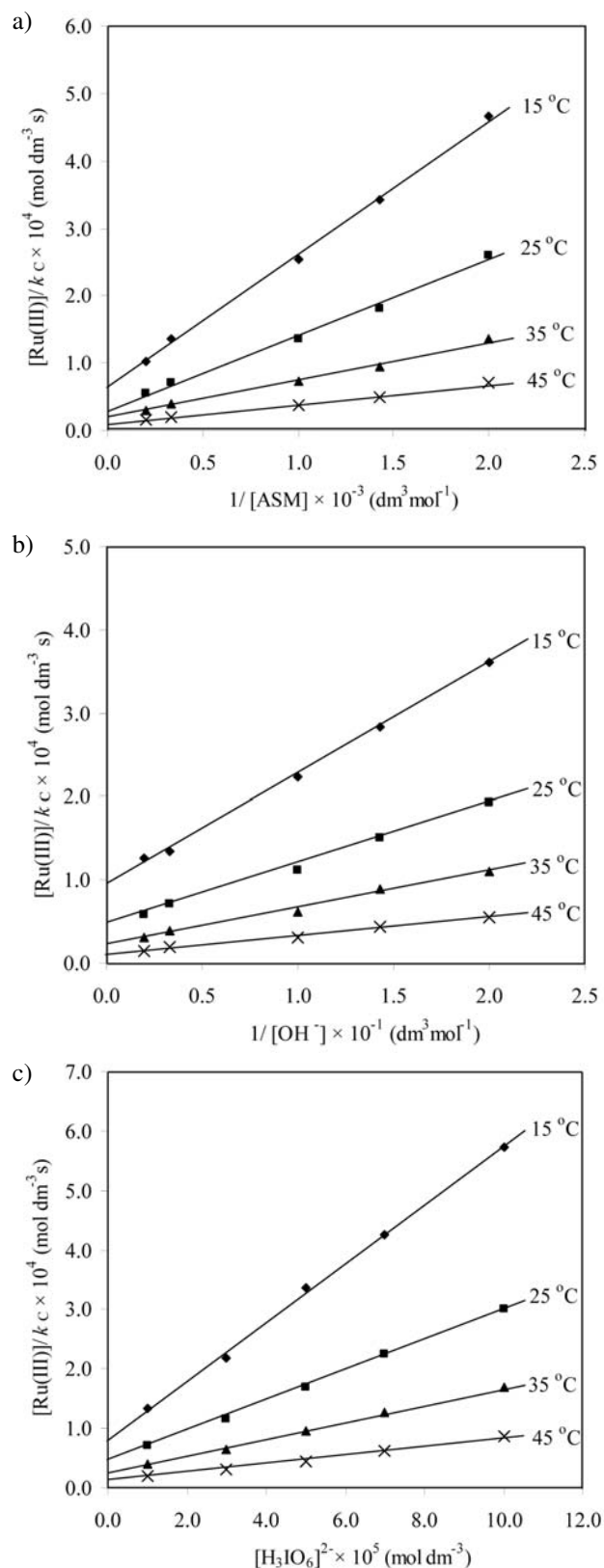


Figure 6. Verification of rate law (8) for the Ru(III) catalyzed oxidation of atropine sulfate by diperiodatocuprate(III). Plots of (A): $[\text{Ru(III)}]/k_C$ versus $1/[\text{ASM}]$, (B): $[\text{Ru(III)}]/k_C$ versus $1/[\text{OH}^-]$, (C): $[\text{Ru(III)}]/k_C$ versus $[\text{H}_3\text{IO}_6]^{2-}$ at four different temperatures (conditions as in Table 1).

4. Conclusions

In the title reaction among the various species of copper(III) in alkaline medium, monoperoiodocuprate(III), (MPC) $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$ is considered to be the active species. The active species of Ru(III) is found to be $[\text{Ru}(\text{H}_2\text{O})_5\text{OH}]^{2+}$. The reaction rates revealed that Ru(III) catalyzed reaction is about seven-fold faster than the uncatalyzed reaction. It becomes apparent that, in carrying out this reaction, the role of reaction medium is crucial. Activation parameters were evaluated for catalyzed reactions. Catalytic constants and the activation parameters with reference to catalyst were also computed. Plausible mechanisms and related rate laws have been designed. It can also be concluded that Ru(III) acts as an efficient catalyst in the facile oxidation of ASM by DPC in alkaline medium

5. Acknowledgements

One of the authors (Kirthi S. Byadagi) gratefully acknowledges the UGC, New Delhi for the award of Research Fellowship in Science for Meritorious Students (RFSMS).

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Povzetek

Atropin sulfat monohidrat (ASM) je zdravilna učinkovina s širokim spektrom antiholinergičnega delovanja. V tem delu smo proučevali kinetiko oksidacije ASM z diperjodatokuperatom (DPC) v prisotnosti mikrokoličin (10^{-6}) katalizatorja Ru(III). Proces smo s pomočjo spektrofotometra spremljali v alkalnem vodnem mediju z $I = 0.50 \text{ mol dm}^{-3}$. Ugotovili smo, da reakcija med DPC in ASM poteka v razmerju 1:2 (ASM:DPC) in je 1. reda glede na [DPC] in [Ru(III)], medtem ko je red reakcije glede na [ASM] in $[\text{OH}^-]$ manjši od ena. Red reakcije pada s porastom koncentracije DPC. Z uporabo katalizatorja je reakcija približno sedemkrat hitrejša. Kinetični eksperimenti kažejo, da je v kompleksu $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$ reaktivno stanje Cu(III) in v $[\text{Ru}(\text{H}_2\text{O})_5\text{OH}]^{2+}$ stanje Ru(III).