Research Article

Kinetics and Mechanism of Oxidation of Amoxicillin by Copper (III) Periodate Complex in Alkaline Medium

Yuv Raj Sahu[1], Narendra K. Chaudhary[1], Parashuram Mishra[*]

[1]Bio-inorganic and Materials Chemistry Research Laboratory, Department of Chemistry, Mahendra Morang Adarsha Multiple Campus, Biratnagar, (Tribhuwan University), Nepal.

***Corresponding author's E-mail:** prmmishra@rediffmail.com

Received: 10-11-2019; **Revised:** 23-12-2019; **Accepted:** 02-01-2020.

ABSTRACT

Oxidation of amoxicillin was investigated by copper (III) periodate complex by UV-Visible spectrophotometer to study its kinetics and mechanism in alkaline medium at ionic strength of 0.1 mol dm-3 and 298 K. The oxidation of amoxicillin and DPC (III) was of 1:2 stoichiometry (AMX: DPC-III) in alkaline medium. Spot test, FT-IR and LC-MS spectral studies supported to identify the reaction products. It was of pseudo-first order reaction with respect to diperiodatocuprate (III) and fractional order with respect to amoxicillin as well as alkali. A negative fractional order was observed by periodate. The main active species for the proposed oxidation reaction was monoperiodatocuprate (MPC-III) as [Cu (H2IO6) (H2O)2]. Determination of activation parameters from different rate constants, spectral evidences and proposal of a plausible mechanism consistent with experimental results supported the reaction properly.

Keywords: Amoxicillin, Kinetics, Mechanism, Diperiodatocuprate, Rate constant.

INTRODUCTION

For the continuation of our ongoing research in modifications in structural design and in vitro antibiotic study of amoxicillin derived complexes[1], the current study is an attempt to familiarize kinetic and mechanistic aspects of degradation of this antibiotic by Cu(III) periodate complex in alkaline medium. The antibiotics are commonly employed in the prevention and treatment of various kinds of diseases in animals and plants. Recently, antibiotic resistance has broken the clinical rules of its applications in the disease treatment process. Unwise and misconduct use of antibiotics is the major cause of antibiotic resistance. Clinically administered antibiotics do not show 100 % activity; rather they come out from livings as unused residue and even release in the environment from the drug manufacturing industries and promote pollution. The industrial effluents coming out from the drug manufacturing industries accumulate in wastewater treatment plants and if release untreated, can pollute natural water reservoirs. This contamination of antibiotics in natural water can lead to the development of antibacterial resistance in indirect way. Hence antibiotic resistance represents a serious health problem and different advanced oxidation processes (AOPs) have to be applied in the degradation of such emergent chemical pollutants[2-5].

It is a semi-synthetic broad-spectrum β-lactam antibiotic that belongs to the class penicillin [6-9]. Amoxicillin is highly effective in the treatment of various infections or diseases caused by gram-positive and gram-negative bacteria and hence widely used due to its better absorption capacity, low toxicity, and low minimum inhibitory concentration (MIC) value against bacteria[10].It consists of a β-lactam heterocyclic ring fused to thiazolidine ring containing one sulphur atom.

Recent studies on the highest oxidation state transition metals have attracted many researchers in the field of kinetic chemistry to put the plausible mechanism of oxidation reactions. Transition metals can form stable complexes with polydentate ligands like diperiodatocuprate (DPC-III)[11], Diperiodatoargentate (DPA-III)[12], diperiodatonickelate (DPN-IV)[13]. These oxidants are used for the analysis of different organic oxidation reactions including amino acids[14]. Copper (III) complexes have occupied a major role in the oxidation chemistry due to their relative abundance and relevance in biological chemistry[15]. Diperiodatocuprate (III) was first synthesized by Malatesta [16] more than a half-century ago and thence followed by G. P. Panigrahi and A. C. Pathy[17].Many research works have been reported on the determination of the nature of this complex [18]. Synthesis, Stability and redox nature of Cu (III) periodate complex in a micro heterogeneous environment like the surfactant-micelle medium has been reported in recent literature[19].Diperiodatocuprate (III) has a flexible one electron-donating nature and biochemistry, stability as well as sensitivity of trivalent copper are already described in literatures [20]. It acts as an analytical reagent and hence used in many biological and analytical electron transfer reactions [21]. Since Cu (III) is generally involved as an active intermediate species appearing in many electron transfer reactions [22], it becomes quite essential to know the role of Cu (III) / Cu (II) couple, as described in earlier literature [23]. While copper (III) periodate involves multiple equilibrium between different copper (III) species and it would be fascinating to identify the most active species participated in the present reaction.

Several oxidation methods of amoxicillin in acid as well as in alkaline medium have been described in earlier literature like oxidation of amoxicillin by chloramine-T in acid medium [24], oxidative degradation of amoxicillin by thermally activated persulphate [25], oxidation of amoxicillin by hexacyanoferrate (III) in aqueous alkaline medium[26], Co (III) catalyzed oxidation of amoxicillin by DPC (III) in alkaline medium [27]. Now, this is our new attempt to study the kinetics of amoxicillin by DPC (III) without any catalyst to have a comparative study in terms of kinetics of amoxicillin. So, we have undertaken the present research work to investigate the kinetics and mechanism of oxidation of amoxicillin in the alkaline medium in the absence of catalyst and hence to arrive at plausible mechanisms including determination of activation properties.

MATERIALS AND METHODS

Reagents and Chemicals

All the chemicals used were of Analytical Reagent (AR) grade and double distilled water was used throughout the work. Melting point 196 °C (literature m. pt. 194.2 °C) was measured to check the purity of amoxicillin (Sigma Aldrich). The stock solution of amoxicillin (0.01 mol dm^{-3}) was prepared by dissolving 0.3654 g of recrystallized amoxicillin in 100 ml double distilled water. Potassium periodate solution was prepared by dissolving 0.023 g (0.01mol dm^{-3}) of KIO_4 (Sigma Aldrich) in 100 ml double distilled hot water and the solution was used only after 24 hours. The concentration of the potassium periodate solution was determined by the iodometric method at neutral pH maintained by using phosphate buffer[28].

Instrumentation

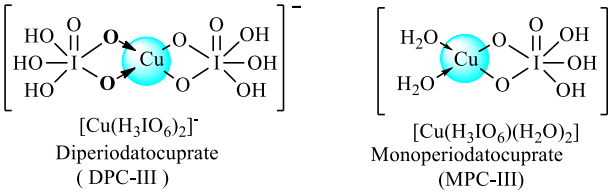
The pH of the solution was measured by ELICO LI 613 pH meter. The electronic absorption spectra were recorded on Varian CARY 5000 UV-VIS spectrophotometer in the range of 200-1000 nm. The infra-red spectra of the complexes were recorded on Thermo Nicolet, Avatar 370 FT-IR spectrometer in the range of 4000-400 cm^{-1} that was run as KBr disc. The mass spectrum of the products was recorded on the UPLC-TQD Mass spectrometer in positive mode in the range of 0 – 1000 m/z.

Synthesis of Reagent

The Copper (III) diperiodate (DPC-III) was prepared [29-30] by mixing copper sulphate (3.54 g), potassium periodate (6.80 g), potassium persulphate (2.20 g) and potassium hydroxide (9.0 g) in a 250 ml double distilled water in a round bottomed flask. The whole mixture was frequently shaken thoroughly and heated on a hot plate for about 2 hours. During this period, the mixture turned to intense red and the flask was heated further for 20 minutes to remove potassium persulphate completely from the mixture by decomposing persulphate. After completion of the reaction, the mixture was cooled and filtered through sintered glass crucible G-4 and the dark red-brown solution was diluted to 250 ml by adding double-distilled water. The aqueous solution of DPC (III) was standardized by iodometric titration ($Na_2S_2O_3$, starch, KI and KH_2PO_4) by thiocyanate method and its exact concentration was ascertained. The existence of DPC (III) was verified by UV-visible spectrophotometer that showed an absorption band with a maximum peak at 415 nm. However, the accurate concentration of DPC (III) was calculated by UV-visible spectrophotometer. DPC (III) has a square planar geometry with dsp^2 hybridization and diamagnetic nature. Similarly, KOH (BDH) and the other required solutions were prepared and stored safely.

Synthesis of Complex

10 ml of amoxicillin solution (0.132 mol dm^{-3}) was taken in a 100 ml RB flask. To this 10 ml DPC (III) (0.528 mol dm^{-3}) was mixed in 1:2 stoichiometric ratio along with 1.0 ml of each KNO_3 (Himedia), KIO_4 and 2.0 ml of KOH solution of fixed molarities and stirred on metal hot plate for 24 hours followed by re-stirring during re-fluxing with condensation for 24 hours. The products were purified and recrystallized in ethanol till the whole solvent evaporated leaving behind crystals only. The appearance of peaks in UV-Visible spectrophotometer showed the formation of the complex. The possible structures of DPC and MPC are given below.



$[Cu(H_3IO_6)_2]^-$
Diperiodatocuprate
(DPC-III)

$[Cu(H_3IO_6)(H_2O)_2]$
Monoperiodatocuprate
(MPC-III)

DPC (III) and MPC (III)

Kinetic Measurements

Since the reaction is very fast, its absorbance was taken quite rapidly along with the progress of the reaction by following pseudo-first-order state when the active mass of AMX was greater than that of DPC at 20°C, 25°C, 30°C and 35°C ± 0.1°C unless specified. The reaction was initiated by mixing required quantities of previously thermo stated solutions of amoxicillin into DPC (III) which already contained a fixed concentration of KIO_4 along with KNO_3 and KOH. Data were obtained from UV-Visible spectrophotometer at pH (9.2-10) and 415 nm wavelength due to DPC by monitoring the decrease in absorbance at the molar extinction coefficient (€) of **6242 ± 50** dm^3 $mol^{-1}cm^{-1}$. The UV visible spectrophotometer was run up to 85% reaction wherein initially added products and dielectric constant didn't exhibit any interference in the reaction.

There was no effect of ubiquitous contamination of initially added carbonate in the reaction. Fresh solutions were nevertheless used to carry out each kinetic run. Regression analysis of experimental data to obtain regression coefficient (r) and standard deviation (s) of points from the regression line was completed with the help of Origin 9.6 (2017) software. Plots of log(abs) versus time gave a straight line and hence rate constants (k_{obs}) were calculated from slopes. The k_{obs} values agreed within ± 5%

error and were the average of at least three independent kinetic runs. A constant concentration of periodate was mixed into reaction mixture all the time. Finally, the total concentration of KIO_4 and KOH were determined by assuming the amount present in DPC and added additionally. To check the effect of periodate, ionic strength, dissolved oxygen, etc, kinetics was also conducted into the N_2 atmosphere wherein no significant changes were observed. Added carbonate and periodate dielectric constant etc., didn't show any effect.

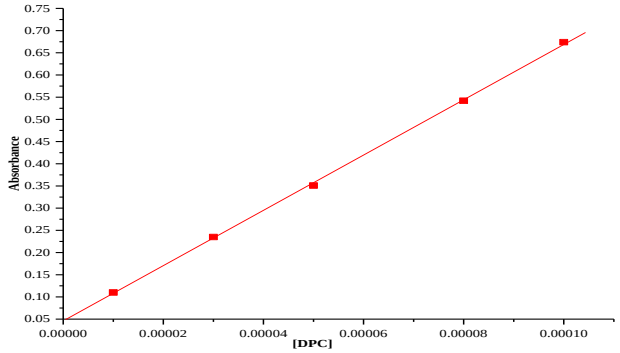


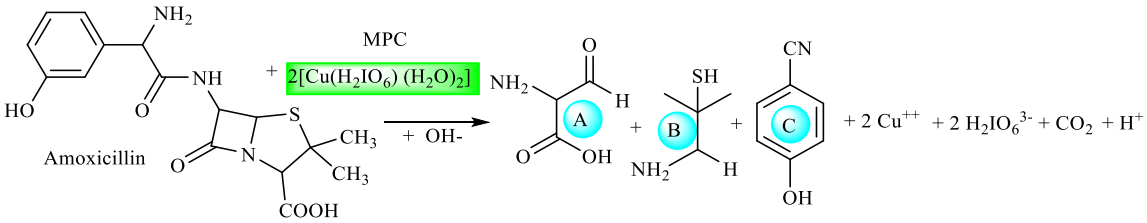
Figure 1: Plot of absorbance vs. [DPC] at 25 °C

The application of Beer-Lambert's law was verified from Figure 1 and found that negligible interference was entertained in the reaction. The maximum wavelength of DPC (III) was noticed at 415 nm.

RESULTS AND DISCUSSION

Stoichiometry and Product Analysis

Several sets of reaction mixtures with varying ratio of DPC to amoxicillin in presence of constant amounts of KOH and KNO_3 were kept for 2.5 hrs in a closed vessel under N_2 atmosphere and the remaining concentration of DPC was analyzed to confirm the accurate stoichiometry by Job's method which was confirmed to be 1:2 for AMX: DPC (III). When amoxicillin reacts with DPC in alkaline medium, 4-hydroxybenzonitrile, 2-amino-2-formylacetic acid and 1-amino-2-methylpropane-2-thiol were formed as the main product which was recrystallized from ethanol, separated by Column Chromatography over neutral alumina by using 80% benzene and 20% chloroform as eluent. Side product CO_2 was qualitatively detected by bubbling N_2 gas through the acidified reaction mixture and passing the gas liberated through the tube filled with lime water. The reaction between Amoxicillin and Diperiodatocuprate (III) in alkaline medium is given as Scheme 1.



Where, A = 2-amino-2-formylacetic acid; B = 1-amino-2-methylpropane-2-thiol; C = 4-hydroxybenzonitrile

Scheme 1: Reaction showing the formation of complex

Similar oxidation products were already isolated in the uncatalyzed oxidation of amoxicillin by hexacyanoferrate (III) in the alkaline medium as reported earlier [8]. The complex showed a molecular ion peak at 686 m/z. The oxidation product 4-hydroxybenzonitrile was identified by the FT-IR spectrum that showed an absorption peak at 2048.13 cm^{-1} due to CN stretch, because of the presence of the hydroxyl group which was evident through the broad peak at 3440.55 cm^{-1}. The products 4-hydroxybenzonitrile, 2-amino-2-formylacetic acid, and 1-amino-2methylpropane-2-thiol showed a molecular ion peak at 119,102 and 106 m/z in LC-MS. Both LC-MS and FT-IR spectrum are presented in Figure **S 1 and S 2**.

Reaction Orders

The orders of reaction were determined from the slope of log k_{abs} versus log (concentration) from different time plots as given in Figure 6 and Table-1 by varying concentrations of amoxicillin, KIO_4, and KOH while keeping the other parameters constant except the concentration of DPC (III).

Effect of [DPC (III)]

The DPC concentrate was varied in the range of 1.0 x 10^{-5} to 1.0 x 10^{-4} mol dm^{-3}. The linearity and almost parallelism plots of log absorbance versus time up to 85% completion of the reaction by keeping other concentrations remaining constant indicated a reaction order of unity in DPC (III). Table 1 and Figure **2** are in the support of pseudo first-order reaction with respect to DPC (III).

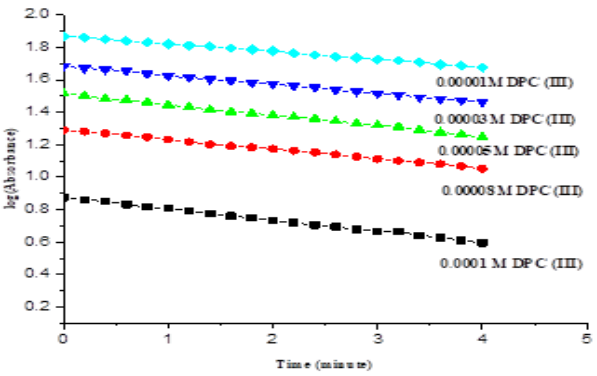


Figure 2: Order Plot of log(abs) vs. time for the oxidation of AMX by DPC (III)

Effect of [AMX]

The effect of [AMX] was studied within a range of 1 x 10^{-4} to 1 x 10^{-3}mol dm^{-3}. The rate constants (k_{obs}), increased with increase in [AMX] and order with respect to amoxicillin was found to be 0.69 (r ≥0.9894, s ≤ 0.0071) which was also confirmed from the plot of (4+ log k_{obs}) vs 5+ log [AMX], **Figure S 3 and Table 1.**

Effect of [Alkali]

The effect of alkali was studied by varying [OH^-] in the range of 0.04 to 0.2 mol dm^{-3} DPC, AMX, as well as ionic strength. Rate constant (k_{obs}) increased with increase in [alkali] and order of reaction with respect to alkali was found to be 0.53 (r ≥0.987, s ≤ 0.00217), confirmed by the linear plot of (4 + log k_{obs}) vs. 4 + log [KOH]), Figure **S 4** and Table 1.

Effect of [Periodate]

The effect of [KIO_4] was observed by varying the concentration range from 1.0 x 10^{-5} to 1.0 x 10^{-4} mol dm^{-3} remaining other active masses and conditions were constant. It was observed that rate constants decreased with an increase in [IO_4^-] and the order of reaction was -0.732 as computed in Table 1.

Table 1: Effect of variation of [DPC]*, [AMX] and [KOH] on the oxidation of Amoxicillin by Diperiodatocuprate (III) in aqueous alkaline medium at 298 K and I = 0.10 / mol dm^{-3}

[DPC] x 10^5	[AMX]x 10^4	[OH^-] x10^1	[IO_4^-] x10^5	K_{obs} x10^4 (s^{-1})	Order
1.0	5.0	0.8	1.0	3.95	
3.0	5.0	0.8	1.0	3.99	
5.0	5.0	0.8	1.0	**3.87**	**1.0**
8.0	5.0	0.8	1.0	3.82	
10.0	5.0	0.8	1.0	3.84	
5.0	**1.0**	0.8	1.0	1.5	
5.0	**3.0**	0.8	1.0	2.12	
5.0	5.0	**0.2**	1.0	1.87	
5.0	**5.0**	0.8	1.0	**3.87**	**0.69**
5.0	**8.0**	0.8	1.0	5.43	
5.0	**10.0**	0.8	1.0	7.56	
5.0	5.0	**0.4**	1.0	2.66	
5.0	5.0	**0.6**	1.0	2.99	
5.0	5.0	**0.8**	1.0	**3.87**	**0.53**
5.0	5.0	**1.0**	1.0	4.52	
5.0	5.0	0.8	**1.0**	**3.87**	**- 0.73**
5.0	5.0	0.8	**3.0**	2.99	
5.0	5.0	0.8	**5.0**	1.98	
5.0	5.0	0.8	**8.0**	1.00	
5.0	5.0	0.8	**10.0**	0.69	

*Concentrations are expressed in mol dm^{-3}.

Effect of Ionic Strength (I) and Dielectric Constant (D)

Ionic strength is applied to know the participation of specific species in the reaction like ion-dipole, ion-ion, dipole-dipole with the same or opposite charge, etc. The effect of ionic strength was studied by varying the concentration of KNO_3 in the range of (0.1 - 0.2 M by keeping the concentration of DPC (III), AMX and KOH constant and we found that increasing ionic strength did not have any significant effect on the rate of reaction. The dielectric constant of the medium (D) can be studied by varying t-butyl alcohol at a constant concentration of DPC (III), AMX, KOH and KNO_3 by using the equation $D = D_1V_1 + D_2V_2$ where D_1 and D_2 are the dielectric constant of water and t-butyl alcohol and V_1 and V_2 are volume fractions of those respectively. There was no effect of dielectric constant on the rate of the catalyzed reaction.

Effect of Initially Added Products

Initially added product ($CuSO_4$ (II)) didn't show any significant effect on the rate of reaction.

Polymerization Study

A known quantity of acrylonitrile[31] monomer was initially added to the reaction mixture and allowed to remain in the inert atmosphere for 3.0 hours. The mixture gave no precipitate on dilution with methanol indicating the absence of free radicals.

Effect of Temperature

The effect of temperature on the rate of oxidation reaction was studied at four different temperatures under the constant concentration of AMX, KOH, and DPC (III) keeping other conditions constant. The rate constants increased with the rise in temperature. Slope obtained from the plot of (log k_{obs} vs. 1/T) helped to calculate the activation

parameter and energy of activation and thence computed in Table 2 and Figure **S 5**.

Table 2: Effect of temperature and activation parameters by rate constants (k_{obs})

Temp (K)	(1/T) 10^3	K_{obs} x 10^4	4 + log k_{obs}
293	3.41	1.86	0.27
298	3.35	3.87	0.59
303	3.30	4.10	0.61
308	3.24	5.76	0.76

Activation Parameters	Values
Ea (K j mol^{-1})	51.43
$\Delta H^{\neq}$ (K j mol^{-1})	49 ± 2
$\Delta S^{\neq}$ (J K^{-1} mol^{-})	-149± 2
$\Delta G^{\neq}$ (k $Jmol^{-1}$)	94 ± 2
LogA	5 ± 0.3

Since DPC (III) is chelating as well as the oxidizing agent, oxidation of different β-lactam antibiotics has been carried out in an alkaline medium. The activity of DPC is a function of pH and is capable of subtle control.DPC (III) is water-soluble oxidizing reagent that exists as $[Cu(HIO_6)_2(OH)_2]^{7-}$ as well as $[HIO_6]^{4-}$ under higher pH condition. It has been evident that it can also exist as $[Cu(H_3IO_6)_2]^{-}$ or $[Cu(H_2IO_6)(OH)_2]^{2-}$ or $[Cu(H_2IO_6)(H_2O)_2]$ or $[Cu(H_3IO_6)(H_2O)_2]$ in aqueous alkaline medium. Periodic acid exists as H_5IO_6 in acid medium. The main species most active for the title work is $[Cu(H_2IO_6)(H_2O)_2]$ as reported in earlier literature. At higher alkali concentration, periodate ion tends to dimerize.

$$H_5IO_6 \rightleftharpoons H_4IO_6^{-} + H^{+}, \quad K_1 = 5.1 \times 10^{-4}$$

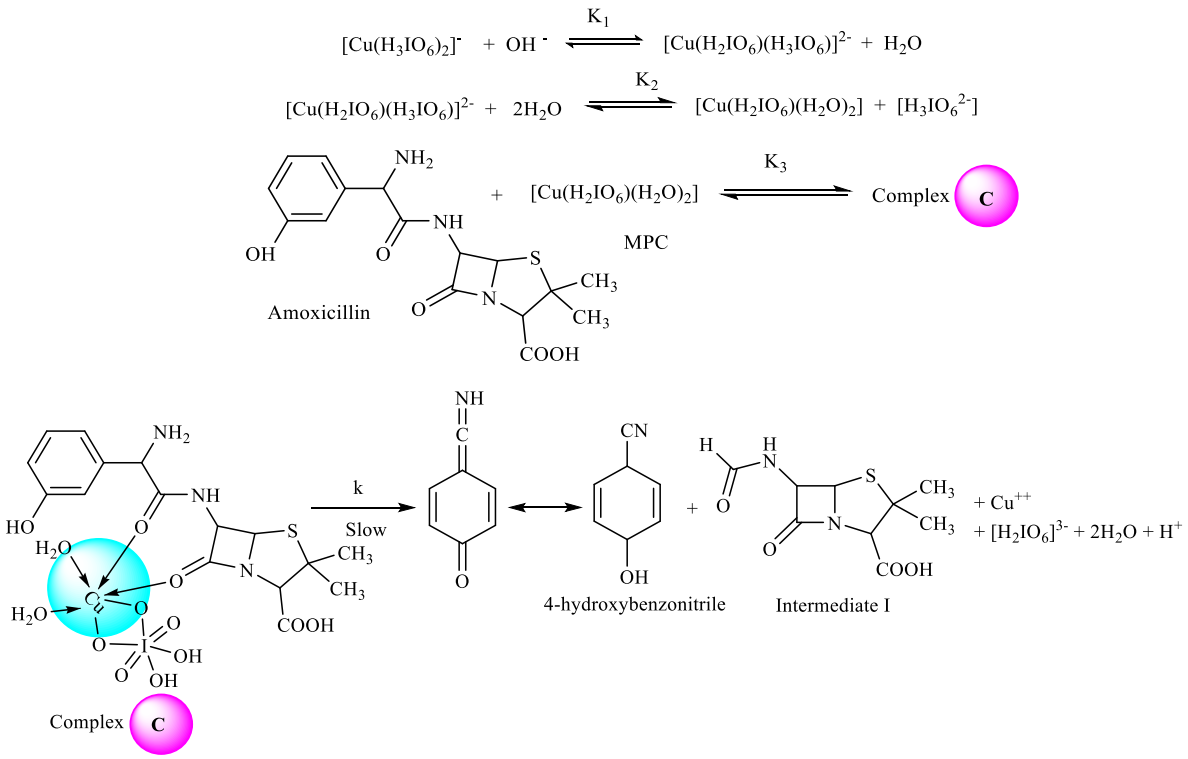
$$H_4IO_6^{-} \rightleftharpoons H_3IO_6^{2-} + H^{+}, \quad K_2 = 4.9 \times 10^{-9}$$

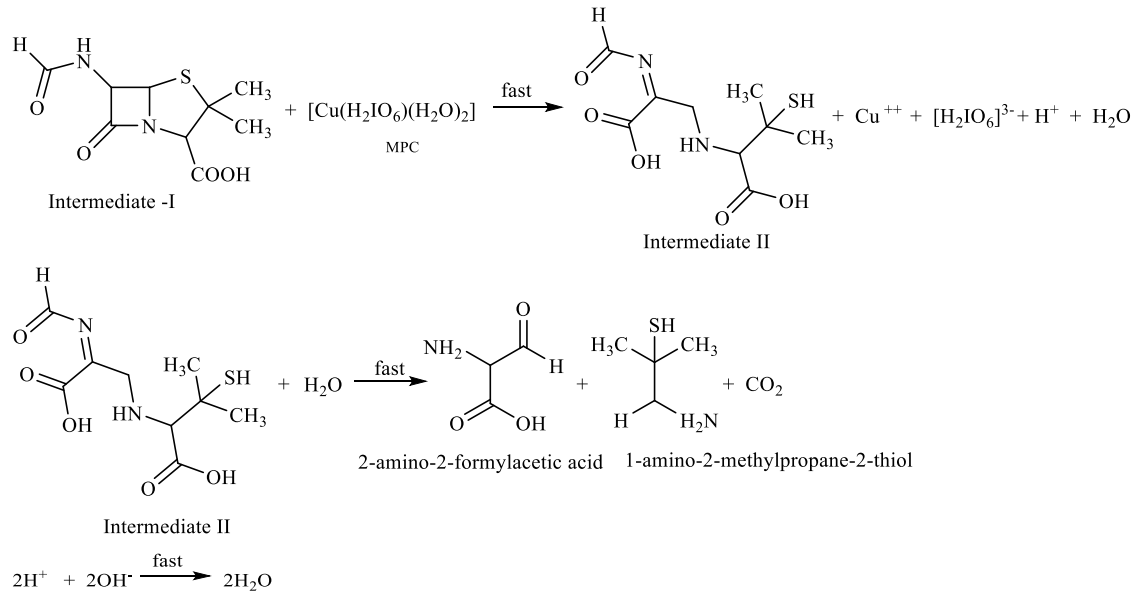
$$H_3IO_6^{2-} \rightleftharpoons H_2IO_6^{3-} + H^{+}, \quad K_3 = 2.5 \times 10^{-12}$$

Probable Mechanism of Reaction

The oxidation reaction between MPC and amoxicillin showed 1:2 stoichiometry and exhibited pseudo-first order reaction with respect to DPC(III), fractional order with respect to amoxicillin and alkali but negative fractional-order periodate. Based on this experimental evidence, a suitable mechanism is proposed along with the proper involvement of all species. In the first step, DPC(III) reacts with the hydroxide ion to form a deprotonated form of DPC which in presence of water yields MPC(III) along with free periodate species. Hence fractional with respect to amoxicillin presumably results due to the formation of the complex by the interaction between amoxicillin and MPC species. This complex interacts with one mole of MPC in a slow step to give 4-hydroxybenzonitrile, an intermediate I along with regeneration of free periodate ion and Cu^{++} ion. In the next step, the intermediate I reacts with one mole of MPC to form intermediate II which undergoes hydrolysis to yield the other final products ie; 2-amino-2-formylacetic acid and 1-amino-2-methylpropane-2-thiol as explained in Scheme 2.

Spectroscopic evidence for the complex formation between reagent DPC(III) and substrate (AMX) was obtained from UV –visible spectra by resisting (5.0×10^{-4} M) AMX, (0.12 M) KOH and a mixture of all. A bathochromic shift was obtained. The Michaelis – Menten plot is in great support for complex formation, Figure **S 5**.





Scheme 2: Detailed Scheme for uncatalyzed oxidation of AMX by DPC(III)

Scheme 2 leads to the rate law equation (6) as -

$$\text{rate} = -\frac{d[DPC]}{dt} = k[C] \qquad [5]$$

$$k_{obs} = \frac{kK_1K_2K_3[DPC][AMX][OH^-]}{[H_3IO_6{}^{2-}] + K_1[OH^-][H_3IO_6{}^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][AMX]} \qquad [6]$$

This equation (6) describes all kinetic orders observed for different species. The rate law equation (6) can be rearranged into equation (7) that suits for verification.

$$\frac{1}{k_{obs}} = \frac{[H_3IO_6{}^{2-}]}{kK_1K_2K_3[AMX][OH^-]} + \frac{[H_3IO_6{}^{2-}]}{kK_2K_3[AMX]} + \frac{1}{kK_3[AMX]} + \frac{1}{k} \qquad [7]$$

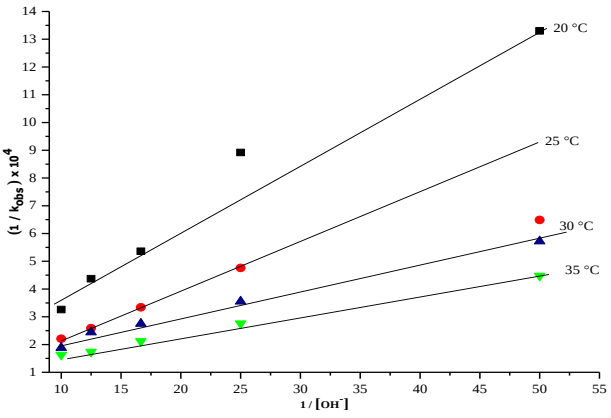


Figure 3: Plot of [1/ k_{obs} vs.1/[KOH]

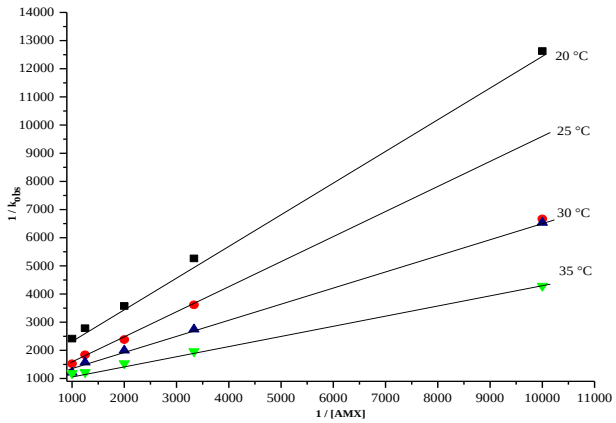


Figure 4: Plot of [1/k_{obs} vs.1/[AMX]

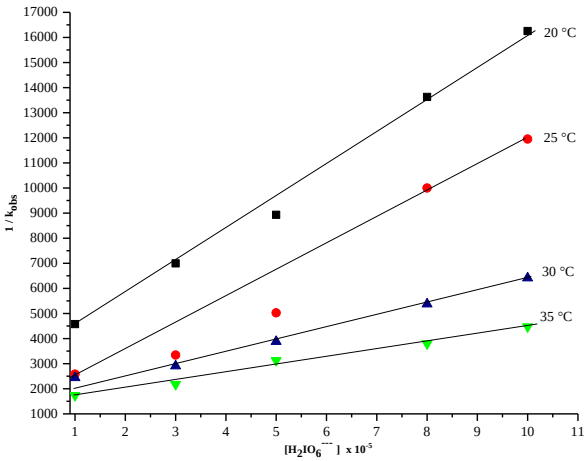


Figure 5: Plot of [1/k_{obs} vs.$[H_2IO_6]^{3-}$

Figure (3-5) represent verification plots for oxidation of AMX by DPC(III) in alkaline medium. According to equation (7), remaining other conditions being constant, the plots of [1 / k_{obs} vs.1 / [KOH] ($r \geq 0.995, \leq s\ 0.00356$), [1 / k_{obs} vs. 1/[AMX] ($r \geq 0.9791, \leq s\ 0.0045$) and [1/ k_{obs} vs. $[H_2IO_6]^{3-}$ (presented in Figure **3, 4** and **5**) should be linear and are found to be so as in Figure 3, 4 and 5. Similarly, activation parameters and thermodynamic parameters for un-catalyzed oxidation of AMX by DPC (III) in aqueous alkaline medium with respect to **slow step** rate constant (k) of Scheme I is presented in Table 3 and Figure **S 6**.

Table 3

Temp (K)	(1/T) 10^3	k x 10^4	4 + log k
293	3.41	7.35	0.87
298	3.35	8.63	0.94
303	3.30	9.75	0.96
308	3.24	12.2	1.09
Activation Parameters		**Values**	
Ea (k J mol^{-1})		24.12	
$\Delta H^{\neq}$ (k J mol^{-1})		21.63 ± 2	
$\Delta S^{\neq}$ (J K^{-1} mol^{-})		-137 ±1	
$\Delta G^{\neq}$ (k J mol^{-1})		62 ± 2	
LogA		1.14 ± 0.4	

Scheme 1 clarifies the participation of neutral species in the reaction due to invariable ionic strength and dielectric constant. The modest values of both enthalpy and entropy of activation, within the range of electron pairing and unpairing process for the loss of degree of freedom and rigid transition state, are favourable for electron transfer reaction. The higher negative value of $\Delta S^{\neq}$ suggests that the intermediate complex is probably highly ordered than the reacting species. The above results, evidences and lower rate constant for slow steps indicate that the oxidation presumably occurs via an inner-sphere mechanism. The reducing property of the substrate is, probably, reduced in the absence of catalyst and the path of the uncatalyzed reaction is extended by increasing the activation energy.

CONCLUSION

The oxidation of Amoxicillin by DPC (III) was studied experimentally in an alkaline medium. (MPC-III) [Cu (H_2IO_6) $(H_2O)_2$] was considered to be the active species for the present work. Activation parameters with respect to rate constant (k_{obs}) at different temperatures were computed. Overall sequences described here are inconsistent with all experimental evidences including product, spectral analysis, mechanistic and kinetics studies.

Supplementary Information: Some of essential Figures and spectrum are arranged into SI file, being attached along with this Manuscript **(SI).**

Acknowledgements: The first author (Y. R. Sahu) is highly acknowledged to Purwanchal Campus, Dharan, Institute of Engineering (IOE), T.U., Nepal for financial support, Prof. Dr. S. T. Nandibewoor and Prof. Dr. S.A. Chimatadar, Karnatak University, Dharwad , India for invaluable guidelines and suggestions and SAIF –IIT, Bombay, STIC-SAIF, Cochin and CDRI-CSIR, Lucknow, India for technical support in providing spectrum results.

REFERENCES

1. Chaudhary NK and Mishra P., Spectral investigation and in vitro antibacterial evaluation of Ni^{II} and Cu^{II} complexes of Schiff base derived from Amoxicillin and α-formalthiophene (αft), Journal of Chemistry, Vol. 2015. Doi.10.1155/2015/136285.
2. Fernando S S, Vanessa V d S, Catiusa K R, Hainzenreder L, Arenzon A & Liliana Al F , Comparison of different advanced oxidation processes for the removal of amoxicillin in aqueous solution, Environmental Technology, Taylor & Francis, Vol. 39, no. 5, 2018, pp.549-557. Doi: 10.1080/09593330.2017.1306116 PMID: 28287908
3. Elmolla E S and Chaudhuri M, Degradation of the antibiotics amoxicillin, ampicillin and cloxacillin in aqueous solution by the photo-Fenton process, Journal of Hazardous Materials, Vol. 172, no. (2-3), 2009, 1476-1481. PMID: 19717236, Doi: 10.1016/j.jhazmat.2009.08.015
4. Filiz Ay, and Fikret Kargi, "Advanced oxidation of amoxicillin by Fenton's reagent treatment," Journal of Hazardous Materials, Vol. 179, no.(1-3), 2010, 622-627. Doi: 10.1016/j.jhazmat.2010.03.048
5. Singh R and Mishra P, Synthesis, spectroscopic, XRPD and computational study of transition metal-organic framework (TMOFs) derived from (6 R)-6-(alpha-phenyl-D-glycylamino) penicillanic acid, Russian Journal of Inorganic Chemistry, Vol. 54, 2009, 1301-1309. Doi: 10.1134/S0036023609080208
6. Kaur S P, Rao R and Nanda S, Amoxicillin, a broad spectrum antibiotic, International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 3, 3, 2011 (ISSN- 0975-1491).
7. Mukherjee G and Ghosh T, Metal ion interaction with penicillin part-vii: mixed ligands complexes formation of Co, Ni, Cu and Zn with ampicillin and nucleus bases, Journal of Inorganic and Biochemistry, Vol. 59, 1995, 827.
8. Alekseev V G, and Samuilova I S, Co-Gly beta lactam antibiotics complex formation in system, Russian Journal of Inorganic Chemistry, Vol. 53, 2008, 327.
9. Sutherland R, Croydon E A and Rolinson G N, Amoxycillin: new semi-synthetic penicillin. Br Med J., 3, 1972, 13 – 6.

   http://www.ncbi.nlm.nih.gov/pubmed/4402672.
10. Antibacterial and Common Infections: Stewardship, Effectiveness, Safety and Clinical Pearls, October 2016. Link: RxFiles.Ca©Oct 2016.
11. Hiremath D C, Kiran T S and Nandibewoor S T, Oxidation of vanillin by diperiodatocuprate (III) in aqueous alkaline medium: A kinetic and mechanistic study by stopped flow technique, International Journal of Chemical Kinetics, Vol. 39, 2007, no. 4. Doi.org/10.1002/kin.20233
12. Hosmani R R and Nandibewoor S T, Mechanistic study of Ruthenium (III) catalyzed oxidation of L-Lysine by Diperiodatoargentate (III) in aqueous alkaline medium, Journal of chemical sciences, 2009, 121, 275-281. www.ias.ac.in/article/fulltext/jcsc/121/03/0275-0281.
13. Shettar R S and Nandibewoor S T, Kinetic, mechanistic and spectral investigations of Ruthenium (III)-catalyzed oxidation of 4-hydroxycoumarin by alkaline diperiodatonickelate (IV) (stopped flow technique), Journal of Molecular Catalysis A: Chemical, Vol. 234, no. 1-2, 2005, pp. 137-143,. Doi.org/10.1016/j.molcata.2005.02.026
14. Reddy K B, Sethuram B and Rao T N , Kinetics of oxidative determination and decarboxylation of some amino acids by diperiodatocuprate (III) in alkaline medium, Indian Journal of Chemistry, Vol. 20A, 1981, pp. 395.
15. Solomon E I, Chen P, Metz M, Lee S K and Palmer A E, Oxygen binding, activation and reduction to water by copper proteins, Angew Chemistry, International Edition, Vol. 40, 2001, no.24, , pp. 4570 -4590. Doi.org/10.1002/1521-3773 (20011217)

16. Malatesta L , Salts of Trivalent Copper and Silver (II), Gazz. Chimica Ital. Vol. 71, 1941, pp. 580-584.

17. Panigrahi G, P. and A. C. Pathy A. C., Kinetics and mechanism of oxidation of potassium thiocyanate by potassium bis(tellurate) cuprate(III), Indian Journal of Chemistry, Vol.25A, 1986, pp. 354-357.

18. Nadimpali S, Padmvasthy J and Yusuff K K M, Determination of the nature of the diperiodatocuprate (III) species in aqueous alkaline medium through a kinetic and mechanistic study on the oxidation of iodide ion, Transition Metal Chemistry, Vol. 26, no. 3 , 2001, pp. 315-321,. Doi.org/10.1023/A:1007116932047

19. Chowdhury B, Mondal M H, Barman M K and Saha B, A study on the synthesis of alkaline Copper (III)-periodate (DPC) complex with an overview of its redox behavior in aqueous micellar media, Research on Chemical Intermediates (Springer), 2018. Doi.org/10.1007/S11164-018-3643-2.

20. Xie H Y, Wang Z R, and Fu Z F, Highly sensitive trivalent copper chelate-luminol chemiluminescence system for capillary electrophoresis chiral separation and determination of ofloxacin enantiomers in urine samples, Journal of pharmaceutical analysis, Science Direct, 4(6), 2014, 412-416. doi.org/10.1016/j.jpha.2014.05.004.

21. Byadagi K S, Nandibewoor S T and Chimatadar S A, Catalytic activity of ruthenium (III) on the oxidation of an Anticholinergic drug-atropine sulphate monohydrate by copper (III) periodate complex in aqueous alkaline medium-Decarboxylation and free radical mechanism, Acta Chimica Slovenica, 60(3), 2013, 617- 627.

22. Sethuram B, Some aspects of electron transfer reaction involving organic molecules, Allied Publishers Pvt. Ltd, New Delhi, 2003, 71-78.

23. Lister M W, The stability of some complexes of trivalent copper, Canadian Journal of Chemistry, Vol. 31, no. 7, 1953, 638-652. doi.org/10.1139/v53-087.

24. Veena M S , Prashanth M K, Kumar K Y, Muralidhara H B and Nayaka Y A, Kinetics and mechanistic study of oxidation of amoxicillin by Chloramine-T in acid medium, Journal of the Chilean Chemical Society, 60(3), 2015. Doi.org/10.4067/S0717-97072015000300019.

25. Zhao J, Sun Y, Wu F, Shi M and Liu X, Oxidative degradation of amoxicillin in aqueous solution by thermally activated persulphate, Journal of Chemistry, Article ID 2505823, Vol. 2019. Doi: org/10.1155/2019/2505823.

26. Durgannavar A K, Patgar M B and Chimatadar S A, Oxidation of amoxicillin by hexacyanoferrate (III) in aqueous alkaline medium- a kinetic and mechanistic Approach, Indian Journal of Chemistry, Vol. 54A, 2015, pp. 1085-1091.

27. Sahu Y R, Mishra P, Chimatadar S A and Nandibewoor S T, A kinetic and mechanistic approach for Co (III) catalyzed oxidation of amoxicillin by copper (III) periodate complexes in alkaline medium, World Journal of Pharmacy and Pharmaceutical Sciences. Vol. 8, no. 9, 2019, pp.1034-1051. Doi: 10.20959/wjpps20199-14676.

28. Jeffery G H, Basset J., Mendham R C and Denney R C, Vogel's Textbook of Qualitative Chemical Analysis, 5th Edition, ELBS, Longman, Essex U.K.455, 1996.

29. Panigrahi G P and Misro P K, Kinetics and mechanism of oxidation of osmium (VIII) catalyzed oxidation of unsaturated acids by sodium periodate, Indian Journal of Chemistry, 15A, 1977, 1066 -1069.

30. Jaiswal P K and Yadava K L, Determination of sugars and organic acids with periodato complex of Cu (III), Indian Journal of Chemistry, Vol. 11, 1973, pp. 837-838.

31. Jagadeesh R V and Puttaswamy J, Chemical transformation in synthetic organic chemistry, Journal of Physical and Organic Chemistry, Vol. 21, no. 10, 2008, pp. 844-858.

Source of Support: Nil, **Conflict of Interest:** None.

APPENDIX

(C) Derivation of rate law

From Scheme 1 $\text{Rate} = -\frac{d[DPC]}{dt} = k[\text{Complex}] = k[C]$ **[A-1]**

From the law of mass action, the third equilibrium constant can be given by $K_3 = \frac{[C]}{[Cu(H_2IO_6)(H_2O)_2[AMX]}$

After rearrangement, we get, $[C] = K_3[Cu(H_2IO_6)(H_2O)_2[AMX]$ **[A-2]**

Substituting the value of C from eq. [A-2], we get, $\text{Rate} = -\frac{d[DPC]}{dt} = K_1K_3[Cu(H_2IO_6)(H_2O)_2[AMX]$ **[A-3]**

The second equilibrium constant can be given by $K_2 = \frac{[Cu(H_2IO_6)(H_2O)_2[H_3IO_6{}^{2-}]}{[Cu(H_2IO_6)(H_3IO_6]^{2-}}$

This can be rearranged into $[Cu(H_2IO_6)(H_2O)_2] = \frac{K_2\,[Cu(H_2IO_6)(H_3IO_6]^{2-}}{[H_3IO_6]^{2-}}$ **[A-4]**

The first equilibrium constant can be given by $K_1 = \frac{[Cu(H_2IO_6)(H_3IO_6]^{2-}}{[Cu(H_3IO_6)_2]^{-}[OH^-]}$

This can be rearranged into $[Cu(H_2IO_6)(H_3IO_6]^{2-} = K_1\,[Cu(H_3IO_6)_2]^{-}[OH^-$ **[A-5]**

Substituting eq. [A-4] to [A-5] in eq. [A-3], we get

$$\text{Rate} = -\frac{d[DPC]}{dt} = \frac{kK_1K_2K_3[AMX]_f[DPC]_f[OH^-]_f}{[H_3IO_6)_2]^-} \quad \textbf{[A-6]}$$

The total concentration of [DPC] can be given as

$$[DPC]_T = [DPC]_f + [Cu(H_2IO_6)(H_3IO_6]^{2-} + [Cu(H_2IO_6)(H_2O)_2] + [C] \quad \textbf{[A-7]}$$

Where T and f denote total and free concentrations $= [DPC]_f + K_1[Cu(H_2IO_6)_2]^-[OH^-] + \frac{K_1K_2[Cu(H_2IO_6)_2]^-[OH^-]}{[H_3IO_6{}^{2-}]} + \frac{K_1K_2K_3[Cu(H_3IO_6)_2]^-[OH^-][AMX]}{[H_3IO_6]^{2-}}$

$$[DPC]_T = [DPC]_f + K_1[DPC]_f[OH^-] + \frac{K_1K_2[DPC]_f[OH^-]}{[H_3IO_6{}^{2-}]} + \frac{K_1K_2K_3[DPC]_f[OH^-][AMX]}{[H_3IO_6{}^{2-}]}$$

$$[DPC]_f = \frac{[DPC]_T[H_3IO_6{}^{2-}]}{[H_3IO_6{}^{2-}] + K_1[OH^-][H_3IO_6{}^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][AMX]} \quad \textbf{[A-8]}$$

The total concentration of [OH^-] can be given by

$$[OH^-]_T = [OH^-]_f + [Cu(H_2IO_6)(H_3IO_6]^{2-} + [Cu(H_2IO_6)(H_2O)_2] + [C]$$

$$[OH^-]_T = [OH^-]_f + K_1[DPC][OH^-]_f + \frac{K_1K_2[DPC][OH^-]_f}{[H_3IO_6]^{2-}} + \frac{K_1K_2K_3[DPC][OH^-]_f[AMX]}{[H_3IO_6]^{2-}} \qquad [OH^-]_T = [OH^-]_f\{1 + K_1[DPC] + \frac{K_1K_2[DPC]}{[H_3IO_6]^{2-}} + \frac{K_1K_2K_3[DPC][AMX]}{[H_3IO_6]^{2-}}\}$$

In view of low concentrations of DPC and $H_3IO_6^{2-}$ used, last three terms inside bracket can be neglected in comparison with unity.

$$[OH^-]_T = [OH^-]_f \quad \textbf{[A-9]}$$

Similarly, in case of low concentrations of DPC and $H_3IO_6^{2-}$ used $[AMX]_T = [AMX]_f$ **[A-10]**

Putting these values of $[DPC]_f$ from eq^n. [A-8], $[OH^-]_f$ from eq^n. [A-9] and $[AMX]_f$ from eq^n. [A-10] in eq^n. [A-6] after omitting subscripts T and f ,we get, Rate = $-\frac{d[DPC]}{dt} = \frac{kK_1K_2K_3[AMX][DPC][OH^-]}{[H_3IO_6{}^{2-}] + K_1[OH^-][H_3IO_6{}^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][AMX]}$

Or, $$\frac{1}{k_{obs}} = \frac{[H_3IO_6{}^{2-}]}{kK_1K_2K_3[AMX][OH^-]} + \frac{[H_3IO_6{}^{2-}}{k\,K_2K_3[AMX]} + \frac{1}{kK_3[AMX]} + \frac{1}{k} \quad \textbf{[A-11]}$$