Mechanistic aspects of Os(VIII) catalysed oxidation of loop diuretic drug furosemide by Ag(III) periodate complex in aqueous alkaline medium

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Abstract. The kinetics of oxidation of a loop diuretic drug furosemide (Fur) by diperiodatoargentate(III) (DPA) has been investigated in the presence of osmium(VIII) (Os(VIII)) used as homogeneous catalyst in alkaline medium at a constant ionic strength of $0.20 \, \text{mol dm}^{-3}$ spectrophotometrically attached with HI-TECH SFA-12 stopped flow accessory. The stoichiometry was 1:2 (Fur:DPA). The order of the reaction with respect to [DPA] was unity while the order with respect to [Fur] was less than unity 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 [Os(VIII)] was unity. The oxidation products were identified as 2-(4-carboxy-2-oxo-but-3-enylamino)-4-chloro-5-sulfamoyl-benzoic acid and Ag(I). A suitable mechanism was proposed. The reaction constants involved in the different steps of the reaction mechanism were calculated. Kinetic experiments suggest that $[\text{Ag(H}_2\text{IO}_6)(\text{H}_2\text{O})_2]$ is the reactive silver(III) species and $[\text{OsO}_4(\text{OH})_2]^{2-}$ is the reactive Os(VIII) species.

Keywords. Kinetics; oxidation; diperiodatoargentate(III); furosemide; Os(VIII) catalysis; mechanism.

1. Introduction

5-Aminosulphonyl-4-chloro-2-furanylmethyl acid (furosemide) (Fur) is a compound belonging to the high ceiling or loop diuretics group. Its pharmacological activity produces an increase in electrolyte urinary excretion and urine flow. It can increase it by a factor of 30 compared with normal excretion. These drugs are clinically used mainly in the treatment of renal disease, liver cirrhoses, oedema and hypertension.[1]

Diperiodatoargentate(III) (DPA) is used as a powerful oxidizing agent in alkaline medium and also as a volumetric reagent for the determination of various organic and inorganic species.[2–4] Jayaprakash Rao and other researchers[5,6] have studied DPA as an oxidizing agent for the kinetics of oxidation of various substrates. They found that the order with respect to both oxidant and substrate was unity and the presence of OH⁻ ions was found to enhance the rate of reaction. But 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 $[\text{Ag(HL)L}]^{(x+1)-}$. However, Anil Kumar and others[7–9] put an effort to give an evidence for the reactive form of DPA in the alkaline pH.

In the present investigation, we have obtained the evidence for the reactive species for the DPA in alkaline medium.

The role of osmium(VIII) as a catalyst in some redox reactions has been reviewed.[10,11] Although the mechanism of catalysis depends on the nature of the substrate, oxidant and on experimental conditions, it has been shown[12] 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,[13] it has been investigated 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,[14] 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,[15] 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 catalysed 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. We

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have observed that, osmium(VIII) catalyses the oxidation of furosemide by diperiodatoargentate(III) in micro amounts in alkaline medium.

There is no report on Os(VIII) catalysed oxidative mechanism of furosemide drug by any oxidant in alkaline medium. Such studies also provide an insight into the interaction of metal ions with the drug in biological systems. Using stopped-flow accessory with UV-visible spectroscopy is an effective method to detect the spectra of intermediate species and for understanding the reaction mechanism. In view of complexity of the title reaction and pharmaceutical importance of furosemide, its detailed study becomes important. In earlier reports,[16] Os(VIII) catalysed DPA oxidation, the order in [OH$^-$] was found to be negative fractional and periodate had no effect in the reaction and diperiodatoargentate(III) (DPA) was considered to be the active species. However, in the present study, we have observed entirely different kinetic observations. That is monoperiodatoargentate(III) (MPA) is found to be active form of oxidant. In order to understand the active species of oxidant, and catalyst and to propose the appropriate mechanism, the title reaction is investigated using a sophisticated accessory stopped flow technique.

2. Experimental

2.1 *Materials and reagents*

All reagents were of reagent grade and millipore water was used throughout the work. A solution of furosemide (Sigma Aldrich) was prepared by dissolving an appropriate amount of recrystallised sample in 0.004 M alkali, because of its less solubility in water. The required concentration of furosemide was obtained from its stock solution. The osmium(VIII) solution was prepared by dissolving OsO$_4$ (Johnson Matthey) in 0.50 mol dm^{-3} NaOH. The concentration of Os(VIII) was ascertained[17] by adding excess [Fe(CN)$_6$]$^{4-}$ and titrating the unreacted [Fe(CN)$_6$]$^{4-}$ with standard Ce(IV) solution in an acidic medium. The ionic strength 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 standard stock solution of IO$_4^-$ was prepared by dissolving a known weight of KIO$_4$ (S.D. Fine) in hot water and used after keeping for 24 h to attain the equilibrium. Its concentration was ascertained iodometrically[18] at neutral pH maintained using phosphate buffer. The pH of the medium in the solution was measured by ELICO (LI 120) pH meter.

2.2 *Preparation of DPA*

DPA was prepared by oxidizing Ag(I) in the presence of KIO$_4$ as described elsewhere;[16,19] the mixture of 28 g of KOH and 23 g of KIO$_4$ in 100 cm^3 of water along with 8.5 g AgNO$_3$ was heated just to boiling and 20 g of K$_2$S$_2$O$_8$ was added in several lots with stirring and then allowed to cool. It was filtered through a medium porosity fritted glass filter and 40 g of NaOH was added slowly to the filtrate, whereupon a voluminous orange precipitate agglomerates. The precipitate is filtered as above and washed three to four times with cold water. The pure crystals were dissolved in 50 cm^3 water and heated to 80°C with constant stirring thereby some solid was dissolved to give a red solution. The resulting solution was filtered when it was hot and on cooling at room temperature, the orange crystals separated out and were recrystallized from water.

The complex was characterized from its UV spectrum, which exhibited three peaks at 216, 255 and 360 nm. These spectral features were identical to those reported earlier for DPA.[18] The magnetic moment study revealed that the complex was diamagnetic. The compound prepared was analysed[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 KI was added to the filtrate for IO$_4^-$. The aqueous solution of DPA was used for the required [DPA] solution in the reaction mixture.

2.3 *Instruments used*

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

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

(iii) For pH measurements, ELICO pH meter model LI 120 was used.

2.4 *Kinetic measurements*

Since the initial reaction (Os(VIII) catalysed reaction) was too fast to be monitored by usual methods, kinetic measurements were performed on a Varian CARY 50 Bio UV-visible spectrophotometer connected to a rapid

kinetic accessory (HI-TECH SFA-12). The kinetics was followed under pseudo first-order condition where [Fur] >> [DPA] at 27°C ± 0.1, unless specified. The reaction was initiated by mixing the DPA to Fur solution which also contained required concentrations of KNO_3, KOH, KIO_4 and Os(VIII) catalyst. The progress of reaction was followed spectrophotometrically at 360 nm by monitoring the decrease in absorbance due to DPA with the molar extinction coefficient, 'ε' to be $13900 ± 100$ dm^3 mol^{-1} cm^{-1}. It was verified that there was a negligible interference from other species present in the reaction mixture at this wavelength. The reaction was followed to more than 90% completion of the reaction. Plots of log (absorbance) versus time lead to the first-order rate constants of the catalysed (k_C) reactions. The plots were linear up to 85% completion of reaction.

The orders for various species were determined from the slopes of plots of log k_C versus log of respective concentrations of species except for [DPA] in which non-variation of 'k_C' was observed as expected to the reaction condition. The rate constants were reproducible within ±5%. During the kinetics, a constant concentration viz. $5.0 × 10^{-5}$ mol dm^{-3} of KIO_4 was used throughout the study unless otherwise stated. Thus, the possibility of oxidation of furosemide by periodate was tested and found that there was no significant interference due to KIO_4 under the experimental condition. 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 nitrogen atmosphere in order to understand the effect of dissolved oxygen on the rate of reaction. No significant difference in the results was observed under a nitrogen 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 rates. The spectral changes during the reaction are shown in figure 1. It is evident from the figure 1 that the concentration of DPA decreases at 360 nm.

In view of the modest concentration of alkali used in the reaction medium, attention was also directed to the effect of the reaction vessel surface on the kinetics. Use of polythene/acrylic wares and quartz or polyacrylate cells gave the same results, indicating that the surface did not have any significant effect on the reaction rates. 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.
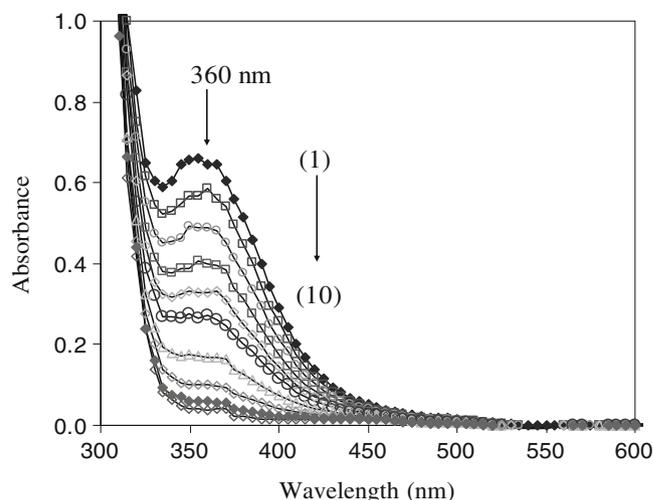

Figure 1. Spectroscopic changes occurring in the oxidation of furosemide by diperiodatoargentate (III) at 27°C, [DPA] = $5.0 × 10^{-5}$, [Fur] = $5.0 × 10^{-4}$, [OH^-] = 0.10 and I = 0.20 mol dm^{-3} with scanning time interval = 1 min.

3. Results

3.1 *Stoichiometry and product analysis*

Different sets of reaction mixtures containing varying ratios of DPA to Fur in the presence of constant amount of OH^-, KIO_4, and KNO_3 and Os(VIII) were kept for 3 h in a closed vessel under nitrogen atmosphere. The remaining concentration of DPA was assayed by measuring the absorbance at 360 nm. The results indicated 1:2 stoichiometry as given in scheme 1. The stoichiometric ratio suggests that the main products were 2-(4-carboxy-2-oxo-but-3-enylamino)-4-chloro-5-sulfamoyl-benzoic acid and Ag(I). Presence of carboxylic and ketone group was identified by spot test.[20]

The nature of the product 2-(4-carboxy-2-oxo-but-3-enylamino)-4-chloro-5-sulfamoyl-benzoic acid was also identified by its IR spectrum, which showed sharp absorption peaks at 1625 cm^{-1}, 1776 cm^{-1} and 1706 cm^{-1} due to acidic $– C = O$ respectively. The LC-MS spectrum showed a molecular ion peak at m/z at 363.0 amu confirming the product. The formation of free Ag^+ in solution was detected by adding KCl solution to the reaction mixture, which produced white turbidity due to the formation of AgCl.

3.2 *Reaction order*

As the diperiodatoargentate(III) oxidation of furosemide in alkaline medium proceeds with a measurable
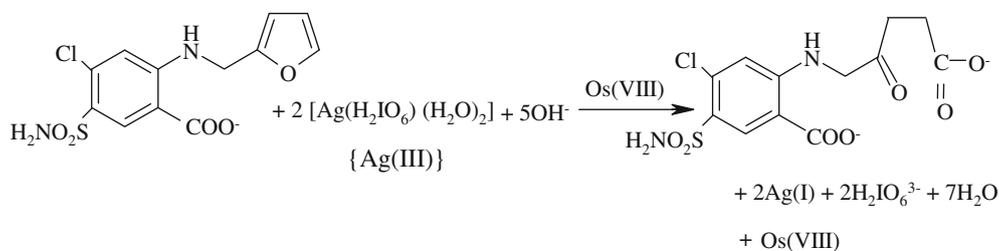
Scheme 1. Stoichiometry of Os(VIII) catalysed oxidation of furosemide by DPA.

rate in the absence of Os(VIII), the catalysed reaction is understood to occur in parallel paths with contributions from both the catalysed and uncatalysed paths. Thus, the total rate constant (k_T) is equal to the sum of the rate constants of the catalysed (k_C) and uncatalysed (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 Fur, IO_4^-, OH^- and catalyst Os(VIII), in turn, while keeping others constant. The rate constant, k_U was evaluated in the absence of catalyst, by the plot of log

(absorbance) versus time by following the progress of the reaction spectrophotometrically at 360 nm.

3.3 *Effect of [diperiodatoargentate(III)]*

The oxidant [DPA] was varied in the range of 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3} at fixed [Fur], [KOH] and [KIO$_4^-$]. The fairly constant pseudo first-order rate constants, k_C, indicate that the order with respect to [DPA] was unity (table 1). This was also confirmed by

Table 1. Effect of [DPA], [Fur], [OH$^-$], [IO$_4^-$] and Os(VIII) on the osmium(VIII) catalysed oxidation of furosemide by DPA in alkaline medium at 27°C, $I = 0.20$ mol dm^{-3}.

10^5 [DPA]	10^4 [Fur]	[OH$^-$]	10^5 [IO$_4^-$]	10^6 [Os(VIII)]	$10^2 k_T$	$10^3 k_U$	$10^2 k_C$ (s^{-1})	
(mol dm^{-3})	(mol dm^{-3})	(mol dm^{-3})	(mol dm^{-3})	(mol dm^{-3})	(s^{-1})	(s^{-1})	Found	Calculated
1.0	5.0	0.10	5.0	1.0	3.82	4.33	3.39	3.25
3.0	5.0	0.10	5.0	1.0	3.62	4.62	3.16	3.25
5.0	5.0	0.10	5.0	1.0	3.55	4.61	3.09	3.25
8.0	5.0	0.10	5.0	1.0	3.67	4.54	3.21	3.25
10.0	5.0	0.10	5.0	1.0	3.59	4.41	3.16	3.25
5.0	2.0	0.10	5.0	1.0	2.14	2.48	1.89	1.80
5.0	5.0	0.10	5.0	1.0	3.55	4.61	3.09	3.25
5.0	10.0	0.10	5.0	1.0	5.08	6.51	4.43	4.45
5.0	15.0	0.10	5.0	1.0	6.11	8.09	5.30	5.08
5.0	20.0	0.10	5.0	1.0	6.92	9.29	5.99	5.62
5.0	5.0	0.02	5.0	1.0	2.01	2.61	1.75	1.72
5.0	5.0	0.06	5.0	1.0	3.04	3.94	2.64	2.83
5.0	5.0	0.10	5.0	1.0	3.55	4.61	3.09	3.25
5.0	5.0	0.15	5.0	1.0	4.21	5.46	3.66	3.51
5.0	5.0	0.20	5.0	1.0	4.56	5.93	3.97	3.66
5.0	5.0	0.10	1.0	1.0	4.75	6.21	4.12	3.99
5.0	5.0	0.10	3.0	1.0	3.98	5.11	3.47	3.59
5.0	5.0	0.10	5.0	1.0	3.55	4.61	3.09	3.25
5.0	5.0	0.10	7.0	1.0	3.22	4.13	2.80	2.97
5.0	5.0	0.10	10.0	1.0	2.95	3.79	2.58	2.63
5.0	5.0	0.10	5.0	0.5	2.16	4.61	1.69	1.63
5.0	5.0	0.10	5.0	0.7	2.70	4.61	2.24	2.28
5.0	5.0	0.10	5.0	1.0	3.55	4.61	3.09	3.25
5.0	5.0	0.10	5.0	3.0	10.40	4.61	9.93	9.75
5.0	5.0	0.10	5.0	5.0	16.26	4.61	15.79	16.24

linearity of the plots of log (absorbance) versus time ($r \geq 0.999$, $S \leq 0.04$) up to 85% completion of the reaction.

3.4 *Effect of [furosemide]*

The effect of furosemide was studied in the range of 2.0×10^{-4} to 2.0×10^{-3} mol dm^{-3} at constant concentrations of DPA, OH$^-$, IO$_4^-$, Os(VIII) and a constant ionic strength of 0.20 mol dm^{-3}. The order with respect to [Fur] was less than unity (table 1). This was also confirmed by the plot of k_C versus [Fur] ($r \geq 0.9982$, $S \leq 0.014$) (figure 2).

3.5 *Effect of [alkali]*

The effect of alkali was studied in the range of 0.02 to 0.20 mol dm^{-3} at constant concentrations of DPA, Fur, IO$_4^-$, Os(VIII) and at a constant ionic strength. The order was found to be less than unity (table 1) ($r \geq 0.9985$, $S \leq 0.017$, for the plot of log (k_C) versus log [OH$^-$]).

3.6 *Effect of [periodate]*

The effect of periodate was studied in the range of 1.0×10^{-5} to 1.0×10^{-4} mol dm^{-3} at constant concentrations of DPA, Fur, OH$^-$, Os(VIII) and a constant ionic strength. The order with respect to IO$_4^-$ was negative fractional (table 1) ($r \geq 0.9830$, $S \leq 0.021$, for the plot of log (k_C) versus log [IO$_4^-$]).
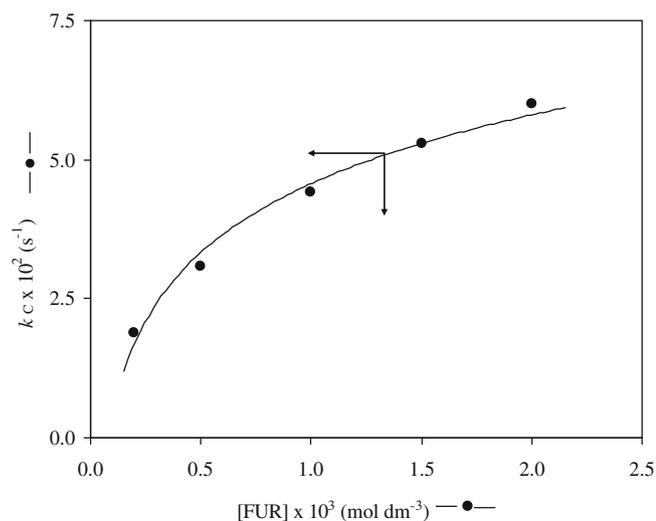

Figure 2. Plot of k_C versus [Fur].

3.7 *Effect of [Os(VIII)]*

The [Os(VIII)] was varied from 5.0×10^{-7} to 5.0×10^{-6} mol dm^{-3} range, at constant concentrations of DPA, Fur, alkali and ionic strength. The order in [Os(VIII)] was found to be unity from the linearity of the plot of k_C versus [Os(VIII)] ($r \geq 0.9986$, $S \leq 0.011$) (table 1).

3.8 *Effect of initially added products*

The externally added products, Ag(I) and 2-(4-carboxy-2-oxo-but-3-enylamino)-4-chloro-5-sulfamoyl-benzoic acid did not have any significant effect on the rate of reaction.

On the basis of above experimental findings, the rate laws for the oxidation of furosemide at low concentrations of DPA in the presence of Os(VIII) as homogeneous catalyst can be proposed in the form of following equations,
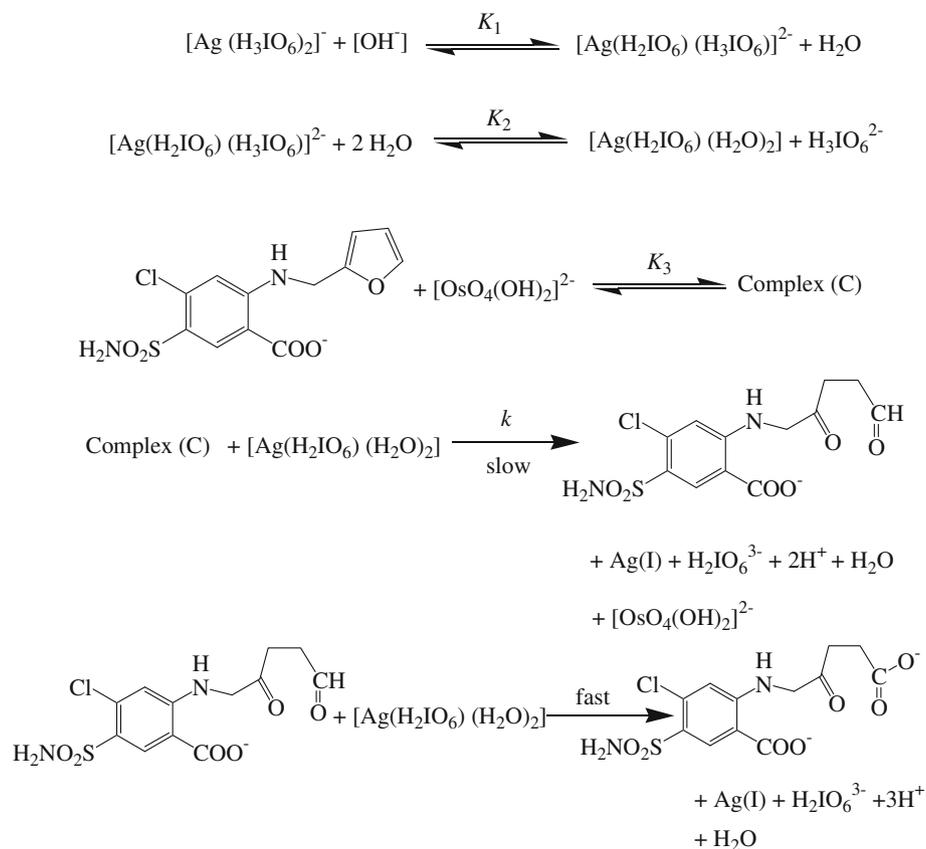
$$\text{Rate} = k_C \, [\text{DPA}]^{1.0} \, [\text{Fur}]^{0.50} \, [\text{OH}^-]^{0.36}$$
$$\times \, [\text{IO}_4^-]^{-0.20} \, [\text{Os (VIII)}]^{0.99}.$$

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

By the addition of KNO$_3$ at constant [DPA], [Fur], [OH$^-$], [IO$_4^-$] and [Os(VIII)] it was found that increasing the ionic strength of the reaction medium increases the rate of reaction; the plot of log k_C versus $\sqrt{I}$ was found to be linear with positive slope. Varying the t-butyl alcohol and water percentage varied dielectric constant of the medium, 'D'. The D values were calculated from the equation $D = D_w V_w + D_B V_B$, where D_w and D_B are dielectric constants of pure water and t-butyl alcohol, respectively and V_w and V_B are the volume fractions of components water and t-butyl alcohol, respectively in the total mixture. The oxidation of t-butyl alcohol–water mixture by DPA in the presence and absence of Os(VIII) was checked and found that there was no significant effect under the experimental conditions. The decrease in dielectric constant of the reaction medium increased the rate and the plot of log k_C versus $1/D$ was linear with positive slope.

3.10 *Effect of temperature (T)*

The kinetics was studied at four different temperatures (290, 295, 300 and 305 K) under varying concen-

$$[Ag\,(H_3IO_6)_2]^- + [OH^-] \xrightleftharpoons{K_1} [Ag(H_2IO_6)\,(H_3IO_6)]^{2-} + H_2O$$

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

$$\text{Complex (C)} + [Ag(H_2IO_6)\,(H_2O)_2] \xrightarrow[\text{slow}]{k}$$

$$+ \; Ag(I) + H_2IO_6{}^{3-} + 2H^+ + H_2O$$

$$+ \; [OsO_4(OH)_2]^{2-}$$

$$+ \; Ag(I) + H_2IO_6{}^{3-} + 3H^+$$

$$+ \; H_2O$$

Scheme 2. Mechanism for the Os(VIII) catalysed oxidation of furosemide by DPA.

trations of furosemide, alkali, periodate and catalyst, keeping other conditions constant. The rate constant was found to increase with increase in temperature. The rate constant (k) of the slow step of scheme 2 was obtained from the slopes and the intercepts of the plots of [Os(VIII)]/k_C versus 1/[Fur] at four different temperatures. The values are given in table 2(A). The activation parameters for the rate determining step were obtained by the least square method of plot of log k versus 1/T ($r \geq 0.9951$, $S \leq 0.019$) and are presented in table 2(B).

3.11 *Test for free radicals (polymerization study)*

To test the intervention of free radicals, the reaction mixture was mixed with acrylonitrile monomer and kept for one hour, under nitrogen atmosphere. On

Table 2. Thermodynamic activation parameters for the osmium(VIII) catalysed oxidation of furosemide by DPA in aqueous alkaline medium with respect to the slow step of scheme 2.

(A) Effect of temperature		(B) Activation parameters (scheme 2)	
Temperature (K)	$10^{-4}\,k$ (dm^3 mol^{-1} s^{-1})	Parameters	Values
290	5.75 ± 0.03	$\Delta H^{\#}$ (kJ mol^{-1})	11.0 ± 0.5
295	6.46 ± 0.09	$\Delta S^{\#}$ (JK^{-1} mol^{-1})	-113 ± 5
300	7.06 ± 0.07		
305	7.66 ± 0.08		

dilution with methanol no precipitate resulted, suggesting there was no participation of free radicals in the reaction.

3.12 *Catalytic activity*

It has been pointed out by Moelwyn–Hughes[21] that in the presence of catalyst, the uncatalysed and catalysed reactions proceed simultaneously, so that,
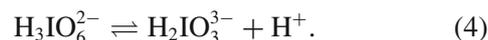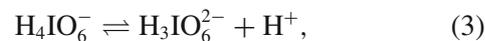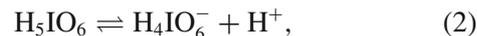
$$k_T = k_U + K_C \left[\text{Catalyst} \right]^x, \qquad (1)$$

here 'k_T' is the total rate constant, 'k_U' the pseudo first-order rate constant for the uncatalysed reaction, '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 was found to be unity. The values of K_C were evaluated at different temperatures and 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. The values of $K_C \times 10^{-4}$ were obtained as 1.70, 2.27, 2.69, and 3.21 at 290, 295, 300, and 305 K, respectively. 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 the catalyst were computed as $Ea = 38.0 \pm 0.5\,\text{kJ mol}^{-1}$, $\Delta H^\# = 35.0 \pm 0.7\,\text{kJ mol}^{-1}$, $\Delta S^\# = -43.0 \pm 0.8\,\text{JK}^{-1}\,\text{mol}^{-1}$, $\Delta G^\# = 48.0 \pm 1.1\,\text{kJ mol}^{-1}$, $\log A = 10.9 \pm 0.3$.

4. Discussion

The kinetics of oxidation of various organic and inorganic substrates have been studied by Ag(III) species due to its strong versatile nature of two electrons oxidant. Among the various species of Ag(III), $Ag(OH)_4^-$, diperiodatoargentate(III) and ethylenebis (biguanide) silver(III) (EBS) are of maximum attention to the researchers due to their relative stability.[22] The stability of $Ag(OH)_4^-$ is very sensitive towards traces of dissolved oxygen and other impurities in the reaction medium whereupon it had not drawn much attention. However, the other two forms of Ag(III)[7–9,23] are considerably stable; the DPA is used in highly alkaline medium and EBS is used in highly acidic medium.

The water soluble diperiodatoargentate(III) (DPA) has a formula $[Ag(IO_6)_2]^{7-}$ with dsp^2 configuration of square planar structure and two bidentate periodate ligands.[19] The same molecule is used in alkaline medium, it is impossible to exist as $[Ag(IO_6)_2]^{7-}$ as periodate is known to be in various protonated forms[24] depending on the pH of the solution as given in following multiple equilibria (2)–(4).

$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+, \qquad (2)$$

$$H_4IO_6^- \rightleftharpoons H_3IO_6^{2-} + H^+, \qquad (3)$$

$$H_3IO_6^{2-} \rightleftharpoons H_2IO_3^{3-} + H^+. \qquad (4)$$

Periodic acid exists as H_5IO_6 in acid medium and 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.[2] However, formation of this species is negligible under conditions employed for kinetic study. On the contrary, the authors[5,6] in their recent studies have proposed the DPA species as $[Ag(HL)_2]^{x-}$ in which 'L' is a periodate with uncertain number of protons and 'HL' is a protonated periodate of uncertain number of protons. This can be ruled out by considering the alternative form[24] 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, diperiodatoargentate(III), may be depicted as $[Ag(H_3IO_6)_2]^-$. The similar speciation of periodate in alkali was proposed[25] for diperiodatonickelate(IV). It is well-known that, in alkali media, furosemide exists fully as anionic form.

Osmium(VIII) is known to form different complexes at different OH^- concentrations[26] as $[OsO_4(OH)_2]^{2-}$ and $[OsO_5(OH)]^{3-}$. At higher concentration of OH^-, $[OsO_5(OH)]^{3-}$ is significant. At lower concentrations of OH^-, as employed in the present study, and since the rate of oxidation increased with increase in $[OH^-]$, it is reasonable that $[OsO_4(OH)_2]^{2-}$ was operative and its formation is important in the reaction. Mechanistically most studies[13] 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 zeroth order kinetics with respect to the main oxidant. In another case,[14] Os(VIII) is regenerated by Os(VI) intervention in view of unit order in each osmium, substrate and oxidant. In some other reports,[15] 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 Os(VIII) catalysed reaction, [DPA] was first order dependence, an apparent order of less than unit order in both [Fur] and [alkali], a negative fractional

order dependence on [periodate] and unit order with respect to Os(VIII) concentrations. No effect of added products was observed. Based on the experimental results, a mechanism is proposed as in scheme 2 for which all the observed orders in each constituent such as [oxidant], [reductant], [catalyst], [OH⁻] and [IO₄⁻] may be well-accommodated.

In the prior equilibrium step 1, the [OH⁻] deprotonates the DPA to give a deprotonated diperiodatoargentate(III); in the second step displacement of 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 MPA is 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, the Os(VIII) species combines with a molecule of anionic species of furosemide to give an intermediate complex (C), which further reacts with one mole of MPA in a rate determining step to give the intermediate species derived from furosemide and regeneration of catalyst, Os(VIII). This intermediate species derived from furosemide further reacts with another molecule of MPA species in further fast step to give the products as given in scheme 2.

Spectroscopic evidence for the complex formation between Os(VIII) and Fur was obtained from UV-vis spectra of (Fur (5.0×10^{-4} mol dm⁻³)), (Os(VIII) (1.0×10^{-6} mol dm⁻³), OH⁻ (0.1 mol dm⁻³)) and a mixture of both. A bathochromic shift of about 7 nm from 273 nm to 280 nm in the spectra of Os(VIII) to mixture of Os(VIII) and Fur was observed. The Michaelis–Menten plot proved the complex formation between catalyst and reductant, which explains less than unit order in [Fur]. Such complex between a catalyst and substrate has also been observed in other studies.[26] The nature of the complex (C) is a chelate complex. An attempt to isolate the complex was not successful. According to scheme 2, the rate law could be derived as,

$$
\begin{aligned}
\text{rate}_T &= \text{rate}_U + \text{rate}_C = \frac{-d\,[DPA]}{dt} \\
&= \frac{kK_1K_2K_3\,[\text{Fur}]\,[\text{OH}^-]\,[\text{Os (VIII)}]\,[\text{DPA}]}{K_1K_2\,[\text{OH}^-] + [H_2IO_6^{-3}] + K_1\,[\text{OH}^-]\,[H_2IO_6^{-3}] + K_1K_2K_3\,[\text{Fur}]\,[\text{OH}^-]},
\end{aligned} \tag{5}
$$

$$
\begin{aligned}
\frac{\text{rate}}{[DPA]} &= k_C = k_T - k_U \\
&= \frac{kK_1K_2K_3\,[\text{Fur}]\,[\text{OH}^-]\,[\text{Os (VIII)}]}{K_1K_2\,[\text{OH}^-] + [H_2IO_6^{-3}] + K_1\,[\text{OH}^-]\,[H_2IO_6^{-3}] + K_1K_2K_3\,[\text{Fur}]\,[\text{OH}^-]},
\end{aligned} \tag{6}
$$

This explains all the observed kinetic orders of different species. The rate law (6) can be rearranged to be equation (7), which is suitable for verification.

$$
\begin{aligned}
\frac{[\text{Os (VIII)}]}{k_C} &= \frac{1}{kK_3\,[\text{Fur}]} + \frac{[H_2IO_6^{-3}]}{kK_1K_2K_3\,[\text{OH}^-]\,[\text{Fur}]} \\
&\quad + \frac{[H_2IO_6^{-3}]}{kK_2K_3\,[\text{Fur}]} + \frac{1}{k}.
\end{aligned} \tag{7}
$$

According to equation (7), the plots of [Os(VIII)]/k_C versus 1/[Fur], [Os(VIII)]/k_C versus 1/[OH⁻] and [Os(VIII)]/k_C versus [IO₄⁻] should be linear and are found to be so. From the intercepts and slopes of such plots, the reaction constants K_1, K_2, K_3 and k were calculated as (0.55 ± 0.06) dm³ mol⁻¹, (1.3 ± 0.05) × 10^{-3} mol dm⁻³, (3.0 ± 0.1) × 10^3 dm³ mol⁻¹ ($7.1 \pm$ 0.4) × 10^4 dm³ mol⁻¹ s⁻¹, respectively. The value K_1 and K_2 obtained are in good agreement with previously reported value.[26] These constants were used to calculate the rate constants and compared with the experimental k_C values and found to be in reasonable agreement with each other, which fortifies the scheme 2.

The thermodynamic quantities for the different equilibrium steps, in scheme 2 can be evaluated as follows. The furosemide, periodate and hydroxide ion concentrations (table 1) were varied at different temperatures. The plots of [Os(VIII)]/k_C versus 1/[Fur] ($r \geq 0.9899$, $S \leq 0.0012$), [Os(VIII)]/k_C versus 1/[OH⁻] ($r \geq 0.9799$, $S \leq 0.0015$) and [Os(VIII)]/k_C versus [IO₄⁻] ($r \geq 0.9847$, $S \leq 0.0019$) were linear at different temperatures. From the slopes and intercepts, the values of K_1, K_2, K_3 were calculated at different temperatures. A vant Hoff's plot was made for the variation of K_1,

K_2, K_3 with temperature (i.e., log K_1 versus $1/T$, log K_2 versus $1/T$ and log K_3 versus $1/T$) and the values of the enthalpy of reaction ΔH, entropy of reaction ΔS and free energy of reaction ΔG, were calculated. These values are also given in table S1. 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.[27]

The increase in the rate with increase in the ionic strength is in favour of a reaction between oppositely charged species of reactant, as presented in scheme 2 of the proposed mechanism. The effect of solvent on the reaction rate is described in detail in the literature.[28] For the limiting case of a zero angle approach between two dipoles or anion-dipole system, Amis,[29] has shown that a plot of log k_C versus $1/D$ gives a straight line, with a negative slope for a reaction between a negative ion and a dipole or two dipoles and with a positive slope for positive ion and dipole interaction. In the present study, the observed plot had a positive slope, which is in the right direction as shown in scheme 2. The moderate $\Delta H^{\#}$ and $\Delta S^{\#}$ values are favourable for electron transfer reaction. The value of $\Delta H^{\#}$ was due to energy of solution changes in the transition state. The negative value of $\Delta S^{\#}$ value suggests that the intermediate complex is more ordered than the reactants.[28] The observed modest enthalpy of activation and a higher rate constant for the slow step indicates that the oxidation presumably occurs via inner-sphere mechanism. This conclusion is supported by earlier observations.[30] The activation parameters evaluated for the reaction explains the catalytic effect on the reaction. The catalyst Os(VIII) forms the complex (C) with substrate which enhances the reducing property of the substrate than that without catalyst. Further, the catalyst Os(VIII) modifies the reaction path by lowering the energy of activation.

5. Conclusions

The Os(VIII) catalysed oxidation of furosemide by diperiodatoargentate(III) was studied. Oxidation products were identified. Among the various species of Ag(III) in alkaline medium, monoperiodatoargentate(III) (MPA) i.e., $[Ag(H_2IO_6)(H_2O)_2]$ is considered as active species for the title reaction. Active species of Os(VIII) is found to be $[OsO_4(OH)_2]^{2-}$. 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 is consistent with all the experimental evidences including the product, spectral, mechanistic and kinetic studies.

Supporting information

Table S1 is given as electronic supplementary data (see www.ias.ac.in/chemsci).

Appendix A

According to scheme 2,

$$\text{Rate} = k\,[C]\left[Ag\,(H_2IO_6)\,(H_2O)_2\right]$$
$$= \frac{kK_1K_2K_3\,[Fur][Os(VIII)][DPA]\left[OH^-\right]}{\left[H_2IO_6^{3-}\right]}. \quad (A)$$

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

$$
\begin{aligned}
[DPA]_T &= [DPA]_f + \left[Ag\,(H_2IO_6)\,(H_3IO_6)\right]^{2-} + \left[Ag\,(H_2IO_6)\,(H_2O)_2\right] \\
&= [DPA]_f\left[\frac{K_1K_2\left[OH^-\right] + \left[H_2IO_6^{3-}\right] + K_1\left[OH^-\right]\left[H_2IO_6^{3-}\right]}{\left[H_2IO_6^{3-}\right]}\right].
\end{aligned}
$$

Therefore,

$[DPA]_f$

$$= \left[\frac{[DPA]_T\left[H_2IO_6^{3-}\right]}{K_1K_2\left[OH^-\right] + \left[H_2IO_6^{3-}\right] + K_1\left[OH^-\right]\left[H_2IO_6^{3-}\right]}\right]. \quad (B)$$

Similarly,

$$
\begin{aligned}
[Fur]_T &= [Fur]_f + (C) \\
&= [Fur]_f + K_3\,[Fur]_f\,[Os\,(VIII)] \\
&= [Fur]_f\,[1 + K_3\,[Os\,(VIII)]].
\end{aligned}
$$

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

$$[Fur]_T = [Fur]_f. \qquad (C)$$

Similarly,

$$\left[OH^-\right]_T = \left[OH^-\right]_f \text{ and } \left[H_2IO_6^{3-}\right]_T = \left[H_2IO_6^{3-}\right]_f, \quad (D)$$

$$[Os\,(VIII)]_T = [Os\,(VIII)]_f + (C)$$
$$= [Os\,(VIII)]_f + K_3\,[Fur]\,[Os\,(VIII)]_f$$
$$[Os\,(VIII)]_f = \left[\frac{[Os\,(VIII)]_T}{\{1 + K_3\,[Fur]\}}\right]. \qquad (E)$$

Substituting (B), (C), (D) and (E) in (A) and omitting the subscripts T and f, we get

$$\text{rate} = \frac{-d\,[DPA]}{dt} = \frac{k\,K_1 K_2 K_3\,[Fur]\left[OH^-\right][Os\,(VIII)]\,[DPA]}{K_1 K_2\left[OH^-\right] + \left[H_2IO_6^{3-}\right] + K_1\left[OH^-\right]\left[H_2IO_6^{3-}\right] + K_1 K_2 K_3\,[Fur]\left[OH^-\right]}.$$

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