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Kinetics and Mechanism of Electron-Transfer Reactions: Oxidation of Nalidixic Acid by Diperiodatocuprate (III) in Aqueous Alkaline Medium

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ABSTRACT

The kinetics and mechanism of oxidation of nalidixic acid by diperiodatocuprate (III) in aqueous alkaline medium has been studied spectrophotometrically at 303 K. The reaction exhibits first order with respect to oxidant but substrate dependence is complex. The stoichiometry of the reaction has been observed to two moles of the oxidant for a mole of the substrate. The oxidation product of the substrate is 1-ethyl-2-hydroxy-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid as established spectrally. The active species of diperiodatocuprate (III) is understood to be as monoperiodatocuprate (III). The activation parameters were also determined and discussed. The activation parameters and thermodynamics quantities were also determined and discussed. A plausible reaction mechanism has been suggested to account for experimental observations.

INTRODUCTION

In recent years, the study of highest oxidation state of transition metals has frame-upped by many researchers. Transition metals in a higher oxidation state can be stabilized by chelation with suitable polydentate ligands. Metal chelate with such as diperiodatocuprate(III), diperiodatoargenate(III) and diperiodatonickelate(IV) are good oxidants [1-3]. Diperiodatocuprate(III) (DPC) is a versatile one-electron oxidant for various organic compounds in alkaline medium and its use as an analytical reagent is now well recognized [4]. Copper complexes have engaged a major place in oxidation chemistry due to their prosperity and applicability in biological chemistry [5]. The study using DPC is novel and confined to few cases owing to its limited solubility and stability [6-13].

Fluoroquinolones are a family of synthetic antibacterial agents with a rising popularity. These antibiotics display a broad spectrum of antibacterial activity including strong effects on gram-negative aerobic and anaerobic organisms as well as on gram-positive and typical pathogens [14,15]. But these are not fully metabolized in the body and are partially excreted in its pharmaceutically active form [16,17]. Due to the limited biodegradability and widespread use of these antibiotics, an incomplete removal is obtained in typical waste water treatment plants and analogous huge quantities are discharged into the environment. As a result, numerous antibiotics can be found in surface waters producing injurious effects on aquatic organisms [18,19]. For the removal of these fluoroquinolone many studies are used, in which oxidation process is mostly used and degrade them from the environment [20,21]. Wang et al have select ClO_2 as an oxidant to understand degradation of drugs in possible products [22]. Zhang et al. used MnO_2 as oxidant in drug oxidation for the elucidation of their oxidant product [23]. However Nalidixic acid (NA) was not used in their studies, neither in quantification nor in the kinetic studies of oxidative degradation with DPC. Nalidixic acid (NA) with molecular formula $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ (1-ethyl-3, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid) is the first synthesized antimicrobial quinolone. NA is an ionizable, non-biodegradable photosensitive molecule [24,25] with a carboxylic acid function having a pKa of 5.95 [26]. NA is an antibacterial drug still widely used for urinary tract infections [27]. However the kinetics of oxidation of medicinally important compound such as NA with the following view point: first, identify the active species of DPC in aqueous alkaline medium, secondly, whether or not the substrate forms any intermediate complex before undergoing to

final reaction products. Hence, the present investigation is aimed to elucidate the reactivity of NA towards DPC, to arrive at a plausible mechanism and to understand the reactive species.

MATERIALS AND METHODS

Chemicals

All chemicals used were of analytical grade and standard solution of NA (KORES India Limited) was prepared by dissolving calculating quantity of pure drug in double distilled water. A stock solution of periodate was prepared by dissolving known amount of KIO_4 (MERCK) in hot water and used after 24 h and concentration was determined iodometrically [28]. The complex of copper(III) periodate was prepared [29] and standardized by a known method [30]. KOH and KNO_3 (BDH) were employed to maintain the required alkalinity and ionic strength respectively in reaction solutions. Doubly distilled water was employed throughout the study.

Instrumentation

For kinetic study, a Peltier accessory (temperature-Controlled) attached to a double beam U.V.3000⁺, UV-Visible spectrophotometer (LABINDIA) with U.V. path length 1.0 cm in the spectral range 200-800 nm, was used. Liquid Chromatography-Mass Spectroscopy (LC-MS), (Q-TOF Micromass, WATERS Company, UK) and Fourier Transform Infrared (FT-IR) Spectrophotometer (ALPHA-T, Bruker, Germany) were used for product analysis.

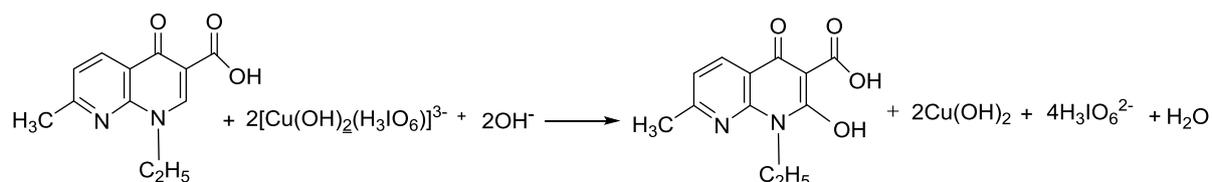
Kinetic procedure

All reaction ingredients except DPC were taken in flask and the reaction was initiated by adding requisite volume of temperature pre-equilibrated solution of DPC. The progress of the reaction was followed by measuring the absorbance of unreacted DPC in the reaction mixture by UV-Visible spectrophotometer at 415 nm. The application of Beer's law of DPC at 415 nm has been verified. The molar absorptivity index of DPC was found to be $\epsilon = 6230 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$ [31]. Since kinetics was studied under pseudo first order conditions ($[\text{NA}] \gg 10[\text{DPC}]$). Pseudo first order plots were obtained and pseudo-first-order rate constants (k_{obs}) were calculated from these plots. The value of k_{obs} was reproducible within $\pm 5\%$.

RESULTS AND DISCUSSION

Stoichiometry and product analysis

The stoichiometry of the reaction was calculated by taken excess of DPC over NA in a flask thermostated at $30 \pm 0.1^\circ\text{C}$. The estimation of excess DPC corresponds to the stoichiometry of the reaction as represented



Nalidixic acid

(1)

The main oxidation product of NA 1-ethyl-2-hydroxy-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid was isolated with the help of TLC and characterized by LC-MS, FT-IR spectral analysis. LC/MS analysis of the reaction indicated the presence of a product with molecular ion of m/z 248 corresponds to 1-ethyl-2-hydroxy-1, 4-dihydro-7-methyl-4-oxo-1, 8-naphthyridine-3-carboxylic acid (Figure 1). The molecular ion of NA is m/z 232.2. The IR spectroscopy shows a broad peak at 3382.39 cm^{-1} which is due to -OH stretching (Figure 2) and the remaining peaks are of the parent compound.

WATERS, Q-TOF MICROMASS (LC-MS)

Nalidixic acid-1- 14 (0.278) Cm (6:14)

SAIF/CIL,PANJAB UNIVERSITY,CHANDIGARH

TOF MS ES+
2.06e3

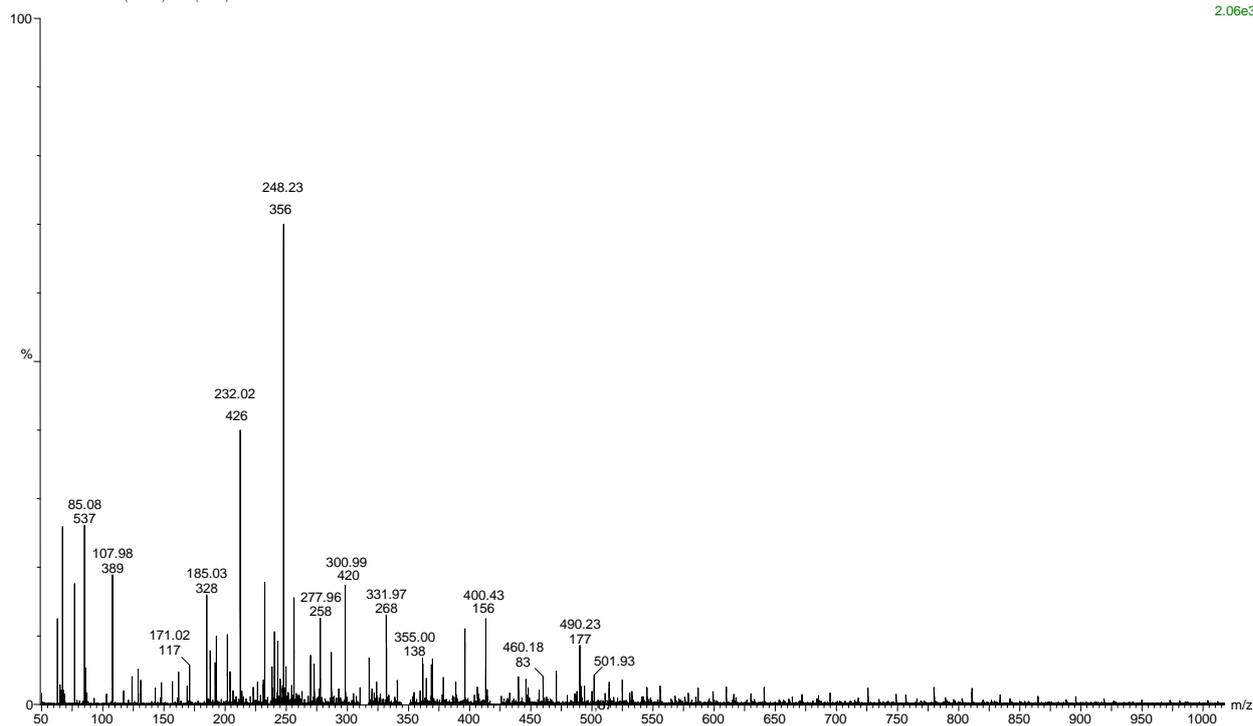


Figure 1 LC-MS spectra of oxidation product of NA.

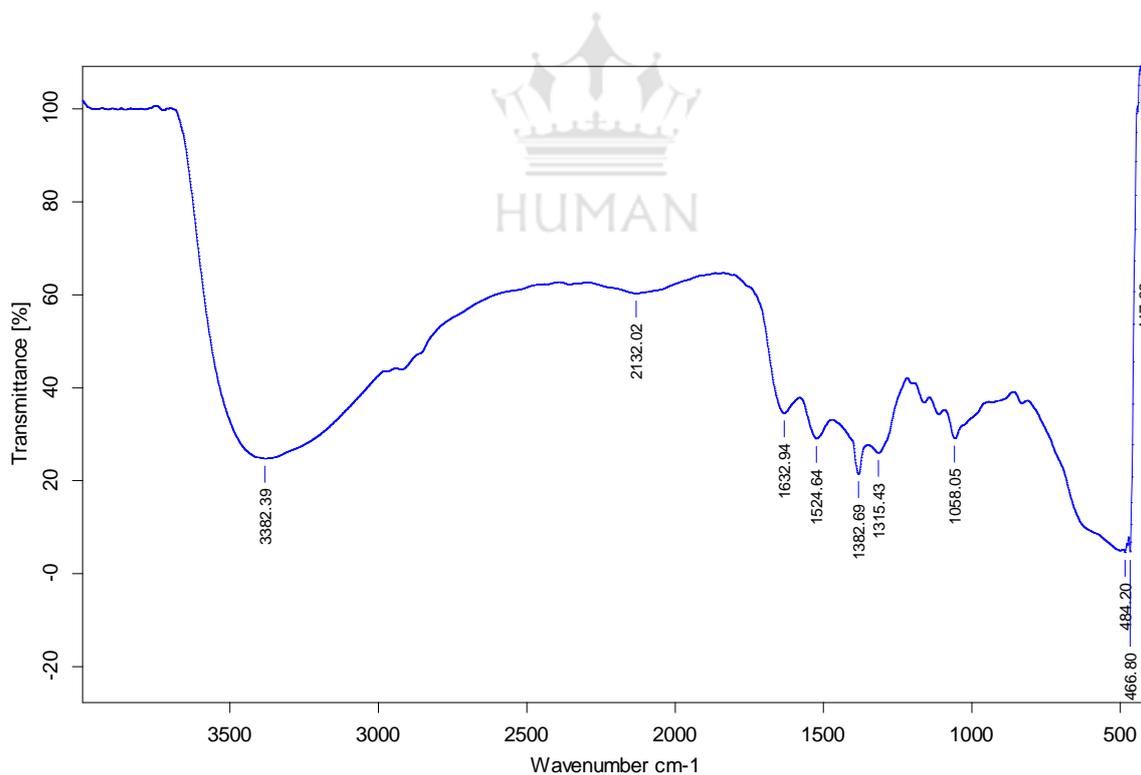


Figure 2 FT-IR spectra of the product of oxidation of NA by DPC.

Diperiodatocuparate(III) dependence

The concentration of DPC was varied from 1.0×10^{-5} to $10.0 \times 10^{-5} \text{ mol dm}^{-3}$ at $[\text{NA}] = 5.0 \times 10^{-4} \text{ mol dm}^{-3}$, alkali = 0.05 mol dm^{-3} and $I = 0.10 \text{ mol dm}^{-3}$ at 30°C temperature. The plot of \log absorbance versus time was linear (Figure 3) indicating the reaction is first order with respect to [DPC]. The observed pseudo first order rate constant (k_{obs}) were independent of the initial concentration of DPC (Table 1).

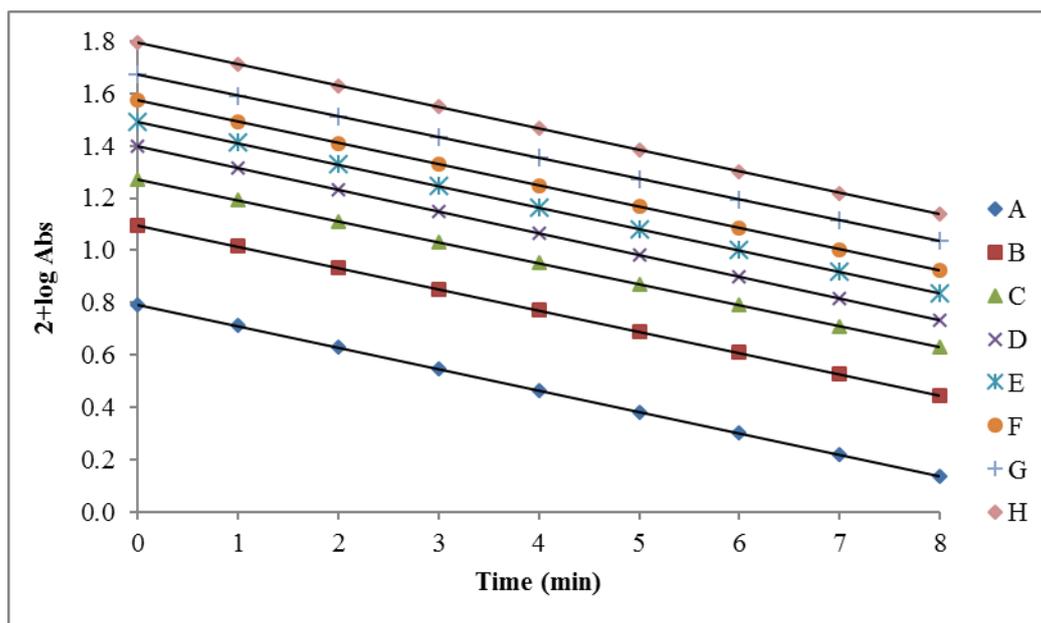


Figure 3 First order plots of the variation of DPC concentration at 30°C .

Conditions: $[\text{NA}] = 5.0 \times 10^{-4}$, $[\text{OH}^-] = 5.0 \times 10^{-2}$, $[\text{IO}_4^-] = 5.0 \times 10^{-5}$ and $I = 0.1 \text{ mol dm}^{-3}$. $[\text{DPC}] \times 10^{-5} \text{ mol dm}^{-3} = (\text{A}) 1.0, (\text{B}) 2.0, (\text{C}) 3.0, (\text{D}) 4.0, (\text{E}) 5.0, (\text{F}) 6.0, (\text{G}) 7.5, (\text{H}) 10.0$.

Nalidixic acid dependence

The concentration of NA was varied from 1.0×10^{-4} to $10.0 \times 10^{-4} \text{ mol dm}^{-3}$ at constant concentration of DPC, alkali, IO_4^- and ionic strength at 25° , 30° and 35°C respectively. The rate of reaction increases with increasing concentration of NA initially but levels off at higher concentration indicating complex order with respect to NA (Table 1). This was confirmed by the plot of $1/k_{\text{obs}}$ versus $1/[\text{NA}]$ which was linear with a positive intercept.

Hydroxyl ion dependence

Hydroxyl ion concentration was varied from 2.0×10^{-2} to $10.0 \times 10^{-2} \text{ mol dm}^{-3}$ at fixed concentration of other reaction ingredients $[\text{DPC}] = 5.0 \times 10^{-5}$, $[\text{NA}] = 5.0 \times 10^{-4}$, $[\text{IO}_4^-] = 2.0 \times 10^{-5}$, $I = 0.1 / \text{mol dm}^{-3}$ at three temperature 25° , 30° , 35°C respectively. Pseudo first order rate constant (k_{obs}) was found to increase with increase in $[\text{OH}^-]$ (Table 1). A plot of $\log k_{\text{obs}}$ versus $\log [\text{OH}^-]$ was linear with a fractional slope of 0.56. This was confirmed by the plot of $1/k_{\text{obs}}$ versus $1/[\text{OH}^-]$.

Periodate ion dependence

The effect of concentration of KIO_4 was studied by different periodate concentration from 1.0×10^{-5} to $1.0 \times 10^{-4} \text{ mol dm}^{-3}$, keeping other reactant concentrations constant. It was found added periodate had a retarding effect on the rate of reaction (Table 1). The order with respect to periodate concentration was found to be less than unity with negative slope.

Effect of ionic strength and dielectric constant

At constant concentration of reactants and other conditions, the ionic strength was varied by different concentration of sodium nitrate from 0.20 to 0.50 mol dm^{-3} . The rate of reaction is unaffected by variations of ionic strength. The effect of the dielectric constant (D) was studied by different t-butanol-water content (v/v) in the reaction mixture with all other conditions maintained constant. The dielectric constant of the reaction medium has no effect on the rate of reaction.

Test for free radical

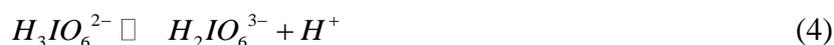
Acrylonitrile was added in the reaction mixture and kept in an inert atmosphere then diluted with methanol. White precipitate comes, indicating the formation of free radicals during reaction.

Table 1. First order rate constants (k_{obs}) for the reaction of NA with DPC in aqueous alkaline medium at $I = 0.1 \text{ mol dm}^{-3}$ and Temperature = 303 K

$10^5 [\text{DPC}]$ (mol dm^{-3})	$10^4 [\text{NA}]$ (mol dm^{-3})	$10^2 [\text{OH}^-]$ (mol dm^{-3})	$10^4 [\text{KIO}_4]$ (mol dm^{-3})	$10^4 k_{obs}$ (s^{-1})
1.0	5.0	5.0	5.0	3.16
2.0	5.0	5.0	5.0	3.12
3.0	5.0	5.0	5.0	3.08
4.0	5.0	5.0	5.0	3.18
5.0	5.0	5.0	5.0	3.15
6.0	5.0	5.0	5.0	3.12
7.5	5.0	5.0	5.0	3.05
10.0	5.0	5.0	5.0	3.15
5.0	1.0	5.0	5.0	0.99
5.0	2.0	5.0	5.0	1.71
5.0	3.0	5.0	5.0	2.32
5.0	4.0	5.0	5.0	2.81
5.0	5.0	5.0	5.0	3.15
5.0	6.0	5.0	5.0	3.43
5.0	7.5	5.0	5.0	3.72
5.0	10.0	5.0	5.0	3.91
5.0	5.0	2.0	5.0	1.42
5.0	5.0	3.0	5.0	2.01
5.0	5.0	4.0	5.0	2.65
5.0	5.0	5.0	5.0	3.15
5.0	5.0	6.0	5.0	3.45
5.0	5.0	7.5	5.0	3.92
5.0	5.0	10.0	5.0	4.50
5.0	5.0	5.0	1.0	6.85
5.0	5.0	5.0	2.5	5.05
5.0	5.0	5.0	5.0	3.15
5.0	5.0	5.0	7.5	2.35
5.0	5.0	5.0	10.0	1.97

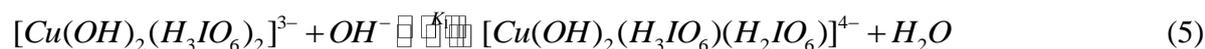
Mechanism

The present investigation carried out in aqueous alkaline medium so involvement of periodate in multiple equilibria (2-4) depending upon the pH of solution [32].

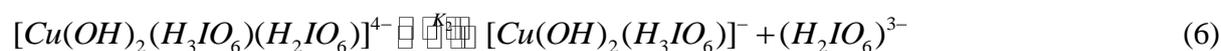


In acid medium periodate acid exist as $H_5IO_6^-$ and at $pH = 7$ as $H_4IO_6^-$. In this study employed alkaline medium, the main species are expected to be $H_3IO_6^{2-}$ and $H_2IO_6^{3-}$. Thus soluble copper(III) periodate complex exist as $[Cu(OH)_2(H_3IO_6)_2]^{3-}$ [33].

The stiochiometry of the reaction between diperiodatocuprate(III) complex and NA is an alkaline medium has 1:2. The rate of reaction increases with alkali concentration can be explained by formation of $[Cu(OH)_2(H_3IO_6)]^{4-}$ from $[Cu(OH)_2(H_3IO_6)_2]^{3-}$ by equation (5).

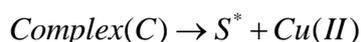


The rate of reaction decrease with increase in periodate concentration suggests that equilibrium of Cu(II) periodate complex to form monoperiodato cuprate(III) (MPC) [31].



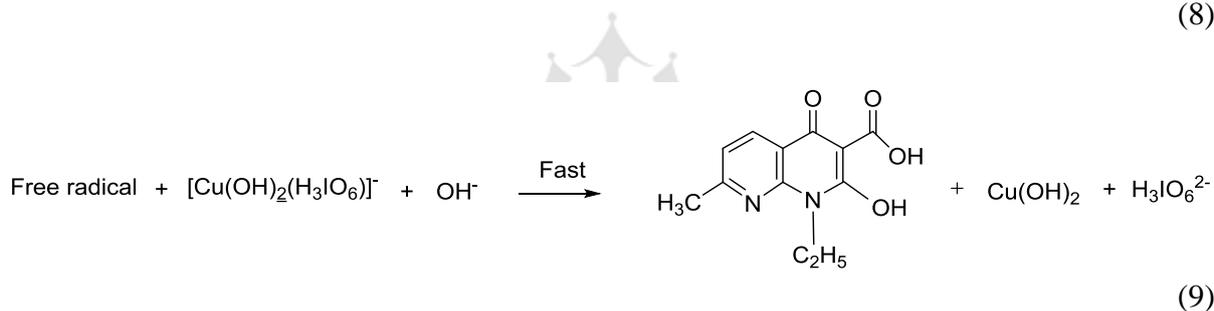
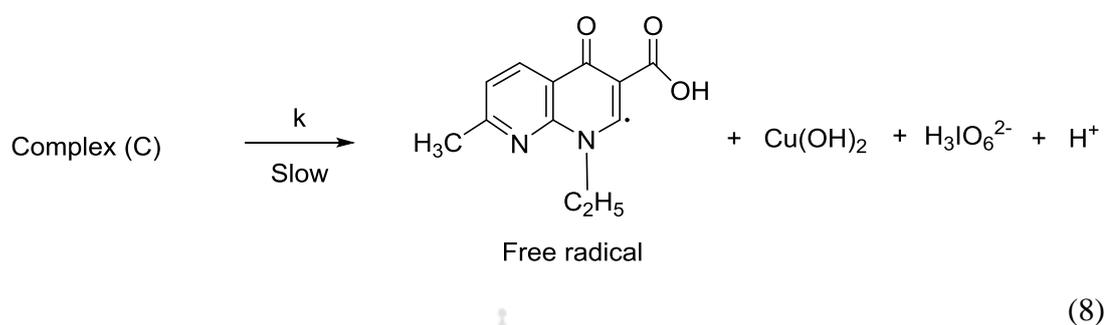
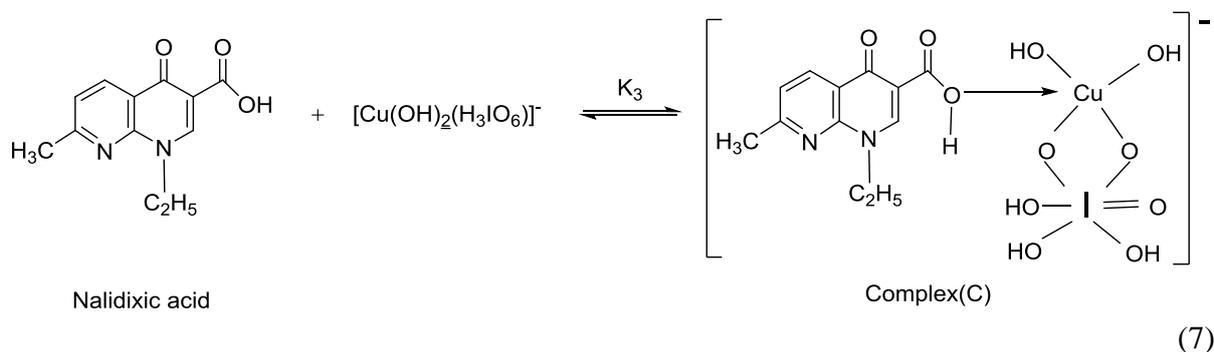
It can also possible that [MPC] is more important than [DPC] in the reaction.

The experimental results shows fractional order with respect to NA concentration indicates complex formation with NA and DPC species [34] before the rate determining step. The braking of this complex (C) is assigned as slowest step, leading to formation of NA radical intermediate. The radical intermediate reacts with other molecules of MPC species, to give final products (scheme 1). The effect of ionic strength on the rate explains qualitatively the involvement of neutral molecule in the reacts on the basis of results, mechanism are as follows.



So, the detailed mechanistic scheme for the oxidation of nalidixic acid by DPC is as follows:





Scheme 1

From the above mechanism the following rate law (10) –(20) can be derived.

$$Rate = -\frac{d[DPC]}{dt} = k[C] = \frac{kK_1K_2K_3[Cu(OH)_2(H_3IO_6)]^- [NA][OH^-]}{[H_3IO_6^{3-}]}$$

(10)

The total concentration of DPC is given by equation (11)

$$[DPC]_t = [DPC]_f + [Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-} + [Cu(OH)_2(H_3IO_6)]^- + [Complex(C)]$$

(11)

$$[DPC]_t = [DPC]_f + K_1[DPC][OH^-] + \frac{K_1K_2[DPC][OH^-]}{[H_2IO_6^{3-}]} + \frac{K_1K_2[DPC][NA][OH^-]}{[H_2IO_6^{3-}]}$$

$$[DPC]_t = [DPC]_f \left\{ \frac{[H_2IO_6^{3-}] + K_1[H_2IO_6^{3-}][OH^-] + K_1K_2[OH^-] + K_1K_2[DPC][NA][OH^-]}{[H_2IO_6^{3-}]} \right\} \quad (12)$$

$$[DPC]_f = \frac{[DPC]_t [H_2IO_6^{3-}]}{[H_2IO_6^{3-}] + K_1[H_2IO_6^{3-}][OH^-] + K_1K_2[OH^-] + K_1K_2[DPC][NA][OH^-]} \quad (13)$$

Where $[DPC]_t$ and $[DPC]_f$ presents total and free concentrations of DPC respectively. Similarly total concentration of Nalidixic acid is given by

$$[NA]_t = [NA]_f + [C]$$

$$[NA]_t = [NA]_f + \frac{K_1K_2K_3[DPC][NA][OH^-]}{[H_3IO_6^{3-}]}$$

$$[NA]_t = \frac{[NA]_f [H_3IO_6^{3-}] + K_1K_2K_3[DPC][OH^-]}{[H_3IO_6^{3-}]}$$

$$[NA]_f = \frac{[NA]_t [H_3IO_6^{3-}]}{[H_3IO_6^{3-}] + K_1K_2K_3[DPC][OH^-]} \quad (14)$$

At low concentration of DPC, OH^- and $H_2IO_6^-$ used.

$$[NA]_f = [NA]_t \quad (15)$$

Similarly,

$$[OH^-]_t = [OH^-]_f + [Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-} + [Cu(OH)_2(H_3IO_6)]^- + [Complex(C)]$$

$$[OH^-]_t = [OH^-]_f + K_1[OH^-][Cu(OH)_2(H_3IO_6)_2]^- + \frac{K_1K_2[Cu(OH)_2(H_3IO_6)_2]^{3-}[OH^-]}{[H_2IO_6^{3-}]} + \frac{K_1K_2[Cu(OH)_2(H_3IO_6)_2]^{3-}[NA]}{[H_2IO_6^{3-}]}$$

(16)

At low concentration of DPC, [NA] and $H_2IO_6^{3-}$ used,

$$[OH^-]_f = [OH^-]_t$$

(17)

Substituting equations (13),(15),(17) in equation (10) and omitting ‘t’ and ‘f’ subscripts.

$$Rate = -\frac{d[DPC]}{dt} = \frac{kK_1K_2K_3[DPC][NA][OH^-]}{[H_2IO_6^{3-}] + K_1[H_2IO_6^{3-}][OH^-] + K_1K_2[OH^-] + kK_1K_2[NA][OH^-]}$$

(18)

or

$$k_{obs} = -\frac{Rate}{[DPC]} = \frac{kK_1K_2K_3[NA][OH^-]}{[H_2IO_6^{3-}] + K_1[H_2IO_6^{3-}][OH^-] + K_1K_2[OH^-] + kK_1K_2[NA][OH^-]}$$

(19)

The equation (19) can be rearranged as

$$\frac{1}{k_{obs}} = \frac{[H_2IO_6^{3-}]}{kK_1K_2K_3[NA][OH^-]} + \frac{[H_2IO_6^{3-}]}{kK_2K_3[NA]} + \frac{1}{kK_3[NA]} + \frac{1}{k}$$

(20)

According to equation (20) the plot of $1/k_{obs}$ versus $1/[OH^-]$, $1/k_{obs}$ versus $1/[NA]$ and $1/k_{obs}$ versus $[H_2IO_6^{3-}]$ are linear (Figure 4, 5, 6 respectively). The slopes and intercept of such plots gives the value of K_1 , K_2 , K_3 and k are $(7.04) \text{ mol}^{-1} \text{ dm}^3$, $(17.78) \times 10^{-2} \text{ mol}^{-1} \text{ dm}^3$, $(25.1) \times 10^5 \text{ mol dm}^{-3}$ and $(6.58) \times 10^{-3} \text{ s}^{-1}$ respectively. The equilibrium constant K_1 is greater than K_2 , which indicates the greater tendency to undergo hydrolysis compared to the dissociation of species in alkaline medium.

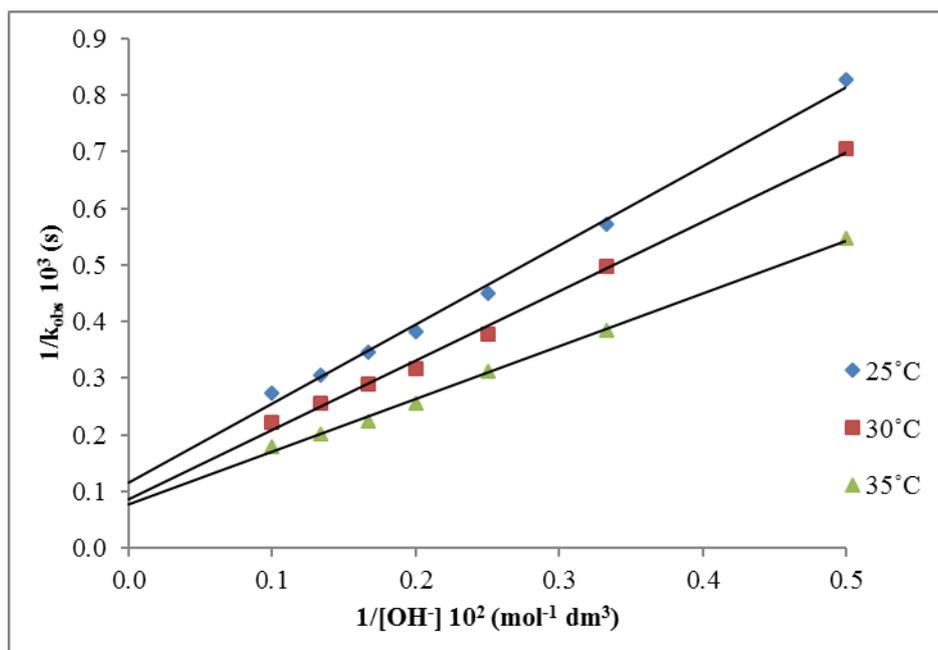


Figure 4 Plot of $1/k_{obs}$ versus $1/[OH^-]$ at $30^\circ C$.

$[DPC] = 5.0 \times 10^{-5}$, $[NA] = 5.0 \times 10^{-4}$, $[IO_4^-] = 5.0 \times 10^{-4}$ and $I = 0.1 / \text{mol dm}^{-3}$.

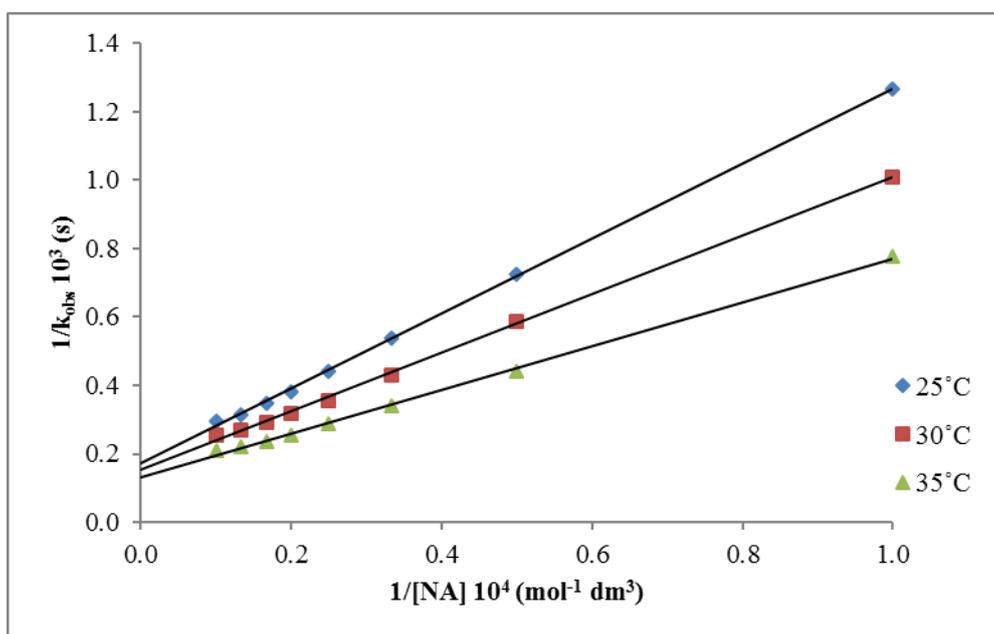


Figure 5 Plot of $1/k_{obs}$ versus $1/[NA]$ at $30^\circ C$.

$[DPC] = 5.0 \times 10^{-5}$, $[OH^-] = 5.0 \times 10^{-2}$, $[IO_4^-] = 5.0 \times 10^{-4}$ and $I = 0.1 / \text{mol dm}^{-3}$.

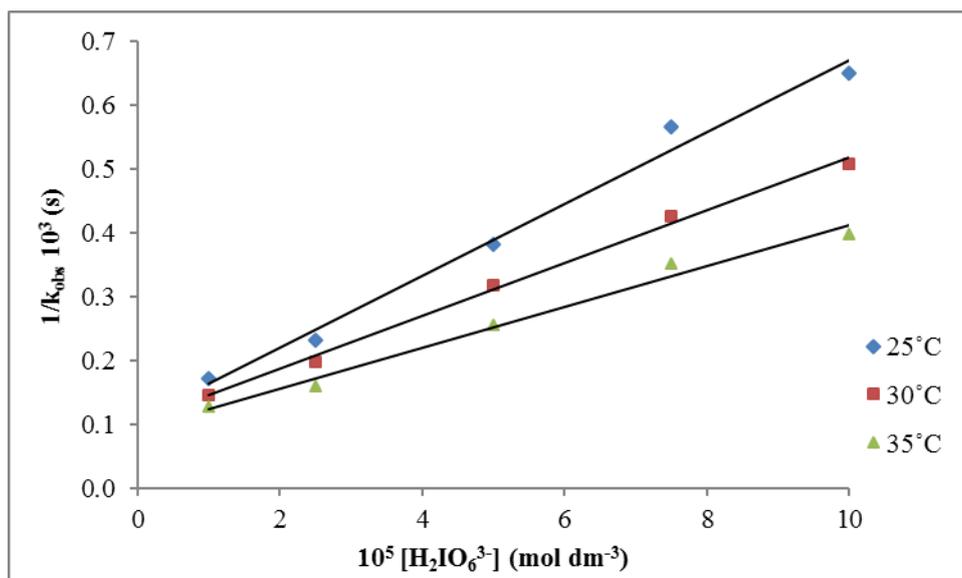


Figure 6 Plot of $1/k_{\text{obs}}$ versus $[\text{H}_2\text{IO}_6^{3-}]$ at 30°C.

$[\text{DPC}] = 5.0 \times 10^{-5}$, $[\text{NA}] = 5.0 \times 10^{-4}$, $[\text{OH}^-] = 5.0 \times 10^{-2}$ and $I = 0.1 \text{ /mol dm}^{-3}$.

The thermodynamics quantities of the first, second and third equation steps of scheme 1 were calculated by variation of $[\text{H}_2\text{IO}_6^{3-}]$, $[\text{NA}]$, $[\text{OH}^-]$ at three temperatures (Table 1). The plots of $1/k_{\text{obs}}$ versus $1/[\text{OH}^-]$, $1/k_{\text{obs}}$ versus $1/[\text{NA}]$ and $1/k_{\text{obs}}$ versus $[\text{H}_2\text{IO}_6^{3-}]$ are obtained linear (Figure 4, 5, 6 respectively). From the slopes and intercept, the values of K_1 were calculated at three temperatures (Table 2). A Von't Haff plot was made by $\log K_1$ versus $1/T$ and values of enthalpy of reaction (ΔH), entropy of reaction (ΔS) and free energy of reaction (ΔG) were calculated. A comparison of latter values with those obtained for the slow step of reaction, clearly indicates the reaction before rate determining step is fast with low activation energy [35]. In the similar way the K_2 and K_3 values were calculated and thermodynamics quantities are given in table 2.

The negative value of ΔS^\ddagger indicates complex is more ordered than reactants [35]. The value of ΔH^\ddagger and ΔS^\ddagger were favourable for electron transfer reactions. The value of entropy of activation and low value of activation and higher value of rate constant of slow step indicates the oxidation reaction occurs via inner-sphere mechanism [36].

Table 2. Activation parameters and thermodynamics quantities for the oxidation of nalidixic acid by DPC in aqueous alkaline medium.

Temperature (K)	$10^3 k (s^{-1})$	Activation parameters	
298	5.88	$E_a (kJ mol^{-1})$	19.47
303	6.58	$\Delta H^\ddagger (kJ mol^{-1})$	16.95
308	7.58	$\Delta S^\ddagger (J K^{-1} mol^{-1})$	-183.43
		$\Delta G^\ddagger (kJmol^{-1})$	86.91
Temperature (K)	$K_1 (mol^{-1} dm^3)$	$10^2 K_2 (mol^{-1} dm^3)$	$K_3 10^5 (mol dm^{-3})$
298	8.17	15.53	19.11
303	7.04	17.78	25.10
308	5.78	20.72	29.70
Thermodynamic quantities	Values from K_1	Values from K_2	Values from K_3
$\Delta H (kJ mol^{-1})$	-26.29	21.92	22.52
$\Delta S (J K^{-1} mol^{-1})$	-315.54	-187.07	-48.25
$\Delta G (kJmol^{-1})$	69.16	78.60	37.06

CONCLUSION

Among the various species of copper(III) in alkaline medium, monoperiodatocuprate(III), $[Cu(H_2IO_6)(H_2O)_2]$ is assumed to be active species for the title reaction. The results indicate that, the rate of pH in the reaction medium is important. Rate constant of the slow step and other equation constants involved in the mechanism evaluated and activation parameters with respect to slow step indicates the oxidation reaction takes place via inner-sphere mechanism.

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