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ORIGINAL PAPER

Mechanistic investigations of ruthenium(III) catalyzed oxidation of pentoxifylline by copper(III) periodate complex in aqueous alkaline medium

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Abstract The kinetics of the oxidation of ruthenium(III)-catalyzed oxidation of pentoxifylline (PTX) by diperiodatocuprate(III) (DPC) in aqueous alkaline medium at a constant ionic strength of 0.30 mol dm^{-3} was studied spectrophotometrically. The reaction between PTX and DPC in alkaline medium in the presence of Ru(III) exhibits 1:2 stoichiometry (PTX:DPC). The reaction was of first order in DPC, less than the unit order in [PTX] and [OH$^-$] and negative fractional order in [IO$_4$$^-$]. The order in [Ru(III)] was unity. Intervention of free radicals was observed in the reaction. The main products were identified by TLC and spectral studies including LC-MS. The oxidation reaction in alkaline medium has been shown to proceed via a Ru(III)-PTX complex, which reacts with monoperiodatocuprate(III) to decompose in a rate determining step followed by a fast step to give the products. The reaction constants involved in different steps of the mechanism were calculated. The activation parameters with respect to the slow step of the mechanism were computed and discussed, and thermodynamic quantities were also determined. The active species of catalyst and oxidant have been identified.

Keywords Kinetics · Mechanism · Diperiodatocuprate(III) · Pentoxifylline · Ruthenium(III) catalysis

Introduction

In recent years, diperiodatocuprate(III) (DPC) has been used as an oxidant in alkaline medium [1]. The oxidation studies of DPC are scanty in view of its limited solubility and stability in aqueous medium. Its use as an analytical reagent is now well recognized [2]. The copper(III) periodate complex exhibits different multiple equilibria involving different copper(III) species in aqueous alkaline medium. It is interesting to know which of the copper(III) species is the active oxidant.

Pentoxifylline (3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-purine-2,6-dione, PTX), a trisubstituted purine and xanthine derivative, is a hemorheolgic agent used for the treatment of peripheral arterial disease [3] and intermittent claudication. PTX improves blood flow through the peripheral circulation by decreasing blood viscosity, inhibiting platelet aggregation, enhancing erythrocyte flexibility, and diminishing fibrinogen concentration [4]. The drug is gaining acceptance for conservative treatment of Peyronie's disease and neuropathic injuries. It also helps to prevent strokes, manage sickle cell disease, improve blood flow to the brain, improve effects of diabetes, or treat nausea and headaches in high places (high-altitude sickness). It has been shown to reduce mortality in acute alcoholic and non-alcoholic steatohepatitis, presumably through its ability to inhibit TNF-alpha. Its anti-TNF properties indicate its potential for the treatment of ALD, alcoholic liver disease. A study demonstrated the possible use of pentoxifylline administered in conjunction with vitamin E for reducing the extent of fibrotic lesions induced by radiation therapy for breast cancer [5].

Transition metals are known to catalyze many oxidation-reduction reactions since they involve multiple oxidation states. In recent years the use of transition metal ions, such as ruthenium, osmium, palladium, manganese,

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chromium, and iridium, either alone or as binary mixtures, as catalysts in various redox processes have attracted considerable interest [6]. Ru(III) acts as a catalyst in the oxidation of many organic and inorganic substrates [7, 8]. The catalyzed mechanism can be quite complicated because of the formation of different intermediate complexes and different oxidation states of ruthenium(III). Although the mechanism of catalysis depends on the nature of the substrate, oxidant, and experimental conditions, it has been shown [9] that metal ions act as catalysts by one of these different paths, such as the formation of complexes with reactant or oxidation of the substrate itself, or through the formation of free radicals.

A literature survey revealed that there are no reports on ruthenium(III)-catalyzed oxidation of PTX by DPC in alkaline medium. We have observed that micro amounts of ruthenium catalyze the oxidation of PTX by DPC in alkaline medium. In earlier reports [10] of DPC oxidation, both periodate and alkali had a retarding effect in most of the reactions. However, in the present study we made entirely different kinetic observations. In view of the medicinal value and potential pharmaceutical importance of PTX, it is important to understand the active species of oxidants and catalysts to compute the activity of the catalyst and to propose the appropriate mechanism. Hence, the title reaction is investigated in detail. An understanding of the mechanism allows the chemistry to be interpreted, understood, and predicted.

Results and discussion

Reaction orders

As the diperiodatocuprate(III) oxidation of pentoxifylline in alkaline medium proceeds with a measurable rate in the absence of ruthenium(III), 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 lg k_C versus lg(concentration) plots by varying the concentrations of PTX, OH^-, IO_4^-, and Ru(III), while in turn keeping the others constant. The uncatalyzed reaction was followed under the conditions $[PTX] = 2.0 \times 10^{-3}$; $[DPC] = 5.0 \times 10^{-5}$; $[OH^-] = 0.20$; $I = 0.30$ mol dm^{-3}. The rate constants of uncatalyzed reaction (k_U) and catalyzed reaction (k_C) were obtained by the plot of lg(absorbance) versus time by following the progress of the reaction spectrophotometrically at 415 nm.

Effect of [diperiodatocuprate(III)]

The DPC concentration was varied in the range of 1.0×10^{-5}–1.0×10^{-4} mol dm^{-3}. The linearity of the plots of lg(absorbance) versus time up to 85% completion of the reaction indicates a reaction order of unity in (DPC). This is also confirmed by varying [DPC], which did not result in any change in the pseudo first-order rate constants k_C (Table 1).

Effect of [pentoxifylline]

The pentoxifylline concentration was varied in the range of 6.0×10^{-4}–6.0×10^{-3} mol dm^{-3} at constant concentrations of DPC, OH^-, IO_4^-, and at a constant ionic strength of 0.30 mol dm^{-3} in the presence of Ru(III) catalyst at 298 K. The k_C values increased with the increase in concentration of pentoxifylline, indicating an apparent less than unit order dependence on [PTX] ($r \geq 0.9978$, $S \leq 0.027$; Table 1) under the concentrations of the experiment done. This is also confirmed in the plot of k_C versus $[PTX]^{0.79}$, which is linear rather than the direct plot of k_C versus [PTX] (Fig. 1).

Effect of [alkali]

The effect of increase in concentration of alkali on the reaction was studied in the range of 0.03–0.30 mol dm^{-3} at constant concentrations of DPC, PTX, IO_4^-, and at a constant ionic strength of 0.30 mol dm^{-3} in the presence of the Ru(III) catalyst at 298 K. The rate constants increased with increasing [alkali] (Table 1), indicating apparent less than unit order dependence of the rate on alkali concentration, i.e., 0.67 ($r \geq 0.9936$, $S \leq 0.007$). This less than unit order is also confirmed by the plot of k_C versus $[OH^-]^{0.67}$, which is linear rather than the direct plot of k_C versus $[OH^-]$ (Fig. 2).

Effect of [periodate]

The effect of an increase in concentration of periodate on the reaction was studied in the range of 5.0×10^{-6}–5.0×10^{-5} mol dm^{-3} at constant concentrations of DPC, PTX, OH^-, and at a constant ionic strength of 0.30 mol dm^{-3} in the presence of the Ru(III) catalyst at 298 K. It was found that the added periodate had a retarding effect on the rate of reaction. The order with respect to periodate concentration was a negative fractional order, i.e., −0.76 ($r \geq 0.9981$, $S \leq 0.004$; Table 1).

Table 1 Effect of variation of [DPC], [PTX], [OH^-], [IO_4^-], and [Ru(III)] on the ruthenium(III) catalyzed oxidation of pentoxifylline by diperiodatocuprate(III) in aqueous alkaline medium at 298 K and $I = 0.30$ mol dm^{-3}

10^5 [DPC] (mol dm^{-3})	10^3 [PTX] (mol dm^{-3})	10^1 [OH^-] (mol dm^{-3})	10^5 [IO_4^-] (mol dm^{-3})	10^6 [Ru(III)] (mol dm^{-3})	10^2 k_T (s^{-1})	10^3 k_U (s^{-1})	10^2 k_C (s^{-1})	
							Found	Calculated
1.0	2.0	2.0	1.0	5.0	1.05	1.70	0.88	0.90
3.0	2.0	2.0	1.0	5.0	1.04	1.85	0.86	0.90
5.0	2.0	2.0	1.0	5.0	1.06	1.93	0.87	0.90
8.0	2.0	2.0	1.0	5.0	1.05	1.60	0.89	0.90
10.0	2.0	2.0	1.0	5.0	1.00	1.42	0.86	0.90
5.0	0.6	2.0	1.0	5.0	0.36	0.63	0.29	0.30
5.0	1.0	2.0	1.0	5.0	0.57	0.98	0.47	0.50
5.0	2.0	2.0	1.0	5.0	1.06	1.93	0.87	0.90
5.0	4.0	2.0	1.0	5.0	1.74	3.10	1.43	1.50
5.0	6.0	2.0	1.0	5.0	2.28	4.29	1.85	1.93
5.0	2.0	0.3	1.0	5.0	0.27	0.46	0.23	0.23
5.0	2.0	0.6	1.0	5.0	0.51	0.85	0.42	0.41
5.0	2.0	1.0	1.0	5.0	0.71	1.21	0.59	0.59
5.0	2.0	2.0	1.0	5.0	1.06	1.93	0.87	0.90
5.0	2.0	3.0	1.0	5.0	1.34	2.41	1.09	1.09
5.0	2.0	2.0	0.5	5.0	1.63	3.00	1.33	1.35
5.0	2.0	2.0	0.8	5.0	1.25	2.28	1.02	1.04
5.0	2.0	2.0	1.0	5.0	1.06	1.93	0.87	0.90
5.0	2.0	2.0	3.0	5.0	0.44	0.85	0.36	0.39
5.0	2.0	2.0	5.0	5.0	0.29	0.54	0.24	0.25
5.0	2.0	2.0	1.0	2.0	0.58	1.93	0.39	0.36
5.0	2.0	2.0	1.0	5.0	1.06	1.93	0.87	0.90
5.0	2.0	2.0	1.0	8.0	1.68	1.93	1.49	1.45
5.0	2.0	2.0	1.0	10.0	2.01	1.93	1.82	1.81
5.0	2.0	2.0	1.0	20.0	3.69	1.93	3.49	3.62

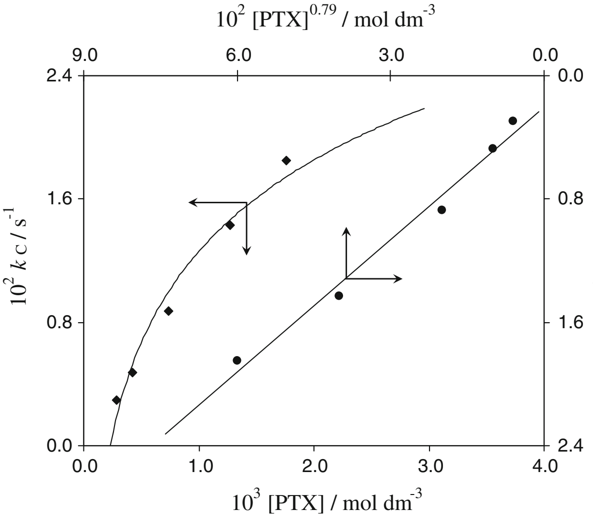


Fig. 1 Plot of k_C versus [PTX]$^{0.79}$ and k_C versus [PTX] (conditions as in Table 1)

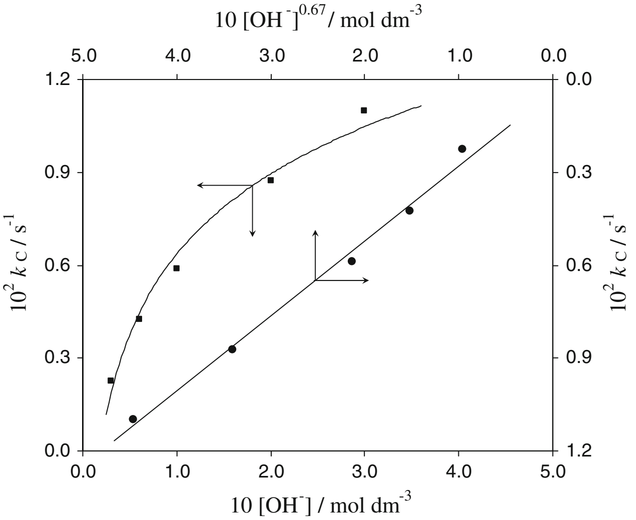


Fig. 2 Plot of k_C versus [OH^-]$^{0.67}$ and k_C versus [OH^-] (conditions as in Table 1)

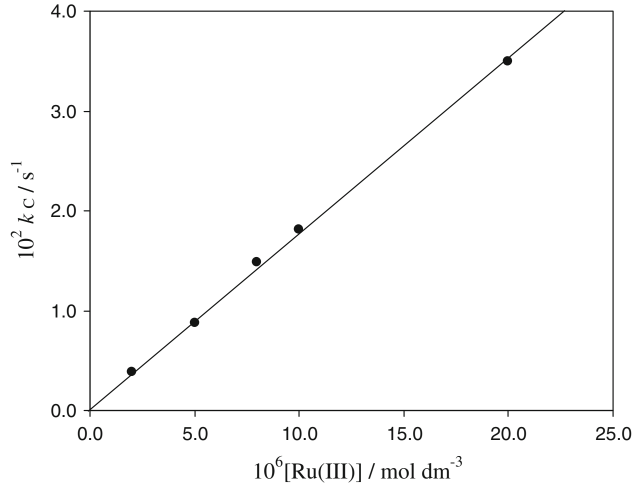


Fig. 3 Unit order plot of k_C versus [Ru(III)]

Table 2 Activation parameters with respect to the slow step of Scheme 1 and thermodynamic quantities for the ruthenium(III)-catalyzed oxidation of pentoxifylline by diperiodatocuprate(III) in aqueous alkaline medium

T (K)	$10^{-4}\ k$ (dm^3 mol^{-1} s^{-1})
(a) Effect of temperature	
288	0.52
298	0.90
308	1.91
318	3.74

Parameters	Values
(b) Activation parameters (Scheme 1)	
E_a (kJ mol^{-1})	50.8 ± 2.4
$\Delta H^\ddagger$ (kJ mol^{-1})	48.3 ± 2.2
$\Delta S^\ddagger$ (JK^{-1} mol^{-1})	−7.0 ± 0.8
$\Delta G^\ddagger$ (kJ mol^{-1})	50.4 ± 4.2
lg A	12.8 ± 0.5

T (K)	K_1 (dm^3 mol^{-1})	$10^5\ K_2$ (mol dm^{-3})	$10^{-2}\ K_3$ (dm^3 mol^{-1})
(c) Effect of temperature to calculate K_1, K_2, and K_3 for the Ru(III) catalyzed oxidation of pentoxifylline by diperiodatocuprate(III) in alkaline medium			
288	0.39	2.18	8.25
298	1.29	1.05	7.02
308	2.50	0.69	6.05
318	6.15	0.50	5.46

Thermodynamic quantities	Values from K_1	Values from K_2	Values from K_3
(d) Thermodynamic quantities using K_1, K_2, and K_3			
ΔH (kJ mol^{-1})	68 ± 3	−37 ± 2	−10.6 ± 1.3
ΔS (JK^{-1} mol^{-1})	230 ± 20	−220 ± 18	19 ± 2
ΔG_{298} (kJ mol^{-1})	−0.64 ± 0.04	28.4 ± 0.8	−16.2 ± 0.6

[DPC] = 5.0×10^{-5}, [PTX] = 2.0×10^{-3}, [OH$^-$] = 0.20, [IO$_4^-$] = 1.0×10^{-5}, [Ru(III)] = 5.0×10^{-6}, I = 0.30 mol dm^{-3}

Effect of [Ru(III)]

The ruthenium(III) concentration was varied from 2.0×10^{-6} to 2.0×10^{-5} mol dm^{-3} range, at constant concentrations of DPC, PTX, OH$^-$, IO$_4^-$, and a constant ionic strength. The order in [Ru(III)] was found to be unity from the linearity of the plot of k_C versus [Ru(III)] ($r \geq 0.9994$, $S \leq 0.019$; Table 1; Fig. 3).

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

By addition of KNO$_3$ at constant [DPC], [PTX], [Ru(III)], [OH$^-$], and [IO$_4^-$], it was found that an increase in ionic strength had a negligible effect on the rate of reaction.

The dielectric constant of the medium, D, was studied by varying the *t*-butyl alcohol and water percentage. The decrease in the dielectric constant of the reaction medium had a negligible effect on the rate of the reaction.

Effect of initially added products

Initially added products, copper(II) (CuSO$_4$) and 3,7-dihydro-1-(4-hydroxybutyl)-3,7-dimethylpurine-2,6-dione, did not have any significant effect on the rate of reaction.

Thus, from the observed experimental results, the rate law for Ru(III) catalyzed reaction is given as:

$$\text{Rate} = k_C[\text{DPC}]^{1.0}[\text{PTX}]^{0.79}[\text{OH}^-]^{0.67}\left[\text{IO}_4^-\right]^{-0.76}[\text{Ru(III)}]^{1.0}$$

Effect of temperature (T)

The influence of temperature on the k_C values was studied at 288, 298, 308, and 318 K. The rate constant, k, of the slow step in the mechanism was obtained from the intercept of [Ru(III)]/k_C versus 1/[PTX] plots at four different temperatures. The values are given in Table 2. The activation parameters for the rate-determining step were obtained by the least square method of plot of lg k versus 1/T and are presented in Table 2.

Test for free radicals

The intervention of free radicals was examined as follows: the reaction mixture, to which a known quantity of acrylonitrile monomer had been added initially, was kept in an inert atmosphere for 2 h. 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 PTX alone with acrylonitrile did not induce any polymerization under the same conditions as those induced for the reaction mixture. Initially added acrylonitrile decreased the rate of reaction, indicating free radical intervention, as was the case in earlier work [11].

It was also examined using an electron spin resonance spectrophotometer whose spectrum showed a peak at 3,325.000 G with a *g*-value of 2.0023 indicating the intervention of free radicals [12].

Catalytic activity

It has been pointed out by Moelwyn-Hughes [13] that in the presence of the catalyst, the uncatalyzed and catalyzed reactions proceed simultaneously, so that

$$k_T = k_U + K_C\,[\text{Catalyst}]^x \qquad (1)$$

Here k_T is the observed pseudo first-order rate constant in the presence of Ru(III) catalyst; k_U is the pseudo first-order rate constant for the uncatalyzed reaction; K_C is the catalytic constant, and '*x*' is the order of the reaction with respect to [Ru(III)]. In the present investigation, the value of *x* for the standard run was found to be 1.0. Then the value of K_C can be calculated using the equation

$$K_C = \frac{k_T - k_U}{[\text{Catalyst}]^x} = \frac{k_C}{[\text{Catalyst}]^x} \quad (\text{where } k_T - k_U = k_C) \qquad (2)$$

The values of $K_C \times 10^{-3}$ were obtained as 0.89, 1.74, 3.69, and 7.59 at 288, 298, 308, and 318 K, respectively. Further, plot of lg 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 $E_a = 54.4 \pm 2.1$ kJ mol^{-1}, $\Delta H^{\ddagger} = 51.9 \pm 0.4$ kJ mol^{-1}, $\Delta S^{\ddagger} = -8.5 \pm 0.8$ JK^{-1} mol^{-1}, $\Delta G^{\ddagger} = 84.7 \pm 4.2$ kJ mol^{-1}, lg $A = 12.8 \pm 0.3$.

The water-soluble copper(III) periodate complex is reported [14] to be $[Cu(HIO_6)_2(OH)_2]^{7-}$. However, in an aqueous alkaline medium and at the high pH range employed in the study, periodate is unlikely to exist as HIO_6^{4-} (as present in the complex) as is evident from its involvement in the multiple equilibria [15] (3)–(5), depending on the pH of the solution.

$$H_5IO_6 \rightleftharpoons H_4IO_6^- + H^+ \qquad (3)$$

$$H_4IO_6^- \rightleftharpoons H_3IO_6^{2-} + H^+ \qquad (4)$$

$$H_3IO_6^{2-} \rightleftharpoons H_2IO_6^{3-} + H^+ \qquad (5)$$

Periodic acid exists as H_5IO_6 in acid medium and as $H_4IO_6^-$ near pH 7. Hence, under alkaline conditions as employed in this study, the main species are expected to be $H_3IO_6^{2-}$ and $H_2IO_6^{3-}$. Thus, at the pH employed in this study, the soluble copper (III) periodate complex might be $[Cu(OH)_2(H_3IO_6)_2]^{3-}$, a conclusion also supported by earlier work [16, 17].

Ruthenium(III) chloride acts as an efficient catalyst in many redox reactions, particularly in an alkaline medium [18]. It is interesting to identify the probable ruthenium(III) chloride species in alkaline media. In the present study it is quite probable that the $[Ru(H_2O)_5OH]^{2+}$ species might assume the general form $[Ru(III)(OH)_x]^{3-x}$. The x value would always be less than six because there are no definite reports of any hexahydroxy ruthenium species. The remainder of the coordination sphere would be filled by water molecules. Hence, under the conditions employed, e.g., $[OH^-] \gg [Ru(III)]$, ruthenium(III) is mostly present as the hydroxylated species, $[Ru(H_2O)_5OH]^{2+}$. Similar equilibria have been reported between Ru(III) catalyzed oxidation of several other substrates with various oxidants in alkaline medium [19].

The reaction between the Ru(III) catalyzed oxidation of pentoxifylline by diperiodatocuprate(III) complex in alkaline medium has the stoichiometry 1:2 (PTX:DPC) with a first order dependence on [DPC] and [Ru(III)], and an apparent order of less than unity in [substrate], [alkali], and negative fractional order dependence on [periodate]. No effect of added products was observed. Based on the experimental results, a mechanism is proposed for which all the observed orders in each constituent such as [catalyst], [oxidant], [reductant], $[OH^-]$, and $[IO_4^-]$ may be well accommodated.

In most of the reports [10] on DPC oxidation, both periodate and OH^- had a decreasing effect on the rate of the reaction. However in the present kinetic study, different kinetic results have been obtained. In this study OH^- increased and periodate retarded the rate of the reaction. The results of an increase in the rate of reaction with increase in alkalinity (Table 1) can be explained in terms of the prevailing equilibrium of formation of $[Cu(H_2IO_6)(H_3IO_6)]^{2-}$ from $[Cu(H_3IO_6)_2]^-$ as given in the following Eq. (6).

$$[Cu(H_3IO_6)_2]^- + OH^- \overset{K_1}{\rightleftharpoons} [Cu(H_2IO_6)_2(H_3IO_6)]^{2-} + H_2O \qquad (6)$$

Also the decrease in rate with an increase in $[H_3IO_6^{2-}]$ (Table 1) suggests that the displacement of a ligand periodate takes place to give free periodate and the equilibrium of copper(III) periodate complex to form monoperiodatocuptrate(III) (MPC) species as given in Eq. (7) is established.

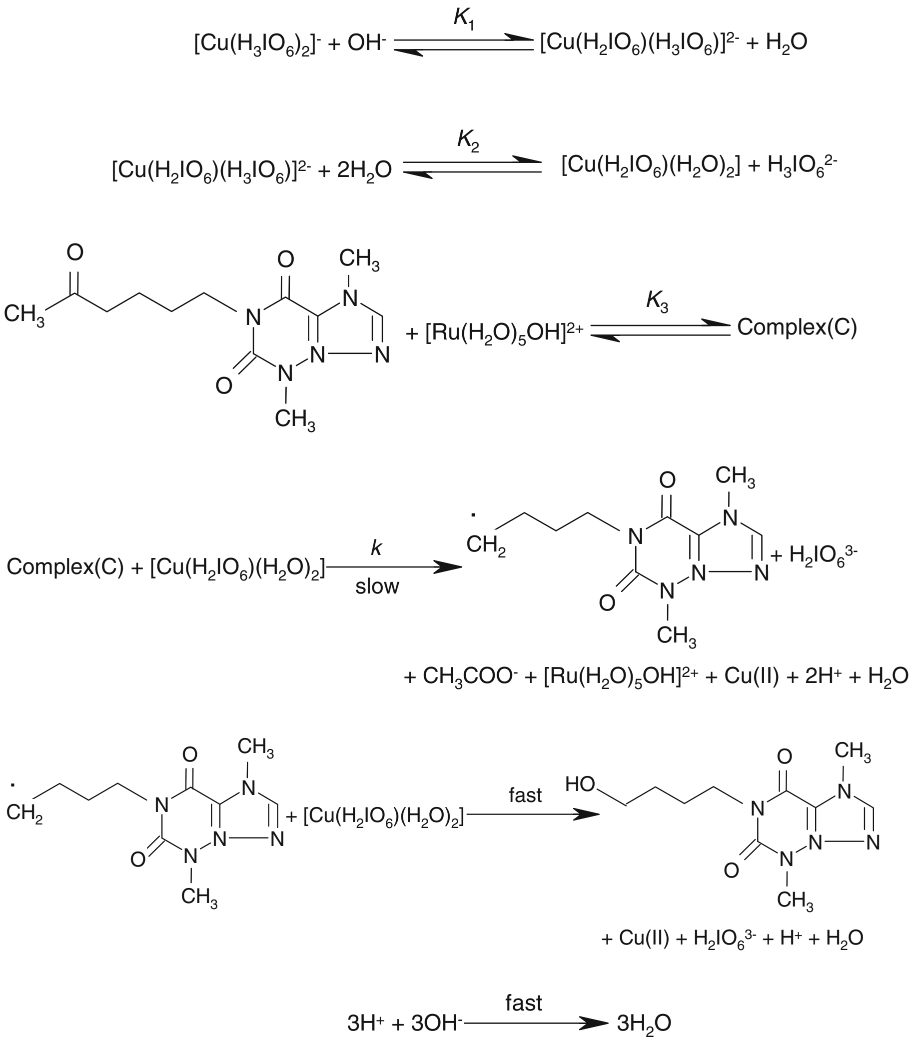
$$[Cu(H_2IO_6)(H_3IO_6)]^{2-} + 2H_2O \overset{K_2}{\rightleftharpoons} [Cu(H_2IO_6)(H_2O)_2]^- + H_3IO_6^{2-} \qquad (7)$$

Such types of equilibria as (6) and (7) have been well noticed in literature [19]. It may be expected that a lower periodate complex such as monoperiodatocuprate(III) (MPC) is more important in the reaction than the DPC. The inverse fractional order in [$H_3IO_6^{2-}$] might also be for this reason. Therefore, MPC might be the main reactive form of the oxidant.

The less than unit order in [PTX] presumably results from the formation of a complex (C) between the ruthenium(III) species and PTX prior to the formation of the products. This complex (C) reacts with one mole of MPC in a slow step to give the intermediate species of free radical derived from PTX, Cu(II) with the regeneration of catalyst, Ru(III). This free radical species further reacts with one more molecule of MPC in a fast step to form the products such as 3,7-dihydro-1-(4-hydroxybutyl)-3,7-dimethylpurine-2,6-dione, Cu(II), and periodate as given in Scheme 1.

Since Scheme 1 is in accordance with the generally well accepted principle of non-complementary oxidations taking place in sequence of one-electron steps, the reaction between the substrate and oxidant would afford a radical intermediate. A free radical scavenging experiment revealed such a possibility. This type of radical intermediate has also been observed in earlier work [10]. Spectroscopic evidence for the complex formation between Ru(III) and PTX was obtained from UV-Vis spectra of PTX (2.0×10^{-3}), Ru(III) (5.0×10^{-6}, $[OH^-] = 0.20$ mol dm^{-3}) and a mixture of both. A bathochromic shift of about 4 nm from 271 to 275 nm in the spectra of PTX to the mixture of Ru(III) and PTX was observed (Fig. 4). However, the Michaelis-Menten plot also proved the complex formation between catalyst and reductant, which explains the less than unit order dependence on [PTX]. Such a type of complex between a substrate and a catalyst has been observed in other studies [21].

Scheme 1



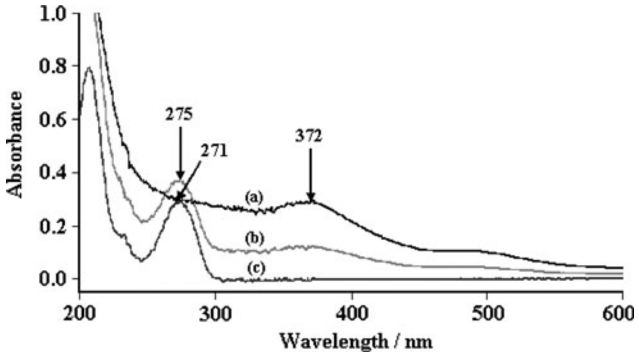


Fig. 4 Spectroscopic evidence for the complex formation between Ru(III) and PTX. **a** UV-Vis spectra of Ru(III) (372 nm); **b** UV-Vis spectra of a mixture of Ru(III) and PTX (275 nm and 372 nm); **c** UV-Vis spectra of PTX (271 nm)

From Scheme 1, the rate law (8) can be derived as

$$\text{Rate} = \frac{-\mathrm{d}[\mathrm{DPC}]}{\mathrm{d}t} = \frac{kK_1K_2K_3[\mathrm{DPC}][\mathrm{PTX}][\mathrm{OH}^-][\mathrm{Ru(III)}]}{[\mathrm{H_3IO_6^{2-}}] + K_1[\mathrm{OH}^-][\mathrm{H_3IO_6^{2-}}] + K_1K_2[\mathrm{OH}^-] + K_1K_2K_3[\mathrm{OH}^-][\mathrm{PTX}]} \tag{8}$$

$$\frac{\text{Rate}}{[\mathrm{DPC}]} = k_\mathrm{C} = k_\mathrm{T} - k_\mathrm{U} = \frac{kK_1K_2K_3[\mathrm{PTX}][\mathrm{OH}^-][\mathrm{Ru(III)}]}{[\mathrm{H_3IO_6^{2-}}] + K_1[\mathrm{OH}^-][\mathrm{H_3IO_6^{2-}}] + K_1K_2[\mathrm{OH}^-] + K_1K_2K_3[\mathrm{OH}^-][\mathrm{PTX}]} \tag{9}$$

The rate law (9) can be rearranged into the following form suitable for verification:

$$\frac{[\mathrm{Ru(III)}]}{k_\mathrm{C}} = \frac{[\mathrm{H_3IO_6^{2-}}]}{kK_1K_2K_3[\mathrm{OH}^-][\mathrm{PTX}]} + \frac{[\mathrm{H_3IO_6^{2-}}]}{kK_2K_3[\mathrm{PTX}]} + \frac{1}{kK_3[\mathrm{PTX}]} + \frac{1}{k} \tag{10}$$

The plots of [Ru(III)]/k_C versus 1/[PTX], [Ru(III)]/k_C versus 1/[OH$^-$], and [Ru(III)]/k_C versus [$\mathrm{H_3IO_6}^{2-}$] should be linear and were found to be so (Fig. 5). From the intercepts and slopes of such plots, the reaction constants K_1, K_2, K_3, and k were calculated as (1.3 ± 0.02) dm^3 mol^{-1} (1.1 ± 0.04) × 10^{-5} mol dm^{-3} (7.0 ± 0.2) × 10^2 dm^3 mol^{-1}, and (9.04 ± 0.30) × 10^3 dm^3 mol^{-1} s^{-1}, respectively. The values of K_1 and K_2 are in good agreement with previously reported work [20]. The equilibrium constant K_1 is far greater than K_2. This may be attributed to the greater tendency of DPC to undergo hydrolysis compared to the dissociation of hydrolyzed species in alkaline medium. These constants were used to calculate the rate constants over different experimental conditions, and when compared with the experimental k_C

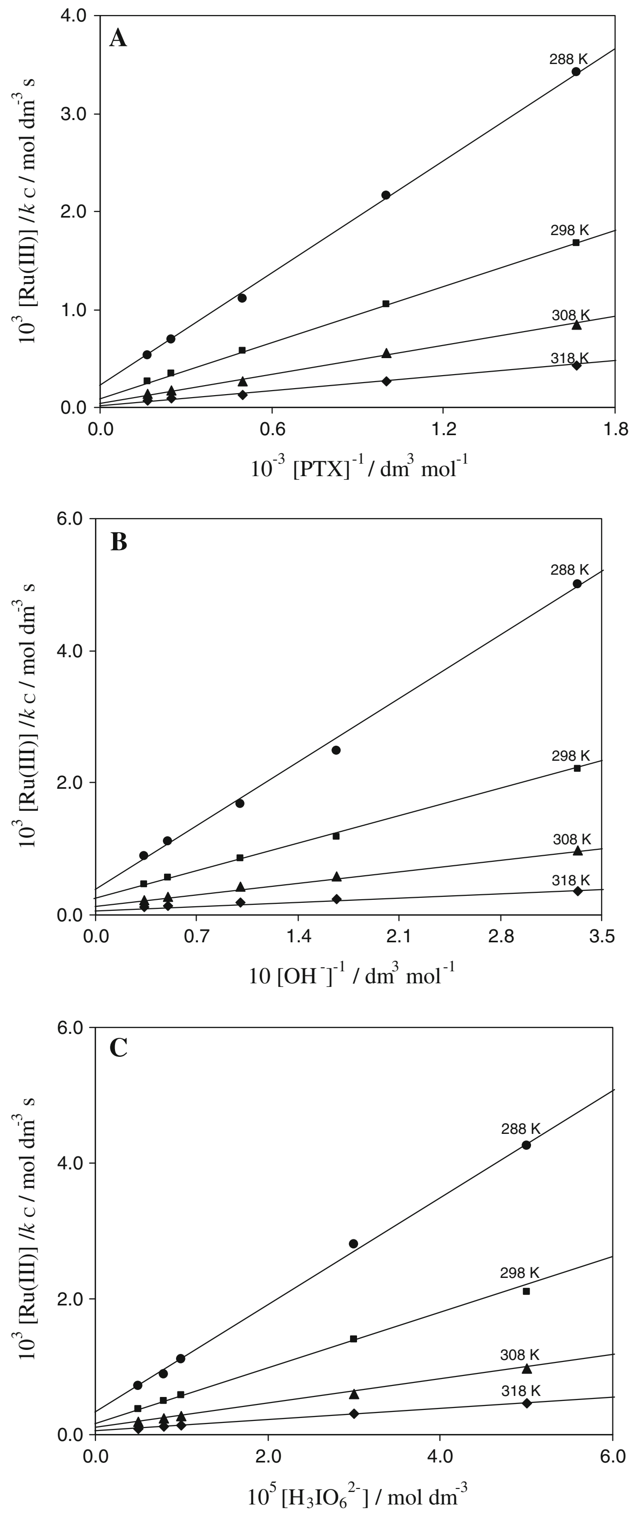


Fig. 5 Verification of rate law (9) for the Ru(III)-catalyzed oxidation of pentoxifylline by diperiodatocuprate(III). Plots of **a** [Ru(III)]/k_C versus 1/[PTX], **b** [Ru(III)]/k_C versus 1/[OH$^-$], and **c** [Ru(III)]/k_C versus [$\mathrm{H_3IO_6}^{2-}$], at four different temperatures (conditions as given in Table 1)

values, they are found to be in reasonable agreement with each other, which fortifies Scheme 1.

The effect of ionic strength and dielectric constant of the medium on the rate explains quantitatively the reaction between the 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 [PTX], [OH$^-$], and [$H_3IO_6^{2-}$] (Table 1) were varied at four different temperatures. The plots of [Ru(III)]/k_C versus 1/[PTX] ($r \geq 0.9999$, $S \leq 0.00131$), [Ru(III)]/k_C versus 1/[OH$^-$] ($r \geq 0.9992$, $S \leq 0.00097$), and [Ru(III)]/k_C versus [$H_3IO_6^{2-}$] ($r \geq 0.9993$, $S \leq 0.00131$) should be linear and were found to be so, as shown in Fig. 5. From the slopes and intercepts, the values of K_1, K_2, and K_3 were calculated at four different temperatures. A van't Hoff's plot was made for the variation of K_1, K_2, K_3 with temperature (i.e., lg K_1 versus 1/T, lg K_2 versus 1/T, and lg K_3 versus 1/T). The values of the enthalpy of reaction ΔH, entropy of reaction ΔS, and free energy of reaction ΔG were calculated for the first, second, and third equilibrium steps. These values are also given in Table 2. A comparison of the ΔH value (68 ± 2) from K_1 with that of $\Delta H^{\ddagger}$ (48.3 ± 2.0) of the rate limiting step supports that the first step of Scheme 1 is fairly slow since it involves a high activation energy [22].

The values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were both favorable for electron transfer processes. The favorable enthalpy was due to the release of energy on solution changes in the transition state. The negative value of $\Delta S^{\ddagger}$ suggests that the intermediate complex is more ordered than the reactants [23]. The observed modest enthalpy of activation and a higher rate constant for the slow step indicate that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by earlier observations [24, 25]. The activation parameters evaluated for the reaction explain the catalytic effect on the reaction. The catalyst Ru(III) forms the complex (C) with the substrate, which enhances the reducing property of the substrate compared to that without the Ru(III) catalyst. Further, the Ru(III) catalyst modifies the reaction path by lowering the energy of activation.

Conclusion

The Ru(III) catalyzed oxidation of pentoxifylline by diperiodatocuprate(III) was studied. Oxidation products were identified. Among various species of Cu(III) in alkaline medium, monoperiodatocuprate(III), $Cu(H_2IO_6)(H_2O)_2$, is considered to be the active species for the title reaction. The active species of Ru(III) is found to be $[Ru(H_2O)_5OH]^{2+}$. Activation parameters were evaluated. Catalytic constant and activation parameters with reference to the catalyst were also computed.

Experimental

Materials and reagents

All chemicals used were of reagent grade, and double distilled water was used throughout the work. Stock solution of PTX (Sigma-Aldrich, St. Louis, MO) was prepared by dissolving the appropriate amount of sample in double-distilled water. The required concentration of PTX was used from its aqueous stock solution. A standard stock solution of Ru(III) was prepared by dissolving $RuCl_3$ (S.D. Fine-chem Ltd., Mumbai, India) in 0.20 mol dm^{-3} HCl. The concentration was determined [26] by EDTA titration.

The copper(III) periodate complex was prepared [27] and standardized by a standard procedure [28]. The UV-Vis spectrum with maximum absorption at 415 nm verified the existence of copper(III) complex. Periodate solution was prepared by weighing the required amount of sample in hot water and used after 24 h to complete the equilibrium. Its concentration was ascertained iodometrically [29] at neutral pH maintained using phosphate buffer. KOH (BDH) and KNO_3 (AR) were employed to maintain the required alkalinity and ionic strength, respectively. The temperature was maintained constant to within ±0.1 °C.

Instruments used

For kinetic measurements, a Peltier Accessory (temperature control) attached to a Varian CARY 50 Bio UV-Vis spectrophotometer (Varian, Victoria-3170, Australia) was used. For product analysis, a Nicolet 410-FT-IR spectrometer (Thermo, USA), a 300-MHz ^{1}H NMR spectrometer (Bruker, Germany), and a LC-MS Agilent 1100 series-API 2000 mass spectrometer using the EI ionization technique were used. For intervention of free radicals, an ESR spectrophotometer (Bruker BioSpin GmbH) was used. For pH measurements an ELICO pH meter model LI 120 was used.

Kinetic measurements

The kinetics were followed under pseudo first-order conditions where [PTX] > [DPC] at 25.0 ± 0.1 °C, unless otherwise specified. The reaction was initiated by mixing the DPC to PTX solution, which also contained required concentrations of Ru(III), KNO_3, KOH, and KIO_4. The progress of the reaction was followed spectrophotometrically at 415 nm by monitoring the decrease in absorbance due to DPC with the molar absorbancy index ε at 6,235 ± 100 $dm^3 mol^{-1} cm^{-1}$ (literature ε = 6,230 [27]). It was verified that there is negligible interference from other species present in the reaction mixture at this wavelength. The pseudo-first order rate constants, k_T, were determined from the lg(absorbance) versus time plots. The plots were linear up to 85% completion of the reaction under the range of $[OH^-]$ used.

During the kinetics a constant concentration of 1.0×10^{-5} mol dm^{-3} of KIO_4 was used throughout the study unless otherwise stated. Since the excess of periodate is present in DPC, the possibility of oxidation of pentoxifylline by periodate in alkaline medium at 298 K was tested. The progress of the reaction was followed iodometrically. However, it was found that there was no significant reaction under the experimental conditions employed compared to the DPC oxidation of PTX. The total concentrations of periodate and OH^- were calculated by considering the amount present in the DPC 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 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 rates. The spectral changes during the reaction are shown in Fig. 6. It is evident from the figure that the concentration of DPC decreases at 415 nm.

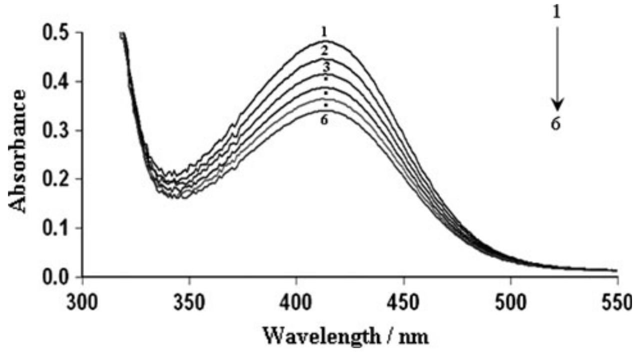


Fig. 6 Spectroscopic changes occurring in the oxidation of PTX by alkaline DPC at 298 K, [DPC] = 5.0×10^{-5}, [PTX] = 2.0×10^{-3}, $[OH^-] = 0.20$, $[IO_4^-] = 1.0 \times 10^{-5}$, [Ru(III)] = 5.0×10^{-6}, and $I = 0.30$ mol dm^{-3} with scanning time of (1) 0.5, (2) 1.0, (3) 1.5, (4) 2.0, (5) 2.5, and (6) 3.0 min

Stoichiometry and product analysis

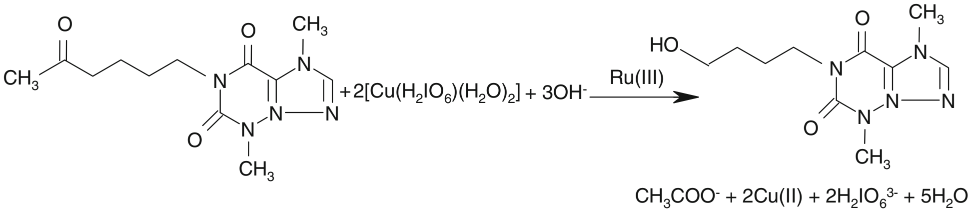
Different sets of reaction mixtures containing varying ratios of DPC to PTX in the presence of constant amounts of OH^-, IO_4^-, KNO_3, and Ru(III) were kept for 6 h in a closed vessel under inert atmosphere. The remaining DPC concentration was estimated by measuring the absorbance at 415 nm spectrophotometrically. The results indicated 1:2 stoichiometry as given in Scheme 2.

The main reaction product was eluted with chloroform and was identified as 3,7-dihydro-1-(4-hydroxybutyl)-3,7-dimethylpurine-2,6-dione. The product was characterized by FT-IR, ^{1}H NMR, and LC-MS studies.

The IR spectrum showed the absence of aliphatic C=O stretching at 1,719 cm^{-1}, which was shown for the parent molecule, the band at 3,431 cm^{-1} indicating the presence of an alcoholic OH group. The product was also characterized by an NMR spectrum ($CDCl_3$) showing a peak at a chemical shift of $\delta = 1.82$ ppm (s, 1H), which disappeared on D_2O exchange. Further, the product was subjected to LC-MS analysis. The mass spectrum (Fig. 7) showed a molecular ion peak (M+1) at $m/z = 253.1$, confirming the formation of product. Sodium acetate was confirmed by a spot test [30]. It was observed that 3,7-dihydro-1-(4-hydroxybutyl)-3,7-dimethylpurine-2,6-dione did not undergo further oxidation under the present kinetic conditions.

Regression analysis of experimental data to obtain the regression coefficient r and standard deviation S of point

Scheme 2



$CH_3COO^- + 2Cu(II) + 2H_2IO_6^{3-} + 5H_2O$

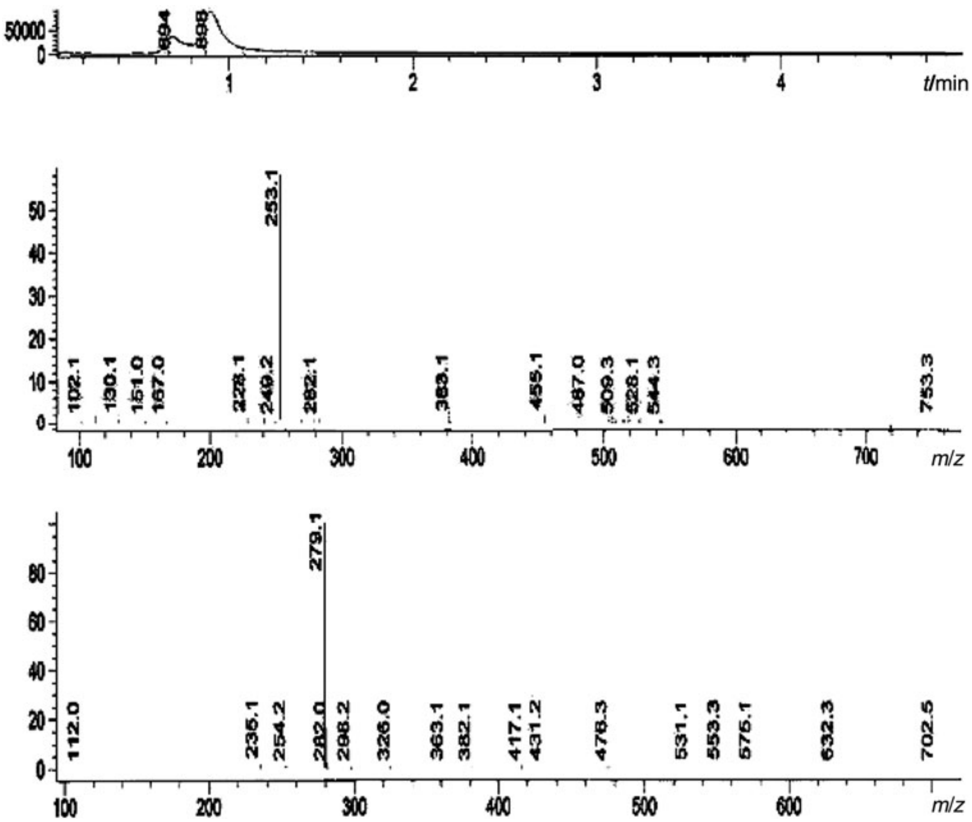


Fig. 7 LC-MS spectrum of 3,7-dihydro-1-(4-hydroxybutyl)-3,7-dimethylpurine-2,6-dione with its molecular ion peak (M+1) at $m/z = 253.1$

from the regression line was performed using the Microsoft Excel 2003 program.

Appendix

According to Scheme 1,

$$\text{Rate} = \frac{-\mathrm{d}[\mathrm{DPC}]}{\mathrm{d}t} = k[\mathrm{C}]\left[\mathrm{Cu(H_2IO_6)(H_2O)_2}\right] = \frac{kK_1K_2K_3[\mathrm{DPC}][\mathrm{PTX}][\mathrm{OH^-}][\mathrm{Ru(III)}]}{\left[\mathrm{H_3IO_6^{2-}}\right]} \tag{11}$$

The total concentration of DPC, $[\mathrm{DPC}]_\mathrm{T}$, is given by (subscripts T and f stand for total and free, respectively)

$$[\mathrm{DPC}]_\mathrm{T} = [\mathrm{DPC}]_\mathrm{f} + [\mathrm{Cu(H_2IO_6)(H_3IO_6)}]^{2-} + \left[\mathrm{Cu(H_2IO_6)(H_2O)_2}\right]$$

$$[\mathrm{DPC}]_\mathrm{T} = [\mathrm{DPC}]_\mathrm{f} + K_1[\mathrm{OH^-}][\mathrm{DPC}] + \frac{K_2[\mathrm{Cu(H_2IO_6)(H_3IO_6)}]^{2-}}{\left[\mathrm{H_3IO_6^{2-}}\right]}$$

$$[\mathrm{DPC}]_\mathrm{T} = [\mathrm{DPC}]_\mathrm{f}\left[1 + K_1[\mathrm{OH^-}] + \frac{K_1K_2[\mathrm{OH^-}]}{\left[\mathrm{H_3IO_6^{2-}}\right]}\right]$$

$$[\mathrm{DPC}]_\mathrm{f} = \frac{[\mathrm{DPC}]_\mathrm{T}\left[\mathrm{H_3IO_6^{2-}}\right]}{\left[\mathrm{H_3IO_6^{2-}}\right] + K_1[\mathrm{OH^-}]\left[\mathrm{H_3IO_6^{2-}}\right] + K_1K_2[\mathrm{OH^-}]} \tag{12}$$

Similarly,

$$[\mathrm{Ru(III)}]_\mathrm{T} = [\mathrm{Ru(III)}]_\mathrm{f} + [\mathrm{C}] = [\mathrm{Ru(III)}]_\mathrm{f} + K_3[\mathrm{PTX}][\mathrm{Ru(III)}]_\mathrm{f}$$

$$[\mathrm{Ru(III)}]_\mathrm{f} = \frac{[\mathrm{Ru(III)}]_\mathrm{T}}{1 + K_3[\mathrm{PTX}]} \tag{13}$$

$$[\mathrm{PTX}]_\mathrm{f} = \frac{[\mathrm{PTX}]_\mathrm{T}}{1 + K_3[\mathrm{Ru(III)}]}$$

In view of the low concentrations of Ru(III) used, we have

$$[\mathrm{PTX}]_\mathrm{T} = [\mathrm{PTX}]_\mathrm{f} \tag{14}$$

Similarly,

$$[\mathrm{OH^-}]_\mathrm{T} = [\mathrm{OH^-}]_\mathrm{f} \tag{15}$$

Substituting Eqs. (12), (13), (14), and (15) in Eq. (11) and omitting the T and f subscripts, we get

$$\text{Rate} = \frac{-\mathrm{d}[\mathrm{DPC}]}{\mathrm{dt}} = \frac{kK_1K_2K_3[\mathrm{DPC}][\mathrm{PTX}][\mathrm{OH}^-][\mathrm{Ru(III)}]}{\left[\mathrm{H_3IO_6^{2-}}\right] + K_1[\mathrm{OH}^-]\left[\mathrm{H_3IO_6^{2-}}\right] + K_1K_2[\mathrm{OH}^-] + K_1K_2K_3[\mathrm{OH}^-][\mathrm{PTX}] + K_3\left[\mathrm{H_3IO_6^{2-}}\right][\mathrm{PTX}] + K_1K_2[\mathrm{PTX}][\mathrm{OH}^-]\left[\mathrm{H_3IO_6^{2-}}\right]}$$

The terms ($K_3[H_3IO_6{}^{2-}][PTX]$) and ($K_1K_3[PTX][OH^-][H_3IO_6{}^{2-}]$) of the denominator are neglected in view of their lower values as compared to the periodate used in the study. Therefore,

$$\text{Rate} = \frac{-\mathrm{d}[\mathrm{DPC}]}{\mathrm{dt}} = \frac{kK_1K_2K_3[\mathrm{DPC}][\mathrm{PTX}][\mathrm{OH}^-][\mathrm{Ru(III)}]}{\left[\mathrm{H_3IO_6^{2-}}\right] + K_1[\mathrm{OH}^-]\left[\mathrm{H_3IO_6^{2-}}\right] + K_1K_2[\mathrm{OH}^-] + K_1K_2K_3[\mathrm{OH}^-][\mathrm{PTX}]} \quad (16)$$

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