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UNCATALYSED OXIDATION OF ALLOPURINOL BY DIPERIODATOARGENTATE(III) COMPLEX IN AQUEOUS ALKALINE MEDIUM

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ABSTRACT

The oxidation of allopurinol (ALO) by diperiodatoargentate(III) (DPA) has been investigated spectrophotometrically the absence in alkaline medium at a constant ionic strength of 0.10mol $dm^{-3}$and Ag(I). The stoichiometry is i.e., [ALO]:[DPA] = 1:1. In the uncatalysed the order with respect to DPA concentration was unity while the order with respect to ALO concentration was < 1 over the concentration range studied. The rate increased with an increase in OH^- concentration and decreased rate with an increase in IO_4^- ion concentration. The mechanisms proposed and derived rate laws are consistent with the observed experimental kinetics. Kinetic experiments suggest that $Ag(H_2IO_6)(H_2O)_2$ is the reactive species of oxidant. The activation parameters were evaluated with respect to slow step of the mechanism.

KEYWORDS: Allopurinol (ALO), Diperiodatoargentate(III), Oxidation, Kinetics.

INTRODUCTION

Allopurinol sold under the brand name zyloprim and generics, is a medication used primarily to treat excess uric acid in the blood and its complication including chronic gout.[1] It is a xanthine oxidase inhibitor which is administered orally. It is on the world health organization list of essential medicines, a list of the most important medication needed in basic health system.

Medical uses

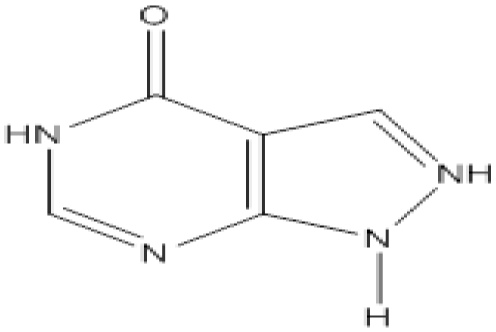
Allopurinol inhibits the breakdown (catabolism) of the thioupurine drug mercaptopurine and was specifically invented by Gertrude Elion to enhance the action of mercaptopurine in treatment of acute lymphoblastic leukemia.

It is used to treatment for

1) Gout and hyperuricemia
2) Tumorlysis syndrome
3) Thiopurine co-therapy
4) Reperfusion injury
5) Renal disease, heart failure and angina
6) Epilepsy
7) Blood pressure

Side effect

Allopurinol it is not a uricosuric. It can be used in patients with poor kidney function. Diperiodatoargentate(III) (DPA) is a powerful oxidizing agent in alkaline medium with the reduction potential 1.74V.[2] It is widely used as a volumetric reagent for the determination of various organic and inorganic species.[3-4] Jayaprakash Rao and other researchers have studied DPA as an oxidizing agent for the kinetics of oxidation of some organic substrates.[5] 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 at 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*[6-7] put an effort to give an evidence for the reactive form of DPA in large scale of alkaline pH. Ag(III) complexes can be stabilized in alkaline medium by periodate or tellurate ions.[8-9] When the Ag(III) species are involved, it would be interesting to know which of the species is the active oxidant. In the present investigation, we have obtained the evidence for the active species of DPA in alkaline medium.



Structure of Allopurinol

There is no report on the kinetics of oxidation of allopurinol by any oxidant in presence and absence of any catalyst. The authors found that, in alkaline medium, the reaction between allopurinol and DPA occurs in the absence of catalyst osmium(VIII). In view of potential pharmaceutical importance of allopurinol, to know the active species of Ag(III). Hence, the present investigation is aimed at checking the reactivity of allopurinol towards DPA in uncatalysed reactions and to arrive at the plausible mechanisms.

EXPERIMENTAL SECTION

All reagents were of analytical grade and double distilled water was used throughout the study. A stock solution of allopurinol (ALO) was prepared by dissolving an appropriate amount of recrystallised sample in double distilled water. The purity of allopurinol (ALO) was checked by its m.p.132^{o}C (Lit.m.p.130-135^{o}C). The IR spectrum agreed with literature. The required concentration of allopurinol was used from its stock solution. The ionic strength in the reaction mixture was maintained by adding KNO_3 solution and the pH value was regulated with KOH (BDH) solution. An aqueous solution of $AgNO_3$ was used to study the product effect, Ag(I). A stock solution of IO_4^- was prepared by dissolving a known weight of KIO_4 (Riedel-de-Hean) in hot water and used after 24h. Its concentration was ascertained iodometrically[10] at neutral pH maintained using phosphate buffer. The pH of the medium in the solution was measured by pH meter. Solutions of allopurinol and DPA were always freshly prepared before use.

Preparation of DPA

DPA was prepared by oxidizing Ag(I) in presence of KIO_4 as described elsewhere.[11] 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.[11] The magnetic moment study revealed that the complex was diamagnetic. The compound prepared was analyzed[12] 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 KI was added to the filtrate for IO_4^-. The aqueous solution of DPA was used for the required DPA concentration in the reaction mixture.

Instrument used

(a) For kinetic measurements, double beam UV–Vis Spectrophotometer were used.

(b) For pH measurement, digital pH meter were used.

Kinetic measurements

The kinetics runs were performed under pseudo first-order condition by ensuring an excess of [ALO] > [DPA] atleast 10 times in uncatalysed reactions at 25.0 ± 0.1ºC, unless specified. In the absence of catalyst the reaction was initiated by mixing DPA with the allopurinol solution which also contained required concentrations of KNO_3, KOH and KIO_4 the course of reaction was followed by monitoring the decrease in absorbance of DPA in a 1-cm quartz cell placed in the thermo stated compartment of double beam UV-Vis Spectrophotometer connected to a rapid kinetic accessory at its absorption maximum of 360 nm as a function of time. Application of Beer's law had been verified between 1.0×10^{-5} to 1.0×10^{-4} of DPA at 360 nm and 'ε' was found to be 13900 ±100 $dm^3 mol^{-1} cm^{-1}$. The spectral changes during the chemical reaction for the standard condition at 25^0C are given in (Fig. 1.). It was verified that there was no interference from other species in the reaction mixture at this wavelength.

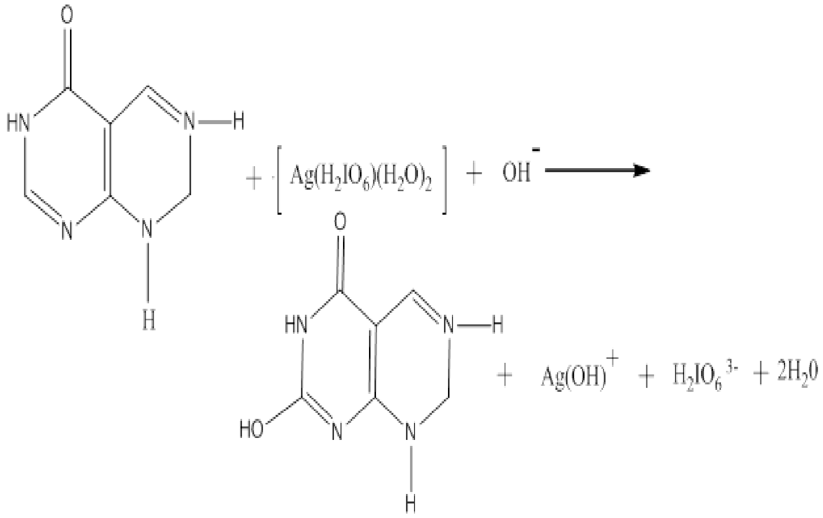
In the kinetic studies it was observed that, under the present experimental conditions in the absence of Os(VIII), the oxidation of ALO by DPA occurs slowly, but in measurable quantities. Hence, during the calculation of pseudo-first order rate constants, k_{obs}, the uncatalysed rate has also to be taken in to account. Due to this, kinetic run, a parallel kinetic run under similar conditions in the absence of catalyst were carried out. The kinetic runs were followed more than 90% completion of the reaction and good first order kinetics were observed. The pseudo-first order rate constants in absence (k_u) calculated from the slopes of the plots of log (absorbance) versus time. The pseudo first order plots in almost all cases, were linear over 85% completion of the reaction. The (k_u) values were reproducible within ± 5% and are the average of at least, three independent kinetic runs (Table 1).

In the kinetic studies a constant concentration, *viz.* $1.0 \times 10^{-5} mol\ dm^{-3}$ of KIO_4 was used throughout, unless otherwise stated. Thus, the possibility of oxidation of allopurinol (ALO) by periodate was verified and found that there was no significant reaction between allopurinol (ALO) and KIO_4 under present experimental conditions. The total concentrations of periodate and OH^- was calculated by considering the amount present in the DPA solution and that additionally added. Kinetic 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 in the presence and absence of nitrogen. In view of the ubiquitous contamination of carbonate in the basic medium, the effect of carbonate was also studied. Added carbonate had no effect on the reaction rates.

RESULTS AND DISSCUSSION

Stoichiometry and product analysis

Different sets of reaction mixtures containing varying ratios of DPA to allopurinol in presence of constant amount of OH^-, KIO_4 and KNO_3 in uncatalysed reaction were kept for 3 hrs in a closed vessel under nitrogen atmosphere. The remaining concentration of DPA was assayed by measuring the absorbance at 360 nm. The reaction products were identified as (4H-Pyrazolo[3,4]Pyrimidine-4-one and Ag(I). The results indicated 1:1 stoichiometry for uncatalysed reactions as given in Eq. (1).



Reaction order

The reaction orders have been determined form the slopes of $\log k_{obs}$ versus log (concentration) plots in case of uncatalysed reaction and while keeping the others constant in the variation of each reactant.

Effect of [DPA]

The oxidant, DPA concentration was varied in the range of 1.0 x 10^{-5} to 1.0 x 10^{-4} at fixed ALO, KOH and KIO_4 concentrations in uncatalysed reactions. The fairly constant pseudo first-order rate constants, k_{obs}, indicate that the order with respect to DPA concentration was unity (Table 1). This was also confirmed by the linearity of the plots of log (absorbance) versus time up to 85% completion of the reaction.

Effect of [Allopurinol]

The effect of allopurinol was studied in the range of 1.0 x 10^{-4} to 1.0 x 10^{-3}mol dm^{-3} at constant concentrations of DPA, OH^-, IO_4^- and a constant ionic strength of 0.10 mol dm^{-3} in uncatalysed reaction. In the case of uncatalysed reaction, at constant temperature, k_{obs} values increased with increase in ALO concentration (Table 1). The order with respect to ALO concentration was less than unity. This was also confirmed by the plots of k_{obs} versus [ALO] and k_{obs} versus [ALO] which were linear.

Effect of [OH^-]

The effect of alkali was studied, in absence of catalyst, in the range of 0.01 to 0.10 mol dm^{-3} at constant concentrations of DPA, allopurinol, IO_4^- and at constant ionic strength. The rate constants increased with increase in [alkali] and the order was found to be less than unity (Table 1).

Effect of [IO_4^-]

The effect of periodate was studied for uncatlysed cases, in the range of 1.0 x 10^{-5} to 1.0 x 10^{-4}mol dm^{-3} at constant concentrations of DPA, ALO, OH^- and at constant ionic strength. The experimental results indicated that the k_{obs} values decreased with increase in the [IO_4^-] (Table 1). The order with respect to IO_4^- was negative fractional.

Effect of ionic strength and dielectric constant

The effect of ionic strength was studied by varying KNO_3 concentration and dielectric constant of the medium 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 in uncatalysed reactions.

Effect of initially added products

Initially added products, Ag(I), (4H-Pyrazolo[3,4]Pyrimidine-4-one did not have any significant effect on the rate of reaction.

Polymerization study

For uncatalysed reactions, the involvement of free radicals in the reaction was verified as follows: The reaction mixture, to which a known quantity of acrylonitrile (i.e., 2 ml scavenger) had been added initially, was kept for 2 hrs in an inert atmosphere. On diluting the reaction mixture with methanol, a white precipitate was formed, indicating the intervention of free radicals in the reactions.

Effect of temperature

The kinetics were studied at four different temperatures, 25, 30, 35 and 40^{0}C, for uncatalysed reactions under varying concentrations of allopurinol, alkali and periodate, keeping other conditions constant. It was observed that, as temperature increases the rate of reaction also increases. The rate constant, k, of the slow step of Scheme 1 was obtained from the slopes and the intercepts of the plots of $1/k_{obs}$ versus 1/[ALO] at four different temperatures. The values are given in Table 2. The energy of activation was obtained from the plot of logk versus 1/T and from which other activation parameters were calculated (Table 2). Due to strong versatile nature of two oxidant, the kinetics of oxidation various organic and inorganic substrate has been studied by Ag(III) species. The literature survey[11] reveals that, the water soluble diperiodatoargentate(III) (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. In the alkaline medium, the dissociative equilibria (4-6) of the IO^-_4 were detected and the corresponding equilibrium constants were determined at 298.2 K by Aveston.[13]

$$2IO_4^- + 2OH^- \rightleftharpoons H_2I_2O_{10}^{4-} \qquad \log \beta_1 = 15.05 \qquad (4)$$

$$IO_4^- + OH^- + H_2O \rightleftharpoons H_3IO_6^{2-} \qquad \log \beta_2 = 6.21 \qquad (5)$$

$$IO_4^- + 2\,OH^- \rightleftharpoons H_2IO_6^{3-} \qquad \log \beta_3 = 8.67 \qquad (6)$$

The distribution of all species of periodate in aqueous alkaline solution can be calculated from equilibria (4-6). In the [OH$^-$] range used in this work the amount of dimer ($H_2I_2O_{10}^{-4}$) and IO_4^- species can neglected. The main species of periodate are $H_2IO_6^{-3}$ And $H_3IO_6^{-2}$, which are consistent with result calculated from Crouthamel's data.[14] Hence, DPA could be as

$[Ag(H_3IO_6)_2]^-$ or $[Ag(H_2IO_6)_2]^{-3}$ in alkaline medium. Therefore, under the present experimental conditions, diperiodatoargentate(III), may be depicted as $[Ag(H_3IO_6)_2]^-$. The similar speciation of Periodate in alkali was proposed for diperiodatonickelate(IV).[15] The reaction between DPA and ALO in alkaline medium presents a 1:1 stoichiometry of oxidant to reductant. Since, the reaction was enhanced by OH^- ion concentration added periodate retarded the rate and first order dependency in DPA concentration and fractional order in ALO and OH^- concentration, plausible reaction mechanism has been proposed which also explains all other experimental observations (scheme 1).

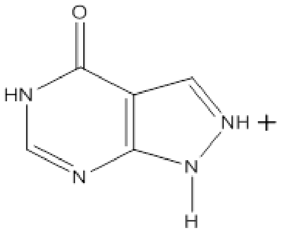
Mechanism for uncatalysed reaction

In view of the observed experimental results, allopurinol (III) (ALO) is considered to be the active species. The fractional order dependence of k_{obs} on $[OH^-]$ suggests that OH^- takes part in the pre-equilibrium step 1 with DPA to give a deprotonated diperiodatoargentate(III). The plot of $1/k_{obs}$ versus $[IO_4^-]$ is linear with a positive intercept indicating a dissociative equilibrium in which the DPA loses a periodate ligand from its coordination sphere, forming a reactive allopurinol(III) complex (ALO) in the second step, which is evidenced by decrease in the rate with increase in $[IO^-{}_4]$. It may be expected that lower Ag(III) periodate species such as ALO will be more important in the reaction than DPA. The fractional order with respect to ALO presumably results from the complex formation between ALO and DPA prior to the slow step. Indeed it is to be noted that a plot of $1/k_{obs}$ versus 1/[ALO] are linear and shows an intercept in agreement with the complex formation which slowly decomposes to form a free radical derived from allopurinol, with formation of Ag(II) species. This free radical species further reacts with Ag(II) species in further fast steps to yield the products. All these results may be interpreted.

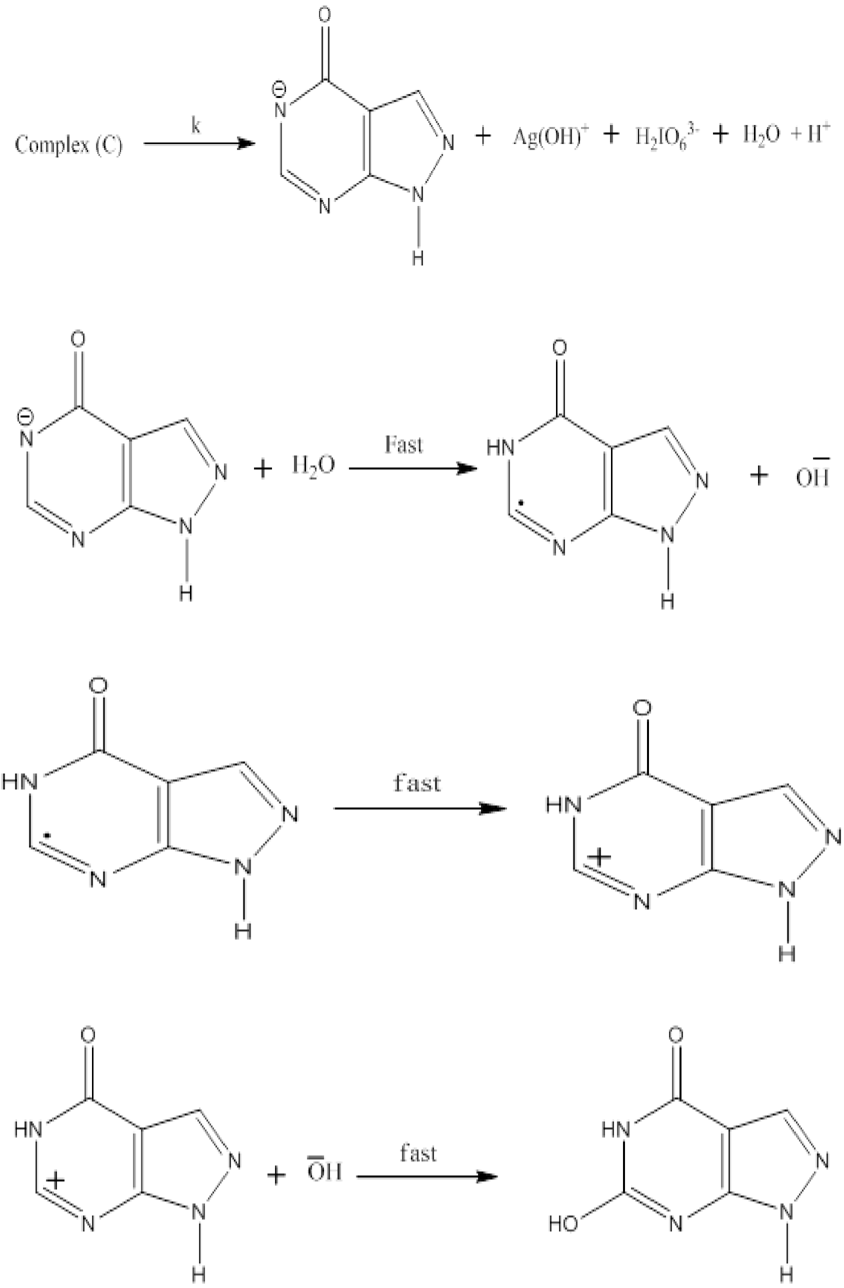
Mechanism

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

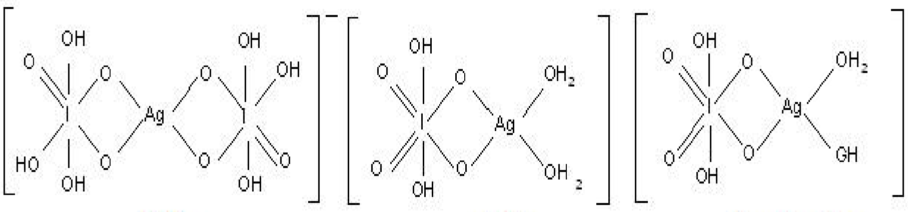
$$[Ag(H_2IO_6)(H_3IO_6)]^{2-} + 2H_2O \overset{K_2}{\rightleftharpoons} [Ag(H_2IO_6)(H_2O)_2] + H_3IO_6^{2-}$$



$$+ \; [Ag(H_2IO_6)(H_2O)_2] \xrightarrow{K_3} \text{Complex (C)}$$



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



DPA MPA Complex C$_1$

Spectroscopic evidence for the complex formation between DPA and ALO was obtained from UV-Vis spectra of ALO (5.0 x 10^{-4}), $[OH^-]$ = (0.05 mol dm^{-3}) and a mixture of both. A bathochromic shift of about 10 nm from 360 to 370 nm in the spectra of the mixture of DPA and allopurinol was observed (Fig. 2.). The Michaelis-Menten plot proved the complex formation between oxidant and substrate, which explains less than unit order in ALO concentration. Such a complex between a oxidant and substrate has also been observed in other studies.[14]

From Scheme 1, the rate law (7) can be derived, while explain all the observed.

$$\text{Rate} = -\frac{d[DPA]}{dt} = \frac{kK_1K_2K_3[DPA][ALO][OH^-]}{[H_3IO_6^{2-}] + K_1[OH^-][H_3IO_6^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][ALO]}$$

$$k_U = \frac{\text{Rate}}{[DPA]} = \frac{kK_1K_2K_3[ALO][OH^-]}{[H_3IO_6^{2-}] + K_1[OH^-][H_3IO_6^{2-}] + K_1K_2[OH^-] + K_1K_2K_3[OH^-][ALO]}$$

Which explains all the observed kinetic orders of different species.
The rate law (7) can be rearranged into the following form which is suitable for verification.

$$\frac{1}{k_U} = \frac{[H_3IO_6^{2-}]}{kK_1K_2K_3[OH^-][ALO]} + \frac{[H_3IO_6^{2-}]}{kK_2K_3[ALO]} + \frac{1}{kK_3[ALO]} + \frac{1}{k}$$

According to Eq.(9), other conditions being constant, plots of $1/k_{obs}$ versus 1/[ALO], $1/k_{obs}$ versus1/$[OH^-]$ and $1/k_{obs}$ versus $[H_3IO_6^{2-}]$ should be linear and are found to be so (Fig 3a, 3b and 3c). The slopes and intercepts of such plots lead to the values of K_1, K_2, K_3 and *k* (Table 2). The value of K_1 is in good agreement with the literature.[15] Using these constants, the rate constants were calculated over different experimental conditions by using Eq. (9) and there is a good agreement between the calculated and the experimental values (Table 1), which fortifies the proposed mechanism (Scheme 1). The equilibrium constant K_1 is far greater than K_2 which may be attributed to the greater tendency of DPA to undergo deprotonation compared to the formation of hydrolysed species in alkaline medium. The thermodynamic quantities for the different equilibrium steps, in Scheme 1 can be evaluated as follows. The ALO, OH^- and $H_3IO_6^{2-}$ concentrations (Table 1) were varied at four different temperatures. The plots of $1/k_{obs}$ versus 1[ALO], $1/k_{obs}$ versus 1/$[OH^-]$ and $1/k_{obs}$ versus $[H_3IO_6^{2-}]$ should be linear. From the slopes and intercepts, the values of K_1, K_2 and K_3 were calculated at different temperatures (Table 2). A van't Hoff 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 H, entropy of reaction S and free energy of reaction G were calculated for the first, second and third equilibrium steps. These values are given in Table 2. A comparison of the H value (18.2 kJ mol^{-1}) from K_2 with determining step is fairly fast as it involved low activation energy.[16] A negative value of $S^{\#}$ (-76 ± 5 JK^{-1} mol^{-1}) suggest that intermediate complex is more ordered than the reactants.[17]

In the prior equilibrium step 1, the OH^- deprotonates the DPA to give a deprotonated diperiodatoargentate(III); 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 IO_4^- ion concentration (Table 2). In view of this it may be expected that lower Ag(III) periodate species such as ALO is more important active species in the reaction than DPA. The inverse fractional order in $[H_3IO_6^{2-}]$ might also be due to this reason.

Table – I: Effect of variation of DPA, ALO, OH^- and IO_4^- concentrations on the oxidation of allopurinol, by diperiodatoargentate(III) in aqueous alkaline medium at 25^0C and I = 0.10 mol dm^{-3}

$[DPA] \times 10^5$ (mol dam^{-3})	$[ALO] \times 10^4$ (mol dam^{-3})	$[OH^-] \times 10^2$ (mol dam^{-3})	$[IO_4^-] \times 10^5$ (mol dam^{-3})	$K_u \times 10^5$ (S^{-1}) Found
1.0	5.0	5.0	1.0	4.4
3.0	5.0	5.0	1.0	4.6
5.0	5.0	5.0	1.0	4.8
8.0	5.0	5.0	1.0	4.7
10.0	5.0	5.0	1.0	4.9
5.0	1.0	5.0	1.0	2.6
5.0	3.0	5.0	1.0	2.8
5.0	5.0	5.0	1.0	3.6
5.0	8.0	5.0	1.0	4.1
5.0	10.0	5.0	1.0	4.6
5.0	5.0	1.0	1.0	2.8
5.0	5.0	3.0	1.0	3.4
5.0	5.0	5.0	1.0	3.6
5.0	5.0	3.0	1.0	4.1
5.0	5.0	10.0	1.0	4.6
5.0	5.0	5.0	1.0	4.4
5.0	5.0	5.0	3.0	4.2
5.0	5.0	5.0	5.0	3.6

5.0	5.0	5.0	8.0	3.1
5.0	5.0	5.0	10.0	3.0

Table –II: Activation parameters and thermodynamic quantities for the oxidation of ALO by diperiodatoargentate(III) in aqueous alkaline medium with respect to the slow step of Scheme1

(a) Effect of temperature and activation parameters

Temperature (K)	$K \times 10^3$ (s^{-1})	Parameters	Values
288	1.0	Ea (KJmol^{-1})	49 ± 2
		$H^{\#}$ (KJmol^{-1})	46 ± 0.1
293	1.9	$S^{\#}$ (KJmol^{-1})	-76 ± 5
298	1.3	$G^{\#}$ (KJmol^{-1})	83 ± 3
303	2.0	Log A	7.2 ± 0.3

(b) Effect of temperature on first, second and third equilibriumstep of Scheme 1

Temperature (K)	K_1 (dm^{-3} mol)	$K_2 \times 10^3$ (dm^{-3} mol)	$K_3 \times 10^3$ (dm^{-3} mol)
288	3.5	2.3	1.4
293	4.6	3.3	1.0
298	8.1	1.4	2.0
303	1.2	5.1	4.4

(c) Thermodynamic quantities with respect to K_1, K_2 and K_3

Thermodynamic quantities	Values from K_1	Values from K_2	Values from K_3
Δ H (kJ mol^{-1})	61.9	52.1	-52.5
Δ S (Jk^{-1} mol^{-1})	217	103	124
Δ G (kJ mol^{-1})	-4.5	20	-23.3

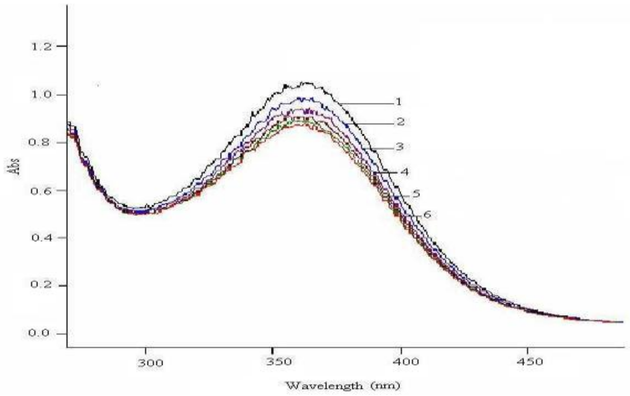


Fig –I: UV-vis. spectral changes during the oxidation of ALO by alkaline DPA at 25^{0}C, [DPA] = 5.0 X 10^{-5}, [ALO] = 5.0 X 10^{-4}, [OH$^-$] = 0.05 mol dm^{-3} and I = 0.10 mol dm^{-3} with scanning time interval of: (1) 1.0, (2) 2.0, (3) 3.0, (4) 4.0, (5) 5.0 and (6) 6.0 min.

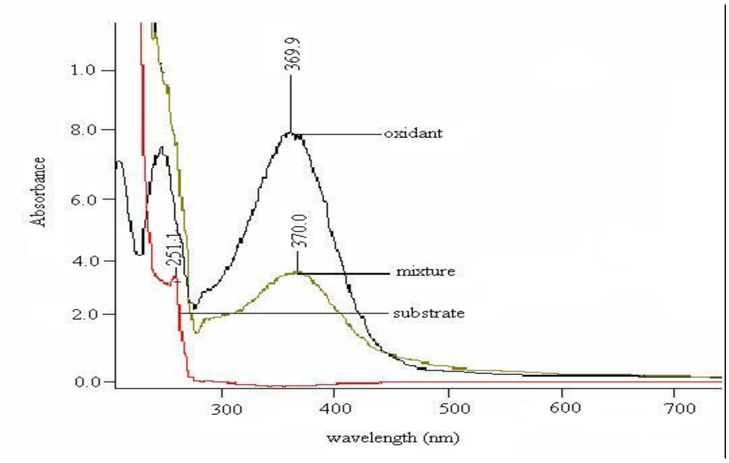


Fig –II: Spectroscopic evidence for the complex formation between ALO and DPA

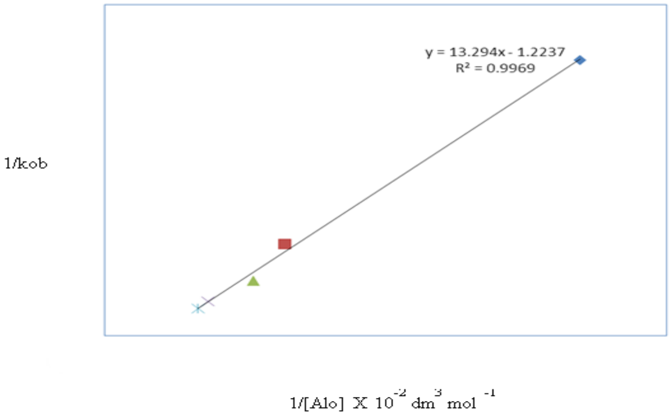


Fig.3a: Verification of rate law (3) for the oxidation of allopurinol diperiodatoargentate (III) at 25^{0}c.

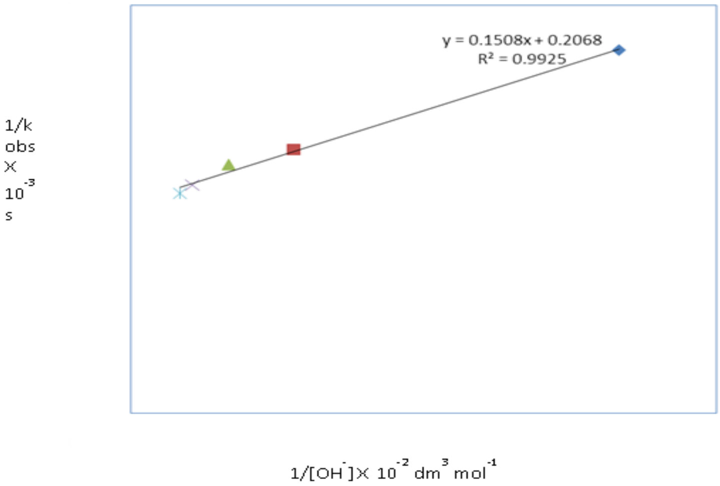


Fig - 3b plots of 1/k$_{obs}$ and versus 1/[OH$^-$] (condition as in Table 1)

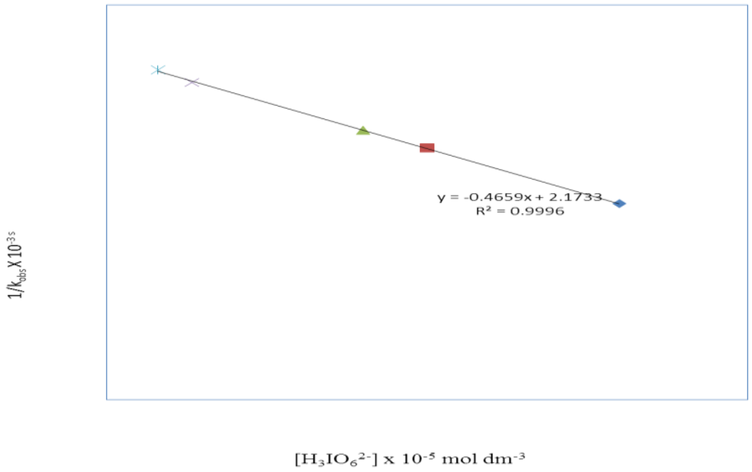


Fig - 3c. Plot of $1/k_{obs}$ versus $[H_3IO_6^{2-}]$ (conditions as in table 2)

CONCLUSION

Through the kinetics study, we proposed the reaction mechanisms for uncatalysed oxidation of allopurinol by diperiodatoargentate(III). Among the various species of silver(III) in alkaline medium, $[Ag(H_2IO_6)(H_2O)_2]$ is considered to be the active species for the title reaction. It becomes apparent that in carrying out this reaction, the role of reaction medium is crucial. Activation parameters were evaluated for uncatalysed reactions. The overall sequence described here is consistent with product, mechanistic, and kinetic studies.

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