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Uncatalyzed Oxidation of Anti Tuberculosis drug, Pyrazinamide by Cu(III) Complex in Aqueous Alkaline Media: A Kinetic Approach.

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ABSTRACT

The kinetics of oxidation of Pyrazinamide (PZA) by diperiodatocuprate(III) (DPC) in alkaline medium at a constant ionic strength of 0.05 mol dm^{-3} was studied spectrophtometrically. The reaction between DPC and Pyrazinamide in alkaline medium shows 1:1 stoichiometry (PZA:DPC).The reaction is first order in [DPC] and has negative fractional order in [IO_4^-]. It has less than unit order in [PZA] and [OH^-]. Based on the observed orders and experimental evidences, a mechanism involving the monoperiodatocuprate (III) (MPC) as the reactive oxidant species has been proposed. The products were identified and characterized by spectral studies. The activation parameters with respect to slow step of the mechanism were calculated and discussed. The thermodynamic quantities were also concluded for different equilibrium steps.

Keywords: kinetics, Mechanism, Oxidation, Anti-tuberculosis, Pyrazinamide, Diperiodatocuprate(III).

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INTRODUCTION

Pyrazinamide is an antituberculosis drug generally administered in initial stages of tuberculosis treatment to shorten chemotherapy course and is given along with combination of Rifampin, isoniazid. It was synthesized in 1936 by Dalmer and Walter [1] and confirmed as anti-tuberculosis drug in 1952. Pyrazinamide is active against Mycobacterium tuberculosis which shows activity at little less than neutral pH. Although the mechanism of the action of PZA is not clearly understood [2]. But literature study reveals that, PZA is converted into Pyrazinoic acid by the enzyme pyrazinamidase present in cytoplasm [3, 4] of the bacteria, where it interferes with fatty acid synthase (FAS). This hinders the ability of bacteriumto synthesize new fatty acids which is needed for the growth and reproduction. Pyrazinamide also has some side effects such as liver injury, arthralgias, anorexia, nausea and vomiting, dysuria, malaise, fever, and sideroblastic anaemia. Therefore, monitoring the PZA level in human body fluids is quite important to find the possible lowest relative concentration that can provide an effective therapeutic dosage and toxicity [5] and [6]. It is also important to control the dosage of PZA in biological fluids to minimize unwanted effects.

Numerous analytical methods have been developed such as multivariate calibration methods [7], capillary electrophoresis [8] and chromatographic methods [9]. Its determination and invivo study of metabolites were carried out using HPLC [10] technique. Further the reduction of pyrazinamide was studied using cyclic voltametric technique[11]. The determination of anti-tuberculosis drugs in mixtures was studied by Alonso Lomillo et.al. [12] by using differential pulse polarography (DPP) combined with the partial least-squares method. This procedure was applied for the determination of PZA in pharmaceutical dosage form and biological fluids. Determination of PZA in drug mixtures was also reported by Maher and Youssef [13] using square-wave polarography.

In recent years, oxidizing property of transition metals in higher oxidation state has fascinated many researchers. Moreover transition metals in a higher oxidation state are stabilized by chelation with suitable polydentate ligands. Metal chelates, such as diperiodatocuprate(III) [14], diperiodatoargentate(III) [15] and diperiodatonickelate(IV) [16] are prepared and reported as fairly good oxidants in a medium with an appropriate pH value. Several organic compounds are analysed by Periodate and tellurate complexes of copper in its trivalent state. Ramreddy et al [17] observed, Copper(III) as an intermediate in the copper(II)-catalysed oxidation of amino acids by peroxydisulphate. The oxidation reactions usually involves the copper(II)-copper(I) couple and such aspects are detailed in different reviews [18].

Copper(III) is fairly good oxidant and it surpasses dichromate and permanganate in its oxidizing property in alkaline media. It has covered vast area in oxidative study due to its abundance and significance in biological chemistry [19]. It has vital role in biological electron transfer reactions and now days realized as one of the analytical reagents. It is one electron oxidant in alkaline media for diverse organic compounds[20]and also used in estimation of aminoacids. The study using diperiodatocuparate(III) is novel and confined to few cases owing to its limited solubility and stability.DPC shows multiple equilibria between its different species and it would be quite exciting to ascertain which of the species is behaving as active oxidant.

An exhaustive survey of literature shows that oxidative study of PZA has been done by Bromamine-T [21] in perchloric acid. However, there are no reports on oxidation of pyrazinamide by diperiodatocuprate. This prompted us to study its oxidation by DPC which may help to explore further understanding of drug action mechanism.

EXPERIMENTAL

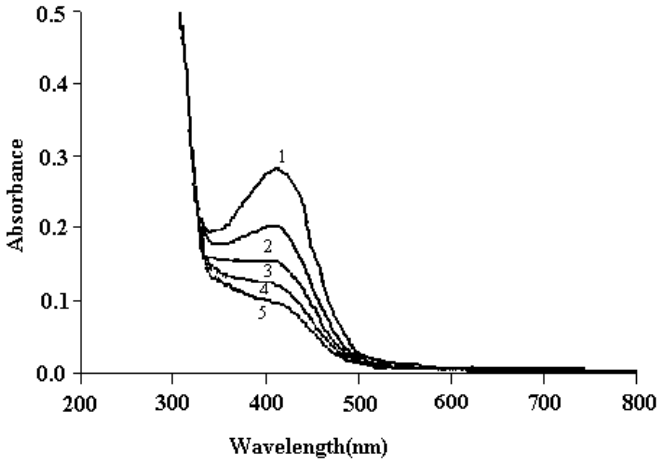
Materials and reagents: All Chemicals used were of analytical grade and double distilled water was used throughout the experiment. Pyrazinamide was obtained as gift sample from Amsal Pvt Ltd. The copper (III) periodate complex was prepared [22]and standardized by referring standard procedure [23]. A periodate solution was prepared by dissolving a known amount of potassium metaperiodate in warm water and it was allowed to stand for 24 hours [23]. Potassium hydroxide (CDH) and Potassium nitrate (Molychem) were added to maintain desired alkalinity and ionic strength respectively in the reaction mixture.

Preparation of DPC: Diperiodatocuprate(III) was prepared by oxidizing,$CuSO_4.5H_2O$ in aqueous alkaline media. Copper sulfate (3.54g), potassium metaperiodate (6.8 g), potassiumpersulphate (2.2g) and potassium hydroxide (9g) were added to 250 $cm^3$of water. Now, the mixture was heated to boiling with constant stirring until the solution turned dark brown and the solution was further boiled for another 25 minutes to ensure the completion of reaction. The mixture was then cooled to ambient temperature and filtration was done through a sintered glass crucible (G-4). Now, the filtrate obtained was diluted to250 cm^3 with distilled water and was stored in amber colored volumetric flask a kept in dark to avoid photochemical reactions. The solution obtained was fairly stable at ambient temperature. The complex was characterized by recording UV visible spectrum from Analytika Jena, Germany using WinASPECT software, which exhibits two strong broad absorption bands at 416 nm and 265 nm. The DPC obtained was standardized by using iodometric and gravimetric [24] methods. There is a possibility periodate of reaction with pyrazinamide & periodate, because periodate is an oxidant and was in excess in DPC solution .The reaction was conducted iodometrically and no significant reaction was observed in experimentally employed conditions at 25 °C.

Experimental details of kinetic measurements: The kinetics was monitored by maintaining pseudo-first order condition, where [PYZ] >[DPC] at 25±0.1°C, unless specified using Analytika Jena, Germany UV–visible spectrophotometer with WinASPECT software. The reaction was initiated by mixing the DPC to PYZ solution which was containing 0.1M, 0.05M and $1x10^{-5}$M concentration of KNO_3, KOH and KIO_4 respectively. The progress of the reaction was followed spectrophotometrically at 416 nm by monitoring the decrease in absorbance of DPC with the molar absorbency index, 'ε' to be 6,250± 50 dm^3 mol^{-1} cm^{-1} (Literature ε = 6500 ± $dm^3.mol^{-1}.cm^{-1}$ [25]). It was confirmed that there is hardly any interference from other species present in the reaction mixture at 416.nm.

The pseudo first-order rate constants, 'k_{obs}' were determined from the log(absorbance) versus time plots. The plots were linear up to 80% completion of reaction under the range of [OH^-] used. The order for various species were determined from the slopes of plots of log k_{obs} versus respective concentration of species except for [DPC] in which non variation of 'k_{obs}' was observed as expected for the reaction condition. During the kinetics a constant concentration, 1.0 x 10^{-5} mol dm^{-3} of KIO_4 was used throughout the study unless otherwise stated. The total concentration of periodate and OH^- were calculated by considering the amount present in the DPC solution and that additionally added. Kinetic measurements were also conducted in nitrogen atmosphere in order to comprehend the effect of dissolved oxygen on the rate of reaction. No substantial disparities in the results were obtained under a nitrogen atmosphere and in the presence of air. 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. The spectral changes during the reaction are shown in Fig.1. It is evident from the figure that the concentration of DPC decreases at 416.nm.

Fig 1: Spectroscopic changes occurring in the oxidation of PZA by DPC at 298 K
[DPC] = 5.0 × 10^{-5} mol dm^{-3}; [PZA] = 5.0 × 10^{-4} mol dm^{-3}; [OH^-] = 0.05 mol dm^{-3}; and I = 0.05 mol dm^{-3} with scanningtime interval of 1min



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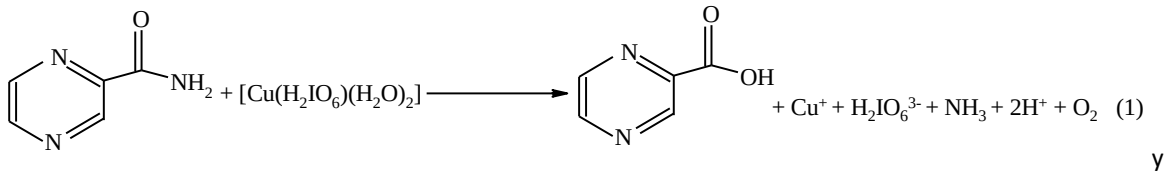
RESULTS

Stoichiometry and product analysis: Different sets of reaction mixtures containing excess of DPC to pyrazinamide in presence of constant amounts of OH^- and KNO_3 were kept for 6 h in closed vessel under inert atmosphere. The remaining DPC concentration was estimated spectrophotometrically at 416 nm. The results indicated a 1:1 stoichiometry as given in equation (1).



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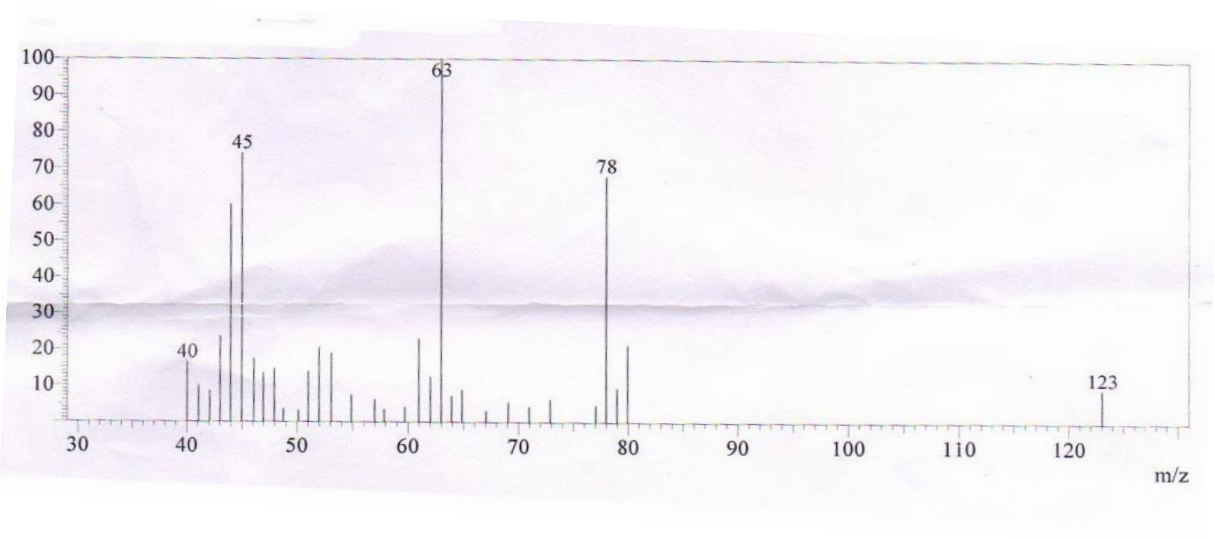
The oxidation product identified was pyrazinoic acid and characterized by its melting point, IR and GC-MS. The nature of pyrazinoic acid was confirmed by its IR spectrum, which showed a -OH stretching frequency at 3386 cm^{-1} and C=O stretching frequency at 1630 cm^{-1}. Also confirmed by the GC-mass spectral analysis. GC-MS data was obtained on a QP-2010S Shimadzu gas chromatograph mass spectrometer. The mass spectral data showed m/z at 123 (m+1) corresponding to the molecular weight of pyrazinoic acid (Fig. 2). The presence of Cu(I) was confirmed by UV-visible spectra.



Regression analysis of experimental data to obtain the regression coefficient r and standard deviation s from the regression line was performed using Microsoft Excel-2007.

Reaction order: The reaction order were determined from the slope of log k_{obs}versus log [concentration] plots by varying the concentration of PZA, alkali in turn while keeping all other concentrations and conditions constant.

Effect of [diperiodatocuprate(III)]: The oxidation of DPC concentration was varied in the range of 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3} and fairly constant k_{obs}value indicate that order with respect to [DPC] was unity (Table1). This was also confirmed by linearity of the plots of log [absorbance] versus time to 85% completion of reaction Fig-3.

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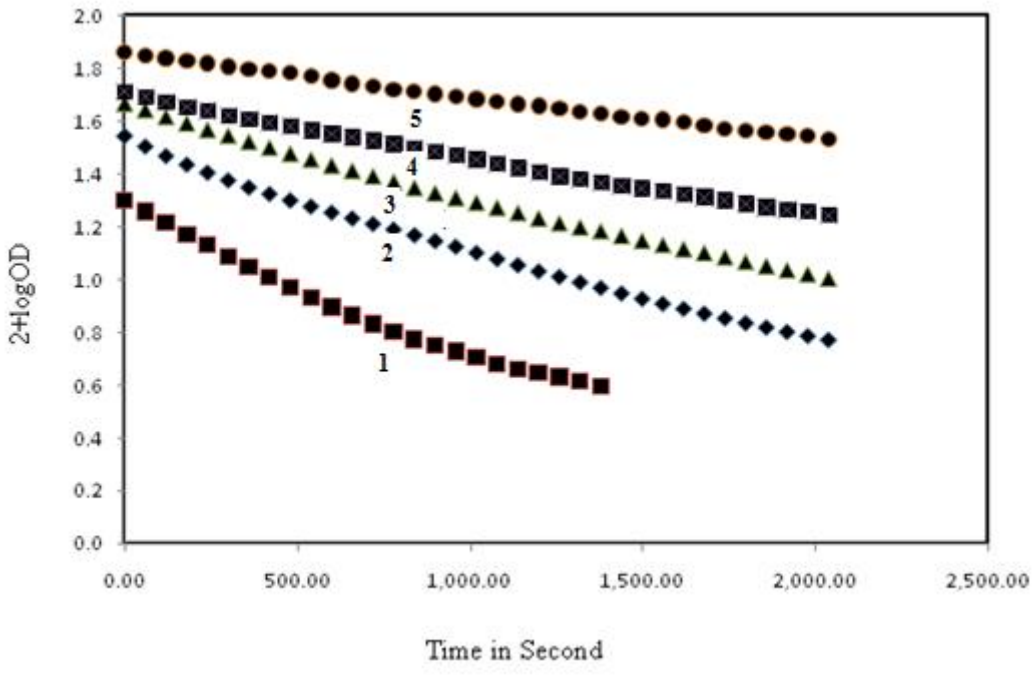
Table 1: Effect of [DPC], [PZA], [OH^-] and [IO_4^-] on the oxidation of pyrazinamide by DPC in alkaline medium at 298 KI = 0.1 mol dm^{-3}

[DPC]×10^5 (mol dm^3)	[PZA] ×10^4 (mol dm^{-3})	[OH^-] (mol dm^{-3})	[IO_4]×10^5 (mol dm^{-3})	k_{obs}×10^3 (s^{-1})	k_{cal}×10^3 (s^{-1})
1.0	5.0	0.05	1.0	3.9	3.9
3.0	5.0	0.05	1.0	3.8	3.8
5.0	5.0	0.05	1.0	3.9	3.9
8.0	5.0	0.05	1.0	3.7	3.7
10.0	5.0	0.05	1.0	3.8	3.8
5.0	1.0	0.05	1.0	1.2	1.1
5.0	3.0	0.05	1.0	2.9	2.8
5.0	5.0	0.05	1.0	3.8	4.0
5.0	8.0	0.05	1.0	4.9	5.23
5.0	10.0	0.05	1.0	5.9	5.8
5.0	5.0	0.01	1.0	2.6	2.4
5.0	5.0	0.03	1.0	3.4	3.5
5.0	5.0	0.05	1.0	3.8	4.0
5.0	5.0	0.08	1.0	4.2	4.2
5.0	5.0	0.1	1.0	4.4	4.6
5.0	5.0	0.05	0.5	4.5	4.4
5.0	5.0	0.05	0.8	4.2	4.2
5.0	5.0	0.05	1.0	3.8	4.0
5.0	5.0	0.05	3.0	2.9	3.0
5.0	5.0	0.05	5.0	2.3	2.3

Fig 3: First order plots for the oxidation of pyrazinamide by diperiodatocuprate(III) in aqueous alkaline medium. [diperiodatocuprate(III)]×10^5(mol dm^{-3}): 1) 1.0, 2) 3.0, 3) 5.0, 4) 8.0,and 5)10.0.



Effect of [pyrazinamide]: The effect of PZA on the rate of reaction was studied at constant concentration of alkali, DPC and periodate at constant ionic strength of 0.05 mol dm^{-3}. The substrate PZA was varied in

the range of 1.0×10^{-4} to 1.0×10^{-3} mol dm^{-3}. The k_{obs} values increased with increase in concentration of PZA. The apparent order with respect to [pyrazinamide] was found to be less than unity (Table 1).

Effect of [alkali]: The effect of increase in concentration of alkali on the reaction was studied at constant concentration of PZA, DPC and periodate at constant ionic strength of 0.1 $moldm^{-3}$ at 298 K. The rate of reaction increases with increase in alkali concentrations (Table 1), indicatingpositive fractional order dependence of rate on alkali concentration.

Effect of [periodate]: The effect of periodate concentration was studied by varying the concentration of periodate from 0.5×10^{-5} to 5.0×10^{-5} mol dm^{-3} keeping all other reactants concentration constant. It was found that added periodate had retarding result on the rate of reaction.

Effect of ionic strength (I) and dielectric constant of medium (D): The addition of KNO_3 at constant [DPC], [PZA], [OH^-] and [IO_4^-] was found that increasing ionic strength of the reaction medium showed no effect on the rate of reaction. The effect of change in dielectric constant of the medium on the rate of reaction was studied by varying percentage of t-butyl alcohol and water. The D values were calculated from the equation $D = D_wV_w + D_BV_B$, where D_w and D_B are dielectric constants of pure water and t-butyl alcohol, respectively, and V_w and V_B the volume fractions of components of water and t-butyl alcohol, respectively, in the total mixture. The decrease in dielectric constant of the reaction medium decreased the rate of reaction. The plot of log k_{obs}versus 1/D was linear with negative slope (Fig-4).

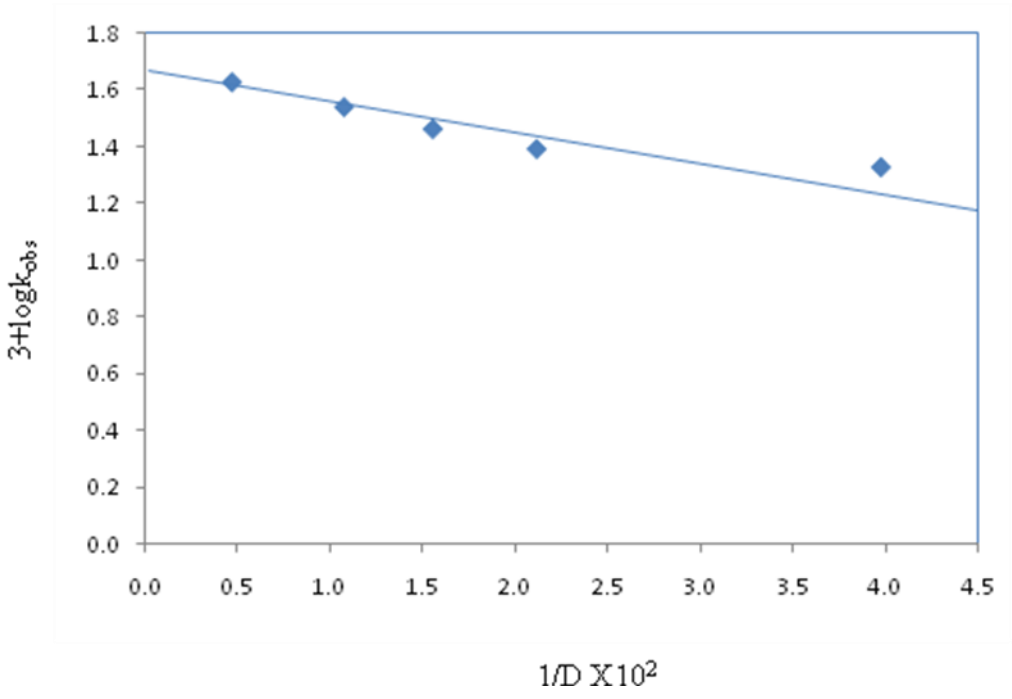


Fig 4: Effect of dielectric constant of the medium on oxidation of PZA by Cu(III) at 25°C

Effect of initially added products: The externally added product Cu(I) and pyrazinoic acid did not have any significant effect on the rate of reaction.

Polymerisation study: The intervention of free radicals in the reaction was examined as follows. The reaction mixture, to which a known quantity of acrylonitrile monomer added, was kept for 2 hours in an inert atmosphere which on dilution with methanol doesn't gave any precipitate. This indicates no intervention of free radicals in the reaction [14]. The blank experiments of either DPC or pyrazinoic acid alone with acrylonitrile did not induce any polymerisation under the same conditions as those induced for the reaction mixture. Initially, added acrylonitrile increased the rate of reaction indicating no free radical intervention, which is the case in earlier work [14, 16].

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Effect of temperature: The kinetics was studied at four different temperatures (20°C, 25°C, 30°C and 35°C) under varying concentrations of PZA, alkali and periodate keeping all other conditions constant. The rate constants (k) of the slow step of the reaction mechanism were obtained from the slopes and intercepts of the plots of $1/k_{obs}$ versus 1/[PZA]at four different temperatures and were used to calculate the activation parameters. The energy of activation corresponding to these constants was evaluated from the Arrhenius plot of log k versus 1/T and other activation parameters obtained are tabulated in Table2.b

Table 2: Thermodynamic activation parameters for the oxidation of pyrazinamide by DPC in aqueous alkaline medium with respect to the slow step of Scheme 1

a. Effect of temperature

Temperature (K)	$k\times10^2$ (s^{-1})
293	0.38
298	0.53
305	0.64
308	0.85

b. Activation parameters (Scheme 1)

Parameters	Value
E_a (kJ mol^{-1})	38.80
ΔH^*(kJ mol^{-1})	36.32
ΔS^* (JK^{-1} mol^{-1})	-161.04
ΔG^* (kJ mol^{-1})	84.31
log A	4.8

c. Effect of temperature to calculate K_1, K_2 and K_3 for the oxidation of pyrazinamide by DPC in alkaline medium

Temperature (K)	K_1 (dm^3 mol^{-1})	$K_2\times10^3$ (mol dm^{-3})	$K_3\times 10^{-3}$ (dm^3 mol^{-1})
293	0.42	0.73	2.30
298	0.64	0.58	3.04
305	0.89	0.42	3.64
308	1.23	0.33	4.47

d. Thermodynamic parameters using K_1, K_2 and K_3

Thermodynamic parameters	Values from K_1	Values from K_2	Values from K_3
ΔH (kJ mol^{-1})	53.36	-40.38	32.58
ΔS ($J K^{-1}$ mol^{-1})	178.12	-198.41	177.61
ΔG (kJ mol^{-1})	-0.453	17.83	-19.23

Thus, from the observed experimental results the rate law for the reaction is given as follows:

$$rate = k_{obs}[DPC]^{1.0}[PZA]^{0.63}[OH^-]^{0.32}[IO_4^-]^{-0.26}$$

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DISCUSSION

The water soluble copper (III) periodate complex is reported [26] to be $[Cu(HIO_6)_2 (OH)_2]^{7-}$. However, in an aqueous alkaline medium and at a high pH range employed in the study, periodate is unlikely to exist as HIO_6^{4-} (as present in the complex) which is evident from its involvement in the multiple equilibria [27] depending on the pH of the solution.

Periodic acid exists as H_5IO_6 in acid medium and as $H_3IO_6^{2-}$ near pH 7. Hence, under alkaline conditions as employed in this study, the main species are expected to be $H_3IO_6^{2-}$ and $H_2IO_6^{3-}$. Thus, at the pH employed in this study, the soluble copper (III) periodate complex might be $[Cu(OH)_2(H_3IO_6)_2]^{3-}$, a conclusion also supported by earlier work [28].

The reaction between the diperiodatocuprate (III) complex and pyrazinamide in alkaline medium has the stoichiometry 1:1 **(**PZA: DPC**)** with a first order dependence on [DPC] and an apparent order of less than unit order in [substrate], [alkali] and a negative fractional order dependence on [periodate]. No effect of added product was observed. Based on the experimental results, a mechanism is proposed for which all the observed orders in each constituent such as [oxidant], [reductant], $[OH^-]$ and $[IO4^-]$ may be well accommodated. In most report [28] on DPC oxidation, periodate had a retarding effect and OH^- had an increasing effect on the rate of reaction. However, in the present kinetic study, different kinetic results have been obtained. In this study OH^- had less than unit order and periodate retarded the rate of reaction with increase in alkalinity (Table 1) can be explained in terms of prevailing equilibrium of formation of $[Cu(OH)_2(H_3IO_6)]^{3-}$ from $[Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4-}$ hydrolysis as given in the following equation:

$$[Cu(H_3IO_6)_2]^- + [OH^-] \underset{}{\overset{K}{\rightleftharpoons}} [Cu(H_2IO_6)(H_3IO_6)]^{2-} + H_2O \qquad (2)$$

Also, decrease in the rate of reaction with increase in $[H_3IO_6^{2-}]$ (Table1) suggests that equilibrium of copper(III)periodate complex to form monoperiodatocuptrate(III) (MPC) species as given in equation (3) is established.

$$[Cu(H_2IO_6)(H_3IO_6)]^{2-} + 2\,H_2O \underset{}{\overset{K}{\rightleftharpoons}} [Cu(H_2IO_6)(H_2O)_2] + [H_3IO_6]^{2-} \qquad (3)$$

Such equilibria (2) and (3) have been well documented in literature [17]. It may be expected that a periodate complex such as monoperiodatocuptrate(III) (MPC) is more important in the reaction than the DPC. The inverse fractional order in $[H_3IO_6^{2-}]$ might also be due to this reason. Therefore, MPC might be the main reactive form of the oxidant.

Mechanism: Since Scheme 1 is in accordance with the generally well accepted principle of non-complementary oxidations taking place in sequence of one-electron steps, the reaction between the substrate and the oxidant would afford a radical intermediate. A free radical scavenging experiment exposed such a possibility. This type of radical intermediate has also been observed in earlier work [27]. A direct plot of k_{obs} versus [PZA] was drawn to characterize the parallel reaction if any along with interaction of oxidant and reductant. However, the plot of k_{obs} versus [PZA] was not linear. Thus, in Scheme 1, the parallel reaction and involvement of one molecule of pyrazinamide in the complex are excluded. The fractional order with respect to PZA presumably results from the complex formation between MPC and PZA prior to the slow step. Indeed it is to be noted that a plot of $1/k_{obs}$ versus 1/[PZA] was linear and shows an intercept in agreement with the complex formation which slowly decomposes to form the product. In the rate-determining stage, this monoperiodatocuprate(III) (MPC) combines with molecule of pyrazinamide to give a complex(I) which decomposes in a slow step to give pyrazinium cation and Cu(II) species. pyrazinium catiion combines with water in a fast step to give pyrazinium hydroxide, further it reacts with another mole of MPC in a fast step to give pyrazinioic acid and Cu(I) species. All these results may be interpreted in the form of scheme 1

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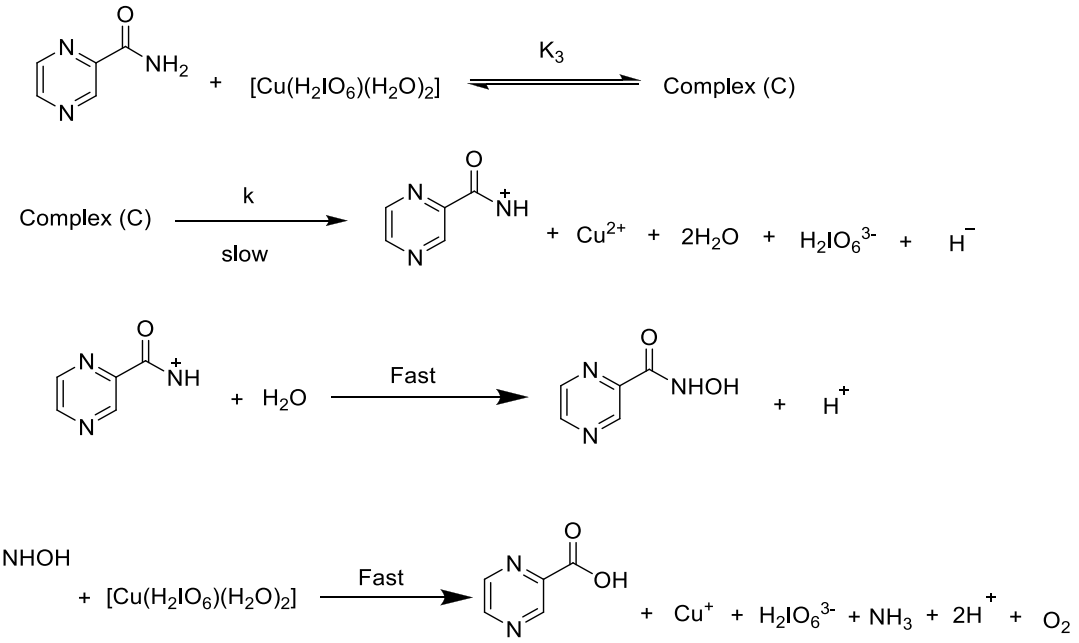
Scheme 1

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

$$[Cu(H_2IO_6)(H_3IO_6)]^{2-} + 2\,H_2O \overset{K_2}{\rightleftharpoons} [Cu(H_2IO_6)(H_2O)_2] + [H_3IO_6]^{2-}$$



Spectroscopic evidence for the complex formation between oxidant and substrate was obtained from UV-visible spectra of pyrazinamide (5 x 10^{-4}), DPC (5 x 10^{-5}), [OH^-] = 0.05mol dm^{-3} and a mixture of both. A hypsochromic shift of about 8 nm from 288 to 280 nm in the spectra of DPC was observed. Complex formation between DPC and

$$\text{Rate} = -\frac{d[DPC]}{dt} = \frac{kK_1K_2K_3[DPC][PZA][OH^-]}{[H_3IO_6^{2-}]+K_1[OH^-][H_3IO_6^{2-}]+K_1K_2[OH^-]+K_1K_2K_3[OH^-][PZA]} \quad (4)$$

pyrazinamide was proved by Michalis-Menten plot. Such a complex between an oxidant has been observed in other studies [29]. Scheme 1 leads to the following rate law:

$$k_{obs} = \frac{\text{Rate}}{[DPC]} = \frac{kK_1K_2K_3[PZA][OH^-]}{[H_3IO_6^{2-}]+K_1[OH^-][H_3IO_6^{2-}]+K_1K_2[OH^-]+K_1K_2K_3[PZA][OH^-]} \quad (5)$$

This explains all the observed kinetic orders of different species. In equation (6) the appearance of [PZA] term both in numerator and denominator explains the observed less than unit order in [pyrazinamide]. Similarly the appearance of [$H_3IO_6^{2-}$] and [OH^-] in the denominator agrees with the observed negative less than unit order [$H_3IO_6^{2-}$] and [OH^-], respectively. This explains all the observed kinetic orders of different species.

Rate law (5) can be rearranged into the following form which is suitable for verification:

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$$\frac{1}{k_{obs}} = \frac{[H_3IO_6^{2-}]}{kK_1K_2K_3[PZA]OH^-} + \frac{[H_3IO_6^{2-}]}{kK_2K_3[PZA]} + \frac{1}{kK_3[PZA]} + \frac{1}{k} \quad (6)$$

According to equation (6), other conditions being constant, plot of $1/k_{obs}$versus 1/[PZA] $1/k_{obs}$versus$1/[OH^-]$ and $1/k_{obs}$ versus$[H_3IO_6^{2-}]$ should be linear and are fond to be so (Fig. 5a, b and c). The slopes and intercepts of these plots lead to the value of K_1, K_2, K_3 and k as 0.64 $dm^3\ mol^{-1}$, 0.58×10^{-3} mol dm^{-3}, $3.04 \times 10^3\ dm^3\ mol^{-1}$ and $0.50 \times 10^{-2}\ s^{-1}$, respectively. The values of K_1 and $K_2$are in good agreement with those reported earlier in literature [30]. These constants were used to calculate the rate constant and compared with the experimental k_{obs}values and found to be in reasonable agreement with each other which fortifies Scheme 1.

Fig 5: Verification of rate law (3) for the oxidation of PZA by DPC

Fig 5a: $1/k_{obs}$versus 1/[PZA] at room temperatures(condition as in Table 1)

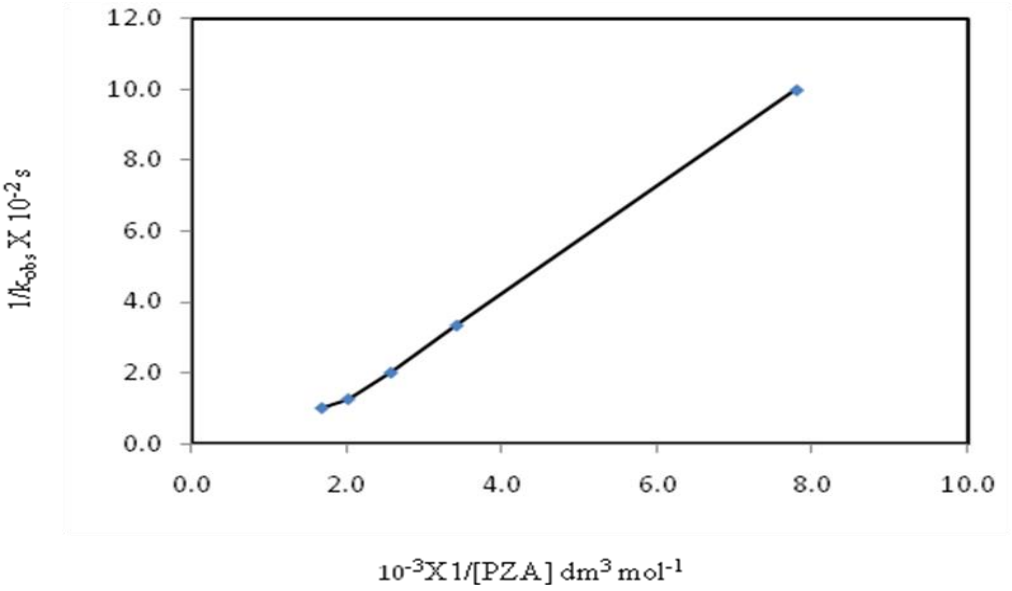

Fig 5b: $1/k_{obs}$versus $1/[OH^-]$ at room temperature (condition as in Table 1)

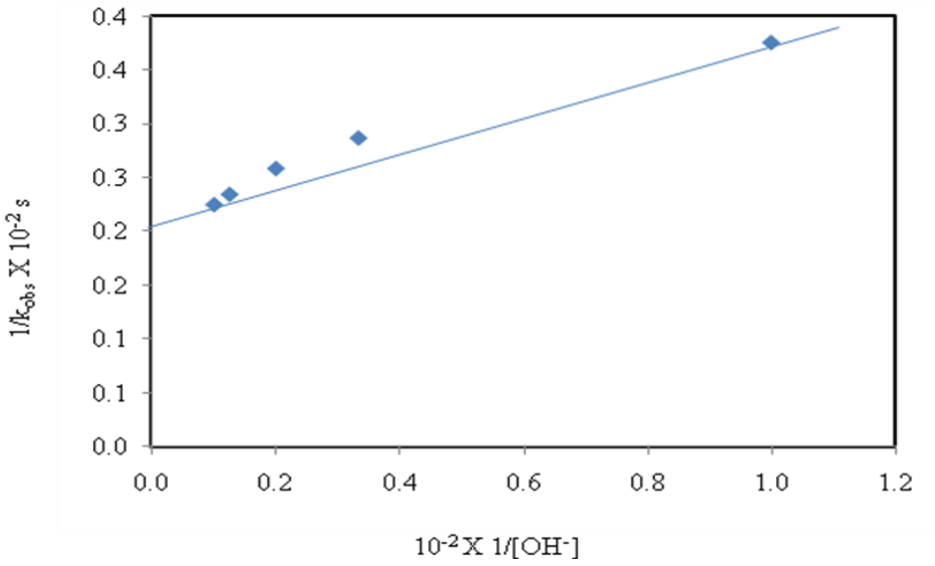

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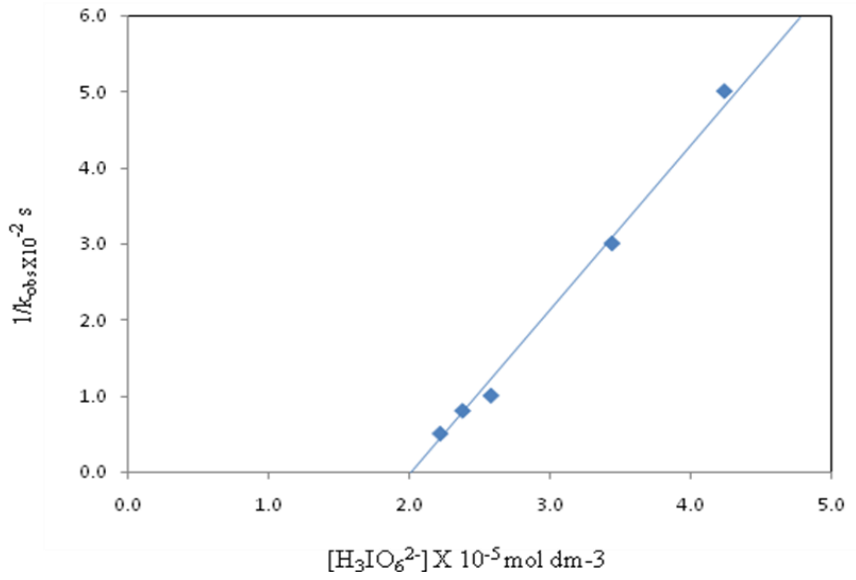
Fig 5c: $1/k_{obs}$versus $[H_3IO_6]^{2-}$ at room temperature (condition as in Table 1)



The negligible effect of ionic strength on the rate explains qualitatively the reaction between one negatively charged ion and neutral molecule, as seen in Scheme 1. The effect of solvent on the rate has been described in details in literature. Increasing the content of t-butyl alcohol in the reaction medium leads to an increased effect on the rate of reaction, which seems to be contrary to the expected reaction between neutral and anionic species in media of lower relative permittivity. However, an increase in the rate of reaction with decreasing relative permittivity may be due to stabilisation of the complex (C) at relative permittivity, which is less solvated than DPC at higher relative permittivity because of its larger size.

The thermodynamic parameters for the first, second and third equilibrium steps of Scheme 1 can be evaluated as follows: [PZA], $[OH^-]$ and $[IO_4]^-$ (Table 1) were varied at 4 different temperatures. The plot of $1/k_{obs}$versus 1/[PZA], $1/k_{obs}$versus $1/[OH^-]$ and $1/k_{obs}$versus$[H_3IO_6^{2-}]$ should be linear. From the slopes and intercepts, the values of K_1, K_2 and K_3were calculated at 4 different temperatures and these values are given in Table 2. The Vant Hoff plots were made for variation of K_1, K_2 and K_3 with temperatures (log K_1versus 1/T) (log K_2versus 1/T) and (log K_3versus 1/T) and 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 thermodynamic parameters of Scheme 1 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 before rate-determining step is fairly fast and involves low activation energy [31]. The values ΔH^* and ΔS^* were both favorable for electron transfer processes. The negative value of ΔS^* suggests that the intermediate complex is more ordered than the reactant [26]. The observed modest enthalpy of activation and a higher rate constant for the slow step indicates that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by earlier observations [32].

CONCLUSIONS

In conclusion, the oxidation of anti-tuberculosis drug pyrazinamide is studied using DPC in aqueous alkaline medium. Among the various species of DPC in alkaline medium, MPC i.e. $[Cu(H_2IO_6)(H_2O)_2]$ is considered as active species for the title reaction. The results indicated that the role of pH in the reaction medium is crucial. Rate constant of slow step and other equilibrium constants involved in the mechanism were evaluated and activation parameters with respect to slow step of reaction were computed. The overall mechanistic sequence described is consistent with product studies, mechanistic and kinetic studies.

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