

## Research Article

# Kinetics and Mechanism of Oxidation of Carbenicillin by Copper (III) Periodate Complex in Aqueous Alkaline Medium

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Kinetics and mechanism of oxidation of carbenicillin by diperiodatocuprate [DPC-III] in aqueous alkaline medium were studied spectrophotometrically at 298 K and an ionic strength of  $0.10 \text{ mol-dm}^{-3}$ . The reaction between DPC (III) and carbenicillin in the alkaline medium showed (CRBC : DPC-III) 1 : 4 stoichiometry. The reaction products were identified by the CHNS test, FT-IR, and LC-MS spectral reports. The reaction was of pseudo-first order with respect to DPC (III) and fractional order with respect to carbenicillin as well as alkali but retarding effect with respect to periodate. Monoperiodatocuprate (MPC-III) was found to be the main active species in the alkaline medium in the form of  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$ . Activation and thermodynamic parameters with respect to uncatalyzed rate constants ( $k_u$ ) and slow step rate constant ( $k$ ) as well as equilibrium constants were determined. The plausible mechanism consistent with experimental results was proposed and discussed in detail.

## 1. Introduction

Penicillanic acid derivatives (PADs) are composed of beta lactam ring and thiazolidine ring as the integral part which have growing demands in daily life, medicines, health tonics, etc. [1]. Carbenicillin, one of the PADs, is the 4<sup>th</sup> generations' semisynthetic [2] analogue of naturally occurring benzylpenicillin with carboxyl and benzyl group penicillin which is synthesized from the 6-aminopenicillanic acid nucleus, discovered at Beecham as "Pyopen." It is active against *Pseudomonas aeruginosa* in vitro [3] and hence used successfully in the treatment of pseudomonal infections [4–6] due to sensitivities of many strains of *P. aeruginosa* to carbenicillin within a reasonably narrow range of concentrations which can be safely obtained in vivo [7]. It is an acid liable antibiotic that inhibits bacterial cell wall synthesis and is commonly used in place of ampicillin to reduce the production of satellite colonies. It is more stable than ampicillin at low pH, which usually arises during bacterial fermentation.

It is soluble in water (solubility 451 mg/L). Its molecular formula, molar mass, and IUPAC name are  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_6\text{S}$ ,  $378.401 \text{ g mol}^{-1}$ , and (2S, 5R, 6R)-6-[[carboxy (phenyl) acetyl] amino]-3,3-dimethyl-7-oxo-thia-1-azabicyclo [3.2.0] heptanes-2-carboxylic acid or 6-(a-carboxy-phenyl acetamido) penicillanic acid, respectively. Its structure is given in Figure 1.

Ampicillin, amoxicillin, dicloxacillin, carbenicillin, tetracycline, etc. belong to PADs family that are widely applied in hospitals, households, sewages [8], veterinary drugs, cosmetics [9], and fragrances or nutraceutical products [10] against different diseases to improve quality of personal health for the whole ecosystem. Characteristics, distribution, and source analysis of the main persistent toxic substances in karst groundwater have been reported [11]. These PADs do not degrade and mix into aquatic environment directly/indirectly, accumulate in natural water reservoirs, and contaminate drinking water, discharge or wastes, surface water, and ground water as well as air and soil. These effects enhance bacterial or viral resistance [12, 13] against different

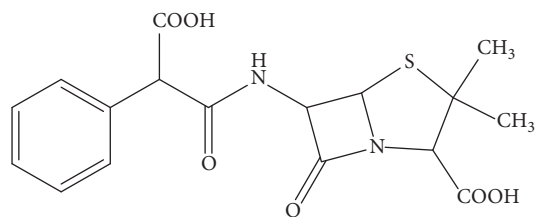


FIGURE 1: Carbenicillin.

PADs, and hence, it is a great challenge before researchers and drug manufacturers [14] to modify their composition along with updated specific function with a view to get fast relief from the illness. Personal care products (PCPs) [15–17] and antibiotic resistance represent a serious health problem, and different advanced oxidation processes (AOPs) have to be applied to degrade such emergent chemical pollutants [18–20] because most of the intermediates, formed transiently, can be definitely mineralized into  $\text{CO}_2$ , water, and mineral species due to possible oxidation-degradation reactions. The proposed work will disclose a novel application in the field of pharmaceuticals as well as kinetics for degradation of drugs and will be adequately applied in wastewater treatment at the sites polluted by PADs antibacterial agents.

Transition metals can form stable complexes with polydentate ligands such as diperiodatocuprate (DPC-III) [21, 22], diperiodatoargentate (DPA-III) [23], diperiodatonickelate (DPN-IV) [24], ditelluratocuprate (DTC-II) [25, 26], and hexacyanoferrate (HCF-III) [27]. At first, Malatesta had synthesized DPC (III) more than a half century ago, and Panigrahi and Pathy [28] followed that method. Determination of the nature of the diperiodatocuprate (III) species in the aqueous alkaline medium through a kinetic and mechanistic study on the oxidation of iodide ion has been reported in the previous literature [29]. DPC (III) has a square planar geometry with  $\text{dsp}^2$  hybridization and diamagnetic nature. Cu (III) appears as an active intermediate species in many electron transfer reactions [30] and supports to know the role of Cu (III)/Cu (II) couple, as described in earlier literature [31]. Review of literature regarding carbenicillin is quite scanty. Only limited previous literature studies could have been included herewith. Some studies are voltammetric oxidation of carbenicillin and its electroanalytical applications at gold electrode [32], in vitro effects of carbenicillin combined with Gentamicin or polymyxin B against *Pseudomonas aeruginosa* [33], interactions of carbenicillin and Ticarcillin with gentamicin [34], interaction between aminoglycoside antibiotics and carbenicillin or ticarcillin [35], effect of time and concentration upon interaction between gentamicin, tobramycin, netilmicin, or amikacin and carbenicillin or ticarcillin [36], in vivo inactivation of gentamicin by carbenicillin and ticarcillin [37], administration of carbenicillin and ticarcillin-pharmaceutical aspects [38], Carbenicillin and ticarcillin [39], synergy between Ticarcillin and Tobramycin against *Pseudomonas aeruginosa* and enterobacteriaceae in vitro and in vivo [40], Carbenicillin administration in patients with severe renal failure [41], etc.

The present research work aimed to investigate the kinetics and mechanism of oxidation of carbenicillin without any catalyst and thence to arrive at plausible mechanism including determination of order of reaction, activation, and thermodynamic properties with respect to uncatalyzed rate constant ( $k_u$ ), slow step rate constant ( $k$ ), and equilibrium constants ( $K_1$ ,  $K_2$ , and  $K_3$ ) at different temperatures.

## 2. Materials and Methods

**2.1. Reagents and Chemicals.** Chemicals used were of Analytical Reagent (AR) grade and double distilled water was used throughout the work. The stock solution of carbenicillin (Sigma Aldrich ( $0.01 \text{ mol}\cdot\text{dm}^{-3}$ )) was prepared by dissolving 0.378 g of recrystallized carbenicillin in 100 ml double distilled water. Potassium periodate solution was prepared by dissolving 0.023 g ( $0.01 \text{ mol}\cdot\text{dm}^{-3}$ ) of  $\text{KIO}_4$  (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 [42].

**2.2. 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 infrared spectra of the complexes were recorded on Thermo Nicolet, Avatar 370 FT-IR spectrometer, in the range of  $4000\text{--}400 \text{ cm}^{-1}$  that was run as KBr disc. The mass spectrum of the products was recorded on the UPLC-TQD mass spectrometer in the positive mode in the range of 0–1000 m/z.

**2.3. Synthesis of Reagents.** (DPC-III) was prepared [43, 44] 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 RB flask. After collecting all chemicals, the whole mixture was frequently shaken thoroughly and heated on a hot plate for about 2 hours. As the mixture turned to intense red, the flask was heated again 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 ( $\text{Na}_2\text{S}_2\text{O}_3$ , starch, KI, and  $\text{KH}_2\text{PO}_4$ ) by the thiocyanate method, and its exact concentration was ascertained. The existence of DPC (III) was verified by using a UV-visible spectrophotometer that showed an absorption band with a maximum peak at 415 nm. However, the accurate concentration of DPC was calculated by using a UV-visible spectrophotometer. Similarly, KOH (BDH) and the other required solutions were prepared and stored safely. A study on the synthesis of alkaline copper (III) periodate (DPC) complex with an overview of its

redox behavior in aqueous micellar media including stability and redox nature of Cu (III) periodate complex in a microheterogeneous environment has been reported in the recent literature [45].

**2.4. Synthesis of Complex.** 10 ml of carbenicillin solution ( $0.132 \text{ mol}\cdot\text{dm}^{-3}$ ) was taken in a 100 ml RB flask. To this, 10 ml DPC (III) ( $0.528 \text{ mol}\cdot\text{dm}^{-3}$ ) was mixed in 1:4 stoichiometric ratio along with 1.0 ml of  $\text{KNO}_3$  (HiMedia) and  $\text{KIO}_4$  (Sigma Aldrich) and 2.0 ml of KOH (HiMedia) solution of fixed molarities and stirred on a hot plate followed by restirring during refluxing with condensation for 24 hours. Then, the mixture was cooled naturally for 3 days and filtered by using a Whatman No. 1 filter paper. 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 (III) and MPC (III) are given in Figure 2.

**2.5. 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 CRBC was greater than that of DPC (III) at  $20^\circ\text{C}$ ,  $25^\circ\text{C}$ ,  $30^\circ\text{C}$ , and  $35^\circ\text{C} \pm 0.1^\circ\text{C}$  unless specified. The reaction was initiated by mixing required quantities of previously thermostated solutions of CRBC into DPC (III) that already contained a definite concentration of  $\text{KIO}_4$  along with  $\text{KNO}_3$  and KOH. Data were obtained from a UV-visible spectrophotometer at pH (9.0–9.2) and 415 nm wavelength due to DPC (III) by monitoring the decrease in absorbance at the molar extinction coefficient ( $\epsilon$ ) of  $6144 \pm 50 \text{ dm}^3\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ . The UV-visible spectrophotometer was run up to 85% reaction wherein initially added products and dielectric constant did not 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  $\log(\text{abs})$  versus time gave a straight line and hence uncatalyzed rate constants ( $k_u$ ) were calculated from slopes. The  $k_u$  values agreed within  $\pm 5\%$  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 concentrations of  $\text{KIO}_4$  and KOH were determined by assuming the amount present in DPC (III) and added additionally. No significant changes could be observed by conducting kinetics into nitrogen gas atmosphere with a view to check the effect of periodate, ionic strength, dissolved oxygen, added carbonate, etc. The application of Beer-Lambert's law was verified from plot of absorbance vs. [DPC-III], presented in Figure 3 ( $r \geq 0.999$ ,  $s \leq 0.0003$ ), and it was found that negligible interference was entertained in the

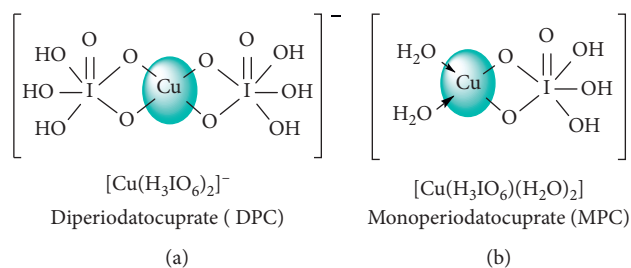


FIGURE 2: Structure of (a) DPC (III) and (b) MPC (III).

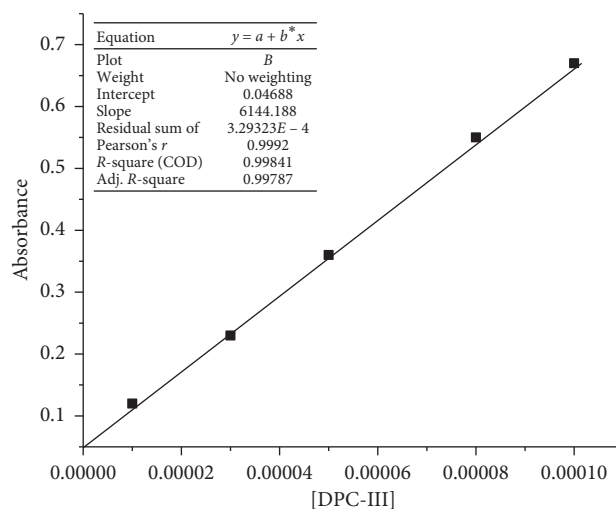


FIGURE 3: Plot of absorbance vs. [DPC] at  $25^\circ\text{C}$ .

reaction. The maximum wavelength of DPC (III) was noticed at 415 nm.

### 3. Results and Discussion

**3.1. Stoichiometry and Product Analysis.** Several sets of reaction mixtures with varying ratio of DPC (III) to CRBC in presence of constant amounts of KOH and  $\text{KNO}_3$  were kept for 2.5 hours in a closed vessel under  $\text{N}_2$  atmosphere and the remaining concentration of DPC (III) was analyzed to confirm the accurate stoichiometry by Job's method which was confirmed to be 1:4 for CRBC:DPC. When CRBC reacts with DPC (III) in alkaline medium, 2-phenylmalonic acid ( $\text{C}_9\text{H}_8\text{O}_4$ ) and 2-(amino (carboxy) methyl)-5, 5-dimethyl-4, 5-dihydrothiazole-4-carboxylic acid-1-oxide ( $\text{C}_8\text{H}_{12}\text{N}_2\text{O}_4\text{S}$ ) were formed as the main products which were recrystallized from ethanol, separated by Column Chromatography over neutral alumina by using 80% benzene and 20% chloroform as eluent. Side product  $\text{CO}_2$  was qualitatively detected by bubbling  $\text{N}_2$  gas through the acidified reaction mixture and passing the gas liberated through the tube filled with lime water.

The reaction between carbenicillin and diperiodatocuprate (III) in alkaline medium is given as



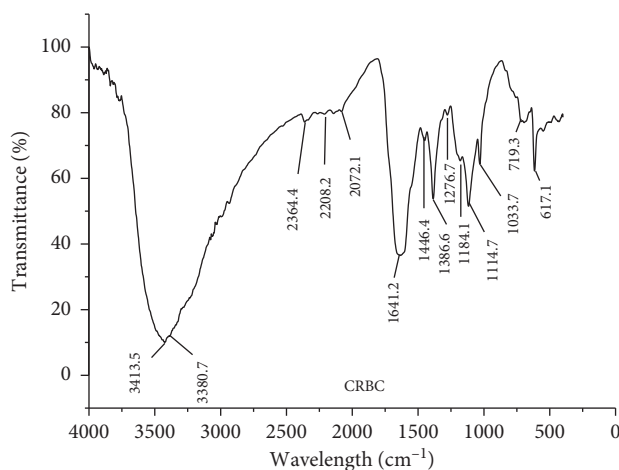


FIGURE 4: FT-IR spectrum for oxidation of CRBC by DPC (III) in alkaline medium.

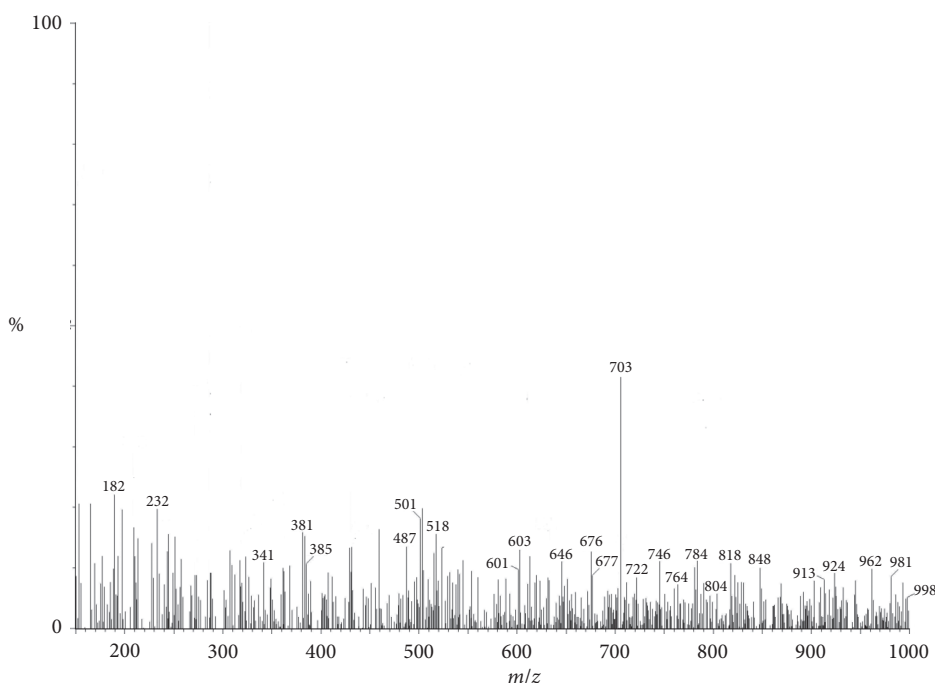


FIGURE 5: LC-MS spectrum of complex and products.

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.

**3.10. Effect of Temperature.** The effect of temperature on the rate of oxidation reaction was studied at four different temperatures under the constant concentration of CRBC, KOH, and DPC (III) keeping other conditions constant. Rate constants increased with the rise in temperature. The energy of activation and other activation parameters were calculated by the least square method from the plot of  $\log k_u$  versus  $1/T$  and thence computed in Table 2 and Figure 10.

The energy of activation and other activation parameters were calculated by using least square method from the plot

of  $(4 + \log k)$  versus  $1/T$  and thence computed in Table 3 and Figure 11.

Since DPC (III) is chelating as well as the oxidizing agent, oxidation of different  $\beta$ -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  $[\text{Cu}(\text{HIO}_6)_2(\text{OH})_2]^{7-}$  as well as  $[\text{HIO}_6]^{4-}$  under higher pH condition. It has been evident that it can also exist as  $[\text{Cu}(\text{H}_3\text{IO}_6)_2]^-$  or  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{OH})_2]^{2-}$  or  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$  or  $[\text{Cu}(\text{H}_3\text{IO}_6)(\text{H}_2\text{O})_2]$  in aqueous alkaline medium. Periodic acid exists as  $\text{H}_5\text{IO}_6$  in acid medium. The main species most active for the title work is  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$  as reported in earlier literature. At higher alkali concentration, periodate ion tends to dimerize.

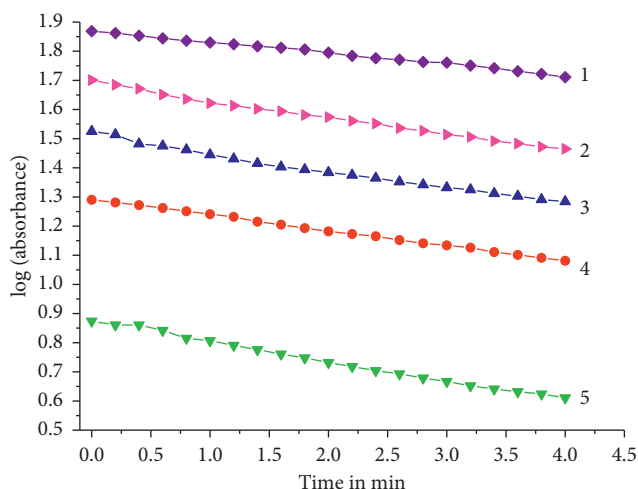
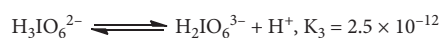
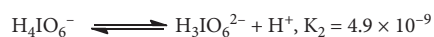
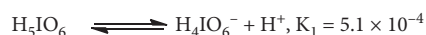


FIGURE 6: Order plot of log (abs) vs. time for the oxidation of CRBC by DPC (III).

TABLE 1: Effect of variation of [DPC]<sup>\*</sup>, [CRBC], and [KOH] on the oxidation of carbenicillin by diperiodatocuprate (III) in aqueous alkaline medium at 298 K and  $I=0.10/\text{mol dm}^{-3}$ .

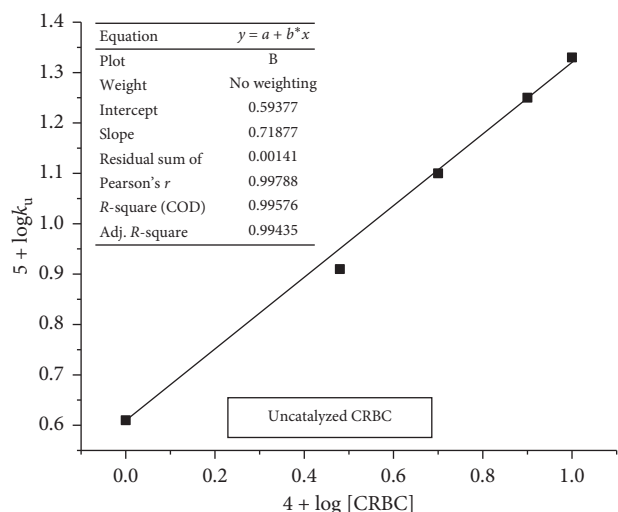
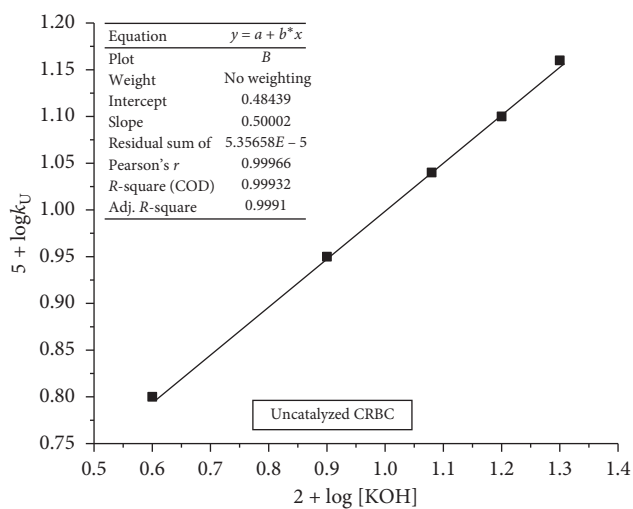
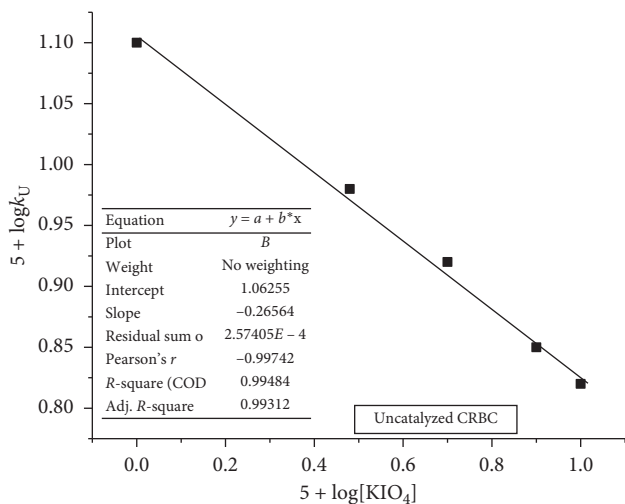
[DPC] $\times 10^5$	[CRBC] $\times 10^4$	[OH <sup>-</sup> ] $\times 10^2$	[IO <sub>4</sub> <sup>-</sup> ] $\times 10^5$	$k_u \times 10^{-4}$ (s <sup>-1</sup> )	Order
<b>1.0</b>	5.0	0.8	1.0	1.22	
<b>3.0</b>	5.0	0.8	1.0	1.24	
<b>5.0</b>	5.0	0.8	1.0	<b>1.25</b>	
<b>8.0</b>	5.0	0.8	1.0	1.21	
<b>10.0</b>	5.0	0.8	1.0	1.22	
5.0	<b>1.0</b>	0.8	1.0	0.41	
5.0	<b>3.0</b>	0.8	1.0	0.81	
5.0	<b>5.0</b>	0.8	1.0	<b>1.25</b>	<b>0.718</b>
5.0	<b>8.0</b>	0.8	1.0	1.80	
5.0	<b>10.0</b>	0.8	1.0	2.34	
5.0	5.0	<b>0.2</b>	1.0	0.62	
5.0	5.0	<b>0.4</b>	1.0	0.82	
5.0	5.0	<b>0.6</b>	1.0	1.01	
5.0	5.0	<b>0.8</b>	1.0	<b>1.25</b>	<b>0.50</b>
5.0	5.0	<b>1.0</b>	1.0	1.61	
5.0	5.0	0.8	<b>1.0</b>	<b>1.25</b>	
5.0	5.0	0.8	<b>3.0</b>	1.05	
5.0	5.0	0.8	<b>5.0</b>	0.85	
5.0	5.0	0.8	<b>8.0</b>	0.72	<b>-0.265</b>
5.0	5.0	0.8	<b>10.0</b>	0.68	

\*Concentrations are expressed in  $\text{mol dm}^{-3}$ . Bold values in [DPC]  $\times 10^5$ , [CRBC]  $\times 10^4$ , [OH<sup>-</sup>]  $\times 10^2$ , and [IO<sub>4</sub><sup>-</sup>]  $\times 10^5$  signify the variable concentration of each solution for each kinetic run, whereas other values signify constant concentration of solutions used in experiments. Bold values in  $k_u \times 10^{-4}$  (s<sup>-1</sup>) signify the average rate constant calculated after conducting the experiment for the corresponding bold value (concentration) of that solution only. Bold values in order signify the exact order of reaction as obtained from the plot.

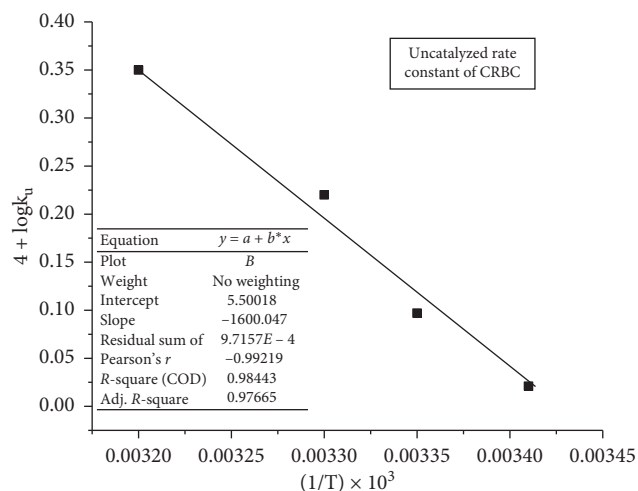


**3.11. Probable Mechanism of Reaction.** The oxidation reaction between MPC (III) and carbenicillin showed 1:2 stoichiometry and exhibited pseudo-first-order reaction with respect to DPC (III), fractional order with respect to carbenicillin and alkali, but negative fractional-order

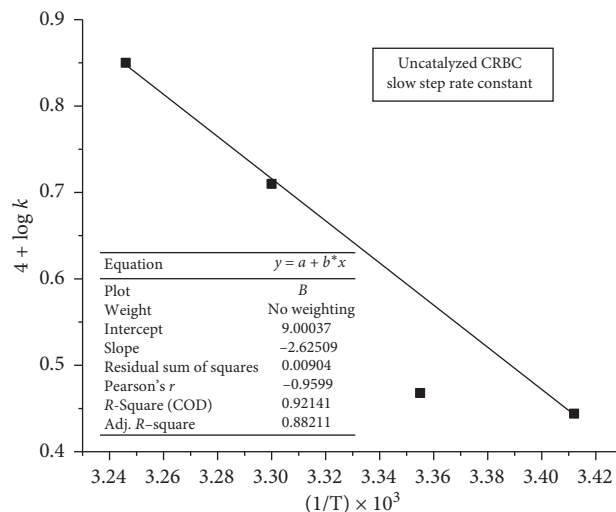
periodate. Based on this experimental evidence, a suitable mechanism is proposed along with the proper involvement of all species. In the first step, DPC (III) reacts with the hydroxide ion to form a deprotonated form of DPC (III) which in presence of water yields MPC (III) along with free periodates species. Hence fractional order with respect to carbenicillin presumably results due to the formation of the complex by the interaction between carbenicillin and MPC (III) species. This complex interacts with one mole of MPC (III) in a slow step to give intermediate A along with regeneration of free periodate ion and Cu<sup>++</sup> ion. In the next step, intermediate A reacts with fresh mole of MPC (III) to

FIGURE 7: Plot of  $(5 + \log k_u)$  vs.  $4 + \log [\text{CRBC}]$ .FIGURE 8: Plot of  $(4 + \log k_u)$  vs.  $2 + \log [\text{KOH}]$ .FIGURE 9: Plot of  $(5 + \log k_u)$  vs.  $5 + \log [\text{KIO}_4]$ .TABLE 2: Activation parameters with respect to uncatalyzed rate constant ( $k_u$ ).

Parameters	Values
$E_a$ (K J mol <sup>-1</sup> )	30.94
$\Delta H^\ddagger$ (K J mol <sup>-1</sup> )	$28 \pm 1$
$\Delta S^\ddagger$ (J K <sup>-1</sup> mol <sup>-1</sup> )	$-205 \pm 3$
$\Delta G^\ddagger$ (kJ mol <sup>-1</sup> )	$89 \pm 2$
LogA	$2.5 \pm 0.6$

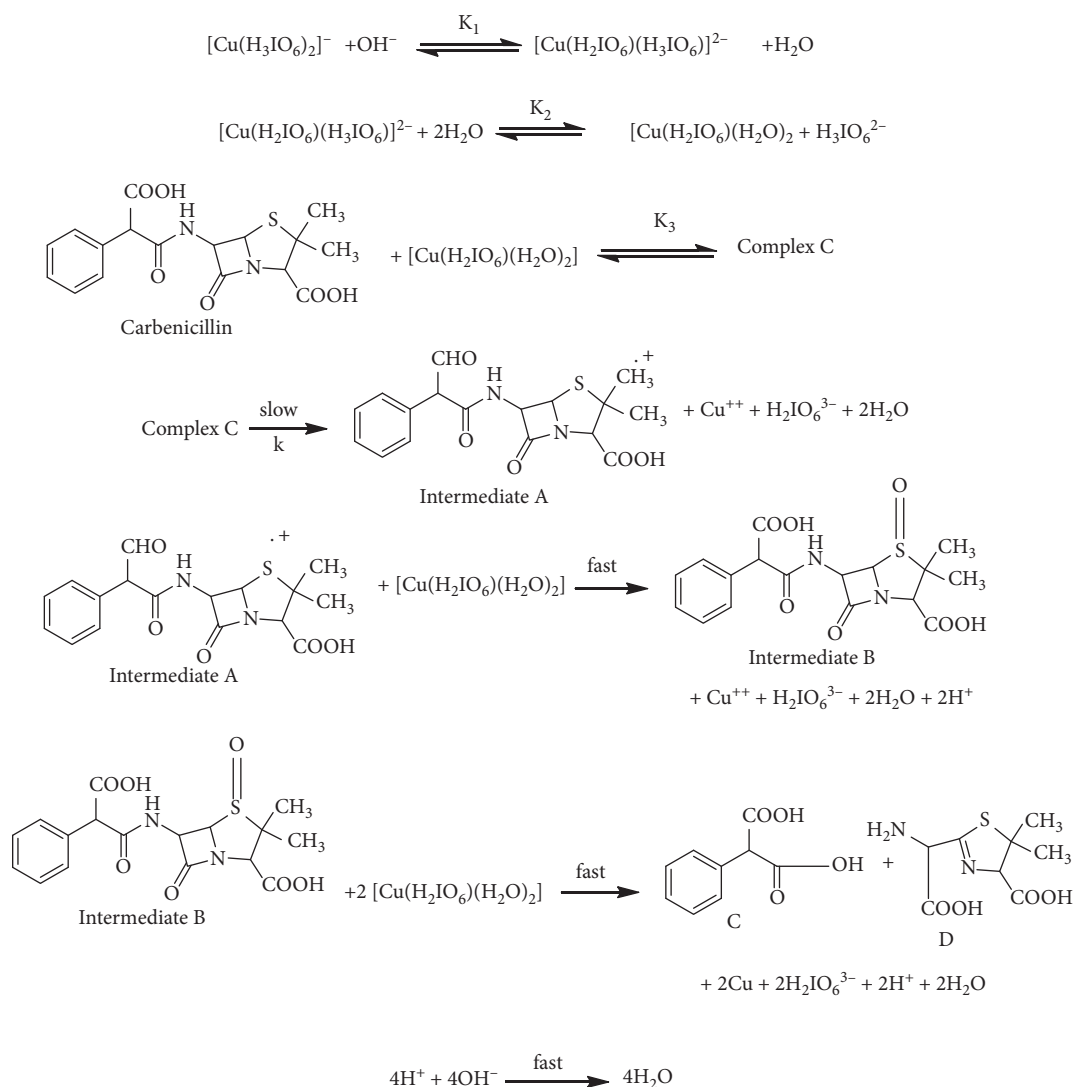
FIGURE 10: Plot of  $(4 + \log k_u)$  vs.  $(1/T) \times 10^3$ .TABLE 3: Activation parameters with respect to slow step rate constants ( $k$ ).

Parameters	Values
$E_a$ (K J mol <sup>-1</sup> )	50.45
$\Delta H^\ddagger$ (K J mol <sup>-1</sup> )	$48 \pm 1$
$\Delta S^\ddagger$ (J K <sup>-1</sup> mol <sup>-1</sup> )	$-150 \pm 2$
$\Delta G^\ddagger$ (kJ mol <sup>-1</sup> )	$92 \pm 2$
LogA	$5.3 \pm 0.2$

FIGURE 11: Plot of  $(4 + \log k)$  vs.  $(1/T) \times 10^3$ .

form intermediate B which undergoes hydrolysis to yield the other final products, i.e., 2-phenylmalonic acid gave  $m/z$  at 182 ( $m+2$ ) and the second product 2-(amino (carboxy)

methyl)-5, 5-dimethyl-4, 5-dihydrothiazole-4-carboxylic acid-1-oxide) as explained in Scheme 1.



The probable structure of complex C is given as follows:

Spectroscopic evidence for the complex formation between reagent DPC (III) and substrate (CRBC) was obtained

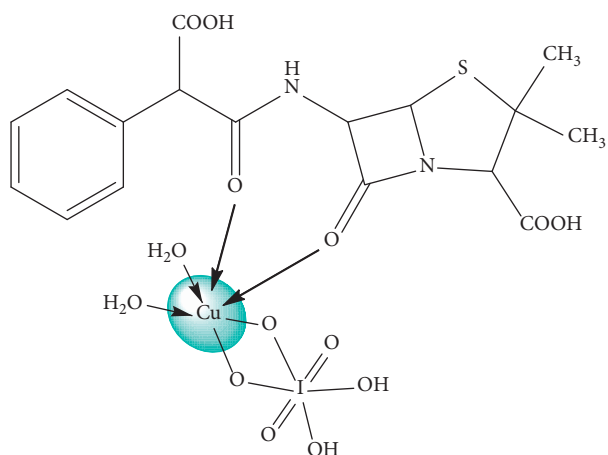
from UV-visible spectra by resting CRBC ( $5.0 \times 10^{-4}$  M), KOH (0.12 M), and a mixture of all. A bathochromic shift was obtained. The Michaelis-Menten plot is in great support for complex formation, Figure 9.

scheme 1 leads to rate law equation (2) as

$$\text{rate} = -\frac{d[\text{DPC}]}{dt} = k[\text{C}] \quad (1)$$

$$k_{\text{obs}} = \frac{kK_1K_2K_3[\text{DPC}][\text{CRBC}][\text{OH}^-]}{[\text{H}_3\text{IO}_6^{2-}] + K_1[\text{OH}^-][\text{H}_3\text{IO}_6^{2-}] + K_1K_2[\text{OH}^-] + K_1K_2K_3[\text{OH}^-][\text{CRBC}]} \quad (2)$$





SCHEME 1: Detailed scheme for uncatalyzed oxidation of CRBC by DPC (III).

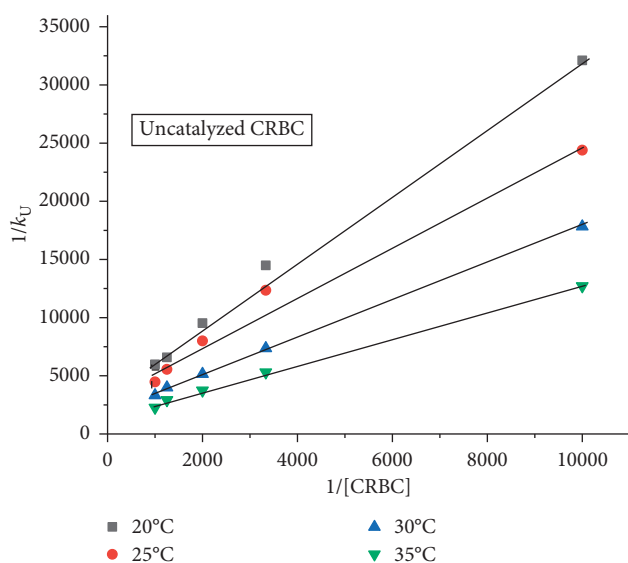


FIGURE 12: Plot of  $[1/k_u \text{ vs. } 1/[\text{CRBC}]]$ .

Equation (2) describes all kinetic orders observed for different species. The rate law equation (2) can be rearranged into equation (3) that suits for verification:

$$\frac{1}{k_{\text{obs}}} = \frac{[\text{H}_3\text{IO}_6^{2-}]}{kK_1K_2K_3[\text{CRBC}][\text{OH}^-]} + \frac{[\text{H}_3\text{IO}_6^{2-}]}{kK_2K_3[\text{CRBC}]} + \frac{1}{kK_3[\text{CRBC}]} + \frac{1}{k} \quad (3)$$

The basic rule to calculate the activation energy and other activation parameters and the complete rate law derivation are given in Appendices A and B, respectively.

Figures 12–14 represent verification plots for oxidation of CRBC by DPC (III) in alkaline medium. According to equation (3), other remaining conditions being constant, the plots of  $[1/k_u \text{ vs. } 1/[\text{KOH}]]$  ( $r \geq 0.999$ ,  $s \leq 0.003$ ),  $[1/k_u \text{ vs. } 1/[\text{CRBC}]]$  ( $r \geq 0.997$ ,  $s \leq 0.004$ ), and  $[1/k_u \text{ vs. } [\text{H}_2\text{IO}_6]^{3-}]$

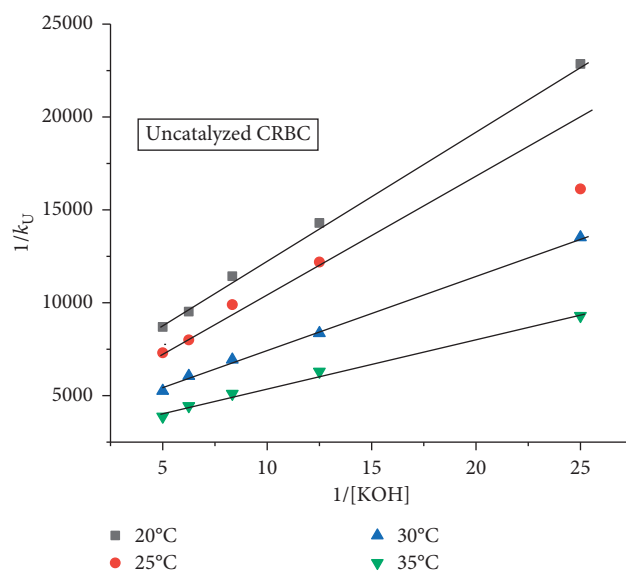


FIGURE 13: Plot of  $[1/k_u \text{ vs. } 1/[\text{KOH}]]$ .

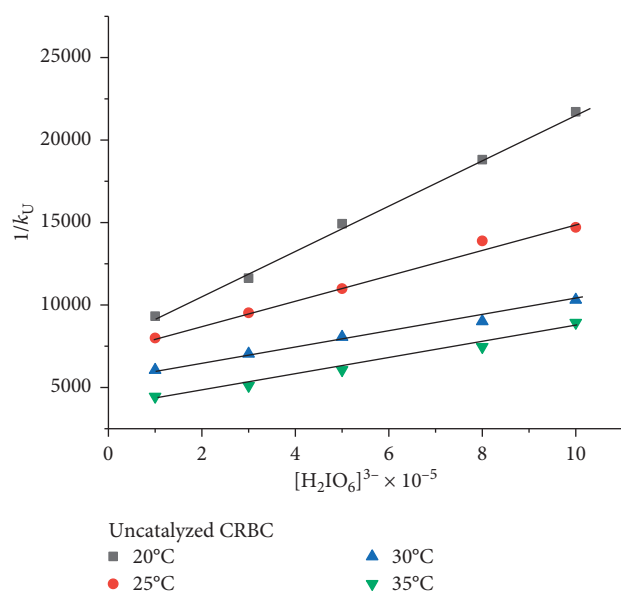


FIGURE 14: Plot of  $[1/k_u \text{ vs. } [\text{H}_2\text{IO}_6]^{3-}]$ .

( $r \geq 0.999$ ,  $s \leq 0.003$ ) should be linear and are found to be so as in Figures 12–14.

Overall slow step rate constants and equilibrium constants are presented in Tables 4 and 5 including thermodynamic parameters at 298 K.

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 reactions. The higher negative value of  $\Delta S^\ddagger$  suggests that the intermediate complex is probably highly ordered compared to the reacting species. The above results, evidences,

TABLE 4: Equilibrium constants and slow step rate constant for CRBC.

Equilibrium constants	Absolute temperatures			
	20°C	25°C	30°C	35°C
$k$ (slow step rate constant) $\times 10^{-4}$	2.78	2.94	5.18	7.2
$K_1$	1.18	1.23	1.417	1.64
$K_2 \times 10^{-4}$	2.09	2.27	3.146	4.2
$K_3$	1719.76	1478.0	1283.91	1036.42

TABLE 5: Thermodynamic parameters from equilibrium constants for CRBC.

Thermodynamic quantities	Values from $K_1$	Values from $K_2$	Values from $K_3$
$\Delta H^\circ_{298}$ (kJ·mol <sup>-1</sup> )	16.98	36.74	-25.03
$\Delta S^\circ_{298}$ (J·K <sup>-1</sup> ·mol <sup>-1</sup> )	59.06	131.027	-23.12
$\Delta G^\circ_{298}$ (kJ·mol <sup>-1</sup> )	-0.59	-2.30	-18.14

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.

#### 4. Conclusions

The oxidation of carbenicillin by DPC (III) was studied experimentally in aqueous alkaline medium. (MPC-III) [Cu(H<sub>2</sub>IO<sub>6</sub>)(H<sub>2</sub>O)<sub>2</sub>] was considered to be the active species for the present work. Activation and thermodynamic parameters with respect to uncatalyzed rate constant ( $k_u$ ), slow step rate constant ( $k$ ), and equilibrium constants at different temperatures were calculated and computed. Overall sequences described here are inconsistent with all experimental evidences including product, spectral analysis, and mechanistic and kinetics studies.

#### Appendix

##### (A). Calculation of Activation Parameters

The energy of activation for the present reaction was calculated by

$$E_a = -2.303 R \text{ slope.} \quad (\text{A.1})$$

The Arrhenius factor "A" was calculated by

$$\log A = \log k_u + \frac{E_a}{2.303 RT}. \quad (\text{A.2})$$

The entropy of activation was calculated by

$$\frac{\Delta S^\ddagger}{4.576} = \log k_u - 10.753 - \log T + \frac{E_a}{4.576T}. \quad (\text{A.3})$$

The enthalpy of activation was calculated by

$$\Delta H^\ddagger = E_a - RT. \quad (\text{A.4})$$

The free energy of activation was calculated by

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger, \quad (\text{A.5})$$

where  $k_u/k_{\text{obs}}$  is uncatalyzed rate constant in sec<sup>-1</sup>,  $T$  is temperature in Kelvin,  $E_a$  is energy of activation in calories,  $R$  is universal gas constant, and  $\ddagger$  is activation parameter.

##### (B). Derivation of Rate Law

From scheme 1,

$$\text{rate} = -\frac{d[\text{DPC}]}{dt} = k[\text{complex}] = k[\text{C}]. \quad (\text{B.1})$$

From the law of mass action, the third equilibrium constant can be given by

$$K_3 = \frac{[\text{C}]}{[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2][\text{CRBC}]} \quad (\text{B.2})$$

After rearrangement, we get

$$[\text{C}] = K_3 [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2][\text{CRBC}] \quad (\text{B.3})$$

Substituting the value of C from equation (B.3), we get

$$\text{rate} = -\frac{d[\text{DPC}]}{dt} = K_1 K_3 [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2][\text{CRBC}] \quad (\text{B.4})$$

The second equilibrium constant can be given by

$$K_2 = \frac{[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2][\text{H}_3\text{IO}_6^{2-}]}{[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)^{2-}]} \quad (\text{B.5})$$

This can be rearranged into

$$[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2] = \frac{K_2 [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)^{2-}]}{[\text{H}_3\text{IO}_6]^{2-}} \quad (\text{B.6})$$

The first equilibrium constant can be given by

$$K_1 = \frac{[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)^{2-}]}{[\text{Cu}(\text{H}_3\text{IO}_6)_2]^- [\text{OH}^-]} \quad (\text{B.7})$$

This can be rearranged into

$$[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)]^{2-} = K_1 [\text{Cu}(\text{H}_3\text{IO}_6)_2]^- [\text{OH}^-] \quad (\text{B.8})$$

Substituting equation (B.6) into (B.8) in equation (B.4), we get

$$\text{Rate} = \frac{d[\text{DPC}]_f}{dt} = \frac{kK_1K_2K_3[\text{CRBC}]_f[\text{DPC}]_f[\text{OH}^-]_f}{[\text{H}_3\text{IO}_6]_2^-} \quad (\text{B.9})$$

The total concentration of [DPC] can be given as

$$[\text{DPC}]_T = [\text{DPC}]_f + [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)]^{2-} + [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2] + [\text{C}] \quad (\text{B.10})$$

where  $T$  and  $f$  denote total and free concentrations:

$$\begin{aligned} &= [\text{DPC}]_f + K_1 [\text{Cu}(\text{H}_2\text{IO}_6)_2]^- [\text{OH}^-] + \frac{K_1K_2[\text{Cu}(\text{H}_2\text{IO}_6)_2]^- [\text{OH}^-]}{[\text{H}_3\text{IO}_6]^{2-}} + \frac{K_1K_2K_3[\text{Cu}(\text{H}_3\text{IO}_6)_2]^- [\text{OH}^-] [\text{CRBC}]}{[\text{H}_3\text{IO}_6]^{2-}} \\ [\text{DPC}]_T &= [\text{DPC}]_f + K_1 [\text{DPC}]_f [\text{OH}^-] + \frac{K_1K_2[\text{DPC}]_f [\text{OH}^-]}{[\text{H}_3\text{IO}_6]^{2-}} + \frac{K_1K_2K_3[\text{DPC}]_f [\text{OH}^-] [\text{CRBC}]}{[\text{H}_3\text{IO}_6]^{2-}} \\ [\text{DPC}]_f &= \frac{[\text{DPC}]_T [\text{H}_3\text{IO}_6]^{2-}}{[\text{H}_3\text{IO}_6]^{2-} + K_1 [\text{OH}^-] [\text{H}_3\text{IO}_6]^{2-} + K_1K_2 [\text{OH}^-] + K_1K_2K_3 [\text{OH}^-] [\text{CRBC}]} \end{aligned} \quad (\text{B.11})$$

The total concentration of  $[\text{OH}^-]$  can be given by

$$\begin{aligned} [\text{OH}^-]_T &= [\text{OH}^-]_f + [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)]^{2-} + [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2] + [\text{C}] \\ [\text{OH}^-]_T &= [\text{OH}^-]_f + K_1 [\text{DPC}] [\text{OH}^-]_f + \frac{K_1K_2[\text{DPC}] [\text{OH}^-]_f}{[\text{H}_3\text{IO}_6]^{2-}} + \frac{K_1K_2K_3[\text{DPC}] [\text{OH}^-]_f [\text{CRBC}]}{[\text{H}_3\text{IO}_6]^{2-}} \\ [\text{OH}^-]_T &= [\text{OH}^-]_f \left\{ 1 + K_1 [\text{DPC}] + \frac{K_1K_2[\text{DPC}]}{[\text{H}_3\text{IO}_6]^{2-}} + \frac{K_1K_2K_3[\text{DPC}] [\text{CRBC}]}{[\text{H}_3\text{IO}_6]^{2-}} \right\} \end{aligned} \quad (\text{B.12})$$

In view of low concentrations of DPC and  $\text{H}_3\text{IO}_6^{2-}$  used, the last three terms inside brackets can be neglected in comparison with unity:

$$[\text{OH}^-]_T = [\text{OH}^-]_f \quad (\text{B.13})$$

Similarly, in case of low concentrations of DPC and  $\text{H}_3\text{IO}_6^{2-}$  used,

$$[\text{CRBC}]_T = [\text{CRBC}]_f \quad (\text{B.14})$$

Putting these values of  $[\text{DPC}]_f$  from equation (B.11),  $[\text{OH}^-]_f$  from equation (B.13), and  $[\text{CRBC}]_f$  from equation (B.14) in equation (B.9) after omitting subscripts  $T$  and  $f$ , we get

$$\begin{aligned} \text{Rate} &= \frac{d[\text{DPC}]}{dt} = \frac{kK_1K_2K_3[\text{CRBC}][\text{DPC}][\text{OH}^-]}{[\text{H}_3\text{IO}_6]^{2-} + K_1[\text{OH}^-][\text{H}_3\text{IO}_6]^{2-} + K_1K_2[\text{OH}^-] + K_1K_2K_3[\text{OH}^-][\text{CRBC}]} \\ \text{or, } \frac{1}{k_{\text{obs}}} &= \frac{[\text{H}_3\text{IO}_6]^{2-}}{kK_1K_2K_3[\text{CRBC}][\text{OH}^-]} + \frac{[\text{H}_3\text{IO}_6]^{2-}}{kK_2K_3[\text{CRBC}]} + \frac{1}{kK_3[\text{CRBC}]} + \frac{1}{k} \end{aligned} \quad (\text{B.15})$$

## Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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