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Mechanistic investigation on the oxidation of ampicillin drug by diperiodatoargentate (III) in aqueous alkaline medium

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The kinetics of oxidation of antibiotic drug, ampicillin (AMP) by diperiodatoargentate (III) (DPA) in alkaline medium at a constant ionic strength of 0.25-mol dm^{-3} was studied spectrophotometrically. The reaction between DPA and AMP in alkaline medium exhibits 1:2 stoichiometry (AMP:DPA). The reaction is of first order in [DPA] and has less than unit order in both [AMP] and [alkali]. Added periodate retarded the rate of reaction and intervention of free radicals was observed in the reaction. The oxidation reaction in alkaline medium has been shown to proceed via a DPA–AMP complex, which decomposes slowly in a rate-determining step followed by other fast steps to give the products. The main products were identified by spot test, IR and NMR studies. The reaction constants involved in the different steps of the mechanism are calculated. The activation parameters with respect to slow step of the mechanism were computed and discussed and thermodynamic quantities were also determined. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: kinetics; mechanism; ampicillin; oxidation; diperiodatoargentate (III)

INTRODUCTION

In recent years, research of the active-intermediate and their related reaction become more and more important in biological science. Ampicillin (AMP), (6R)-6-(α-phenyl-D-glycylamino)penicillanic acid is a semisynthetic penicillin.[1] It is prepared from the benzylpenicillin or penicillin-G,[2] which is prepared by a biosynthetic process using various strains of *Penicillium notatum* and *Penicillium chrysogenum*.[3] Penicillin-G was the first antibiotic to be used in the chemotherapy. It is a bacteriostatic and a drug of choice for the treatment of the infections caused by most of the Gram-positive and Gram-negative bacteria.[4] AMP is a broad spectrum antibiotic.[5] AMP is acidic in nature, and it acts by inhibiting the protein synthesis [6] of the bacterial cell wall. The side chain determines the antibacterial and pharmacological characteristics of this compound.[7]

Diperiodatoargentate (III) (DPA) is a powerful oxidizing agent in alkaline medium with the reduction potential [8] 1.74 V. It is widely used as a volumetric reagent for the determination of various organic and inorganic species.[9,10] Jayaprakash Rao *et al.*[11,12] have used DPA as an oxidizing agent for the kinetics of oxidation of various organic substrates. They normally found that order with respect to both oxidant and substrate was unity and [OH$^-$] was found to enhance the rate of reaction. It was also observed that they did not arrive the possible active species of DPA in alkali, and on the other hand they proposed mechanisms by generalizing the DPA as [Ag(HL)L]$^{(x+1)-}$. However, Kumar *et al.*[13–15] put an effort to give an evidence for the reactive form of DPA in the large scale of alkaline pH. When the silver(III) periodate complex is oxidant and multiple equilibria between different silver(III) species are involved, it would be interesting to know which of the species is the active oxidant.

There is no report on the kinetics of oxidation of AMP drug by any oxidant in alkaline medium. Such oxidation studies may throw some light on the mechanism of conversions of compounds in biological system. In view of the complexity of the title reaction, a detailed study of the reaction becomes important. Hence the title reaction is undertaken to understand the mechanism and active species in such media.

EXPERIMENTAL

Materials and reagents

All chemicals used were of reagent grade and Millipore water was used throughout the work. A solution of AMP (Sigma Aldrich) was prepared by dissolving an appropriate amount of recrystallized sample in Millipore water. The purity of the AMP was checked by its m.p. 207 °C [Lit.m.p. 208 °C]. The IR spectrum agreed with literature. The required concentration of AMP was obtained from its stock solution. KNO$_3$ and KOH (BDH) were used to maintain the ionic strength and alkalinity of the reaction, respectively. An aqueous solution of AgNO$_3$ was used to study the product effect, Ag(I). A stock standard solution of IO$_4^-$ was prepared by dissolving a known weight of KIO$_4$ (Riedel-de Haen) in hot water and used after keeping for 24 h to attain equilibrium. Its concentration was ascertained iodometrically,[16] at neutral pH maintained, using

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phosphate buffer. The pH of the medium in the solution was measured by ELICO (LI613) pH meter.

DPA was prepared by oxidizing Ag(I) in presence of KIO_4 as described elsewhere:[17,18] The complex was characterized from its UV spectrum, which exhibited three peaks at 216, 255, and 362 nm. These spectral features were identical to those reported earlier for DPA.[17] The magnetic moment study revealed that the complex is diamagnetic. The compound prepared was analyzed[19] for silver and periodate by acidifying a solution of the material with HCl, recovering and weighing the AgCl for Ag, and titrating the iodine liberated when excess of KI was added to the filtrate for IO_4^-. The stock solution of DPA was used for the required [DPA] solution in the reaction mixture. During the kinetics a constant concentration *viz.* 1.0×10^{-4} mol dm^{-3} of KIO_4 was used throughout the study unless otherwise stated. Thus, the possibility of oxidation of AMP by periodate was tested and found that there was no significant interference due to KIO_4 under experimental condition. The total concentrations of periodate and OH^- was calculated by considering the amount present in the DPA solution and that additionally added. Kinetics runs were also carried out in 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 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. Added carbonate had no effect on the reaction rate.

Kinetics

The kinetic measurements were performed on a Varian CARY 50 Bio UV–Vis Spectrophotometer under pseudo first order condition where [AMP] > [DPA] at 25 ± 0.1 °C, unless specified. The reaction was initiated by mixing the DPA to AMP solution, which also contained required concentration of KNO_3, KOH, and KIO_4; and the progress of reaction was followed spectrophotometrically at 360 nm by monitoring decrease in absorbance due to DPA (molar absorbancy index, 'ε' to be $13\,900 \pm 100$ dm^3 mol^{-1} cm^{-1}). The spectral changes during the chemical reaction for the standard condition at 25 °C are given in Fig. 1, It was verified that there is a negligible interference from other species present in the reaction mixture at this wavelength.

The pseudo-first order rate constants, 'k_{obs}', were determined from the log (absorbance) *versus* time plots. The plots were linear up to 85% completion of reaction under the range of [OH^-] used. The rate constants were reproducible to within ± 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.

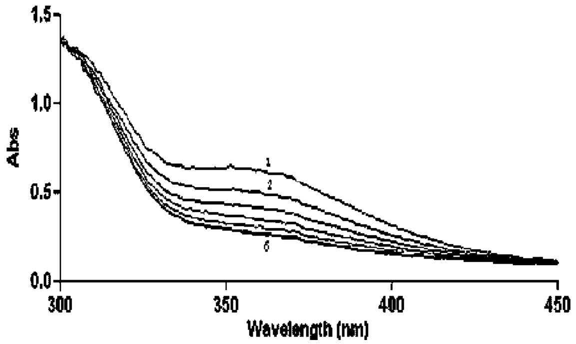
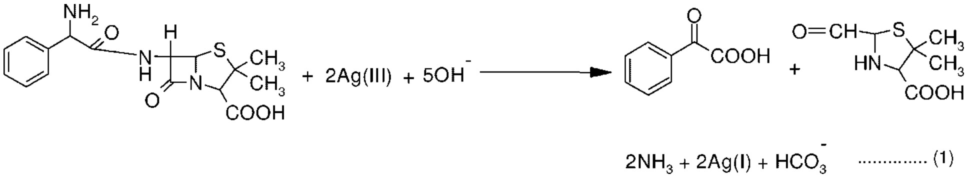


Figure 1. Spectroscopic changes occurring in the oxidation of ampicillin by [diperiodatoargentate(III)] at 298 K, [DPA] = 5.0×10^{-5}, [AMP] = 5.0×10^{-4}, [OH^-] = 0.15, and I = 0.25 mol dm^{-3} with scanning time interval of: (1) 0.5, (2) 1.0, (3) 1.5, (4) 2.0, (5) 2.5, and (6) 3.0 min

RESULTS AND DISCUSSION

Stoichiometry and product analysis

Different sets of reaction mixtures containing varying ratios of DPA to AMP in presence of constant amounts of OH^- and KNO_3 were kept for 4 h in closed vessel under nitrogen atmosphere. The remaining concentration of DPA was estimated by spectrophotometrically at 360 nm. The results indicate that 1:2 stoichiometry as given in



The main two products, oxo-phenyl acetic acid and 2-formyl-5,5-dimethyl-thiazolidine-4-carboxlic acid were separated by column chromatography over neutral alumina using a mixture of benzene and chloroform (80:20 v/v) as eluent. Evaporation of the fractions gave a pure product, which showed a single spot on TLC plate.

IR spectrum of oxo-phenyl acetic acid showed a sharp absorption peak at 1735.1 cm^{-1} (due to ketone C=O stretch), 1651.2 cm^{-1} (due to carboxylic C=O stretch), and a broad peak at 3334.4 cm^{-1} (due to carboxylic OH). ^{1}H NMR (300 MHz, DMSO d_6) δ: 10.9 (s, 1H, carboxylic OH exchangeable with D_2O), 7.38–7.8 (m, 5H, ArH). Further this product was characterized by GC-MS that gives m/z at 149 as (m − 1).

The IR spectrum of 2-formyl-5, 5-dimethyl-thiazolidine-4-carboxylic acid showed a sharp absorption peak at 1738.3 cm^{-1} (due to aldehyde C=O stretch), 1673.4 cm^{-1} (due to carboxylic C=O stretch), and 1378.3 cm^{-1} (due to —CH_3 stretch). N—H stretching shows absorptions at 3430.1 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$ d_6) δ: 1.61 (s, 6H, gem dimethyl), 2.60 (s, 1H, NH exchangeable with D_2O), 4.01(s, 1H, 4C—H), 4.31 (s, 1H, 2C—H), 8.9 (s, 1H, formyl), 10.09 (s, 1H, carboxylic OH exchangeable with D_2O). Further this product was characterized by GC-MS that gives m/z at 190.2 as (m + 1). Both the products showed positive results in spot test.

The by-products were identified as ammonia by Nessler's reagent and the CO_2 was qualitatively detected by bubbling nitrogen gas through the acidified reaction mixture and passing the liberated gas through a tube containing lime water.

Reaction orders

The reaction orders were determined from the slope of log k_{obs} *versus* log (concentration) plots by varying the concentrations of AMP, alkali, and periodate, in turn, while keeping all other concentrations and conditions constant.

Effect of [diperiodatoargentate (III)]

The oxidant DPA concentration was varied in the range of 1.0×10^{-5}–1.0×10^{-4} mol dm^{-3} and the fairly constant k_{obs} values indicate that order with respect to [DPA] was one (Table 1). This was also confirmed by linearity of the plots of log [absorbance] *versus* time ($r \geq 0.996$, $S \leq 0.04$) up to 80% completion of the reaction.

Effect of [ampicillin]

The effect of AMP on the rate of reaction was studied at constant concentrations of alkali, DPA, and periodate at a constant ionic strength of 0.25-mol dm^{-3}. The substrate, AMP was varied in the range of 3.0×10^{-4}–3.0×10^{-3} mol dm^{-3}. The k_{obs} values increased with increase in concentration of AMP. The order with respect to [AMP] was found to be less than unity (Table 1) ($r \geq 0.994$, $S \leq 0.006$).

Effect of [alkali]

The effect of alkali on the reaction has been studied in the range of 0.02–0.2 mol–dm^{-3} at constant concentrations of AMP, DPA, and a constant ionic strength of 0.25 mol dm^{-3} at 25 °C. The rate constants increase with increase in [alkali] and order was found to be less then unity (Table 1).

Effect of [periodate]

Periodate was varied from 5.0×10^{-5} to 5.0×10^{-4} mol dm^{-3} keeping all other reactant concentrations constant. It was observed that the rate constants decreased with increase in [IO_4^-] (Table 1).

Effect of ionic strength (I) and dielectric constant of the medium (D)

Ionic strength and dielectric constant of medium had no effect on the rate of reaction.

Effect of initially added products

The externally added products, Ag(I) did not have any significant effect on the rate of the reaction.

Polymerization study

The reaction mixture was mixed with a known quantity of acrylonitrile monomer and kept for 4 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 DPA or AMP alone with acrylonitrile did not induce any polymerization under the same condition as those induced for reaction mixture. Initially added acrylonitrile decreases the rate of reaction indicating free radical intervention, which is the case in earlier work.[20,21]

Table 1. Effect of [DPA], [AMP], [OH^-], and [IO_4^-] on the oxidation of ampicillin by DPA(III) in alkaline medium at 25 °C, $I = 0.25$ mol dm^{-3}

10^5 [DPA] (mol dm^{-3})	10^4 [AMP] (mol dm^{-3})	[OH^-] (mol dm^{-3})	10^4 [IO_4^-] (mol dm^{-3})	$10^3 k_{obs}$ (s^{-1})	$10^3 k_{cal}$ (s^{-1})
1.0	5.0	0.15	1.0	4.28	4.26
3.0	5.0	0.15	1.0	4.27	4.26
5.0	5.0	0.15	1.0	4.30	4.26
8.0	5.0	0.15	1.0	4.29	4.26
10.0	5.0	0.15	1.0	4.27	4.26
5.0	3.0	0.15	1.0	3.60	3.45
5.0	5.0	0.15	1.0	4.30	4.26
5.0	10.0	0.15	1.0	5.07	5.17
5.0	15.0	0.15	1.0	5.49	5.56
5.0	20.0	0.15	1.0	5.91	5.78
5.0	30.0	0.15	1.0	6.32	6.20
5.0	5.0	0.02	1.0	2.24	2.21
5.0	5.0	0.05	1.0	3.14	3.25
5.0	5.0	0.08	1.0	3.79	3.79
5.0	5.0	0.15	1.0	4.30	4.26
5.0	5.0	0.2	1.0	4.61	4.50
5.0	5.0	0.15	0.5	4.75	4.62
5.0	5.0	0.15	0.8	4.54	4.40
5.0	5.0	0.15	1.0	4.30	4.26
5.0	5.0	0.15	3.0	3.50	3.40
5.0	5.0	0.15	5.0	2.89	2.76

Effect of temperature

The kinetics was studied at, 298, 303, 308, and 313 K, four different temperatures under varying concentrations of AMP, alkali, and periodate, keeping other conditions constant. The rate constants were found to increase with increase in temperature. The rate constants (k) of the slow step of Scheme 1 were obtained from the slopes and intercepts of $1/k_{obs}$ *versus* 1/[AMP], $1/[OH^-]$, and $[H_3IO_6^{2-}]$ plots at four different temperatures. The values of $k \times 10^3$ (s^{-1}) were obtained as 6.56, 7.09, 7.89, and 9.12, at 298, 303, 308, and 313 K, respectively. The activation parameters for the rate determining step were obtained as $E_a(\text{kJ mol}^{-1}) = 16 \pm 1$, $\Delta H^{\#}(\text{kJ mol}^{-1}) = 14 \pm 2$, $\Delta S^{\#}(\text{JK}^{-1}\,\text{mol}^{-1}) = -237 \pm 10$, $\Delta G^{\#}(\text{kJ mol}^{-1}) = 85 \pm 2.0$.

In the later period of 20th century, the kinetics of oxidation of various organic and inorganic substrates have been studied by Ag(III) species which may been due to its strong versatile nature of two electrons' oxidant. Among the various species of Ag(III), $Ag(OH)_4^-$, DPA and ethylenebis (biguanide) (EBS), and silver(III) are of maximum attention to the researchers due to their relative stability.[22] The stability of $Ag(OH)_4^-$ is very sensitive toward traces of dissolved oxygen and other impurities in the reaction medium therefore it had not drawn much attention. However, the other two forms of Ag(III)[11–15,23,24] are considerably stable; the DPA is used in highly alkaline medium and EBS is used in highly acidic medium.

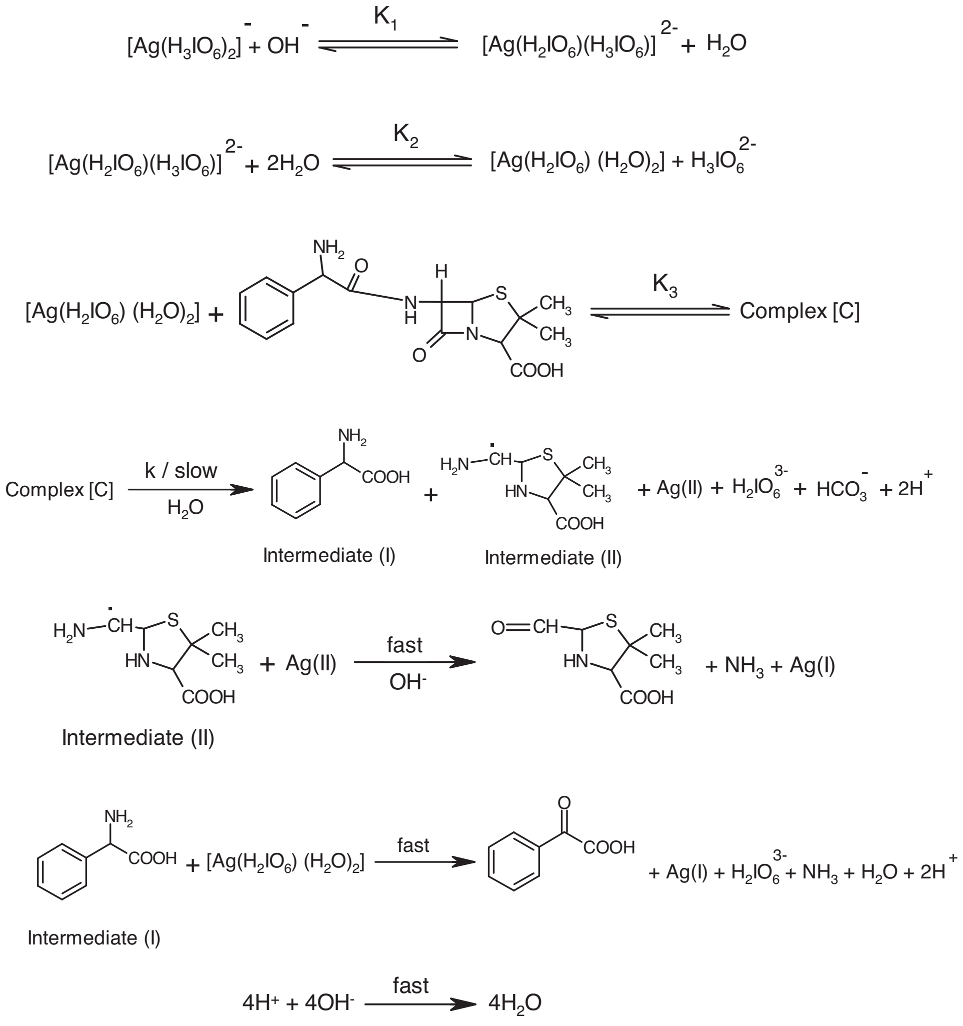
A literature survey[17] reveals that the water soluble DPA has a formula $[Ag(IO_6)_2]^{7-}$ with dsp^2 configuration of square planar structure, similar to diperiodatocopper(III) complex with two bidentate ligands, periodate to form a planar molecule. When the same molecule is used in alkaline medium, it is unlike to be existed as $[Ag(IO_6)_2]^{7-}$ as periodate is known to be in various protonated forms[25,26] depending on pH of the solution as given in following multiple equilibria:

$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+ \tag{2}$$

$$H_4IO_6^- \rightleftharpoons H_3IO_6^{2-} + H^+ \tag{3}$$

$$H_3IO_6^{2-} \rightleftharpoons H_2IO_6^{3-} + H^+ \tag{4}$$

Periodic acid (H_5IO_6) exists in acid medium and also as $H_4IO^-{}_6$ at pH 7. Thus, under the present alkaline conditions, the main species are expected to be $H_3IO_6^{2-}$and $H_2IO_6^{3-}$. At higher concentrations, periodate also tends to dimerise.[27] However, formation of this species is negligible under the conditions employed for this kinetic study. On the contrary, the authors[11,12] in their recent studies have proposed the DPA as $[Ag(HL)_2]^{x-}$ in which 'L' is a periodate with uncertain number of protons and 'HL'



Scheme 1. Detailed scheme for the oxidation of ampicillin by alkaline 0iperiodatoargentate(III)

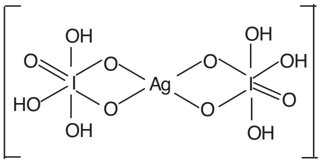
is a protonated periodate of uncertain number of protons. This can be ruled out by considering the alternative form[25,26] of IO_4^- at pH > 7 which is in the form $H_3IO_6^{2-}$ or $H_2IO_6^{3-}$. Hence, DPA could be as $[Ag(H_3IO_6)_2]^-$ or $[Ag(H_2IO_6)_2]^{3-}$ in alkaline medium. Therefore, under the present condition, DPA, may be depicted as $[Ag(H_3IO_6)_2]^-$. The similar speciation of periodate in alkali was proposed[28] for diperiodatonickelate(IV).

Mechanism

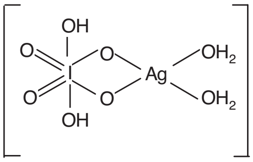
The reaction between DPA and Amicillin in alkaline medium presents a 1:2 stoichiometry of oxidant to reductant. Since, the reaction was enhanced by $[OH^-]$, added periodate retarded the rate and first order dependency in [DPA] and fractional order in [AMP] and $[OH^-]$, the following mechanism has been proposed which also explains all other experimental observations (Scheme 1).

In the prior equilibrium step 1, the $[OH^-]$ deprotonates the DPA to give a deprotonated DPA; in the second step, displacement of a ligand, periodate takes place to give free periodate which is evidenced by decrease in the rate with increase in [periodate] (Table 1). It may be expected that lower Ag(III) periodate species such as monoperiodatoargentate(III) (MPA) will be more important in the reaction than the DPA. The inverse fractional order in $[H_3IO_6^{2-}]$ might also be due to this reason. In the pre-rate-determining stage, this MPA, combines with a molecule of AMP to give a complex. This complex [C] decomposes in a slow step, to form phenyl glycine and a free radical species as intermediates. The formation of intermediate Ag(II) species is evidenced by earlier work.[13–15,29] This free radical species combines with Ag(II) species in a fast step to form carboxylic aldehyde compound. The phenyl glycine then reacts with another molecule of MPA in a fast step to form the product such as oxo-phenyl acetic acid. The oxidation of phenyl glycine is well documented in the literature.[30]

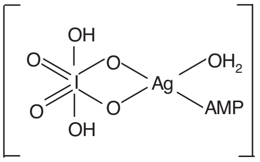
On the basis of square planar structure of DPA, the structure of MPA and complex may be proposed as below:



DPA



MPA



Complex

Spectroscopic evidence for the complex formation between oxidant and substrate was obtained from UV–Vis spectra of AMP [(5.0×10^{-4}), DPA (5.0×10^{-5}), $[OH^-] = 0.15\ mol\ dm^{-3}$)] and mixture of both. A bathochromic shift of about 4 nm from 332 to 336 nm in the spectra of DPA was observed. The rate law for the Scheme 1 could be derived as

$$\text{rate} = -\frac{d[DPA]}{dt} = \frac{k K_1 K_2 K_3 [DPA][OH^-][AMP]}{[H_3IO_6^{2-}] + K_1[OH^-][H_3IO_6^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][AMP]} \quad (5)$$

$$k_{obs} = \frac{k K_1 K_2 K_3 [OH^-][AMP]}{[H_3IO_6^{2-}] + K_1[OH^-][H_3IO_6^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][AMP]} \quad (6)$$

The rate law (6) can be rearranged into the following form for verification:

$$\frac{1}{k_{obs}} = \frac{[H_3IO_6^{2-}]}{k K_1 K_2 K_3 [OH^-][AMP]} + \frac{[H_3IO_6^{2-}]}{k_1 K_2 K_3 [AMP]} + \frac{1}{k K_3 [AMP]} + \frac{1}{k} \quad (7)$$

According to Eqn (7), other conditions being constant, plots of $1/k_{obs}$ *versus* $1/[OH^-]$ $(r \geq 0.995, S \leq 0.012)$, $1/k_{obs}$ *versus* 1/[AMP] $(r \geq 0.997, S \leq 0.016)$, and $1/k_{obs}$ *versus* $[H_3IO_6^{2-}]$ $(r \geq 0.993, S \leq 0.014)$ should be linear as found in Fig. 2. The slopes and intercepts of such plots lead to the values of K_1, K_2, K_3, and k as $(0.55 \pm 0.03)\ dm^3\ mol^{-1}$, $(1.63 \pm 0.02) \times 10^{-3}\ mol\ dm^{-3}$, $(6.65 \pm 0.12) \times 10^3\ dm^3\ mol^{-1}$, and $(6.56 \pm 0.2) \times 10^{-3}\ s^{-1}$, respectively. The value of k_1 is good agreement with earlier literature.[31] Using these constants the rate constants were calculated and compared with experimental values (Table 1). The experimental rate constants were in good agreement with calculated values, which fortifies the proposed mechanism. The negligible effect of ionic strength and dielectric constant on the rate explains qualitatively the involvement of species in the reaction, as seen in Scheme 1.

The thermodynamic quantities for the first, second, and third equilibrium steps of Scheme 1 can be evaluated as follows. The [AMP], $[OH^-]$, and $[H_3IO_6^{2-}]$ as given in Table 1 were varied at four different temperatures. The plots of $1/k_{obs}$ *versus* 1/[AMP], $1/k_{obs}$ *versus* $1/[OH^-]$, and $1/k_{obs}$ *versus* $[H_3IO_6^{2-}]$ should be linear (Fig. 2). From the slopes and intercepts, the values of K_1 were calculated at different temperatures. The values of K_1 $(dm^3\ mol^{-1})$ were obtained as 0.55, 0.97, 1.20, and 2.09 at 298, 303, 308, and 313 K, respectively. A van't Hoff's plot was made for variation of K_1 with temperature (i.e., log K_1 *vs.* $1/T$ $(r \geq 0.9904, S \leq 0.006)$) and the values of enthalpy of reaction ΔH, entropy of reaction ΔS, and free energy of reaction ΔG_{298}, were calculated as $64 \pm 4\ kJ\ mol^{-1}$, $212 \pm 10\ JK^{-1}\ mol^{-1}$, and $1.44 \pm 0.3\ kJ\ mol^{-1}$, respectively. A comparison of the latter values with those obtained for the slow step of the reaction shows that these values mainly refer to the rate limiting step, supporting the fact that the reaction before the rate determining step is fairly slow and involves high activation energy.[32] In the same manner, K_2 and K_3 values were calculated at different temperatures. The values of $K_2 \times 10^3$ $(mol\ dm^{-3})$ were obtained as 1.63, 1.36, 0.82, and 0.47. Thermodynamic quantities are $\Delta H = -64 \pm 0.6\ kJ\ mol^{-1}$, $\Delta S = -270 \pm 8\ JK^{-1}\ mol^{-1}$, and $\Delta G_{298} = 15.9 \pm 0.6\ kJ\ mol^{-1}$. Similarly the values of $K_3 \times 10^{-3}$ $(dm^3\ mol^{-1})$ were obtained as 6.65, 7.10, 11.1, and 14.0. Thermodynamic quantities are

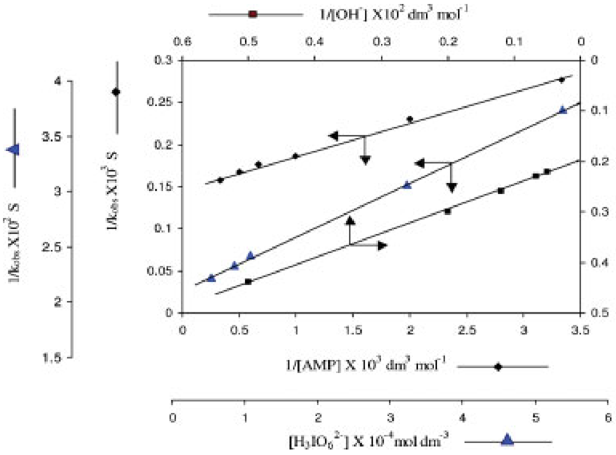


Figure 2. Verification of rate law (6) for the oxidation of ampicillin by diperiodatoargentate(III) at 25 °C.

$\Delta H = 41 \pm 1.0\,\mathrm{kJ\,mol^{-1}}$, $\Delta S = 211 \pm 9\,\mathrm{JK^{-1}\,mol^{-1}}$, and $\Delta G_{298} = -21 \pm 0.8\,\mathrm{kJ\,mol^{-1}}$.

The high negative value of $\Delta S^{\#}(-237\,\mathrm{JK^{-1}\,mol^{-1}})$ suggests that the intermediate complex is more ordered than the reactants.[33] The observed modest enthalpy of activation and a higher rate constant for the slow step indicates that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by earlier observations.[33]

CONCLUSION

Among various species of DPA in alkaline medium, $[Ag(H_2IO_6)(H_2O)_2]$ is considered as active species for the title reaction. It becomes apparent that in carrying out this reaction, the role of the reaction medium is crucial. The overall sequence described here is consistent with product, mechanistic, and kinetic studies.

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APPENDIX

According to Scheme 1

$$\text{rate} = k[C] = \frac{k\,K_1\,K_2\,K_3[\text{DPA}][\text{OH}^-][\text{AMP}]}{[\text{H}_3\text{IO}_6^{2-}]}$$

$$\begin{aligned}[\text{DPA}]_\text{T} &= [\text{DPA}]_\text{f} + [\text{Ag}(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^{2-} + [\text{Ag}(\text{H}_2\text{IO}_6)(\text{H}_2\text{O})_2] + [C] \\ &= [\text{DPA}]_\text{f}\left[1 + k_1[\text{OH}^-] + \frac{K_1\,K_2[\text{OH}^-]}{[\text{H}_3\text{IO}_6^{2-}]} + \frac{K_1\,K_2\,K_3[\text{AMP}][\text{OH}^-]}{[\text{H}_3\text{IO}_6^{2-}]}\right]\end{aligned} \qquad \text{(I)}$$

where T and f refer to total and free concentrations

$$[\mathrm{DPA}]_f = \frac{[\mathrm{DPA}]_T[\mathrm{H_3IO_6^{2-}}]}{[\mathrm{H_3IO_6^{2-}}] + K_1[\mathrm{OH^-}][\mathrm{H_3IO_6^{2-}}] + K_1K_2[\mathrm{OH^-}] + K_1K_2K_3[\mathrm{OH^-}][\mathrm{AMP}]}$$

$$[\mathrm{OH}]_T = [\mathrm{OH^-}]_f + [\mathrm{Ag(H_3IO_6)(H_2IO_6)^{2-}}] + [\mathrm{Ag(H_2IO_6)(H_2O)_2}] \tag{II}$$

$$= [\mathrm{OH}]_f + K_1[\mathrm{DPA}][\mathrm{OH^-}] + \frac{K_1K_2[\mathrm{DPA}][\mathrm{OH^-}]}{[\mathrm{H_3IO_6^{2-}}]}$$

In view of the low concentration of [DPA] and $[\mathrm{H_3IO_6^{2-}}]$ used:

$$[\mathrm{OH}]_T = [\mathrm{OH}]_f \tag{III}$$

Similarly

$$[\mathrm{AMP}]_T = [\mathrm{AMP}]_f + [C] \quad = [\mathrm{AMP}]_f + \frac{K_1K_2K_3[\mathrm{AMP}][\mathrm{DPA}][\mathrm{OH^-}]}{[\mathrm{H_3IO_6^{2-}}]}$$

In view of the low concentration of [DPA], $[\mathrm{OH^-}]$ and $[\mathrm{H_3IO_6^{2-}}]$ used:

$$[\mathrm{AMP}]_T = [\mathrm{AMP}]_f \tag{IV}$$

Substituting Eqns (II–IV) in Eqn (I) and omitting the subscripts T and f, we get

$$\text{rate} = \frac{k\,K_1K_2K_3[\mathrm{DPA}][\mathrm{OH^-}][\mathrm{AMP}]}{[\mathrm{H_3IO_6^{2-}}] + K_1[\mathrm{OH^-}][\mathrm{H_3IO_6^{2-}}] + K_1K_2[\mathrm{OH^-}] + K_1K_2K_3[\mathrm{OH^-}][\mathrm{AMP}]}$$