

## GRAPHICAL ABSTRACT

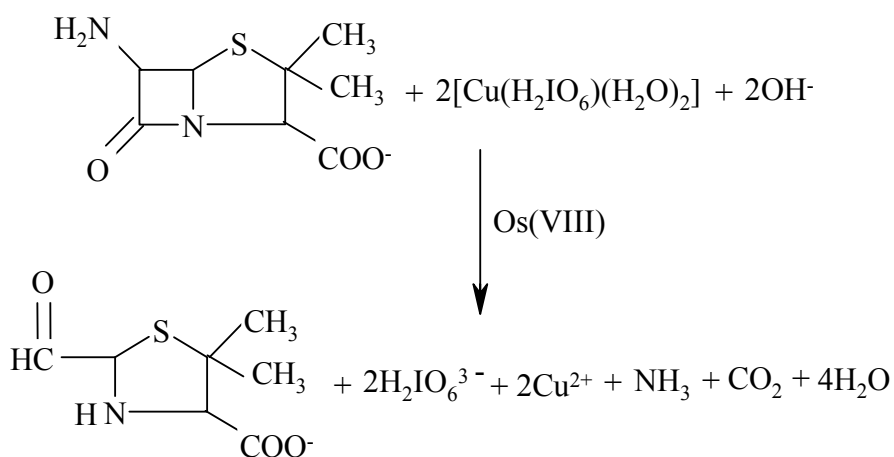
### “Osmium(VIII) Catalyzed Oxidation of 6-Aminopenicillanic Acid by Alkaline Copper(III) Periodate Complex: A Kinetic and Mechanistic Approach”

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The oxidation of 6-aminopenicillanic acid by copper(III) periodate complex in presence of osmium(VIII) catalyst has been studied which showed 6-APA to DPC(III) 1:2 stoichiometry. Active species for copper(III) and Os(VIII) were found to be  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$  and  $[\text{OsO}_4(\text{OH})_2]^{2-}$ .



## RESEARCH HIGHLIGHTS

- Kinetics of oxidation of 6-APA by DPC(III) was studied in presence of Os(VIII) catalyst
- Main oxidation product was 2 formyl-5,5 dimethyl thiazolidine 4-carboxylic acid
- Reaction constants for the different steps of the reaction mechanism were calculated
- Active species for copper(III) and Os(VIII) were found to be  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$  and  $[\text{OsO}_4(\text{OH})_2]^{2-}$

# Osmium(VIII) Catalyzed Oxidation of 6-Aminopenicillanic Acid by Alkaline Copper(III) Periodate Complex: A Kinetic and Mechanistic Approach

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ABSTRACT: The oxidation of 6-aminopenicillanic acid (6-APA) by diperiodatocuprate(III) (DPC) has been investigated in presence of osmium(VIII) catalyst in aqueous alkaline medium at a constant ionic strength of  $0.20 \text{ mol dm}^{-3}$  spectrophotometrically. The stoichiometry was 1:2 (6-APA:DPC). The order of the reaction with respect to [DPC] was unity while the order with respect to [6-APA] was  $< 1$  over the concentration range studied. The rate increased with an increase in  $[\text{OH}^-]$  and decreased with an increase in  $[\text{IO}_4^-]$ . The order with respect to  $[\text{Os(VIII)}]$  was unity. The oxidation products were identified by spectral analysis. Suitable mechanism was proposed. The reaction constants involved in the different steps of the reaction mechanism were calculated. The catalytic constant ( $K_C$ ) was also calculated for catalyzed reaction at different temperatures. The activation parameters with respect to slow step of the mechanism and also the thermodynamic quantities were determined. Kinetic experiments suggest that  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$  is the reactive copper(III) species and  $[\text{OsO}_4(\text{OH})_2]^{2-}$  is the reactive Os(VIII) species.

Keywords: 6-Aminopenicillanic acid; Diperiodatocuprate(III); Os(VIII) catalysis; Oxidation; Kinetics

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## INTRODUCTION

6-Aminopenicillanic acid (6-APA) is an integral  $\beta$ -lactam compound of the various penicillins. Penicillins consist of the heterocyclic group consisting of a thiazolidine ring (with 5 members including one sulphur atom) fused with a  $\beta$ -lactam ring (with 4 members), which are distinguished from each other by the nature of the side chain attached to the amine group in position 6 through a peptide link. 6-Aminopenicillanic acid is the active core body of all penicillins substituted at the 6-amino position resulting in a variety of antibacterial and pharmacologic characteristics. It is a non-hygroscopic crystal that decomposes at 209 °C. 6-Aminopenicillanic acid is a key intermediate in the production of many commercial  $\beta$ -lactam antibiotics. It is produced by enzymatic hydrolysis of penicillin G [1].

Transition metals in their higher oxidation states can generally be stabilized by chelation with suitable polydentate ligands. These metal chelates such as diperiodatocuprate(III) [2], diperiodatoargentate(III) [3] and diperiodatonickelate(IV) [4] are good oxidants in a medium with an appropriate pH value. Diperiodatocuprate(III) is a versatile one-electron oxidant and the oxidation study of DPC is scanty in view of its limited solubility and stability in aqueous medium. Its use as an analytical reagent is now well recognized [5]. Copper complexes have a major role in oxidation chemistry due to their abundance and relevance in biological chemistry [6-8]. Copper(III) is involved in many biological electron transfer reactions [9]. When copper(III) periodate complex is the oxidant and multiple equilibria between different copper(III) species are involved, it would be interesting to know which of the species is the active oxidant.

The reactions catalyzed by transition metal ions are of great interest [10] due to their involvement in many important industrial processes, such as hydrogenation, carbonylation reactions and also low pressure polymerization of ethylene and propene. The role of

osmium(VIII) as a catalyst in some redox reactions has been reviewed [11, 12]. Although the mechanism of catalysis depends on the nature of the substrate, oxidant and on experimental conditions, it has been shown [13] that metal ions act as catalysts by one of these different paths such as the formation of complexes with reactants or oxidation of the substrate itself or through the formation of free radicals. In earlier report [14], it has been observed that Os(VIII) forms a complex with substrate, which is reduced to Os(VI) then osmium(VII) species, followed by the rapid reaction of Os(VII) with one mole of oxidant to regenerate Os(VIII). In another report [15], it has been observed that oxidant-substrate complex reacts with Os(VIII) to form Os(VI) species, which again reacts with oxidant in a fast step to regenerate Os(VIII). In some other reports [16], it is observed that Os(VIII) forms a complex with substrate which is oxidized by the oxidant with the regeneration of Os(VIII). Hence understanding the role of Os(VIII) in the catalyzed reaction is important. Catalysis by osmium(VIII) in redox reactions involves different degrees of complexity, due to the formation of different intermediate complexes and different oxidation states of osmium.

The uncatalyzed and Ru(III) catalyzed oxidation of 6-APA by DPC has been studied [17]. However, the literature survey revealed that no attention has been paid towards the Os(VIII) catalyzed oxidation of 6-APA acid with DPC from the kinetic and mechanistic point of view. It is also observed that, no one has examined the role of this catalyst on the oxidation of this ubiquitous amino acid. We have observed that osmium(VIII) in micro amounts catalyzes the oxidation of 6-APA by DPC in alkaline medium. Such studies are of much significance in understanding the mechanistic profile of 6-APA in redox reactions and provide an insight into the interaction of metal ions with the substrate and its mode of action in biological systems. Also to know the active species of Cu(III) and catalyst Os(VIII), and the complexity of the reaction, a

detailed study of the title reaction becomes important. Hence, the present investigation is aimed at checking the reactivity of 6-APA towards DPC in osmium(VIII) catalyzed reaction and to arrive at the plausible mechanism.

## **EXPERIMENTAL**

### **Chemicals and Materials**

All reagents were of analytical reagent grade and millipore water was used throughout the work. A solution of 6-aminopenicillanic acid (HiMedia Laboratories) was prepared by dissolving an appropriate amount of recrystallized sample in millipore water. The required concentration of 6-APA was obtained from its stock solution. The osmium(VIII) solution was prepared by dissolving  $\text{OsO}_4$  (Johnson Matthey) in  $0.50 \text{ mol dm}^{-3}$  NaOH. The concentration of Os(VIII) was ascertained [18] by determining the unreacted  $[\text{Fe}(\text{CN})_6]^{4-}$  with standard Ce(IV) solution in an acidic medium.

The copper(III) periodate complex was prepared [19, 20] and standardized by a standard procedure [21]. The UV-vis spectrum with maximum absorption at 415 nm verified the existence of copper(III) complex. The ionic strength was maintained by adding  $\text{KNO}_3$  (AR) solution and the pH value was regulated with KOH (BDH) solution. A stock solution of  $\text{IO}_4^-$  was prepared by dissolving a known weight of  $\text{KIO}_4$  (Riedel-de-Haan) in hot water and used after keeping for 24 h to attain the equilibrium. Its concentration was ascertained iodometrically [22], at neutral pH maintained using phosphate buffer.

## Instruments Used

(i) For kinetic measurements, a Peltier Accessory (temperature control) attached Varian CARY 50 Bio UV-vis spectrophotometer (Varian, Victoria-3170, Australia) connected to a rapid kinetic accessory (HI-TECH SFA-12, U.K.) was used.

(ii) For product analysis, LC-MS (Agilent 1100 series-API 2000) mass spectrometer ionization technique, Nicolet 5700-FT-IR spectrometer (Thermo, U.S.A.) were used.

(iii) For pH measurement an Elico pH meter model LI 120 was used.

## Kinetic Measurements

Since the initial rate was too fast to be monitored by usual methods, the kinetic measurements were performed on a Varian CARY 50 Bio UV-visible spectrophotometer attached to a rapid kinetic accessory (HI-TECH SFA-12). The oxidation of 6-APA by DPC was followed under pseudo-first-order conditions where  $[6\text{-APA}] \gg [\text{DPC}]$  at  $25.0 \pm 0.1$  °C, unless otherwise specified. The reaction was initiated by mixing DPC with the 6-APA solution which also contained the required concentrations of  $\text{KNO}_3$ ,  $\text{KOH}$ ,  $\text{KIO}_4$  and  $\text{Os(VIII)}$  catalyst. The progress of the reaction was monitored spectrophotometrically at 415 nm (i.e., decrease in absorbance due to DPC with the molar absorbcency index, ' $\epsilon$ ' to be  $6231 \pm 100 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$  (Literature  $\epsilon = 6230$ )) [23], which is the maximum absorption wavelength of DPC. The concentration of DPC decreases at 415 nm. It was also observed that there was almost no interference from other species in the reaction mixture at this wavelength.

During the kinetics, a constant concentration *viz.*  $1.0 \times 10^{-5} \text{ mol dm}^{-3}$  of  $\text{KIO}_4$  was used throughout the study unless otherwise stated. Since excess of periodate is present in DPC, the possibility of oxidation of 6-APA by periodate in alkaline medium at 25 °C was tested and found

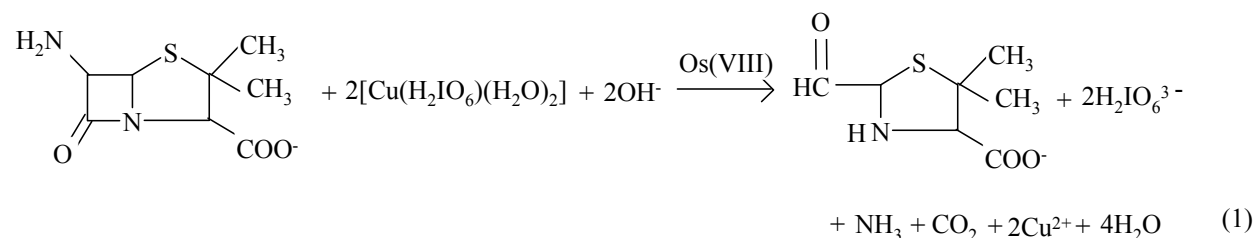
that there was no significant interference due to  $\text{KIO}_4$  under experimental conditions. The total concentrations of periodate and  $\text{OH}^-$  was calculated by considering the amount present in DPC solution and that additionally added. Kinetic runs were also carried out in  $\text{N}_2$  atmosphere in order to understand the effect of dissolved oxygen on the rate of the reaction. No significant difference in the results was obtained under a  $\text{N}_2$  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. The added carbonate had no effect on the reaction rates.

The orders for various species were determined from the slopes of plots of  $\log(k_C)$  versus respective concentration of species except for [DPC] in which non-variation of ' $k_C$ ' was observed as expected to the reaction condition. The rate constants were reproducible to within  $\pm 5\%$ . Regression analysis of experimental data to obtain regression coefficient 'r' and the standard deviation 'S', of points from the regression line, was performed with the Microsoft office Excel-2003 program.

## RESULTS

### Stoichiometry and Product Analysis

Different sets of reaction mixtures containing varying ratios of DPC to 6-APA in the presence of constant amount of  $\text{OH}^-$ ,  $\text{KIO}_4$ ,  $\text{KNO}_3$  and  $\text{Os(VIII)}$  were kept for 4 h in a closed vessel under nitrogen atmosphere. The remaining concentration of DPC was assayed by measuring the absorbance at 415 nm. The results indicated 1:2 stoichiometry as given in Eqn. (1).





The main reaction product was identified as 2 formyl-5,5 dimethyl thiazolidine 4-carboxylic acid. This was characterized by LC-ESI-MS and FT-IR spectral studies. LC-ESI-MS analysis was carried out using reverse phase high performance liquid chromatography (HPLC) system with a phenomenex C-18 column, UV-visible detector and series mass analyzer. 12  $\mu$ L of acidified reaction mixture was injected. The mobile phase consisted of 10 mM ammonium acetate pH 3.0 (eluent A) and acetic acid (eluent B) at a flow rate of 1 ml/min. Gradient elution was run to separate the substrate and reaction products. LC-ESI-MS analysis indicated the presence of main products with molecular ions of m/z at 189 (Fig. 1).

The byproducts were identified as ammonia by Nessler's reagent [21] and CO<sub>2</sub> was qualitatively detected by bubbling nitrogen gas through the acidified reaction mixture and passing the liberated gas through the tube containing lime water. Finally copper(II) was identified by UV-vis spectra.

## Reaction Orders

As the diperiodatocuprate(III) oxidation of 6-aminopenicillanic acid in alkaline medium proceeds with a measurable rate in the absence of Os(VIII), the catalyzed reaction is understood to occur in parallel paths with contributions from both the catalyzed and uncatalyzed paths. Thus the total rate constant ( $k_T$ ) is equal to the sum of the rate constants of the catalyzed ( $k_C$ ) and uncatalyzed ( $k_U$ ) reactions, so  $k_C = k_T - k_U$ . Hence the reaction orders have been determined from the slopes of  $\log k_C$  versus  $\log$  (concentration) plots by varying the concentrations of 6-APA, IO<sub>4</sub><sup>-</sup>, OH<sup>-</sup> and catalyst Os(VIII), in turn while keeping others constant. The rate constant,  $k_U$  was obtained by the plot of  $\log$  (absorbance) versus time by following the progress of the reaction spectrophotometrically at 415 nm.

### **Evaluation of Pseudo-First-Order Rate Constants**

The oxidant [DPC] was varied in the range of  $1.0 \times 10^{-5} - 1.0 \times 10^{-4}$  at fixed [6-APA], [KOH] and  $[\text{KIO}_4^-]$ . The pseudo-first-order rate constant, ( $k_C$ ), was determined from the log (absorbance) versus time plot. The plots were linear up to 85% completion of reaction under the range of  $[\text{OH}^-]$  used ( $r \geq 0.9929$ ,  $S \leq 0.014$ ). The fairly constant pseudo-first-order rate constant,  $k_C$ , indicate that the order with respect to [DPC] was unity (Table I).

### **Effect of Varying [6-Aminopenicillanic Acid]**

The effect of 6-APA was studied in the range of  $6.0 \times 10^{-5} - 6.0 \times 10^{-4} \text{ mol dm}^{-3}$  at constant concentrations of DPC,  $\text{OH}^-$ ,  $\text{IO}_4^-$ , Os(VIII) and a constant ionic strength of  $0.20 \text{ mol dm}^{-3}$ . The  $k_C$  values increased with increase in [6-APA]. The order with respect to [6-APA] was less than unity (Table I) ( $r \geq 0.9979$ ,  $S \leq 0.009$ ). This was also confirmed by the plots of  $k_C$  versus [6-APA]<sup>0.63</sup> which is linear rather than the direct plot of  $k_C$  versus [6-APA] (Fig. 2).

### **Effect of Varying [Alkali]**

The effect of alkali was studied in the range of  $0.02 - 0.20 \text{ mol dm}^{-3}$  at constant concentrations of DPC, 6-APA,  $\text{IO}_4^-$ , Os(VIII) and ionic strength. The rate constants increased with increase in [alkali] and the order was found to be less than unity i.e., 0.40. (Table I) ( $r \geq 0.9956$ ,  $S \leq 0.008$ ). This was also confirmed by the plot of  $k_C$  versus  $[\text{OH}^-]^{0.40}$  which is linear rather than the direct plot of  $k_C$  versus  $[\text{OH}^-]$  (Fig. 3).

### **Effect of Varying [Periodate]**

The effect of periodate was studied in the range of  $5.0 \times 10^{-6} - 5.0 \times 10^{-5} \text{ mol dm}^{-3}$  at constant concentrations of DPC, 6-APA,  $\text{OH}^-$ , Os(VIII) and ionic strength. The experimental results indicated that the  $k_C$  values decreased with increase in  $[\text{IO}_4^-]$ . The order with respect to  $\text{IO}_4^-$  was negative fractional i.e., -0.44. (Table I) ( $r \geq 0.9928$ ,  $S \leq 0.005$ ).

### **Effect of Varying [Os(VIII)]**

The [Os(VIII)] concentration was varied from  $1.0 \times 10^{-7} - 1.0 \times 10^{-6} \text{ mol dm}^{-3}$  range, at constant concentration of DPC, 6-APA, and alkali and constant ionic strength. The order in [Os(VIII)] was found to be unity from the linearity of the plot of  $k_C$  versus [Os(VIII)] (Table I, Fig. 4).

### **Effect of Varying Ionic Strength (I) and Dielectric Constant (D)**

The effect of ionic strength ( $I$ ) was studied by varying  $[\text{KNO}_3]$ . The dielectric constant of the medium ( $D$ ) was studied by varying the *t*-butyl alcohol and water percentage. It was found that there was no significant effect of ionic strength and dielectric constant of the medium on the rate of reaction.

### **Effect of Initially Added Products**

Initially added products, copper(II) ( $\text{CuSO}_4$ ) and 2-formyl-5,5 dimethyl thiazolidine 4-carboxylic acid did not have any significant effect on the rate of reaction.

## Polymerization Study

The possibility of intervention free radicals was detected as follows: the reaction mixture, to which a known quantity of acrylonitrile (scavenger) had been added initially, was kept for 2 h in an inert atmosphere. On diluting the reaction mixture with methanol, a white precipitate was formed, indicating the intervention of free radicals in the reaction. The blank experiments of either DPC or 6-aminopenicillanic acid alone with acrylonitrile did not induce any polymerization under the same condition as those induced for the reaction mixture. Initially added acrylonitrile decreases the rate of reaction indicating free radical intervention, which is the case in earlier work [24].

## Effect of Temperature (T)

The kinetics was studied at four different temperatures 288, 298, 308 and 318 K under varying concentrations of 6-aminopenicillanic acid, alkali, periodate and catalyst, keeping other conditions constant. The rate constant ( $k$ ), of the slow step of [Scheme 1](#) were obtained from the slopes and the intercepts of the plots of  $[\text{Os(VIII)}]/k_C$  versus  $1/[\text{6-APA}]$  at four different temperatures. The values are given in [Table II](#). The energy of activation for the rate determining step was obtained by the least-squares method of plot of  $\log k$  versus  $1/T$  and other activation parameters calculated are presented in [Table II](#).

## Catalytic Activity

It has been pointed out by Moelwyn-Hughes [25] that in the presence of catalyst, the uncatalyzed and catalyzed reactions proceed simultaneously, so that,

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

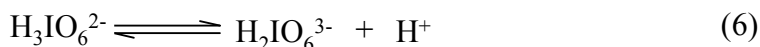
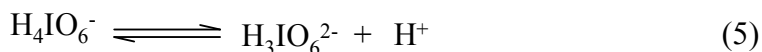
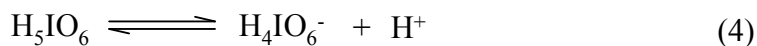
Here,  $k_T$ , is the total rate constant;  $k_U$ , the pseudo-first-order rate constant for uncatalyzed;  $K_C$ , the catalytic constant and 'x' the order of the reaction with respect to Os(VIII). In the present investigations; x values for the standard run were found to be unity. Then, the value of  $K_C$  is calculated using the equation,

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

The values of  $K_C$  were evaluated at different temperatures and were found to vary at different temperatures. Further, plot of  $\log K_C$  versus  $1/T$  was linear and the values of energy of activation and other activation parameters with reference to catalyst were computed. These results are summarized in [Table III](#).

## DISCUSSION

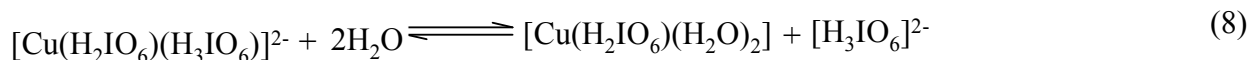
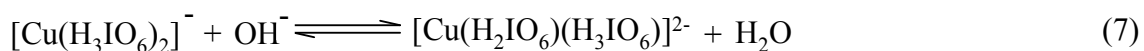
The water-soluble copper(III) periodate complex is reported [26] to be  $[\text{Cu}(\text{HIO}_6)_2(\text{OH})_2]^{7-}$ . However, in an aqueous alkaline medium and at a high pH range as employed in the study, periodate is unlikely to exist as  $\text{HIO}_6^{4-}$  (as present in the complex) as is evident from its involvement in the multiple equilibria [27] (4)-(6) depending on the pH of the solution.



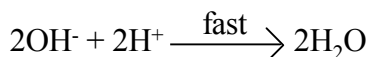
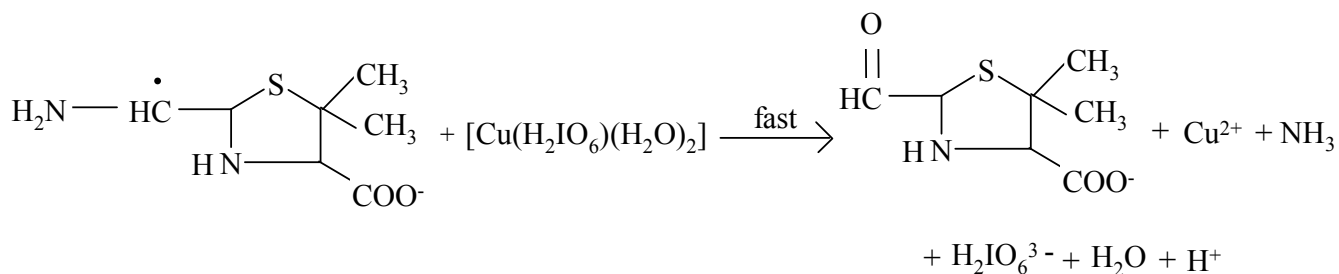
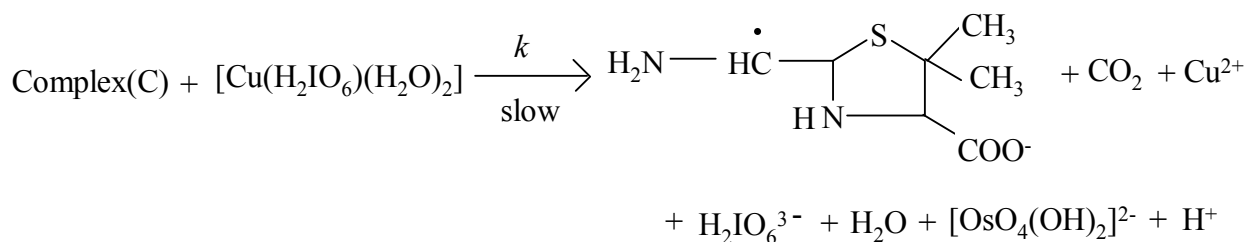
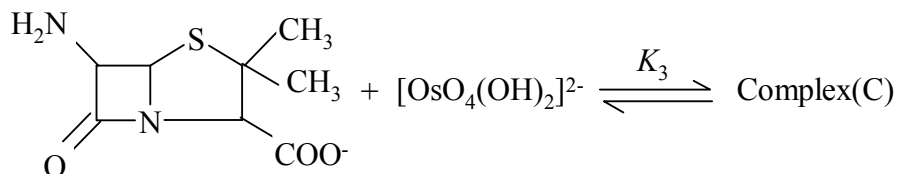
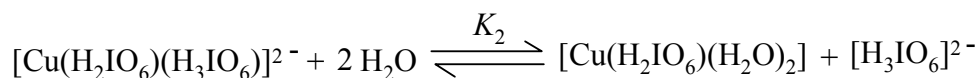
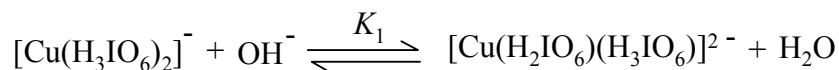
Periodic acid exists as  $\text{H}_5\text{IO}_6$  in an acid medium and as  $\text{H}_4\text{IO}_6^-$  around pH 7. Thus, under the conditions employed in alkaline medium, the main species are expected to be  $\text{H}_3\text{IO}_6^{2-}$  and  $\text{H}_2\text{IO}_6^{3-}$ . At higher concentrations, periodate also tends to dimerise. However, formation of this species is negligible under conditions employed for kinetic study. Hence, at the pH employed in

this study, the soluble copper(III) periodate complex exists as diperiodatocuprate(III),  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)]^{2-}$  a conclusion also supported by earlier work [28, 29]. It is known that in alkali media 6-APA exists fully as anionic form.

Lister [30] proposed the copper(III) periodate in alkaline medium into three forms as diperiodatocuprate(III) (DPC), monoperiodatocuprate(III) (MPC) and tetrahydroxocuprate(III). The latter is ruled out as its equilibrium constant is  $8.0 \times 10^{-11}$  at 40 °C. Hence, in the present study, in view of the negative less than unit order in periodate on rate of reaction, monoperiodatocuprate(III) MPC is considered to be the active species of copper(III) periodate complex. The results of increase in the rate with increase in alkali concentration and decrease in the rate with increase in periodate concentration suggests that equilibria of different copper(III) periodate complexes are possible as in Eqns. (7) and (8).



The inverse fractional order in  $[\text{IO}_4^-]$  might also be due to this reason. Anionic species of 6-APA reacts with osmium(VIII) active species to form a complex (C) which further reacts with one mole of MPC in a slow step to give the free radical species of 6-APA, Cu(II) with regeneration of catalyst, osmium(VIII). Further this free radical species of 6-APA reacts with one more molecule of MPC species in a fast step to form products such as 2 formyl-5,5 dimethyl thiazolidine 4-carboxylic acid, Cu(II) and periodate. All these results may be interpreted in the form of Scheme 1. Similar type of key step in the mechanism has been proposed for the catalyzed reaction in the earlier studies [31].



**Scheme 1.** Mechanism for Os(VIII) catalyzed oxidation of 6-aminopenicillanic acid by alkaline diperidatocuprate(III)

Osmium(VIII) is known to form different complexes at different  $\text{OH}^-$  concentrations [32] as  $[\text{OsO}_4(\text{OH})_2]^{2-}$  and  $[\text{OsO}_5(\text{OH})]^{3-}$ . At higher concentration of  $\text{OH}^-$ ,  $[\text{OsO}_5(\text{OH})]^{3-}$  is significant. At lower concentrations of  $\text{OH}^-$ , as employed in the present study, and since the rate of oxidation

increased with increase in  $[\text{OH}^-]$ , it is reasonable that  $[\text{OsO}_4(\text{OH})_2]^{2-}$  was operative and its formation is important in the reaction. Mechanistically most studies [14] propose electron transfer between the substrate and catalyst in the rate determining steps leading to the products, followed by the rapid oxidation of osmium(VI/VII) to osmium(VIII) by the main oxidants, resulting in zero<sup>th</sup> order kinetics with respect to the main oxidant. In another case [15], Os(VIII) is regenerated by Os(VI) intervention in view of unit order in each osmium, substrate and oxidant. In some other reports [16], it is observed that Os(VIII) forms complex with substrate, in view of apparent less than unit order in substrate concentrations which is oxidized by the oxidant with the regeneration of the catalyst. Hence the study of the behaviour of Os(VIII) becomes significant. In the present investigation, the reaction was enhanced by  $[\text{OH}^-]$ , added periodate retarded the rate, first order dependency in [DPC] and catalyst [Os(VIII)] and fractional order in [6-APA] and  $[\text{OH}^-]$  was observed. To explain the observed orders the following Scheme 1 has been proposed for the reaction considering 6-APA as anionic form of 6-APA in alkaline medium.

Spectroscopic evidence for the complex formation between Os(VIII) and 6-APA was obtained from UV-vis spectra of 6-APA ( $5.0 \times 10^{-4}$ ), Os(VIII) ( $5.0 \times 10^{-7}$ ,  $[\text{OH}^-] = 0.08 \text{ mol dm}^{-3}$ ) and a mixture of both. A bathochromic shift of about 8 nm from 364 to 372 nm in the spectra of Os(VIII) to the mixture of Os(VIII) and 6-APA was observed. The Michaelis-Menten plot proved the complex formation between catalyst and substrate, which explains less than unit order in [6-APA]. Such a complex between a catalyst and substrate has also been observed in other studies [32].



From [Scheme 1](#), the rate law (10) can be derived.

$$\text{rate} = \frac{-d [\text{DPC}]}{dt} = \frac{kK_1K_2K_3[6\text{-APA}][\text{OH}^-][\text{Os(VIII)}][\text{DPC}]}{K_1K_2[\text{OH}^-] + [\text{H}_3\text{IO}_6^{2-}] + K_1[\text{OH}^-][\text{H}_3\text{IO}_6^{2-}] + K_1K_2K_3[6\text{-APA}][\text{OH}^-]} \quad (9)$$

$$\frac{\text{rate}}{[\text{DPC}]} = k_C = k_T - k_U = \frac{kK_1K_2K_3[6\text{-APA}][\text{OH}^-][\text{Os(VIII)}]}{K_1K_2[\text{OH}^-] + [\text{H}_3\text{IO}_6^{2-}] + K_1[\text{OH}^-][\text{H}_3\text{IO}_6^{2-}] + K_1K_2K_3[6\text{-APA}][\text{OH}^-]} \quad (10)$$

The rate law (10) can be rearranged into the following form which is suitable for verification.

$$\frac{[\text{Os(VIII)}]}{k_C} = \frac{1}{kK_3[6\text{-APA}]} + \frac{[\text{H}_3\text{IO}_6^{2-}]}{kK_1K_2K_3[\text{OH}^-][6\text{-APA}]} + \frac{[\text{H}_3\text{IO}_6^{2-}]}{K_2K_3[6\text{-APA}]} + \frac{1}{k} \quad (11)$$

According to Eqn. (11), other conditions being constant, plots of  $[\text{Os(VIII)}]/k_C$  versus  $1/[6\text{-APA}]$ ,  $1/[\text{OH}^-]$  and  $[\text{H}_3\text{IO}_6^{2-}]$  should be linear and are found to be so ([Fig. 5](#)). The slopes and intercepts of such plots lead to the values of  $K_1$ ,  $K_2$ ,  $K_3$  and  $k$  ([Table II](#)). The values of  $K_1$  and  $K_2$  are in good agreement with the literature [[31](#)]. Using these constants, the rate constants were calculated and compared with the experimental  $k_C$  values. There was a reasonable agreement with each other ([Table II](#)), which fortifies the proposed mechanism ([Scheme 1](#)).

The negligible effect of ionic strength and dielectric constant of medium on the rate explains qualitatively the reaction between neutral and positively charged ions, as seen in [Scheme 1](#). The thermodynamic quantities for the different equilibrium steps, in [Scheme 1](#) can be evaluated as follows. The  $[6\text{-APA}]$ ,  $[\text{OH}^-]$  and  $[\text{H}_3\text{IO}_6^{2-}]$  ([Table II](#)) were varied at four different temperatures. The plots of  $[\text{Os(VIII)}]/k_C$  versus  $1/[6\text{-APA}]$ ,  $[\text{Os(VIII)}]/k_C$  versus  $1/[\text{OH}^-]$  and  $[\text{Os(VIII)}]/k_C$  versus  $[\text{H}_3\text{IO}_6^{2-}]$  should be linear and are found to be so. From the slopes and intercepts, the values of  $K_1$ ,  $K_2$  and  $K_3$  were calculated at four different temperatures. A vant Hoff's plot was made for the variation of  $K_1$ ,  $K_2$  and  $K_3$  with temperature ( $\log K_1$  versus  $1/T$ ,  $\log K_2$  versus  $1/T$  and  $\log K_3$  versus  $1/T$ ). The values of enthalpy of reaction  $\Delta H$ , entropy of reaction

$\Delta S$  and free energy of reaction  $\Delta G$  were calculated for the first, second and third equilibrium steps. These values are given in [Table II](#). The observed modest enthalpy of activation and higher rate constant for the slow step indicate that the oxidation presumably occurs *via* an inner-sphere mechanism. This conclusion is supported by earlier observation [33]. The activation parameters evaluated explain the catalytic effect on the reaction. The catalyst Os(VIII) forms the complex (C) with substrate, which enhances the reducing property of substrate than that without catalyst. Further, the catalyst Os(VIII) modifies the reaction path by lowering the energy of activation.

The values of activation parameters for the Os(VIII) catalyzed oxidation of some amino acids by DPC are summarized in [Table IV](#). The entropy of activation for the title reaction falls within the observed range. Variation in the rate within the reaction series may be caused by change in the enthalpy or entropy of activation. Changes in the rate are caused by changes in both  $\Delta H^\ddagger$  and  $\Delta S^\ddagger$ , but these quantities vary extensively in a parallel fashion. A plot of  $\Delta H^\ddagger$  versus  $\Delta S^\ddagger$  is linear according to equation,

$$\Delta H^\ddagger = \beta \Delta S^\ddagger + \text{constant}$$

$\beta$  is called the isokinetic temperature. It has been asserted that apparently linear correlation of  $\Delta H^\ddagger$  with  $\Delta S^\ddagger$  are sometimes misleading and the evaluation of  $\beta$  by means of the above equation lacks statistical validity [34]. Exner [35] advocates an alternative method for the treatment of experimental data. If the rates of several reactions in a series have been measured at two temperatures and  $\log k_2$  (at  $T_2$ ) is linearly related to  $\log k_1$  (at  $T_1$ ), i.e.,  $\log k_2 = a + b \log k_1$ , he proposes that  $\beta$  can be evaluated from the equation,

$$\beta = T_1 T_2 (b - 1) / (T_2 b - T_1)$$

We have calculated the isokinetic temperature as 314.1 K by plotting  $\log k_2$  at 303 K versus  $\log k_1$  at 298 K ( $r \geq 0.9987$ ,  $s \leq 0.005$ ) as in [Fig. 6](#). The value of  $\beta$  (314.1 K) is higher than

experimental temperature (298 K). This indicates that the rate is governed by enthalpy of activation [36]. The linearity and the slope of the plot obtained may confirm that the kinetics of these reactions follow a similar mechanism, as previously suggested.

## CONCLUSIONS

The Os(VIII) catalyzed oxidation of 6-aminopenicillanic acid by diperiodatocuprate(III) was studied. Among the various species of copper(III) in alkaline medium, monoperiodatocuprate(III),  $[\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$  is considered to be the active species for the title reaction. The active species of Os(VIII) is found to be  $[\text{OsO}_4(\text{OH})_2]^{2-}$ . It becomes apparent that, in carrying out this reaction, the role of reaction medium is crucial. Activation parameters were evaluated. Catalytic constants and the activation parameters with reference to catalyst were also computed. The overall sequence described here is consistent with all the experimental evidences including the product, spectral, mechanistic and kinetic studies.

## APPENDIX

According to [Scheme 1](#)

$$\text{Rate} = k[C][\text{DPC}] = \frac{kK_1K_2K_3[6\text{-APA}][\text{Os(VIII)}][\text{DPC}][\text{OH}^-]}{[\text{H}_3\text{IO}_6^{2-}]} \quad (1)$$

The total concentration of DPC is given by (where T and f stands for total and free)

$$\begin{aligned} [\text{DPC}]_T &= [\text{DPC}]_f + [\text{Cu}(\text{H}_2\text{IO}_6)(\text{H}_3\text{IO}_6)]^{2-} + [\text{Cu}(\text{H}_3\text{IO}_6)_2]^- \\ &= [\text{DPC}]_f \left[ \frac{K_1K_2[\text{OH}^-] + [\text{H}_3\text{IO}_6^{2-}] + K_1[\text{OH}^-][\text{H}_3\text{IO}_6^{2-}]}{[\text{H}_3\text{IO}_6^{2-}]} \right] \end{aligned}$$

Therefore,

$$[\text{DPC}]_f = \left[ \frac{[\text{DPC}]_T [\text{H}_3\text{IO}_6^{2-}]}{K_1K_2[\text{OH}^-] + [\text{H}_3\text{IO}_6^{2-}] + K_1[\text{OH}^-][\text{H}_3\text{IO}_6^{2-}]} \right] \quad (2)$$

Similarly

$$\begin{aligned} [6\text{-APA}]_T &= [6\text{-APA}]_f + [C] = [6\text{-APA}]_f + K_3 [6\text{-APA}]_f [\text{Os(VIII)}] \\ &= [6\text{-APA}]_f \left[ 1 + K_3 [\text{Os(VIII)}] \right] \end{aligned}$$

In view of low concentrations of Os(VIII) used,

$$[6\text{-APA}]_T = [6\text{-APA}]_f \quad (3)$$

Similarly,

$$[\text{OH}^-]_T = [\text{OH}^-]_f \text{ and } [\text{H}_3\text{IO}_6^{2-}]_T = [\text{H}_3\text{IO}_6^{2-}]_f \quad (4)$$

$$[\text{Os(VIII)}]_T = [\text{Os(VIII)}]_f + [C] = [\text{Os(VIII)}]_f + K_3 [6\text{-APA}] [\text{Os(VIII)}]_f$$

$$[\text{Os(VIII)}]_f = \left[ \frac{[\text{Os(VIII)}]_T}{\{1 + K_3 [6\text{-APA}]\}} \right] \quad (5)$$

Substituting (2), (3), (4) and (5) in (1) and omitting the subscripts T and f, we get

$$\text{rate} = \frac{-d [\text{DPC}]}{dt} = \frac{kK_1K_2K_3[6\text{-APA}][\text{OH}^-][\text{Os(VIII)}][\text{DPC}]}{K_1K_2[\text{OH}^-] + [\text{H}_3\text{IO}_6^{2-}] + K_1[\text{OH}^-][\text{H}_3\text{IO}_6^{2-}] + K_1K_2K_3[6\text{-APA}][\text{OH}^-]}$$

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## FIGURE CAPTIONS

**Figure 1** Chromatogram and LC- ESI-MS spectra of the product, 2-formyl-5,5 dimethyl thiazolidine 4-carboxylic acid, of oxidation of 6-aminopenicillanic acid by diperiodatocuprate(III).

**Figure 2** Plot of  $k_C$  versus  $[6\text{-APA}]^{0.63}$  and  $k_C$  versus  $[6\text{-APA}]$ .

**Figure 3** Plot of  $k_C$  versus  $[\text{OH}^-]^{0.40}$  and  $k_C$  versus  $[\text{OH}^-]$ .

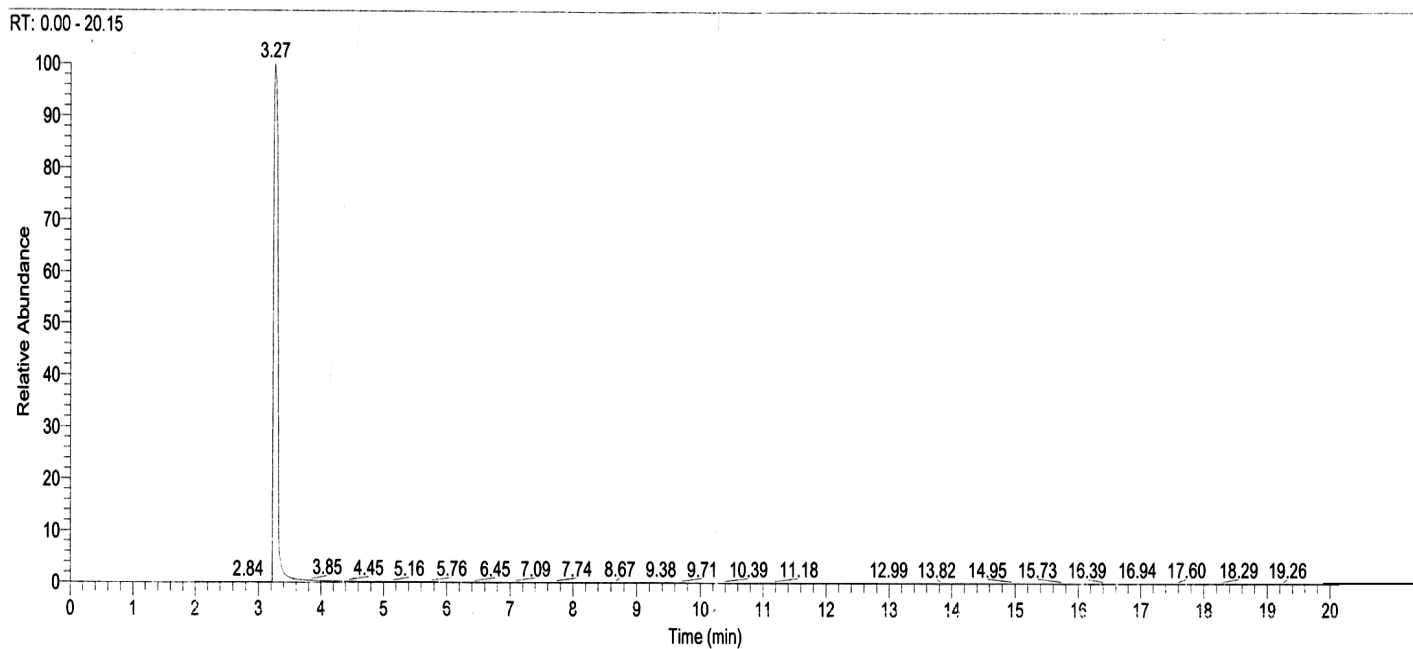
**Figure 4** Unit order plot of  $[\text{Os(VIII)}]$  versus  $k_C$ .

**Figure 5** Verification of rate law (10) of Os(VIII) catalyzed oxidation of 6-APA by DPA at four different temperatures. Plots of (A)  $[\text{Os(VIII)}]/k_C$  versus  $1/[6\text{-APA}]$ , (B)  $[\text{Os(VIII)}]/k_C$  versus  $1/[\text{OH}^-]$ , (C)  $[\text{Os(VIII)}]/k_C$  versus  $[\text{H}_3\text{IO}_6^{2-}]$ .

**Figure 6** Plot of  $\log k_2$  at 303 K versus  $\log k_1$  at 298 K for Os(VIII) catalyzed reaction (conditions as given in Table 4); for (1) Vanillin; (2) L-lysine; (3) L-alanine; (4) 6-aminopenicillanic acid.



Figure 1



38110-1 #75 RT: 3.27 AV: 1 NL: 2.52E8  
T: + p Full ms [50.00-500.00]

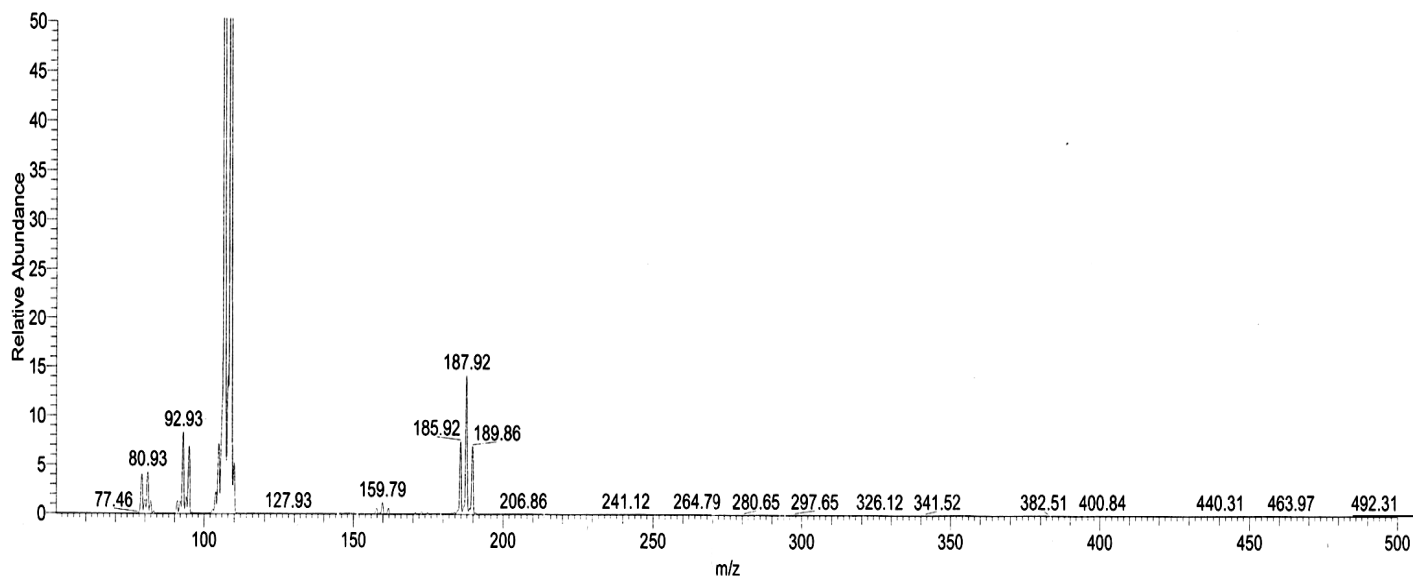


Figure 2

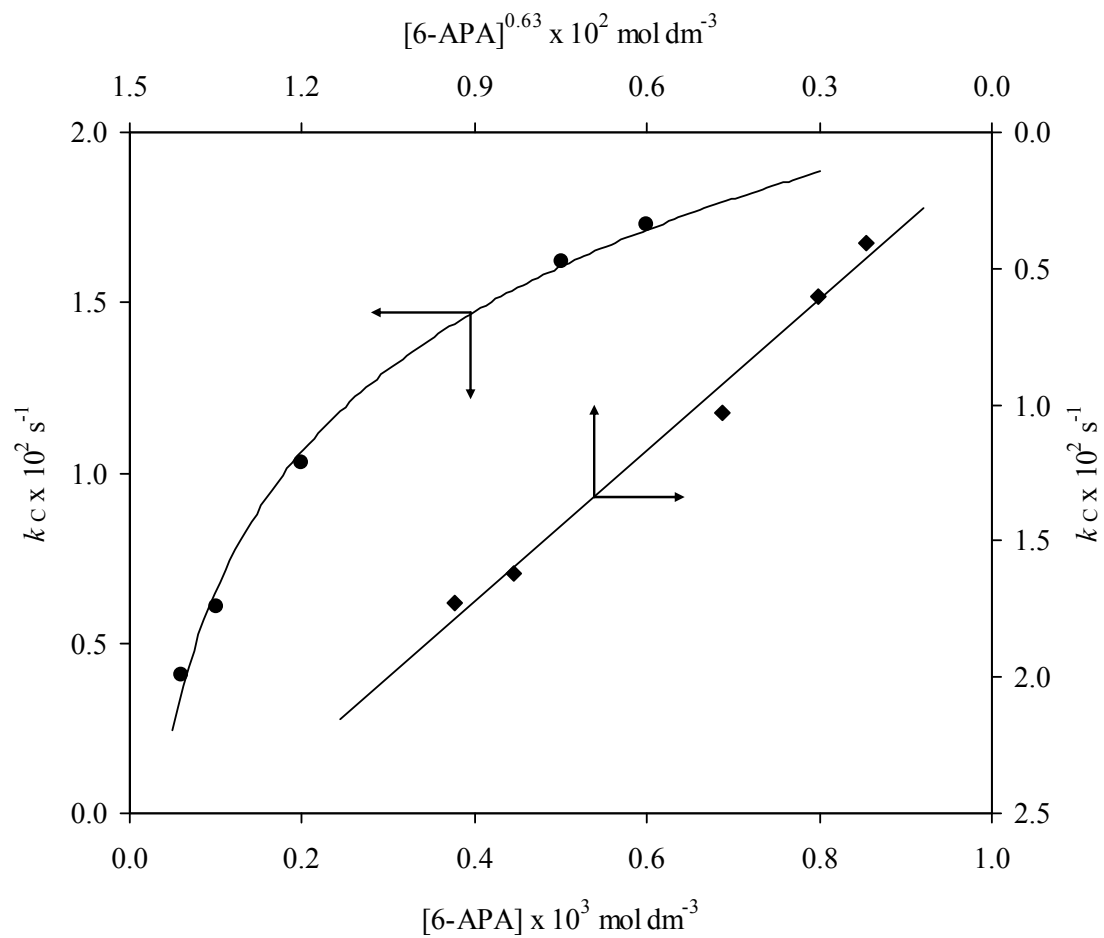


Figure 3

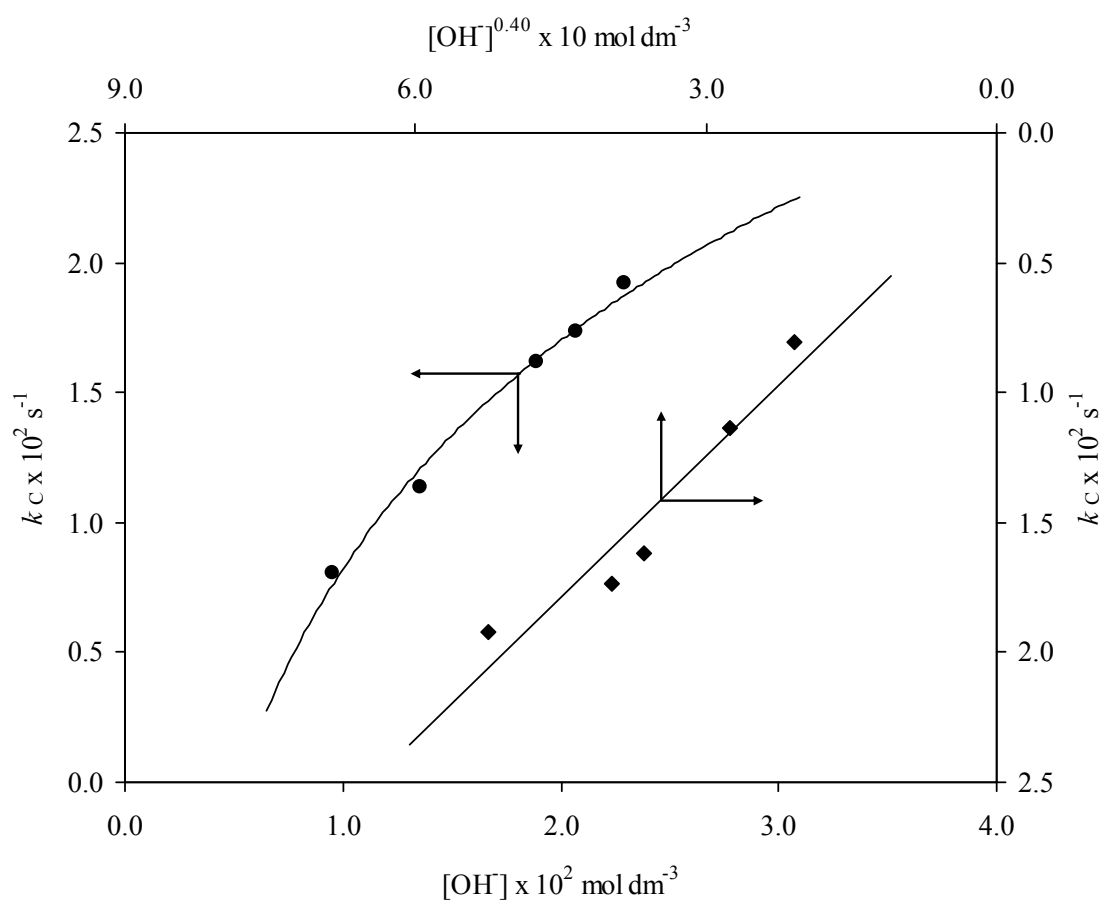


Figure 4

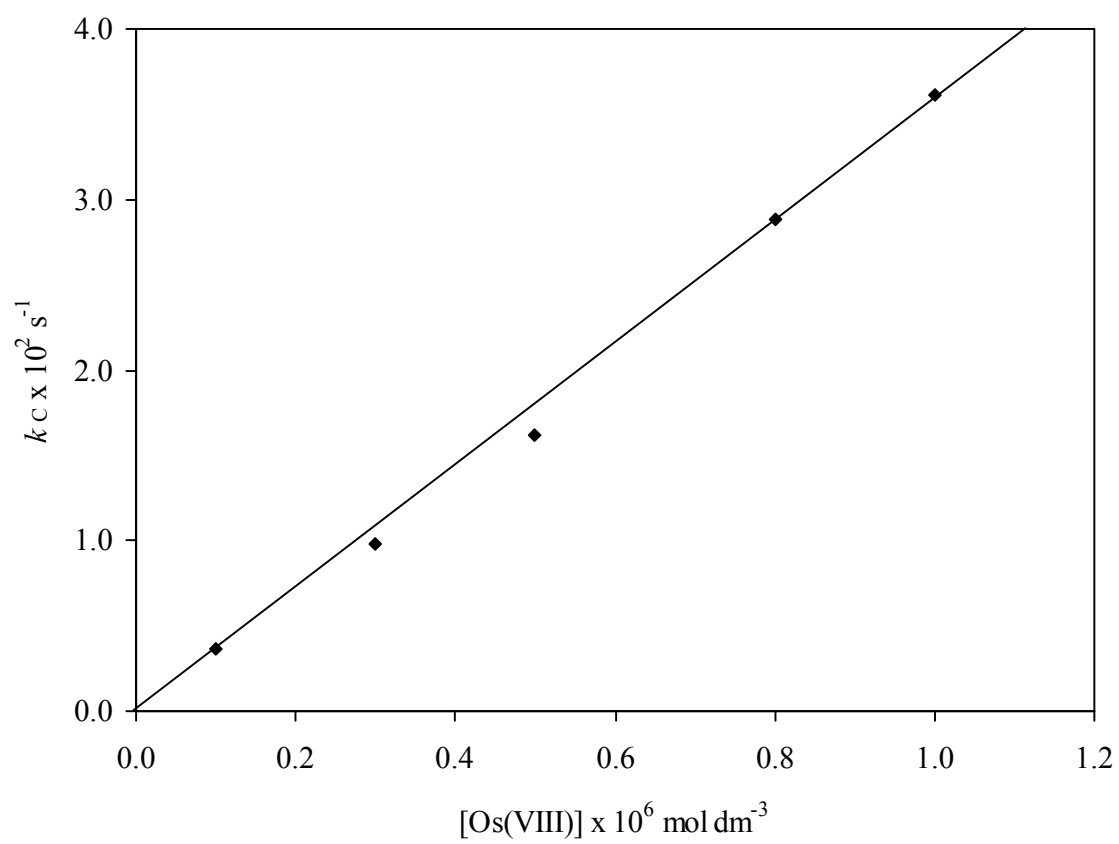
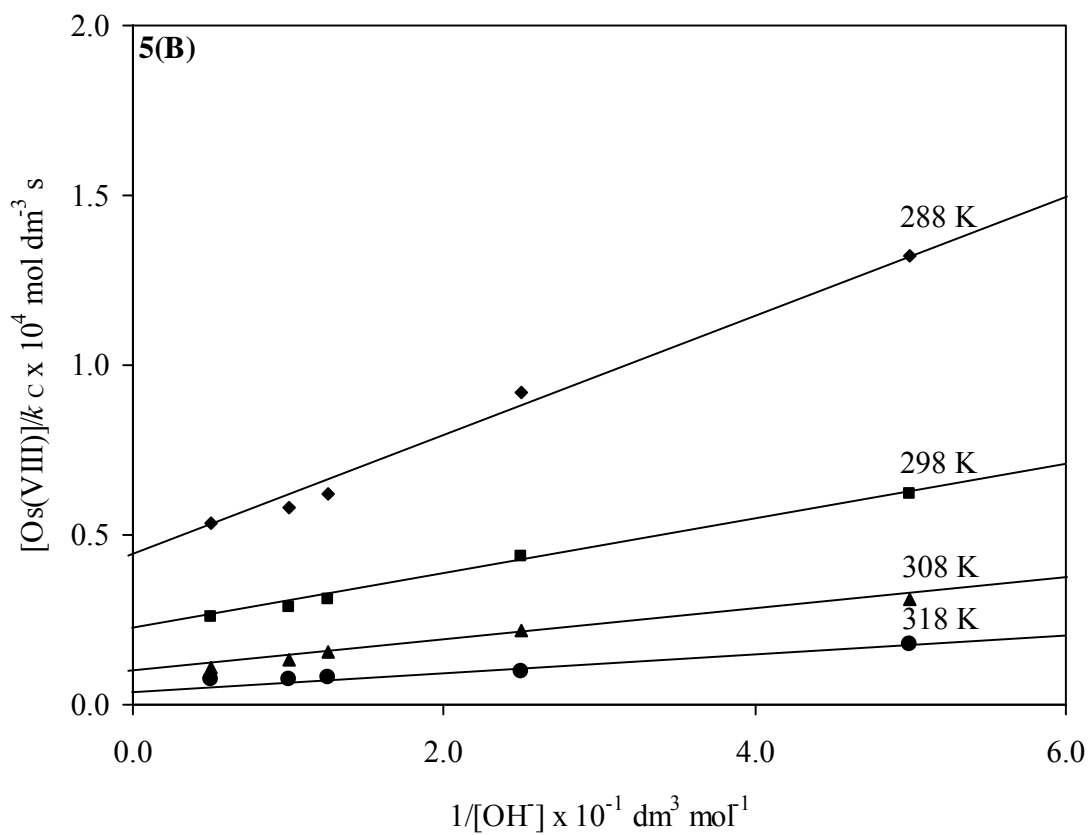
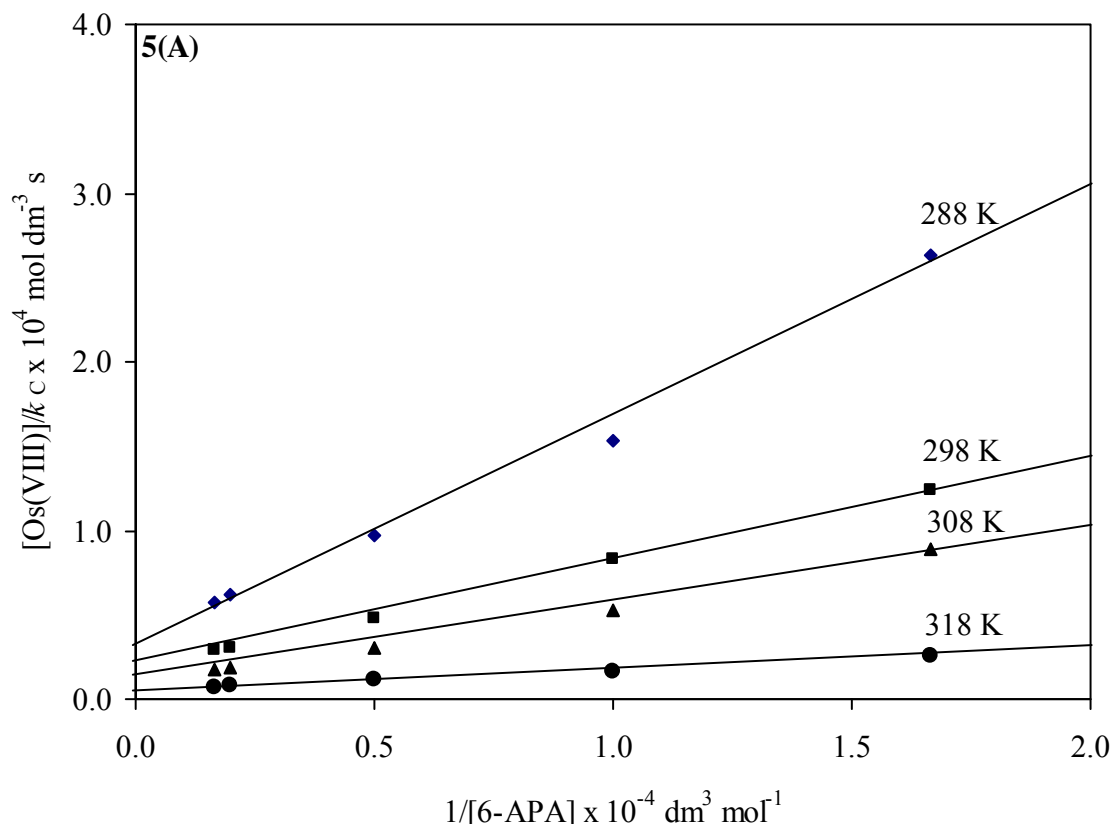


Figure 5



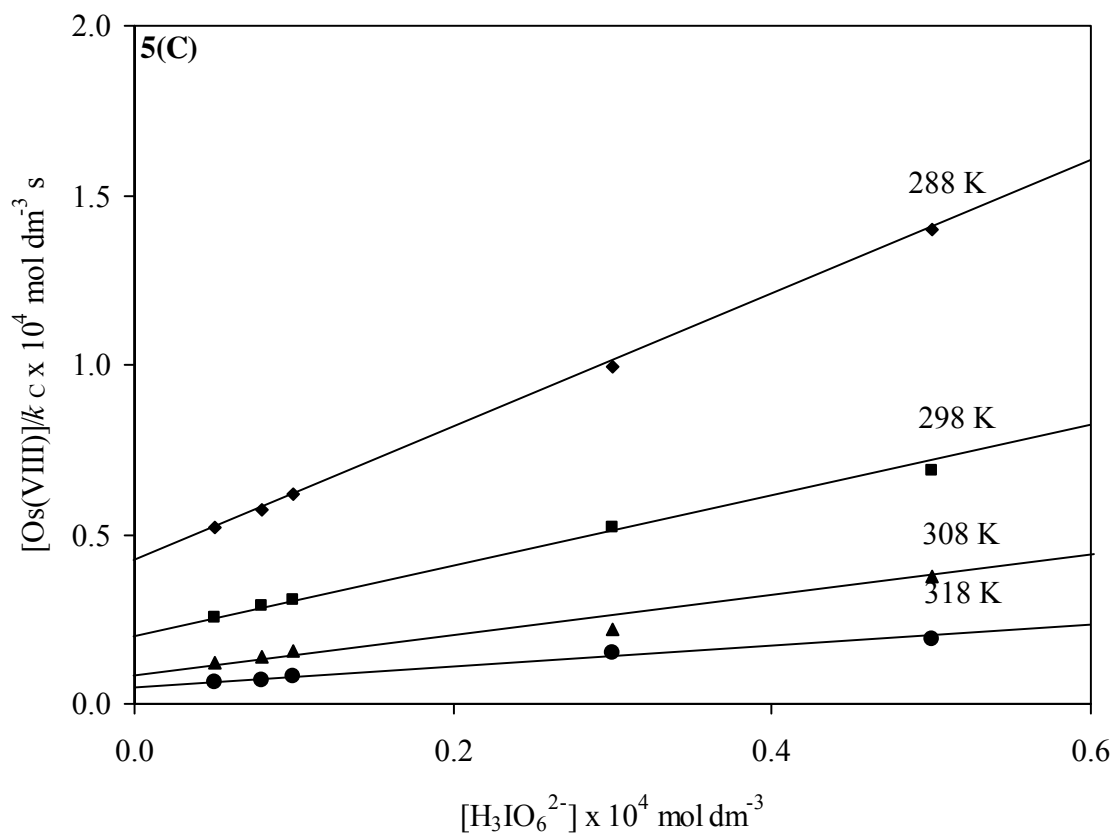
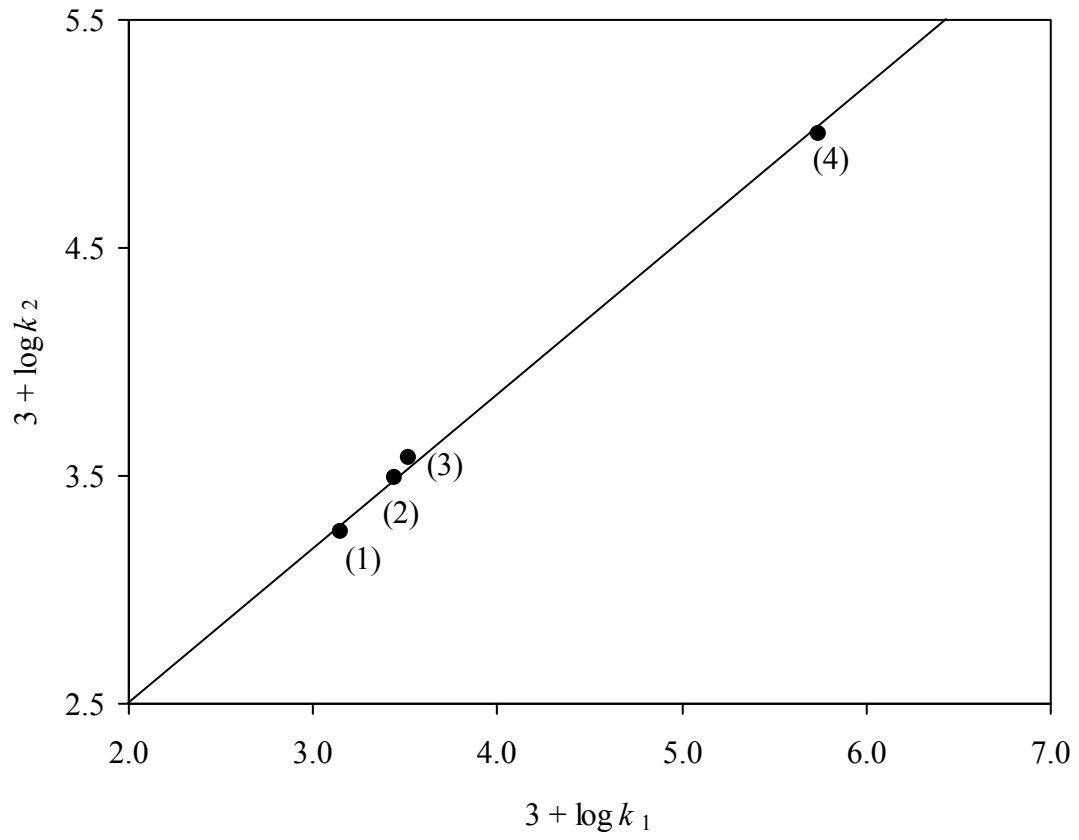


Figure 6



**Table I.** Effect of Variation of [DPC], [6-APA], [OH<sup>-</sup>], [IO<sub>4</sub><sup>-</sup>] and [Os(VIII)] on the Osmium(VIII) Catalyzed Oxidation of 6-Aminopenicillanic Acid by Diperoiodatocuprate(III) in Aqueous Alkaline Medium at 298 K and  $I = 0.20 \text{ mol dm}^{-3}$ .

[DPC]×10 <sup>5</sup> (mol dm <sup>-3</sup> )	[6-APA]× 10 <sup>4</sup> (mol dm <sup>-3</sup> )	[OH <sup>-</sup> ]×10 <sup>1</sup> (mol dm <sup>-3</sup> )	[IO <sub>4</sub> <sup>-</sup> ]×10 <sup>5</sup> (mol dm <sup>-3</sup> )	[Os(VIII)]×10 <sup>7</sup> (mol dm <sup>-3</sup> )	$k_T$ ×10 <sup>2</sup> (s <sup>-1</sup> )	$k_U$ ×10 <sup>3</sup> (s <sup>-1</sup> )	$k_C \times 10^2$ (s <sup>-1</sup> )	
							Found	Calculated
1.0	5.0	0.8	1.0	5.0	1.77	2.85	1.48	1.56
3.0	5.0	0.8	1.0	5.0	1.83	2.96	1.54	1.56
5.0	5.0	0.8	1.0	5.0	1.89	2.72	1.62	1.56
8.0	5.0	0.8	1.0	5.0	1.76	2.53	1.50	1.56
10.0	5.0	0.8	1.0	5.0	1.54	2.40	1.27	1.56
5.0	0.6	0.8	1.0	5.0	0.49	0.86	0.40	0.37
5.0	1.0	0.8	1.0	5.0	0.73	1.28	0.60	0.57
5.0	2.0	0.8	1.0	5.0	1.24	2.08	1.03	0.94
5.0	5.0	0.8	1.0	5.0	1.89	2.72	1.62	1.56
5.0	6.0	0.8	1.0	5.0	2.07	3.38	1.73	1.69
5.0	5.0	0.2	1.0	5.0	0.95	1.49	0.80	0.79
5.0	5.0	0.4	1.0	5.0	1.35	2.15	1.14	1.18
5.0	5.0	0.8	1.0	5.0	1.89	2.72	1.62	1.56
5.0	5.0	1.0	1.0	5.0	2.07	3.36	1.73	1.67
5.0	5.0	2.0	1.0	5.0	2.29	3.75	1.92	1.93
5.0	5.0	0.8	0.5	5.0	2.33	3.81	1.95	1.88
5.0	5.0	0.8	0.8	5.0	2.07	3.30	1.74	1.67
5.0	5.0	0.8	1.0	5.0	1.89	2.72	1.62	1.56
5.0	5.0	0.8	3.0	5.0	1.14	1.86	0.96	0.94
5.0	5.0	0.8	5.0	5.0	0.86	1.33	0.73	0.67
5.0	5.0	0.8	1.0	1.0	0.66	2.72	0.37	0.34
5.0	5.0	0.8	1.0	3.0	1.27	2.72	0.98	0.95
5.0	5.0	0.8	1.0	5.0	1.89	2.72	1.62	1.56
5.0	5.0	0.8	1.0	8.0	3.17	2.72	2.88	2.82
5.0	5.0	0.8	1.0	10.0	3.91	2.72	3.62	3.58

[DPC] =  $5.0 \times 10^{-5}$ , [6-APA] =  $5.0 \times 10^{-4}$ , [OH<sup>-</sup>] = 0.08, [IO<sub>4</sub><sup>-</sup>] =  $1.0 \times 10^{-5}$ ,  $I = 0.20 / \text{mol dm}^{-3}$



**Table II.** Activation Parameters and Thermodynamic Quantities for the Os(VIII) Catalyzed Oxidation of 6-APA by Diperoiodatocuprate(III) in Aqueous Alkaline Medium with respect to the Slow Step of [Scheme 1](#): (A) Effect of Temperature, (B) Activation Parameters ([Scheme 1](#)), (C) Effect of Temperature on  $K_1$ ,  $K_2$  and  $K_3$  for the Os(VIII) Catalyzed Oxidation of 6-APA by Diperoiodatocuprate(III) in Aqueous Alkaline Medium, (D) Thermodynamic Quantities using  $K_1$ ,  $K_2$  and  $K_3$ .

Temperature (K)	$k \times 10^{-4} (\text{dm}^3 \text{mol}^{-1} \text{s}^{-1})$		
(A)			
288.16	3.18		
298.16	5.55		
308.16	11.8		
318.16	20.8		
Parameters	Values		
(B)			
$E_a$ (kJ mol <sup>-1</sup> )	49 ± 2		
$\Delta H^\ddagger$ (kJ mol <sup>-1</sup> )	46 ± 1		
$\Delta S^\ddagger$ (JK <sup>-1</sup> mol <sup>-1</sup> )	0.17 ± 0.01		
$\Delta G^\ddagger$ (kJ mol <sup>-1</sup> )	46 ± 1		
log $A$	13.3 ± 0.3		
Temperature (K)	$K_1 (\text{dm}^3 \text{mol}^{-1})$	$K_2 \times 10^4 (\text{mol dm}^{-3})$	$K_3 \times 10^{-4} (\text{dm}^3 \text{mol}^{-1})$
(C)			
288.16	0.09 ± 0.02	6.1 ± 0.2	0.6 ± 0.1
298.16	0.16 ± 0.05	2.5 ± 0.1	1.1 ± 0.1
308.16	0.29 ± 0.06	0.6 ± 0.05	2.0 ± 0.1
318.16	0.65 ± 0.07	0.2 ± 0.03	3.3 ± 0.2
Thermodynamic quantities	Values from $K_1$	Values from $K_2$	Values from $K_3$
(D)			
$\Delta H$ (kJ mol <sup>-1</sup> )	49 ± 2	-90 ± 2	44 ± 1
$\Delta S$ (JK <sup>-1</sup> mol <sup>-1</sup> )	150 ± 5	-371 ± 9	224 ± 4
$\Delta G_{298}$ (kJ mol <sup>-1</sup> )	3.6 ± 0.1	22.9 ± 0.7	-24.2 ± 0.5
[DPC] = 5.0 × 10 <sup>-5</sup> , [6-APA] = 5.0 × 10 <sup>-4</sup> , [OH <sup>-</sup> ] = 0.08, [IO <sub>4</sub> <sup>-</sup> ] = 1.0 × 10 <sup>-5</sup> , $I = 0.20 / \text{mol dm}^{-3}$			

**Table III.** Values of Catalytic Constant ( $K_C$ ) at Different Temperatures and Activation Parameters Calculated Using  $K_C$  Values.

Temperature (K)	$K_C \times 10^{-4}$
288.16	1.62
298.16	3.24
308.16	6.34
318.16	12.7
$E_a$ (kJ mol <sup>-1</sup> )	52.1
$\Delta H^\ddagger$ (kJ mol <sup>-1</sup> )	49.6
$\Delta S^\ddagger$ (JK <sup>-1</sup> mol <sup>-1</sup> )	5.4
$\Delta G^\ddagger$ (kJ mol <sup>-1</sup> )	48
log $A$	13.5
$[DPC] = 5.0 \times 10^{-5}$ , $[6\text{-APA}] = 5.0 \times 10^{-4}$ , $[\text{OH}^-] = 0.08$ , $[\text{Os(VIII)}] = 5.0 \times 10^{-7}$ , $[\text{IO}_4^-] = 1.0 \times 10^{-5}$ , $I = 0.20 / \text{mol dm}^{-3}$	

**Table IV.** Activation Parameters for the Os(VIII) Catalyzed Oxidation of Some Amino Acids by Diperiodatocuprate(III) (for Isokinetic Temperature).

Amino acids	$k_1 \times 10^{-4}$ ( $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ ) at 298 K	$k_2 \times 10^{-4}$ ( $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ ) at 303 K	$\Delta H^\ddagger$ ( $\text{kJ mol}^{-1}$ )	$\Delta S^\ddagger$ ( $\text{J K}^{-1} \text{mol}^{-1}$ )	Reference
Vanillin	1.4	1.8	41.0	-25.7	[36]
L-lysine	2.8	3.1	15.5	-107	[36]
L-alanine	3.3	3.8	25.2	-6.7	[36]
6-APA	5.5	1.1	46.1	0.17	Present work