



A Thermodynamic and Comparative Study of Pharmaceutical Drug by Ir(III) and Pd(II) Catalyzed Oxidation in Acidic Medium (HClO₄): Kinetic Model

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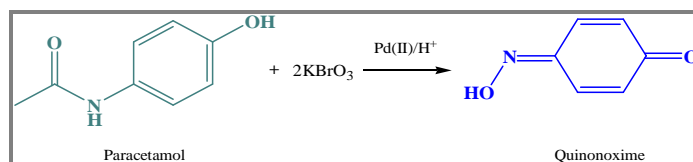
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ABSTRACT

A comparative study of Pharmaceutical drug (Paracetamol) by Ir(III) and Pd(II) catalysed oxidation in acidic medium (HClO₄) at 35 °C to 45 °C. The reaction is carried out in the presence of mercuric acetate as a scavenger for bromide ion. 1-carboxy cyclohexane 1-acetic acid was obtained as the oxidation product and identified chromatographically. The rate law followed a first order and zero order dependence with respect to KBrO₃ and potassium chloride [KCl] respectively. The reaction followed first order with respect to Ir(III) and Pd(II) chloride. Negligible effect of [Hg(OAc)₂] and ionic strength of the medium was observed. The rate of reaction decreased with increasing [H⁺] was observed for the oxidation of paracetamol. Rate of reaction exhibits fractional positive order kinetics with respect to [PA]. The values of rate constants observed at different temperatures (30 to 45 °C) were utilized to calculate the activation parameters. Quinoneoxime and acetic acid have been identified as main oxidation products of the reactions. Feasible mechanism is proposed which are composed with the kinetics, stoichiometry and product of the reaction. The rate law has been derived from obtained kinetic data.

Graphical Abstract



Keywords: Kinetics, Ir(III) chloride, Pd(II) chloride oxidation, Paracetamol, Potassium bromate, Acidic medium.

INTRODUCTION

The transition metal catalyzed reactions are important for the chemical industry from both practical and economic point of view. Transition metal ions are found to be good catalysts and their complexes

are also able to catalyze a wide variety of reactions like hydrogenation, oxidation and polymerization. The applications of transition metal catalyst such as Ru(III) [1, 2], Rh(III) [3, 4], Cu(II)[5, 6], and Pd(II)[7, 8] in kinetic studies of redox reaction involving organic substrate are reported in literature. It was found that these catalysts work efficiently in both acidic and alkaline media. The use of Ir(III) chloride as a non-toxic and homogeneous catalyst has been reported [9-11]. The reaction path depends not only upon the nature of the oxidant and the nature of the substrates but also upon the ways in which reactive species of transition metal ion forms complex with the reactant molecules before changing into final products under experimental conditions. Oxidant such as NBS [13, 14], NBA [14, 15], periodate [16, 17], and iodate [18, 19], have been successfully utilized in kinetic and mechanistic investigations of various organic substrate. Amongst various inorganic oxidants, iodate has been used as an oxidant in the uncatalyzed oxidation of oxalic acid [20], acetophenone [21], and benzaldehyde [22]. Singh *et al.*, [23-26] have introduced various reports in the literature regarding the oxidation of reducing sugars involving Ir(III) as homogeneous catalyst. Potassium bromate is known to be a powerful oxidizing agent with redox potential 1.44 volts and has been used widely in the oxidation of several organic substrates [27]. Potassium bromate is used for oxidation of uncatalyzed reactions by several workers [28, 29]. Uncatalyzed reactions of aldoses and aldosesamines [30], carbohydrates [31] compound oxidation by potassium bromate have also been reported. Ir(III) catalyzed cyclic alcohols [32], cyclic ketones [33] oxidation by potassium bromate has also been reported. Comparatively Ir(III) catalysed oxidation has been dealt than other catalyst and scant attention has been paid with potassium bromate as an oxidant. The kinetics of paracetamol (PAM) oxidation has been studied both spectrophotometrically and iodometrically. Spectrophotometric determination of paracetamol in drug formulation has been a subject of several investigators [34-42]. It is antipyretic and analgesic compound of high therapeutic value [43, 44]. It is also used as an intermediate for pharmaceutical (as a precursor in penicillin) and azo dye [45-47]. Oxidation reactions are important in the synthesis of organic compounds, create new functional groups or modify existing functional groups in a molecule [48, 49]. Various advanced oxidation processes such as electrochemical [50-52] ozonation and H₂O₂ / UV oxidation [53-56] have been employed to remove aqueous paracetamol. Several authors have performed studies using Pd(II) because of the commercial importance of reactions catalyzed by Pd(II). The kinetics for the oxidation of ethylene by aqueous Pd (II) is an example [57, 58]. In this study the effect of chloride ion on the reaction rate was studied in order to establish the active species of the catalyst. Generally the mechanism of catalysis depends on the nature of the substrate, the oxidant, and other experimental conditions [59, 60]. In most of the catalytic studies for organic transformations, the nature of active form of Pd(II) remain obscure. The kinetic methods of analysis are highly sensitive, selective, simple, accurate, and less expensive. The present study examines, in detail the kinetic and mechanistic aspects of the Ir(III) catalyzed oxidation of paracetamol by KBrO₃ in acidic media with the following objective. In this paper it has been tried to consolidate the various work done on the well-known drug that finds extensive application in pharmaceutical industries in the last few decades. In most of the catalytic studies for organic transformations, the nature of active form of Pd(II) remain obscure. The kinetic methods of analysis are highly sensitive, selective, simple, accurate, and less expensive. In recent years, several kinetic Paracetamol (4-hydroxyacetanilide or acetamidophenol) is a well-known drug that is having extensive application in pharmaceutical industries. The present study examines, in detail the kinetic and mechanistic aspects of the Ir(III)/Pd(II) catalyzed oxidation of paracetamol by KBrO₃ in acidic media.

MATERIALS AND METHODS

Materials: Aqueous solution of Paracetamol (CDH), potassium bromate (S.D. Fine A.R.) and mercuric acetate (E. Merck) were prepared by dissolving the weighed amount of sample in triple distilled water. Perchloric acid (60% E. Merck) was used as a source of hydrogen ions. Iridium (III) chloride and palladium chloride (Johnson Matthey) was prepared by dissolving the sample in hydrochloric acid of known strength. All other reagents of analytical grade were available. Sodium perchlorate (E. Merck) was used to maintain the ionic strength of the medium. The reaction stills were blackened from outside to prevent photochemical effect.

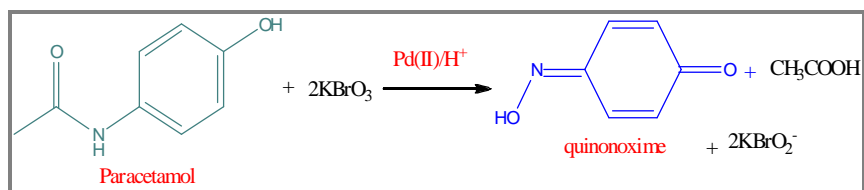
Table 1. Effect of variation of oxidant, substrate, catalyst at 35°C

[Oxidant] x 10 ³ M (Potassium bromate)	[Substrate]x 10 ² M (Paracetamol)	[Pd(II) / Ir(III)] x 10 ⁵ M	(-dc/dt)x10 ⁷ ML ⁻¹ s ⁻¹ Pd(II)	Ir(III)
0.80	1.00	11.2	1.92	4.30
1.00	1.00	11.2	2.60	5.20
1.25	1.00	11.2	2.82	6.45
1.69	1.00	11.2	3.81	8.65
2.50	1.00	11.2	5.32	12.80
5.00	1.00	11.2	10.60	25.50
1.00	0.40	11.2	1.32	3.80
1.00	0.50	11.2	1.60	4.30
1.00	0.66	11.2	2.10	4.62
1.00	1.00	11.2	2.60	5.20
1.00	2.00	11.2	4.25	6.65
1.00	4.00	11.2	6.20	8.25
1.00	1.00	5.60	1.33	2.56
1.00	1.00	11.2	2.60	5.20
1.00	1.00	16.8	4.60	10.30
1.00	1.00	22.4	5.18	15.32
1.00	1.00	33.6	8.35	20.40
1.00	1.00	44.8	10.21	25.90

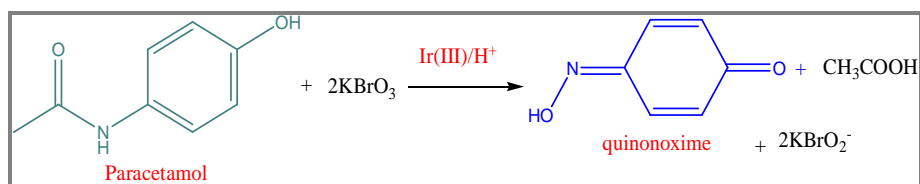
Solution Condition: [HClO₄] = 1.00 X 10⁻³ M, [KCl] = 1.00 X 10⁻³ M, [Hg(OAc)₂] = 1.25 X 10⁻³ M

Kinetic Procedure: A thermostated water bath was used to maintain the desired temperature within $\pm 0.1^\circ\text{C}$. Calculated amount of the reactants i.e. paracetamol, perchloric acid, mercuric acetate, Ir (III)/Pd(II) chloride, KCl and water, except potassium bromate were taken in a reaction vessel which was kept in a thermostatic water bath. After allowing sufficient time to attain the temperature of the experiment, requisite amount of potassium bromate solution, also thermostated at the same temperature was rapidly pipetted out and run into the reaction vessel. The total volume of reaction mixture was 50 mL in each case. Aliquots (5 mL) of the reaction mixture were pipetted out at regular intervals of time and poured in to a conical flask containing 5 mL of 4% KI solution and 5 mL of dilute sulfuric acid. The liberated bromine equivalent to consumed oxidant was estimated with standard sodium thiosulphate solution using starch as an indicator. The rate of reaction (-dc/dt) was determined from the slope of the tangent drawn at a fixed [BrO₃⁻] in each kinetic run. The order of reaction in each reactant was measured with the help of log plot of (-dc/dt) versus concentration of the reactants.

Determination of stoichiometry and product analysis of Pd(II) chloride for the oxidation of paracetamol



Determination of stoichiometry and product analysis of Ir(III) chloride for the oxidation of paracetamol



Different sets of the reaction mixture containing Paracetamol, Ir(III)/Pd(II) chloride, and HClO_4 with excess KBrO_3 were equilibrated for 72 h at 303 K. Estimation of unconsumed KBrO_3 in each set revealed that for the oxidation of 1 mol of Paracetamol, 2 mols of KBrO_3 were consumed. Accordingly, the stoichiometry equation may be expressed as the reaction products were extracted with ether after completion of the reaction (monitored by TLC). Evaporation of the ether layer was followed by column chromatography on silica gel using a gradient elution (from dichloromethane to chloroform). After the initial separation, the products were further purified by recrystallization. Acetic acid and quinine oxime were identified as oxidation products of Paracetamol and 2KBrO_2 was the reduction product of KBrO_3 . The quinone oxime was identified by its IR spectrum (1652 cm^{-1} , C=O stretching; 1615 cm^{-1} , C=N stretching of oxime; 3332 cm^{-1} , O-H stretching). Identification was further confirmed by its melting point of 131°C (literature mp 132°C).

Table 2. Effect of variation of perchloric acid (HClO_4), potassium chloride (KCl), mercuric acetate [$\text{Hg}(\text{Ac})_2$] and sodium perchlorate at 35°C

[HClO_4] x 10^3M	[KCl] x 10^3M	[$\text{Hg}(\text{OAc})_2$] x 10^3M	NaClO ₄ x 10^3M	(-dc/dt) x $10^7\text{ML}^{-1}\text{s}^{-1}$	
				Pd(II)	Ir(III)
0.83	1.00	1.00	1.00	3.12	5.60
1.00	1.00	1.00	1.00	2.60	5.20
1.25	1.00	1.00	1.00	2.41	4.60
1.67	1.00	1.00	1.00	2.00	4.25
2.50	1.00	1.00	1.00	1.22	3.60
5.00	1.00	1.00	1.00	0.82	2.95
1.00	0.83	1.00	1.00	2.23	4.90
1.00	1.00	1.00	1.00	2.60	5.20
1.00	1.25	1.00	1.00	2.00	4.52
1.00	1.67	1.00	1.00	2.81	5.45
1.00	2.50	1.00	1.00	2.52	5.12
1.00	5.00	1.00	1.00	2.42	4.72
1.00	1.00	0.83	1.00	2.21	4.52
1.00	1.00	1.00	1.00	2.60	4.93
1.00	1.00	1.25	1.00	2.60	5.20
1.00	1.00	1.67	1.00	3.00	4.62
1.00	1.00	2.50	1.00	2.42	5.55
1.00	1.00	5.00	1.00	2.51	5.32
1.00	1.00	1.00	0.83	2.00	5.00
1.00	1.00	1.00	1.00	2.60	4.63
1.00	1.00	1.00	1.25	2.00	5.20
1.00	1.00	1.00	1.67	2.22	5.10
1.00	1.00	1.00	2.50	2.10	5.63
1.00	1.00	1.00	5.00	2.00	5.11

Solution Condition: [Oxidant (KBrO_3)] = $1.00 \times 10^{-3}\text{M}$, [Paracetamol (PA)] = $1.00 \times 10^{-2}\text{M}$, [Ir (III) And Pd(II) Chloride] = $11.2 \times 10^{-5}\text{M}$

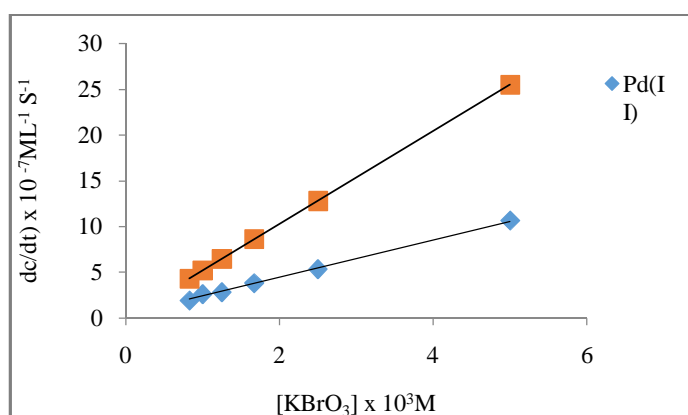
RESULTS AND DISCUSSION

The kinetic results were collected at several initial concentrations of reactants (Table 3). The initial rate $(-\text{dc}/\text{dt})$ in each kinetic run was calculated by the slope of tangent drawn at fixed time for the variation of $[\text{KBrO}_3]$ while in the variation of other [reactants], tangents drawn at fixed $[\text{KBrO}_3]$ which was written as $[\text{KBrO}_3^*]$. The first order rate constant K_1 was calculated as, $K_1 = -(\text{dc}/\text{dt})/[\text{KBrO}_3^*]$.

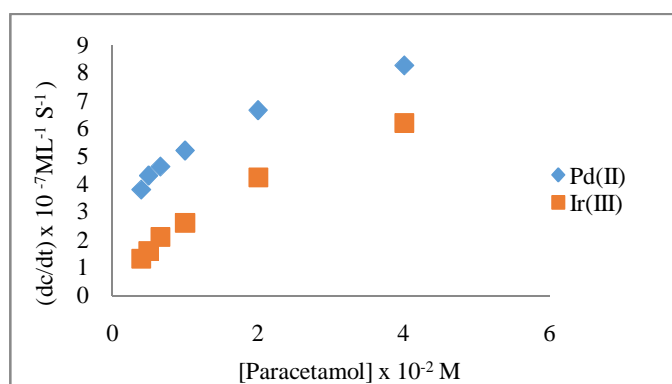
Each kinetic run was studied for two half-lives of the reaction. The observed rates of reaction were reproducible with in $\pm 5\%$ in replicate kinetic run. The order of reaction in each reactant was determined with the help of log-log plot of $(-\text{dc}/\text{dt})$ vs. Concentration of reactant. First order rate constant k_1 i.e. $(-\text{dc}/\text{dt}/\text{KBrO}_3^*)$ were calculated from the plots of unconsumed potassium bromate vs. time. The comparative plots of $\log(-\text{dc}/\text{dt})$ versus $\log(\text{oxidant})$ were linear indicating first order dependence on KBrO_3 (Figure 1). Insignificant effect on the rate was observed on increasing the concentration of $[\text{Cl}^-]$

Table 3. Activation parameters for Pd(II) / Ir(III) chloride catalyzed oxidation of paracetamol by KBrO₃ at 35°C

Parameter	Temperature(T°C)	Paracetamol(-dc/dt)x 10	
		Pd(II)	Ir(III)
$k_1 \times 10^4 \text{s}^{-1}$	30°	1.55	3.70
$k_1 \times 10^4 \text{s}^{-1}$	35°	2.60	5.20
$k_1 \times 10^4 \text{s}^{-1}$	40°	3.18	7.35
$k_1 \times 10^4 \text{s}^{-1}$	45°	5.18	10.12
log A	...	10.80	9.51
ΔE_a^* (kJ mol ⁻¹)	35°	60.98	55.25
ΔG^* (kJ mol ⁻¹)	35°	74.63	76.12
ΔH^* (kJ mol ⁻¹)	35°	71.45	55.52
ΔS^* (JK ⁻¹ mol ⁻¹)	35°	-10.03	-66.82

**Figure 1.** A comparative graph between rate of reaction (-dc/dt) vs [KBrO₃] for the oxidation of paracetamol at 35°C. [HClO₄] = 1.00 x 10⁻³ M, [KCl] = 1.00 x 10⁻³ M, [Hg(OAc)₂] = 1.25 x 10⁻³ M, Paracetamol [PAM] = 1.00 x 10⁻² M, Pd(II)/Ir(III) Chloride = 11.2 x 10⁻⁵ M.

indicating zero order in [KCl], i.e. potassium chloride (Table 2). The rate of reaction increases as the concentration of Iridium (III) chloride and Pd(II) chloride is increased, It was observed that values of (-dc/dt) were doubled when the concentration of iridium(III)/Pd(II) was made two times, showing first order dependence on IrCl₃ / PdCl₂ indicating first order of catalyst i.e. Ir(III) chloride and Pd(II) chloride (Table 1) and comparative graph (Figure 3). Kinetic result obtained on varying concentrations of substrate indicates fractional positive order of paracetamol, which implies that rate of reaction increases when the concentration of [PA] is increased with both catalyst (Table 1) and (Figure 2). With increasing the concentration of [H⁺], the value of reaction rate decreases for both catalyst (Table 2) and

**Figure 2.** A comparative graph between rate of reaction (-dc/dt) vs [Paracetamol] for the oxidation of paracetamol at 35°C. [HClO₄] = 1.00 x 10⁻³ M, [KCl] = 1.00 x 10⁻³ M, [Hg(OAc)₂] = 1.25 x 10⁻³ M, Paracetamol [Ir(III)/Pd(II)] = 11.20 x 10⁻⁵ M, [KBrO₃] = 1.00 x 10⁻³ M.

(Figure 4). This shows negative effect of the reaction rate with respect to $[H^+]$ on the rate of oxidation of paracetamol. The rate measurements were taken at 30°-45°C and specific rate constants were used to draw a comparative graph plot of $\log k$ vs. $1/T$ which was linear (Figure 5).

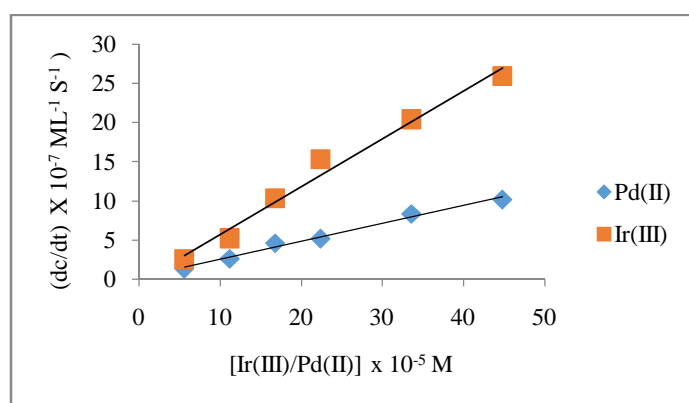


Figure 3. A comparative graph between rate of reaction ($-dc/dt$) vs $[Pd(II)]$ and $[Ir(III)]$ chloride for the oxidation of paracetamol at 35°C. $[HClO_4] = 1.00 \times 10^{-3} M$, $[KCl] = 1.00 \times 10^{-3} M$, $[Hg(OAc)_2] = 1.25 \times 10^{-3} M$, Paracetamol $[PAM] = 1.00 \times 10^{-2} M$, $[KBrO_3] = 1.00 \times 10^{-3} M$.

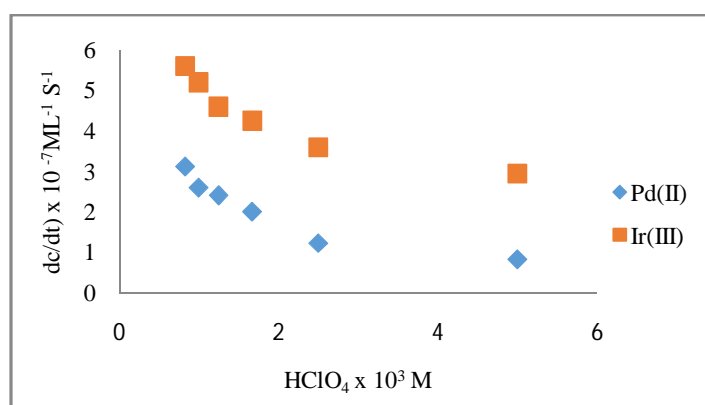


Figure 4. A comparative graph between rate of reaction ($-dc/dt$) vs $[HClO_4]$ for the oxidation of paracetamol at 35°C. $[Ir(III)/Pd(II)] = 11.20 \times 10^{-5} M$, $[KCl] = 1.00 \times 10^{-3} M$, $[Hg(OAc)_2] = 1.25 \times 10^{-3} M$, Paracetamol $[PAM] = 1.00 \times 10^{-2} M$, $[KBrO_3] = 1.00 \times 10^{-3} M$.

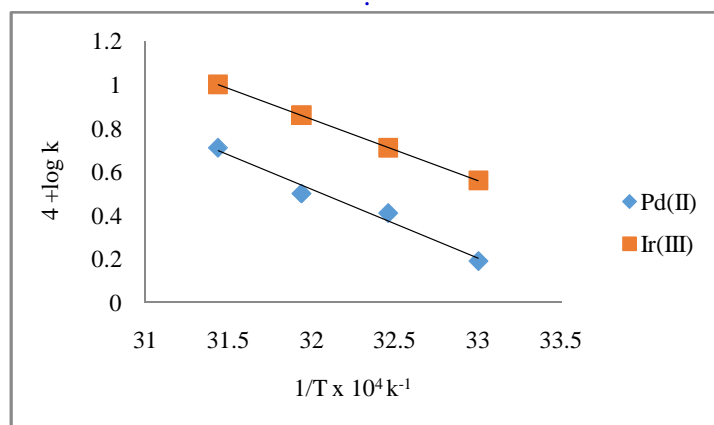
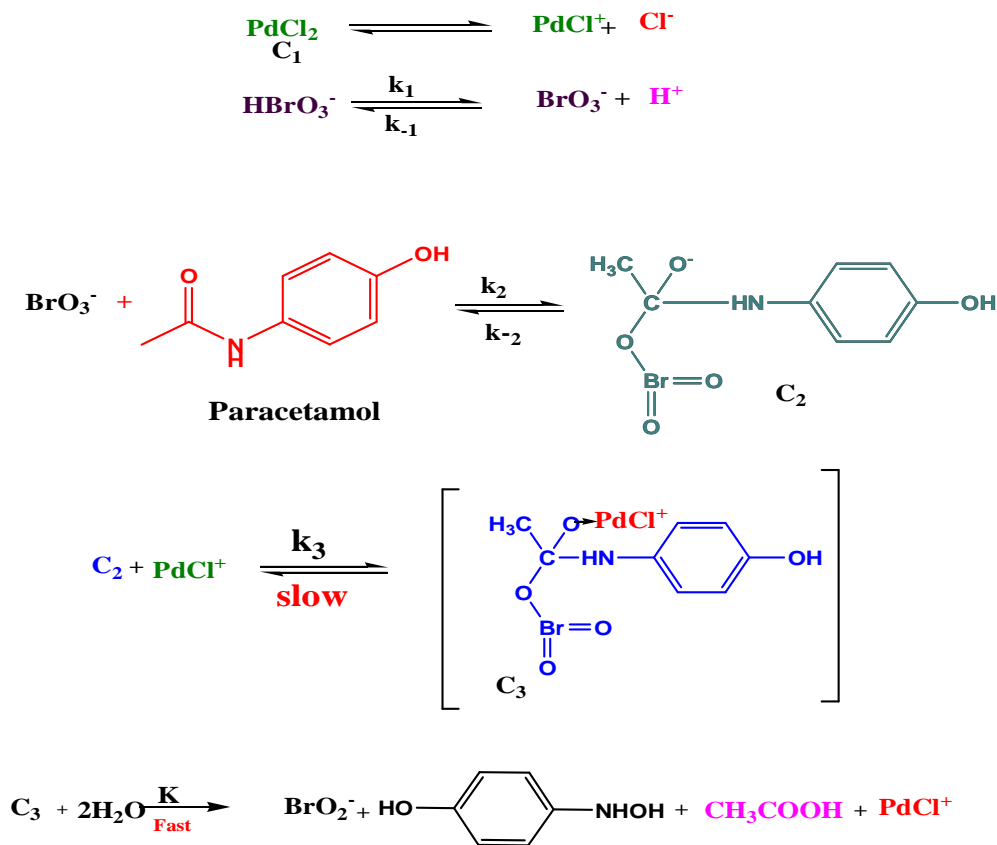


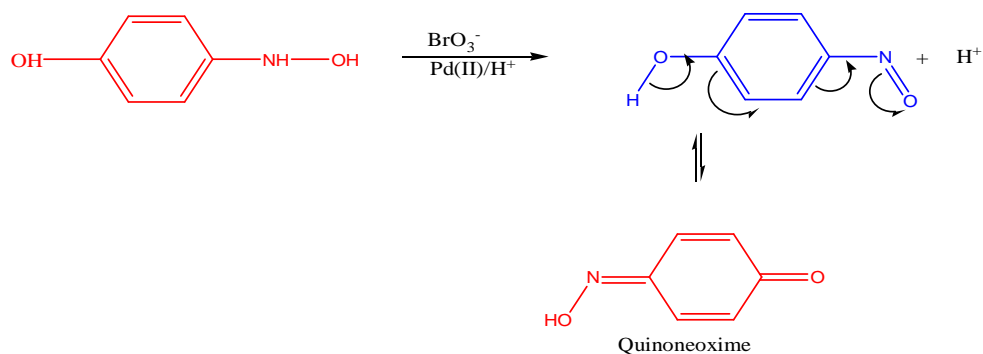
Figure 5. A comparative arrhenius plot of the oxidation of paracetamol on the reaction rate at 35°C $[Pd(II)/Ir(III)]$ Chloride= $11.2 \times 10^{-5} M$, $[KCl]=1.00 \times 10^{-3} M$, $[Hg(OAc)_2]=1.25 \times 10^{-3} M$ [Oxidant ($KBrO_3$)] = $1.00 \times 10^{-3} M$, [Paracetamol]= $1.00 \times 10^{-2} M$, $[HClO_4]=1.00 \times 10^{-3} M$.

Role of Entropy of activation and other activation parameters: The value of energy of Activation (ΔE_a) Arrhenius factor (A), entropy of activation (ΔS^*) and free energy of activation (ΔG^*) were calculated from rate measurement at 30°, 35°, 40°, 45°C and these values have been recorded in table 3. Moderate ΔH^* and ΔS^* values are favorable for electron transfer reaction. The value of ΔH^* was due to energy of solution changes in the transition state. The high positive values of change in free energy of activation (ΔG^*) indicates highly solvated transition state, while fairly high negative values of change in entropy of activation (ΔS^*) suggest the formation of an activated complex with reduction in the degree of freedom of molecule. The observed modest enthalpy of activation and a higher rate constant for the slow step indicates that the oxidation presumably occurs via an inner-sphere mechanism. This conclusion is supported by earlier observations. The high positive values of change in free energy of activation (ΔG^*) indicates highly solvated transition state, while fairly high negative values of change in entropy of activation (ΔS^*) suggest the formation of an activated complex with reduction in the degree of freedom of molecule [61]. The activation parameters evaluated for the catalyzed and uncatalyzed reaction explain the catalytic effect on the reaction. Entropy of activation plays an important role in the case of reaction between ions or between an ion and a neutral molecule or a neutral molecule forming ions. When reaction takes place between two ions of opposite charges, their union will result in a lowering of net charge, and due to this some frozen solvent molecules will be released with increase of entropy but on the other hand when reaction takes place between two similarly charged species, the transition state will be more highly charged ion and due to this, more solvent molecules will be required for separate the ions, leading to decrease the entropy.

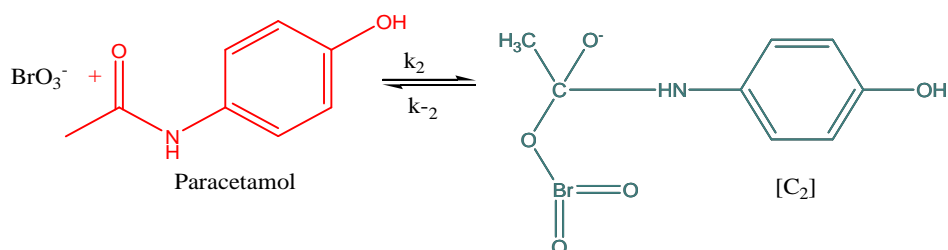
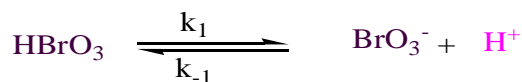
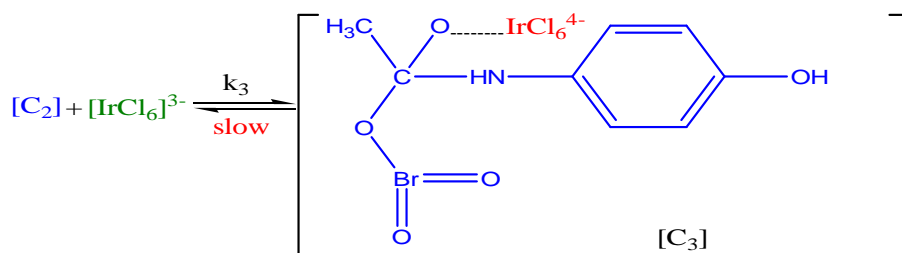
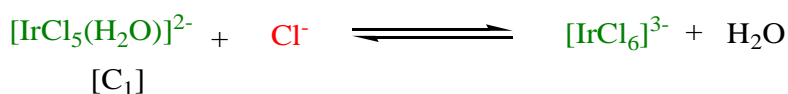
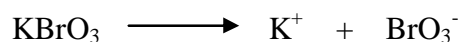
Mechanism and derivation of rate law: The reaction mechanism involves interaction of KBrO_3 with the reactive species of the catalyst to form a complex. The BrO_3^- species has been reported to act as an oxidizing agent in acidic as well as in alkaline medium. Pd (II) and Ir(III) chloride has been reported to give a number of possible chloro species dependent on pH of the solution.

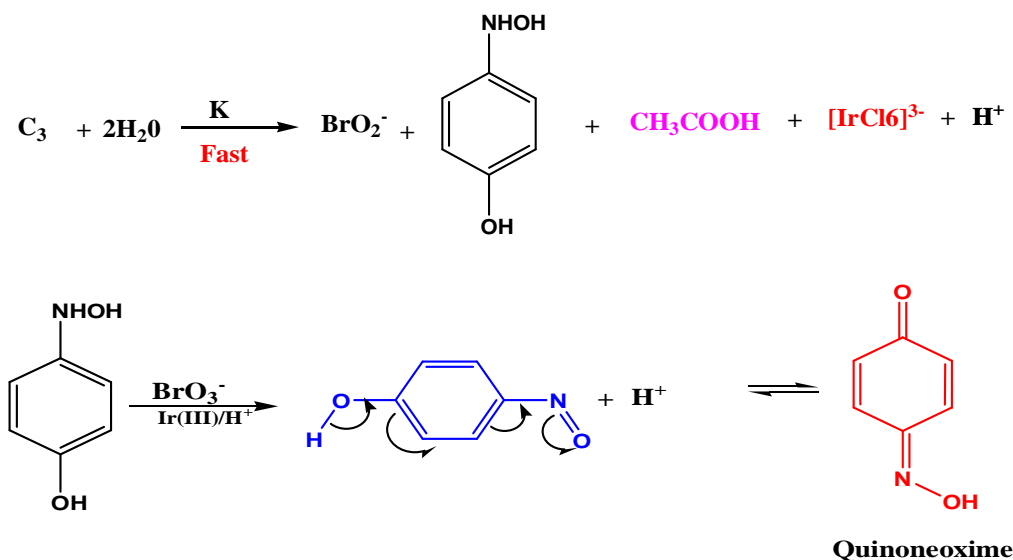
Mechanism 1:





Mechanism 2: It has been already discussed that $[\text{IrCl}_6]^{3-}$ is the reactive species of iridium chloride in acidic medium. In view of the reactive species of Ir(III) chloride and KBrO_3 and other kinetic features with respect to [Substrate], $[\text{H}^+]$, $[\text{Hg}(\text{II})]$, $[\text{Cl}^-]$ and ionic strength of the medium, the following mechanism steps are proposed. In acidic solution of KBrO_3 , quick formation of HBrO_3 has been reported. Negligible effect of mercuric acetate excludes the possibility of its involvement either as a catalyst or as an oxidant because it does not help the reaction proceed without potassium bromate. Hence the function of mercuric acetate is to act as a scavenger for any $[\text{Br}^-]$ ion formed in the reaction. It helps to eliminate the parallel oxidation by Br_2 which would have been formed as a result of interaction between Br^- and bromate ion. Potassium bromate has been used as an oxidant for a variety of compounds in acidic media, sometimes in the presence of a catalyst. In alkaline and acidic medium, potassium bromate is ionized.





Considering the fact that 1 mole of paracetamol is oxidized by 2 mole of bromate for both catalyst Pd(II) and Ir(III) chloride and applying the steady state treatment, with reasonable approximation, the rate law may be written as equation.

$$\text{rate}(R) = \frac{-d [BrO_3]^-}{dt} = 2k[C_3] \quad \dots (1)$$

On the basis of scheme above step (1) to (4) equation 2-5 can be obtained in the following forms respectively as-

$$R = \frac{2k K_1 K_2 K_3 [Pd(II)] / [Ir(III)] [PA] [HBrO_3]}{[H]^+} \quad \dots (2)$$

At any time in the reaction the total concentration of $HBrO_3$ that is $[HBrO_3]_T$ can be expressed as-

$$[HBrO_3]_T = [HBrO_3] + [C_1] + [C_2] + [C_3] \quad \dots (3)$$

Substitution of the variable of $[C_1]$ $[C_2]$ and $[C_3]$ in equation [3]. Equation [4] is obtained.

$$[HBrO_3] = \frac{[HBrO_3]_T}{[H]^+ + K_1 + K_1 K_2 [PA] + K_1 K_2 K_3 [Pd(II)] / [Ir(III)] [PA]} \quad \dots (4)$$

Substituting the value of $[HBrO_3]$ in equation [2] we obtained the expression equation [5].

$$R = \frac{2k K_1 K_2 K_3 [Pd(II)] / [Ir(III)] [PA] [HBrO_3]_T}{[H]^+ + K_1 + K_1 K_2 [PA] + K_1 K_2 K_3 [Pd(II)] / [Ir(III)] [PA]} \quad \dots (5)$$

APPLICATION

The present study examines, in detail the kinetic and mechanistic aspects of the Ir(III) catalyzed oxidation of paracetamol by $KBrO_3$ in acidic media with the following objective. In this paper it has been tried to consolidate the various work done on the well-known drug that finds extensive application in pharmaceutical industries in the last few decades. In most of the catalytic studies for organic transformations, the nature of active form of Pd(II) remain obscure. The kinetic methods of

analysis are highly sensitive, selective, simple, accurate, and less expensive. In recent years, several kinetic Paracetamol (4-hydroxyacetanilide or acetamidophenol) is a well-known drug that is having extensive application in pharmaceutical industries.

CONCLUSION

The present study examines, in detail the kinetic and mechanistic aspects of the Ir(III)/Pd(II) catalysed oxidation of paracetamol by KBrO_3 in acidic media with find the ascertain reactive species of the catalyst and the oxidant. The deduce rate law consistent with the kinetic results. And identify the oxidation products as well as estimate activation parameters. In additional elucidate the plausible reaction mechanism based on the observed reaction rate law and stoichiometry.

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