Ru(III) Catalysed Oxidation of Fluoroquinoline Anitibacterial Agent, Norfloxacin by Diperiodatoargentate (III) in Aqueous Alkaline Medium- A kinetic and Mechanistic Study

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Abstract:

The kinetics of Ru(III) catalysed oxidation of norfloxacin (NF) by diperiodatoargentate(III) (DPA) in alkaline medium at constant ionic strength of 0.10 mol dm^{-3} at 25°C has been studied spectrophotometrically. The reaction exhibits 1:1 stoichiometry and fallow first order kinetics in DPA and Pd(II). The dependence of the rate on substrate concentration has been found to be of Michaelis- Menten type. To calculate thermodynamic parameters, the reactions have been studied at four different temperatures. A complex mechanism involving the complex formation between the catalyst and the substrate has been proposed. The main products were identified by spot test and spectroscopic studies. The activation parameters with respect to slow step of the mechanism are computed and discussed. The probable active species of catalyst and oxidant have been studied. A reaction mechanism has been proposed based on the kinetic data and product analysis.

Key words: Ru(III), diperiodatoargentate(III), oxidation, Norfloxacin.

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1. Introduction:

Diperiodatoargentate(III) (DPA) is a powerful oxidizing agent in alkaline medium with the reduction potential[1] 1.74 V. It was shown by the previous workers that DPA was used as a volumetric reagent for the determination of various organic and inorganic species [2,3]. Jaya Prakash Rao et al[4,5] has used DPA as an oxidizing agent for the kinetics of oxidation of various organic substrates. However, Kumar [6-8] et al. put an effort to give an evidence for the reactive form of DPA in the large scale of alkaline pH.

Norfloxacin, a fluoroquinolone, is a 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7- (1-piperazinyl)-3quinolinecarboxylic acid. It is a synthetic chemotherapeutic antibacterial agent [9,10], occasionally used to treat common as well as complicated urinary tract infections. It also inhibits DNA synthesis and is bactericidal [11-16] and a first generation synthetic fluoroquinolone (quinolone) was developed by Kyorin Seiyaku K.K. It interacts with a number of other drugs, as well as a number of herbal and natural supplements. Such interactions increase the risk of anti-coagulation, formation of non-absorbable complexes as well as increasing the risk of toxicity. As a result of their extensive usage, fluoroquinolones may enter the environment via waste water effluent, biosolids from sewage treatment plants, via manure and litters from food-producing animal husbandry. The presence and accumulation of fluoroquinolone antibiotics in aquatic environments may pose threats to the ecosystem and human health.

The oxidation rate was increased by the use of transition metal ions such as Os, Ru and Pd, either alone or as binary mixtures in various redox processes has attracted considerable interest [17]. Although the mechanism of catalysis depends on the nature of the substrate, the oxidant and experimental conditions, it has been shown that metal ions acts 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 [18]. Ru(III) is known to catalyse various reactions[19] and most studies using Ru(III) as catalyst have employed in the form of Ru(III) chloride [20]

and its active form in such reactions remain obscure.

The oxidation proceeds very slowly in the absence of catalyst while it follows a complex kinetics in the presence of catalyst. Thus to understand about the catalysis of Ru(III) in the oxidation of Norfloxacin by DPA and to explore the mechanism of oxidations in aqueous alkaline medium, the drug Norfloxacin has been selected as substrate.

2. Experimental Section

All chemicals and reagents used were of AR grade. All solutions and reaction mixtures were prepared in double distilled water. The solution of norfloxacin (Sigma-Aldrich) was prepared by dissolving a known amount of the compound in 6.0 ml of 0.3 mol dm^{-3} NaOH and further diluted to 100 ml with double distilled water. The required concentration of norfloxacin was obtained from its stock solution. DPA was prepared by oxidizing Ag (I) in presence of KIO_4 as described elsewhere[21, 22]. Absorbance was recorded on Systronic UV-vis spectrophotometer. The complex was characterized from its UV spectrum, which exhibited three peaks at 215, 254, and 362 nm. These spectral features were identical to those reported earlier for DPA[21]. The magnetic moment study revealed that the complex is diamagnetic. The compound prepared was analysed [22] 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 of KI was added to the filtrate for IO_4^-. The stock solution of DPA was used for the required concentration of DPA solution in the reaction mixture. During the kinetics a constant concentration viz. 1.0 x10^{-4} mol dm^{-3} of KIO_4 was used throughout the study. Thus, the possibility of oxidation of NF by periodate was tested and found that there was no significant interference due to KIO_4 under experimental condition. The total concentrations of periodate and OH^- was calculated by considering the amount present in the DPA solution.

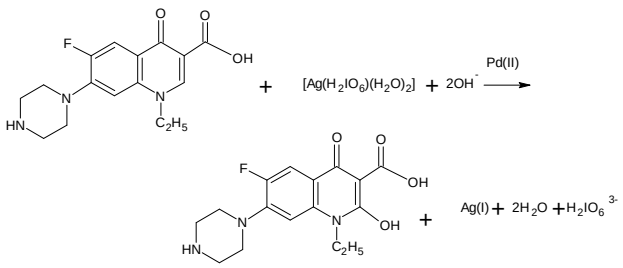
A Ru(III) stock solution was prepared by dissolving known weight of Ru(III) chloride(S.D Fine Chemicals) in 0.20 mol dm^{-3} HCl and standardized against EDTA by known procedure. For some kinetic runs in the absence of Cl^-, the chloride ion in the Ru (III) stock solution was precipitated with $AgNO_3$ and removed by repeated centrifugation. The final strength of Ru(III) solution was kept 1.0 x 10^{-6} mol dm^{-3}. The chloride concentration was maintained between 2.0 x 10^{-5} and 4.0 x 10^{-4} mol dm^{-3} with KCl.

3. Results

3.1 Stoichiometry and Product Analysis

Different sets of reaction mixtures containing varying ratios of DPA to norfloxacin in presence of constant amount of OH^-, KIO_4, KNO_3 and catalyst, were kept for 3h in closed vessel under nitrogen atmosphere. The remaining concentration of DPA was estimated spectrophotometrically at 360 nm. Estimation of the residual oxidant showed that one mole of substrate consumed one mole of DPA(III), corresponding to the stoichiometry as given in Scheme 1.

Scheme 1.



The main reaction products were identified as Ag(I) and 1-ethyl-6-fluoro-2-hydroxy-4-oxo-7-piperazin-1-yl-1,4-hydro-quinoline-3-carboxylic acid, identical to those obtained for the oxidation of NF with permanganate[23]. The oxidation product of norfloxacin, 1-ethyl-6-fluoro-2- hydroxy-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid, was isolated with the help of TLC and other separation techniques and characterized by LC-ESI-MS, FTIR and ^{1}H NMR spectral studies. The presence of a product was confirmed with molecular ion of *m/z* 335 (yield 91%), which corresponds to 1-ethyl-6-fluoro-2-hydroxy-1,4-

dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid.

The IR spectroscopy shows a peak at 1731 cm^{-1} due to acidic C=O stretching ; the peak due to ketonic C=O stretching will appear at 1644 cm^{-1}; 3056 cm^{-1} is due to NH stretching of the piperzine moiety; and the broad peak at 3424 cm^{-1} is due to OH stretching, ^{1}H NMR (DMSO) shows singlet at 8.9 ppm due to acidic OH, NH of piperzine moiety singlet appears in the region of 4.6 ppm and the singlet of phenolic OH at 6.6 ppm, which disappears on D_2O exchange and confirms the formation of product 1-ethyl-6-fluoro-2-hydroxy-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline carboxylic acid as shown in Fig. The formation of free Ag^+ in solution was detected by adding HCl solution to the reaction mixture, which produced white turbidity due to the formation of AgCl. Under the reaction conditions the products were not further oxidized.

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Fig.1: ^{1}H NMR spectra of the product of oxidation of norfloxacin by DPA

3.2 Reaction Orders

Kinetic experiments were made at different concentration of reactant while keeping the concentration of others constant.

3.3 Effect of [diperiodatoargentate (III)]

The oxidant DPA concentration was varied in the range of 0.5 x 10^{-4} to 5.0 x 10^{-4} mol dm^{-3} and the fairly constant values indicate that order with respect to [DPA] was one (Table 1). This was also confirmed by linearity of the plots of log (absorbance) versus time up to 75% completion of the reaction.

3.4 Effect of [Norfloxacin]

The effect of norfloxacin on the rate of reaction was studied at constant concentration of alkali, DPA, Ru(III) catalyst and periodate at a constant ionic strength of 0.25 mol dm^{-3}. The substrate norfloxacin was varied in the range of 0.4 x 10^{-3} to 4.0 x 10^{-3} mol dm^{-3}. The k_{obs} values increased with increase in concentration of norfloxacin. The order with respect to norfloxacin was found to be less than unity (Table 1).

3.5 Effect of [Alkali]

The effect of alkali on the reaction has been studied in the range of 0.05 to 0.5 mol dm^{-3} at constant concentration of NF, DPA, Ru(III) catalyst and a constant ionic strength of 0.25 moldm^{-3} at 25 ^{0}C. A perusal of data reveals less than unity with respect to OH^- concentration (Table 1).

3.6 Effect of [Periodate]

Periodate was varied from 0.5 x 10^{-4} to 5.0 x 10^{-4} mol dm^{-3} keeping all other reactant concentration constant. The k_{obs} values indicate that the order in [IO_4^-] was negative fractional order (Table 1).

The effect of ionic strength was studied by varying the [$NaClO_4$] in the reaction mixture. The ionic strength of reaction medium was varied from 0.01 to 0.10 mol dm^{-3} at constant [DPA], [NF], [Ru(III)], [IO_4^-] and [OH^-]. Increasing ionic strength had no effect on the rate constant. The effect of the dielectric constant (D) was studied by varying the t-butanol–water content (v/v) in the reaction mixture with all other conditions held constant. The rate of reaction increases with increasing t-butanol volume.

3.7 Effect of Temperature

To calculate the thermodynamic parameters, the effect of temperature on the rate of the oxidation was studied by carrying out the reaction at four temperatures 298, 303, 308 and 313 K, with varying concentrations of NF and alkali while keeping other conditions constant. A linear plots of log k versus 1/T indicates that the reaction obeys Arrhenius equation.The activation parameters for the rate determining step were obtained as Ea ($kJmol^{-1}$) = 20.4$\pm$1.1, $\Delta H^{\#}$ ($kJmol^{-1}$) = 17.8$\pm$0.8, $\Delta S^{\#}$ ($J K^{-1} mol^{-1}$) = - 48.7$\pm$1.9, $\Delta G^{\#}$ (kJ mol^{-1}) = 32.4$\pm$1.1. The negative values of entropy of activation suggests the formation of a solvated and charged transition state.

3.8 Effect of [Initially added products]

Initially added products Ag (I) did not have any significant effect on the rate of reaction.

3.9 Effect of [catalyst]

The effect of $RuCl_3$ concentration on the oxidation of norfloxacin was varied from 0.5 x 10^{-5} to 5.0 x 10^{-5} mol dm^{-3} keeping all other reactant concentration constant. The results presented in Table 1 clearly reveal first order kinetics with respect to Ru(III) concentration.

4.0 Polymerization Study

To test for the involvement of free radicals, the reaction mixture is mixed with a known quantity of acrylonitrile scavenger and was kept in an inert atmosphere for 4 hours. On diluting the reaction mixture with methanol, a white ppt was formed,

Table 1. Effect of [DPA], [NF], [OH^-], [IO_4^-] and [Pd(II)] on the Ruthenium(III) catalysed oxidation of Norfloxacin by Diperiodatoargentate(III) in aq.alkaline medium at 25 °C ; I=0.25 mol dm^{-3}

[DPA]x 10^4 (mol dm^{-3})	[NF]x10^3 (mol dm^{-3})	[OH^-] (mol dm^{-3})	[IO_4^-] x10^4 (mol dm^{-3})	Ru(III)x10^5 (mol dm^{-3})	k_Ix10-^{3} (s^{-1})	k_Ux10^4 (s^{-1})	k_C x10^3 (s^{-1})	
							Found	Calculated
0.5	1.0	0.15	1.0	1.0	6.32	5.10	5.81	5.80
0.8	1.0	0.15	1.0	1.0	6.30	5.18	5.78	5.85
1.0	1.0	0.15	1.0	1.0	6.40	5.21	5.88	5.79
2.0	1.0	0.15	1.0	1.0	6.36	5.12	5.85	5.88
5.0	1.0	0.15	1.0	1.0	6.14	5.20	5.62	5.75
1.0	0.4	0.15	1.0	1.0	3.42	2.96	3.12	3.05
1.0	0.8	0.15	1.0	1.0	5.56	4.01	5.16	5.09
1.0	1.0	0.15	1.0	1.0	6.34	5.18	5.82	5.88
1.0	2.0	0.15	1.0	1.0	8.99	6.18	8.37	8.48
1.0	4.0	0.15	1.0	1.0	11.71	6.75	11.03	10.91
1.0	1.0	0.05	1.0	1.0	3.58	4.60	3.12	3.01
1.0	1.0	0.10	1.0	1.0	5.34	4.86	4.75	4.74
1.0	1.0	0.15	1.0	1.0	6.27	5.12	5.76	5.88
1.0	1.0	0.20	1.0	1.0	7.07	5.31	6.54	6.67
1.0	1.0	0.50	1.0	1.0	9.53	5.78	8.95	8.82
1.0	1.0	0.15	0.5	1.0	8.60	5.55	8.04	7.96
1.0	1.0	0.15	0.8	1.0	6.96	5.25	6.43	6.56
1.0	1.0	0.15	1.0	1.0	6.36	5.15	5.84	5.88
1.0	1.0	0.15	3.0	1.0	3.06	4.04	2.66	2.87
1.0	1.0	0.15	5.0	1.0	2.15	3.50	1.86	1.92
1.0	1.0	0.15	1.0	0.5	3.53	5.21	3.01	2.93
1.0	1.0	0.15	1.0	0.8	5.30	5.21	4.78	4.70
1.0	1.0	0.15	1.0	1.0	6.21	5.21	5.69	5.88
1.0	1.0	0.15	1.0	3.0	17.74	5.21	17.22	17.6
1.0	1.0	0.15	1.0	5.0	29.22	5.21	28.7	29.3

indicating the intervention of free radicals in the reaction. Blank experiments with either NF or DPA did not induce polymerization under the same conditions. Initially added acrylonitrile decreases the rate of reaction indicating free radical intervention, which is the case in earlier studies[24,25]

4.1 Catalytic activity

It is known that[26] in presence of the catalyst, the uncatalysed and catalysed reaction proceed simultaneously, so that

$$k_T = k_U + K_C [\text{catalyst}]^x \quad (2)$$

Here k_T is the observed pseudo first order rate constant in presence of Ru(III) catalyst, k_U the pseudo first order rate constant for the uncatalysed reaction, K_C is the catalytic constant and x the order of the reaction with respect to [Ru(III)]. In the present investigation, value of x for the standard run was found to be unity for Ru(III) and the value of k_u has been calculated. The value of K_C is calculated using the equation

$$K_C = \frac{k_T - k_U}{[\text{Catalyst}]^x} = \frac{k_C}{[\text{Catalyst}]^x} \quad (3)$$

where $(k_T - k_U = k_C)$

4.3 Discussion

In the later period of twentieth century the kinetics of oxidation of various organic and inorganic substrates have been studied by Ag(III) species which may be due to its strong versatile nature of two electron oxidant. Among the various species of Ag(III), $Ag(OH)_4^-$, diperiodatoargentate (III) and ethylenebis (biguanide), (EBS), silver(III) are of maximum attention to the researchers due to their relative stability[27]. The stability of $Ag(OH)_4^-$ is very sensitive towards traces of dissolved oxygen and other impurities in the reaction medium whereupon it had not drawn much attention. However, the other two forms of Ag(III) [4,7-8, 28-30] are considerably stable; the DPA is used in highly alkaline medium and EBS is used in highly acidic medium.

A literature survey [20] reveals that the water soluble 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. When the same molecule is used in alkaline medium, it is unlike to be existed as $[Ag(IO_6)_2]^{7-}$ (6) as periodate is known to be in various protonated forms[31, 32] depending on pH of the solution as given in following multiple equilibria: (5) (4)

$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+$$

$$H_4IO_6^- \rightleftharpoons H_3IO_6^{2-} + H^+$$

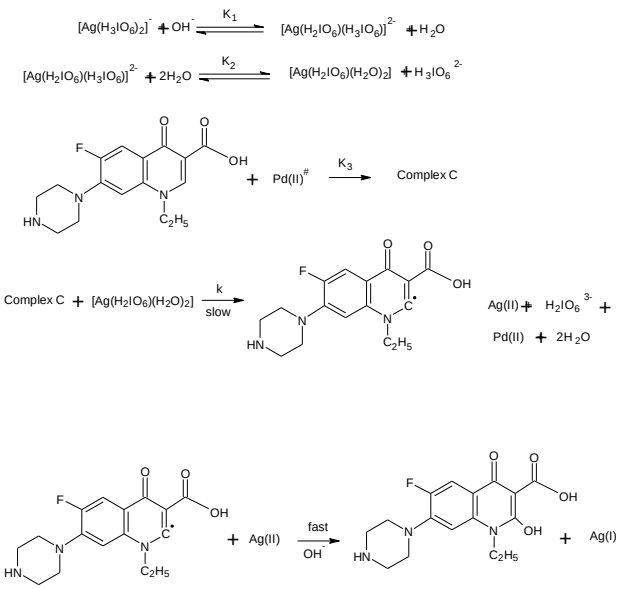
$$H_3IO_6^{2-} \rightleftharpoons H_2IO_6^{3-} + H^+$$

Periodic acid (H_5IO_6) exists in acid medium and also as $H_4IO_6^-$ at pH 7. Thus, under the present 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[33]. The recent studies have proposed the DPA as $[Ag(HL)_2]^{x-}$ in which 'L' is a periodate with uncertain number of protons and 'HL' is a protonated periodate of uncertain number of protons. This can be ruled out by considering the alternative form[31, 32] of IO_4^- at pH>7, which is in the form $H_3IO_6^{2-}$ or $H_2IO_6^{3-}$. Hence, DPA could be as $[Ag(H_3IO_6)_2]^-$ or $[Ag(H_2IO_6)_2]^{3-}$ in alkaline medium. Therefore, under the present condition, DPA, may be depicted as $[Ag(H_3IO_6)_2]^-$

Mechanism

It is interesting to identify the probable Ruthenium (III) chloride species in alkaline medium. Electronic spectral studies[33, 34] have confirmed that ruthenium chloride exists in hydrated form as $[Ru(III)(OH)_x]^{3-x}$, where x value would always be less than six, since there are no definite reports of any hexahydroxy ruthenium species. The remainder of the coordination sphere would be filled by water molecules as shown in **scheme 2,** which is in accordance with earlier work [35]. Keeping in view of the above experimental data, the following mechanistic path has been suggested for the oxidation of norfloxacin by DPA in the presence of Ru(III) as catalyst in aqueous alkaline medium.

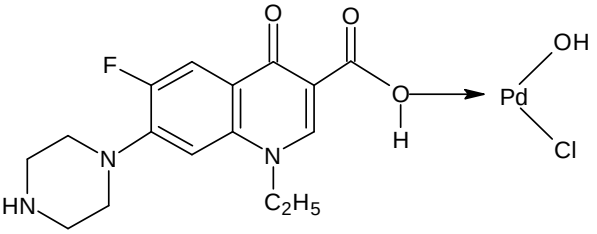
Scheme 2.



In the prior equilibrium step 1, the [OH^-], deprotonates the DPA to give a deprotonated DPA; 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 [periodate] (Table 1). It may be expected that lower Ag(III) periodate species such as monoperiodatoargentate(III) (MPA) will be more important in the reaction than the DPA. The inverse fractional order in [$H_3IO_6^{2-}$] might also be due to this reason. In the pre-rate-determining stage, the Ru(III) reacts with a molecule of NF to give a complex [C], which further reacts with one molecule of MPA in the slow step to give the free radical and Ag(II) species and the catalyst is regenerated. The formation of intermediate Ag(II) species is evidenced by earlier work[6-8, 36, 37]. This free radical species combines with Ag(II) species in a fast step to form the product.

The probable structure of the Complex C is given **in Scheme 3**. Spectroscopic evidence for the complex formation between catalyst and substrate was obtained from UV–Vis spectra of NF Ru(III), [OH^-] and the mixture of both. A bathochromic shift of about 7 nm from 332 to 339nm in the spectra of norfloxacin and Ru(III) was observed. The Michelis-Menten plot proved the complex formation between Ru(III) and NF. Such a complex formation between a substrate and a oxidant has been observed in other studies [38, 39].

Scheme 3



The rate law for the Scheme 1 could be derived as

$$Rate_{cat} = rate_{total} - rate_{uncat}$$

$$Rate = \frac{-d[DPA]}{dt}$$

$$= \frac{kK_1K_2K_3[DPA][NF][OH^-][Ru(III)]}{[H_3IO_6^{2-}] + K_1[OH^-][H_3IO_6^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][NF]} \quad (7)$$

$$\frac{Rate}{[DPA]} = k_T - k_U k_c$$

$$= \frac{kK_1K_2K_3[NF][OH^-][Ru(III)]}{[H_3IO_6^{2-}] + K_1[OH^-][H_3IO_6^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][NF]} \quad (8)$$

The rate law (7) can be rearranged to following form for verification.

$$\frac{[Ru(III)]}{k_C} = \frac{[H_3IO_6^{2-}]}{kK_1K_2K_3[OH^-][NF]} + \frac{[H_3IO_6^{2-}]}{kK_3[NF]} + \frac{1}{kK_2K_3[NF]} + \frac{1}{k} \quad (9)$$

According to Eqn (9), other conditions being constant, plots of Ru(III)/k_{obs} versus [$H_3IO_6^{2-}$] , Ru(III)/k_{obs} versus 1/[NF] and Ru(III)/k_{obs} versus 1/[OH^-] should be linear as found in Fig. 1, 2 and 3. The slopes and intercepts of such plots lead to the

values of K_1, K_2, K_3, and k as (0.65 $\pm$0.16) $dm^3 mol^{-1}$, (1.95$\pm$0.04) x 10^{-4} $moldm^{-3}$, (4.22$\pm$1.03)x10^2 dm^3mol^{-1} and (1.53$\pm$0.11) x 10^3 s^{-1} respectively. Using these values the rate constants were calculated and compared with experimental values (Table1). The experimental rate constants were in good agreement with calculated values, which fortifies the proposed mechanism.

The values of K_1 (dm^3mol^{-1}) were obtained as 0.65 ± 0.11, 0.82 ±.05, 0.98 ± 0.12, and 1.23 ± 0.19 at 298, 303,308, and 313K, respectively. A van't Hoff's plot was made for the variation of K_1 with temperature [i.e. log K_1 vs. 1/T) and the values of the enthalpy of reaction ΔH ($kJmol^{-1}$) = 31.99 ± 1.22, entropy of reaction ΔS ($JK^{-1}mol^{-1}$) = 11.89 ±1.4 and free energy of reaction ΔG ($kJmol^{-1}$) = 28.46 ±1.2, were calculated. A comparison of the latter values with those obtained for the slow step of the reaction shows that these values mainly refer to the rate limiting step, supporting the fact that the reaction before the rate determining step is fairly slow and involves high activation energy[40]. In the same manner, K_2 and K_3 values were calculated at different temperatures. The values of K_2 x 10^{-4} mol dm^3 were obtained as 1.95, 1.41, 1.14, 0.81. Thermodynomic quantities ΔH ($kJmol^{-1}$) = -40.77 ±1.1, entropy of reaction ΔS($JK^{-1}mol^{-1}$) = -45.02 $\pm$0.85 and free energy of reaction ΔG($kJmol^{-1}$) = -27.35 ± 1.06, were calculated. Similarly the values of K_3 x 10^3 dm^3 mol^{-1} are 4.22, 4.75, 5.18, 5.52. Thermodynomic quantities ΔH($kJmol^{-1}$) = 11.88 ± 1.2, entropy of reaction ΔS($JK^{-1}mol^{-1}$) = -92.39 $\pm$1.0 and free energy of reaction ΔG($kJmol^{-1}$) = -39.41 ± 1.81 were calculated.

The negative value of $\Delta S^{\#}$ suggests that the intermediate complex is more ordered than the reactants [41]. The observed modest enthalpy of activation and a low value of entropy of activation indicates that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by earlier observations[42]. The activation parameters evaluated for the catalysed and uncatalysed reaction explain the catalytic effect on the reaction. The catalyst Ru(III) form the complex(C) with substrate, which enhances the reducing property of the substrate than that without catalyst. Further, the catalyst Ru(III) modifies the reaction path by lowering the energy of activation.

Figure : 1

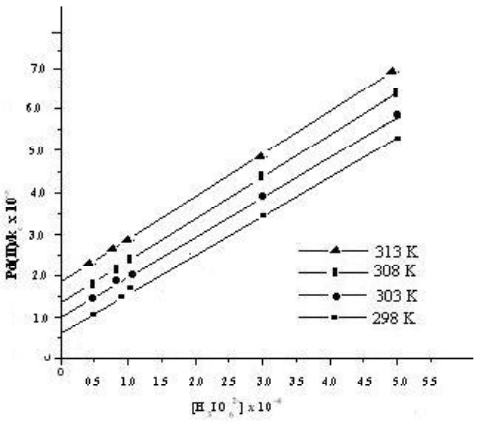


Figure: 2

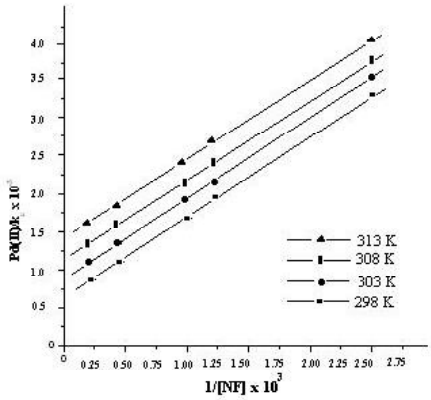
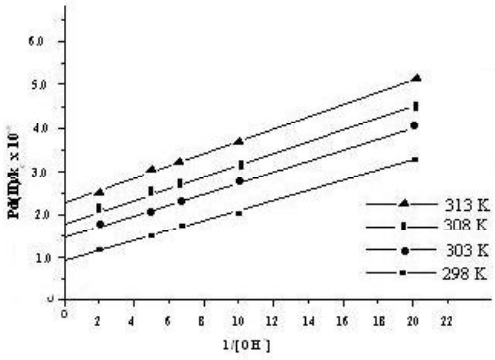


Figure: 3



CONCLUSION

Among the various species of DPA in alkaline medium, in earlier reports the $[Ag(H_2IO_6)(H_2O)_2]$ is considered as the active species for the title reaction. Active species of Ru(III) is found to be $[Ru(H_2O)_5OH]^{2+}$. The difference in the activation parameters for the catalysed and uncatalysed reactions explains the catalytic effect on the reaction. The catalyst Ru(III)) alters the reaction path by lowering the energy of activation. The overall sequence described here is consistent with product, mechanistic and kinetic studies.

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