

## Kinetics of oxidation of Methyldopa by Periodate ion in aqueous medium

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**Abstract:** The oxidation of methyldopa(MDP) by periodate ion in aqueous medium was studied from kinetics point of view spectrophotometrically. Stoichiometry of the reaction was found to be 1 mol MDP reacting with 2 moles of periodate for the initial part of the reaction. The reaction followed second order behaviour, being first order in oxidant and substrate each. Results under pseudo first order conditions, are in agreement with the rate law :

$$\text{Reaction Rate} = kK_w [\text{MDP}]_0 [\text{IO}_4^-] [\text{H}^+] / \{K_2 K_w + (K_w + K_b K_2) [\text{H}^+] + K_b [\text{H}^+]^2\}$$

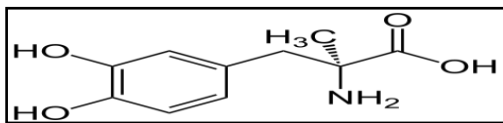
where  $kK$  is the empirical composite rate constant,  $K_w$  is ionic product of water,  $K_2$  is acid dissociation constant of  $\text{H}_4\text{IO}_6^-$ ,  $K_b$  is base dissociation constant of MDP and  $[\text{MDP}]_0$  represents the concentration of methyldopa that has been taken in excess. The rate of reaction was found to be maximum at an optimum pH of 5.0. In agreement with the rate law the  $1/k_2$  versus  $[\text{H}^+]$  profile passes through the minimum. The experimental value matches very well with the calculated pH value corresponding to the rate-pH profile maximum. The rate of reaction increases with increase in dielectric constant of the medium. Free radical scavengers do not affect the reaction rate. Various thermodynamic parameters have been evaluated and the values are reported in this communication.

**Keywords:** Methyldopa, Periodate, Aqueous medium, Kinetics.

### Introduction

Aromatic vic-diols are catechol derivatives in which 3 or 4 position is unsubstituted and these positions are sterically blocked. These derivatives are drugs and now, are widely used in the treatment of bronchial asthma, hypertension, Parkinson's disease, myocardial infarction and cardiac surgery<sup>1</sup>. Antihypertensive drugs like Aldomet, Chloridine, Methyldopa, Minoxidil etc.<sup>2</sup> are used when walls of arteries and arterioles harden, the resistance to blood flow increases and the heart has to contract more forcefully to cope with the peripheral resistance which enhances both systolic and diastolic pressure resulting in the hypertension or high blood pressure. Methyldopa or 3-(3,4-dihydroxy phenyl)-2 methyl-L-alanine sesquihydrate with molecular formula  $\text{C}_{10}\text{H}_{13}\text{NO}_4 \cdot 1\frac{1}{2} \text{H}_2\text{O}$ , molecular weight 238.24 and structure<sup>3</sup> given below, is primarily used as the adrenergic blocker (central and peripheral adrenergic inhibitor) which reduces cardiac output or decreases the peripheral vascular resistance and helps in management of acute or severe hypertension<sup>4,5</sup>. Adverse ocular side effects due to methyldopa are rare and usually insignificant<sup>6-8</sup>. However, it is widely used when hypertension is complicated with renal disease. Its hypertensive properties mainly occur due to the action on the central nervous system<sup>9</sup>. If it is administered independently via oral or parenteral routes, it can provoke sedation, vertigo, psychic depression, dry mouth, nasal congestion, gastrointestinal disturbs, edemas and sexual impotency as secondary effects<sup>10</sup>. It is a supplemental agent used when the initial drug therapy fails to achieve the desired effect. Methyldopa is converted to  $\alpha$ -methyldopamine and  $\alpha$ -methylnorepinephrine and used in

treatment of hypertension<sup>11</sup>. Oxidation of catecholamines by periodate or peroxidase/ H<sub>2</sub>O<sub>2</sub> or horseradish peroxidase and lactoperoxidase produces open chain quinone<sup>11-13</sup>. There is only one report related to using periodate as an oxidant for estimation of methyl dopa in presence of sulphuric acid<sup>11</sup>. This report has no detailed kinetic study of the reaction under consideration. Electrooxidation of some catecholamines in the presence of 4-aminobenzoic acid at different pH values resulted in the formation of corresponding o-benzoquinones<sup>14,15</sup>.

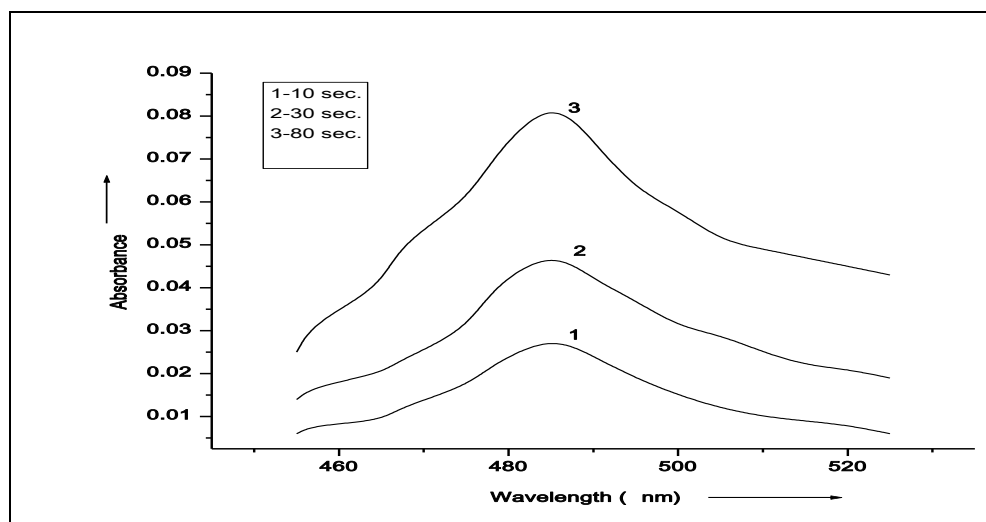


In continuation to our earlier studies using periodate as an oxidant for some aromatic amines<sup>16-30</sup>, the results of periodate oxidation of methyl dopa in aqueous medium are being presented and discussed in the present communication. The results show special effect of pH on reaction rate which is being reported for this reaction for the first time. Also a complete rate law, including the pH dependence, has been worked out for the first time for the periodate oxidation of MDP. The studies shall be of importance as these may be utilized for detection, estimation and treatment of the drug as well as in providing support for understanding its physiological action.

## Experimental

### Reagents and chemicals

Sodium meta periodate (Loba Chemie), methyl dopa (Glenmark), acetone (E. Merck) and all other chemicals of analytical reagent/ guaranteed reagent grade were used after redistillation/ recrystallization. Triply distilled water was used for preparation of the solutions. Thiel, Schultz and Koch buffer<sup>31</sup>, consisting of different volumes of 0.05 M oxalic acid, 0.02 M boric acid, 0.05 M succinic acid, 0.05 M sodium sulphate and 0.05 M borax, was used for maintaining the pH, measured on Systronics digital pH-meter-802. The reactions were studied in a spectrophotometric cell and initiated by adding temperature equilibrated NaIO<sub>4</sub> solution of known concentration to the reaction mixture containing the methyl dopa and buffer and maintained at the desired temperature ( $\pm 0.1^{\circ}\text{C}$ ).



**Fig. 1- Determination of absorption maxima of reaction mixture for periodate oxidation of Methyl dopa in aqueous medium (UV-VIS Scan at different time)**

### Kinetics procedure

On mixing the reactants, the solution becomes pink colour initially followed by its disappearance. These observations indicate the formation of more than one intermediate prior to the formation of final reaction product. The rapid scan of the pink solution showed the  $\lambda_{\text{max}}$  of the intermediate C to be 485 nm. The UV-visible spectra of IO<sub>4</sub><sup>-</sup> and methyl dopa indicated these to show no absorption in visible region. Hence for

following the kinetics the absorbance changes were recorded on Shimadzu double beam spectrophotometer (UV Pharmaspec-1700) at 485 nm.  $\lambda_{\max}$  was not found to change with change in time under experimental conditions (Fig.1). High precision thermostatically controlled water bath with an accuracy of  $\pm 0.1^\circ\text{C}$  was employed for maintaining the desired temperature. Plane mirror and Guggenheim's methods, respectively were used for evaluation of initial rates in terms of change in absorbance with time,  $(dA/dt)$ , and pseudo first order rate constants,  $k_{obs}$ .

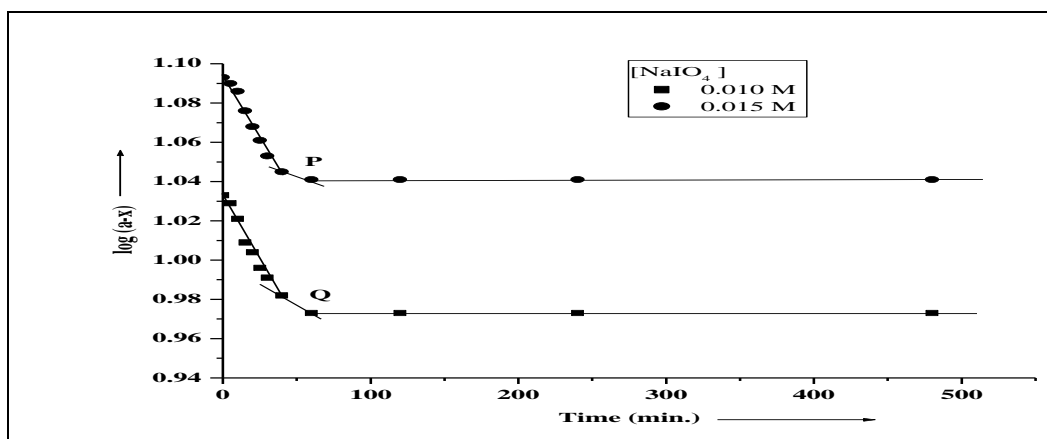
## Product analysis

Reaction mixture containing 0.01M  $\text{NaIO}_4$  + 0.001M MDP, was prepared, shaken and set aside for 24 hours. It developed a pink colour initially followed by its disappearance. An attempt was made for the extraction of pink coloured product in chloroform. It was dried in air and subjected to TLC (plate thickness = 0.5 mm; stationary phase = silica gel 'G'; eluent = chloroform + petroleum ether in 60: 40 volume ratio; elution time = 45 minutes). Three components were separated – dark brown, pale yellow and light pink. Sufficient amount of any of the products could not be separated. Therefore the characterization studies could not be made upto satisfaction. However, the I. R. spectrum of light pink coloured compound showed the strong band at  $1632\text{ cm}^{-1}$ (s) (indicating the presence of C=O on benzoquinone pattern with the possibility that the position of this band got lowered due to +I effect of other group<sup>32</sup>. This compound responded positive for a quinone<sup>33</sup>. It is important to note that the quinones(particularly o-benzoquinones) have also been reported by earlier workers as the main products in the oxidation of MDP by various oxidants<sup>9, 11-13, 34</sup>.

## Results

### Stoichiometry

Excess of  $\text{NaIO}_4$  was allowed to react with MDP. The unconsumed  $\text{NaIO}_4$  was titrated iodimetrically. Log (a-x) versus time plots (where a-x is the concentration of unconsumed periodate) were first order curves with inflexion points P and Q corresponding to completion of initial stage of the reaction (Fig. 2). The results indicate the stoichiometry to be 1 mol MDP: 2 moles periodate.



**Fig. 2- Determination of Stoichiometry of the reaction of periodate oxidation of Methyldopa at  $[\text{MDP}] = 1.0 \times 10^{-3}\text{ mol dm}^{-3}$ , Temp =  $25.0 \pm 0.1^\circ\text{C}$ , pH = 5.5.**

### Rate Law

The kinetics was studied under pseudo order conditions, viz.,  $[\text{IO}_4^-]_0 \gg [\text{MDP}]$  and  $[\text{MDP}]_0 \gg [\text{IO}_4^-]$ . Under both these conditions the reaction displayed first order. Under the condition,  $[\text{MDP}]_0 \gg [\text{IO}_4^-]$ , the results (Table 1) were defined by the eq. (2) and pseudo first order rate constant,  $k_{obs}$ , was equal to  $k_2 [\text{MDP}]_0$ .

$$d[\text{C}]/dt = k_2 [\text{IO}_4^-] [\text{MDP}]_0 \quad (2)$$

where  $k_2$  is a pH-dependent second order rate constant.

On the other hand under the condition  $[\text{IO}_4^-]_0 \gg [\text{MDP}]$ , the rate was defined by eq. (3)

and  $k_{obs}$  was equal to  $k_2 [\text{IO}_4^-]_0$ .

$$d[\text{C}]/dt = k_2 [\text{IO}_4^-]_0 [\text{MDP}] \quad (3)$$

In eqs. (2) and (3)  $[\text{IO}_4^-]_0$  and  $[\text{MDP}]_0$  represent the initial concentrations of reactants in excess.

### Order in oxidant and substrate

**Table 1. Effect of variation of reactants, dielectric constant, and pH on reaction rate at  $25.0 \pm 0.1^\circ\text{C}$ .**

$[\text{NaIO}_4] \times 10^4$ ( $\text{mol dm}^{-3}$ )	$[\text{MDP}] \times 10^4$ ( $\text{mol dm}^{-3}$ )	Acetone (% v/v)	pH	$k_{obs} \times 10^3$ ( $\text{s}^{-1}$ )	$k_2 \times 10^{-1}$ ( $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ )
2.0	0.2	-	5.5	4.0	2.0
2.2	0.2	-	5.5	5.0	2.3
2.4	0.2	-	5.5	5.9	2.5
2.6	0.2	-	5.5	6.5	2.5
2.8	0.2	-	5.5	7.4	2.6
3.0	0.2	-	5.5	8.1	2.7
0.2	2.0	-	5.5	4.0	1.9
0.2	2.2	-	5.5	4.4	2.0
0.2	2.4	-	5.5	5.3	2.2
0.2	2.6	-	5.5	6.1	2.4
0.2	2.8	-	5.5	6.7	2.4
0.2	3.0	-	5.5	7.7	2.6
0.4	4.0	-	3.0	6.1	1.5
0.4	4.0	-	3.5	7.9	1.9
0.4	4.0	-	4.0	8.2	2.1
0.4	4.0	-	4.5	9.6	2.4
0.4	4.0	-	5.0	11.7	3.0
0.4	4.0	-	5.5	9.1	2.3
0.4	4.0	-	6.0	7.9	2.0
0.4	4.0	-	6.5	5.7	1.4
0.4	4.0	-	7.0	4.2	1.0
0.4	4.0	0.5	5.5	6.5	1.6
0.4	4.0	1.0	5.5	4.9	1.2
0.4	4.0	1.5	5.5	3.6	0.9
0.4	4.0	2.0	5.5	2.7	0.7

The values of  $k_2$  determined from  $k_{obs}$  values are given in Table 1. The consistency in the values of  $k_2$  clearly indicates a clear cut first order in each of periodate and methyl dopa.

### Effect of pH

The effect of pH was examined in the range 3.0-7.0. Rate-pH profile indicates a maximum at pH = 5.0 (Table-1) (Fig. 3), which could be due to change in the nature of species and their relative reactivity when the pH is changed.

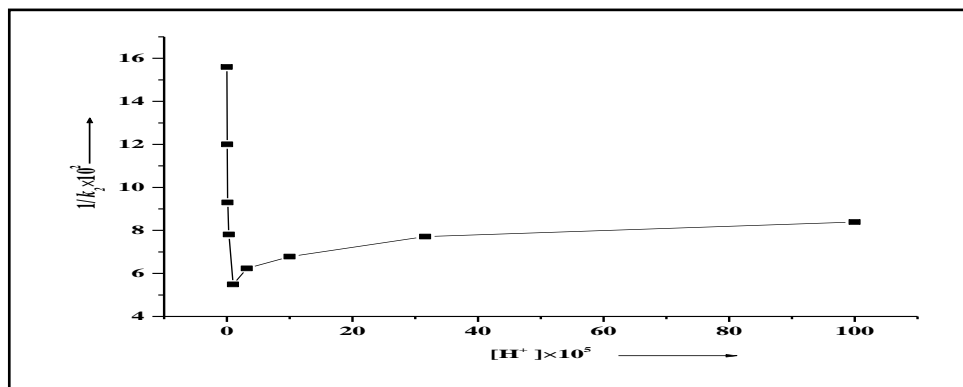


Fig.3 –  $1/k_2$ –  $[H^+]$  profile at  $[MDP] = 4.0 \times 10^{-4} \text{ mol dm}^{-3}$ ,  $[NaIO_4] = 4.0 \times 10^{-5} \text{ mol dm}^{-3}$ , Temp =  $25.0 \pm 0.1^\circ\text{C}$ ,  $\lambda_{\text{max}} = 485\text{nm}$ .

### Effect of dielectric constant of medium

An increase in dielectric constant increased the rate of reaction as indicated by a linear plot between  $\log k_2$  versus  $1/D$  (Fig. 4), where  $D$  is the dielectric constant of the medium. It indicates an ion-dipole type interaction in the rate-determining step, and that the reacting ion is possibly an anion.

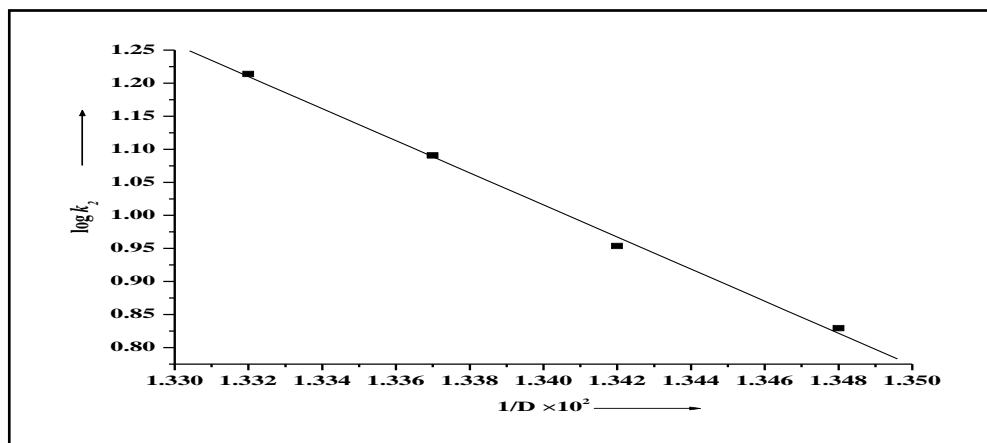


Figure 4: Effect of dielectric constant ( $\log k_2$  vs.  $1/D$  plot).  $[MDP] = 4.0 \times 10^{-4} \text{ mol dm}^{-3}$ ,  $[NaIO_4] = 4.0 \times 10^{-5} \text{ mol dm}^{-3}$ , Temp =  $25.0 \pm 0.1^\circ\text{C}$ ,  $\lambda_{\text{max}} = 485\text{nm}$ , pH = 5.5.

### Effect of free radical scavengers

Free radical scavengers acrylamide and allyl alcohol had no effect of on the reaction rate. This rules out the possibility of reaction showing a free radical mechanism.

### Effect of temperature and evaluation of thermodynamic parameters

$$[MDP] = 4.0 \times 10^{-4} \text{ mol dm}^{-3}, [NaIO_4] = 4.0 \times 10^{-5} \text{ mol dm}^{-3}, \lambda_{\text{max}} = 485\text{nm}, \text{pH} = 5.5.$$

By determining the rate constants at four different temperatures ( $30.0$  to  $45.0^\circ\text{C}$ ), a linear Arrhenius plot was obtained (Fig. 5). The values of different thermodynamic parameters- activation energy ( $\Delta E$ ), Arrhenius frequency factor ( $A$ ), entropy of activation ( $\Delta S^\ddagger$ ), free energy of activation ( $\Delta G^\ddagger$ ) and enthalpy of activation ( $\Delta H^\ddagger$ ) were found and these are reported in Table 2.

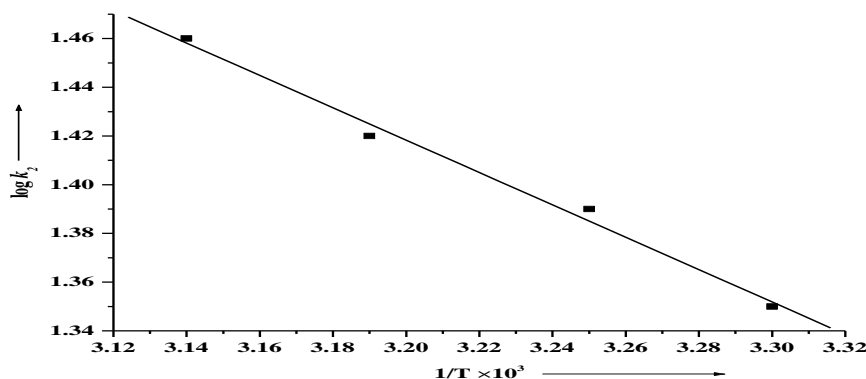


Figure 5: Arrhenius plot

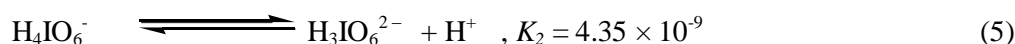
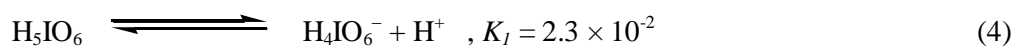
Table 2. Thermodynamic Parameters for periodate oxidation of methyl dopa

[MDP] = 2.0 × 10<sup>-4</sup> mol dm<sup>-3</sup>, [NaIO<sub>4</sub>] = 2.0 × 10<sup>-5</sup> mol dm<sup>-3</sup>, pH = 5.5, λ<sub>max</sub> = 485nm.

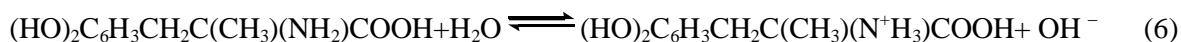
Temp. °C	k <sub>2</sub> × 10 <sup>-1</sup> (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )	ΔE (kJ mol <sup>-1</sup> )	A × 10 <sup>-3</sup> (dm <sup>3</sup> mol <sup>-1</sup> s <sup>-1</sup> )	-ΔS <sup>#</sup> (J mol <sup>-1</sup> K <sup>-1</sup> )	ΔG <sup>#</sup> (kJ mol <sup>-1</sup> )	ΔH <sup>#</sup> (kJ mol <sup>-1</sup> )
30.0	2.25	12.90	3.97	185.19	67.87	10.37
35.0	2.44					
40.0	2.61					
45.0	2.86					

## Discussion

As already stated, the overall reaction involves several steps and possibly several transient intermediates, in addition to comparatively stable one C, are formed during the oxidation of methyl dopa by periodate ion. The kinetic order of one in periodate but requirement of the two periodate molecules for each methyl dopa molecule as per stoichiometry indicates the involvement of only one periodate in the rate determining step and second IO<sub>4</sub><sup>-</sup> ion is consumed in a fast reaction in the formation of the intermediate, C. The concentration of C increases continuously with time and reaches a limiting value. And this has been used in following the kinetics of this reaction. 1/k<sub>2</sub> - pH profile indicates the presence of at least three differently reactive reactant species in the pH region chosen for study<sup>36</sup>. Therefore, it is necessary to consider the speciation of methyl dopa and periodate. In aqueous solutions, periodate exists in three forms governed by the equilibria:

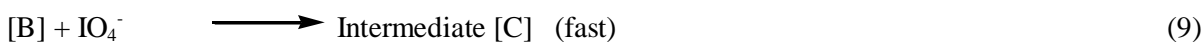
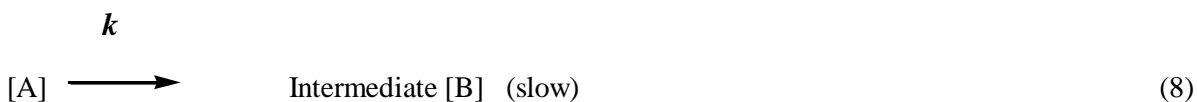
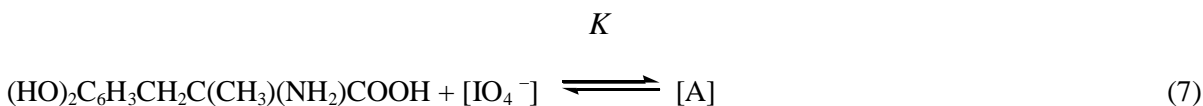


The value of K<sub>1</sub> indicates that in the pH range 5 – 9 species H<sub>5</sub>IO<sub>6</sub> shall be practically non-existent and hence only species H<sub>4</sub>IO<sub>6</sub><sup>-</sup> and H<sub>3</sub>IO<sub>6</sub><sup>2-</sup> need be considered for explaining observed pH - dependence. In case of methyl dopa<sup>35</sup>, in aqueous solution the following acid – base equilibrium with K<sub>b</sub> = 1.58 × 10<sup>-12</sup> operates.



In the studied pH-range, both (HO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>C(CH<sub>3</sub>)(NH<sub>2</sub>)COOH and (HO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>C(CH<sub>3</sub>)(N<sup>+</sup>H<sub>3</sub>)COOH shall exist and both of these have been considered.

Based on the observed kinetic rate laws (2-3) and pH- dependence, the following mechanism, which assumes, (HO)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>C(CH<sub>3</sub>)(NH<sub>2</sub>)COOH and H<sub>4</sub>IO<sub>6</sub><sup>-</sup> to be the reactive species, is proposed.



The intermediate, C, appear to undergo very slow reorganization/ hydrolysis to yield the reaction product.



In the mechanism for simplicity,  $\text{H}_4\text{IO}_6^-$  has been written as  $\text{IO}_4^-$ . Since the elementary reactions in liquid phase are a rarity, the formation of a transient intermediate [C], which could be a collisional complex/reactant pair in a rapid step having a low value of equilibrium constant,  $K$ , is assumed in the proposed mechanism. It is necessary and interesting to discuss the possible molecular mechanism of the reaction. The first step can be taken as a reversible bimolecular reaction between MDP and  $[\text{IO}_4^-]$ . The high negative value of entropy of activation supports the involvement of solvation effects in this reaction. The formation of another intermediate [B] followed by its reaction with another  $\text{IO}_4^-$  to form [C] in a fast step are the expected steps of the mechanism involved. The last step (10) seems to be the slow hydrolysis and rearrangement of (C) to give quinones (D), i.e., the main products expected in this case<sup>9,11-13,34</sup>.

The mechanistic steps (8-9) lead to the rate law:

$$d[\text{C}]/dt = k [\text{A}] \quad (11)$$

$$= kK[(\text{HO})_2\text{C}_6\text{H}_3\text{CH}_2\text{C}(\text{CH}_3)(\text{NH}_2)\text{COOH}][\text{IO}_4^-] \quad (12)$$

Since the observed kinetics shows first order in each of  $[(\text{HO})_2\text{C}_6\text{H}_3\text{CH}_2\text{C}(\text{CH}_3)(\text{NH}_2)\text{COOH}]$  and  $[\text{IO}_4^-]$ , the value of  $K$  must be low.

At affixed pH, under the condition  $[\text{MDP}]_0 \gg [\text{IO}_4^-]$ , the rate of formation of intermediate, C, is given by eq.(13).

$$d[\text{C}]/dt = kK [\text{IO}_4^-] [\text{MDP}]_0 / (1+K[\text{MDP}]_0) \quad (13)$$

Likewise, under the condition  $[\text{IO}_4^-]_0 \gg [\text{S}]$

$$d[\text{C}]/dt = kK [\text{IO}_4^-]_0 [\text{MDP}] / (1+K[\text{IO}_4^-]_0) \quad (14)$$

Since the reaction shows a clean-cut first order in each of  $[\text{MDP}]$  and  $[\text{IO}_4^-]$ , the inequalities  $K[\text{MDP}]_0 \gg 1$  and  $[\text{IO}_4^-]_0 \gg 1$  should operate in eqs.(13) and (14), respectively leading to the rate laws in eqs. (2) and (3).

On substituting the values of concentrations of the reactive species  $[(\text{HO})_2\text{C}_6\text{H}_3\text{CH}_2\text{C}(\text{CH}_3)(\text{NH}_2)\text{COOH}]$  and  $[\text{IO}_4^-]$  in terms of equilibria (4-5) and (6), respectively, in eq. (12), the complete rate law including  $[\text{H}^+]$  - dependence becomes:

$$d[\text{C}]/dt = kK \{([\text{MDP}]_0 [\text{OH}^-] / ([\text{OH}^-] + K_b))\} \{([\text{IO}_4^-] [\text{H}^+] / (K_2 + [\text{H}^+]))\} \quad (15)$$

On replacing  $[\text{OH}^-]$   $[\text{H}^+]$  by  $K_w$  and  $[\text{OH}^-]$  by  $K_w / [\text{H}^+]$  in denominator and on rearranging, we get,

$$d[\text{C}]/dt = k K K_w [\text{MDP}]_0 [\text{IO}_4^-] [\text{H}^+] / \{ K_2 K_w + (K_w + K_b K_2) [\text{H}^+] + K_b [\text{H}^+]^2 \} \quad (16)$$

On comparing eqs.(2) and (16), we get

$$k_2 = kK K_w [H^+] / \{ K_2 K_w + (K_w + K_b K_2) [H^+] + K_b [H^+]^2 \} \quad (17)$$

Equation(17) on rearranging becomes eq. (18).

$$1/k_2 = (K_2 / k K[H^+]) + \{ (K_w + K_b K_2) / k K K_w \} + K_b [H^+] / k K K_w \quad (18)$$

The nature of the rate law shows that a plot of  $1/k_2$  versus  $[H^+]$  shall pass through a minimum<sup>36</sup>. Differentiation of  $1/k_2$  with respect to  $[H^+]$  in eq.(18), gives the value of  $d^2[1/k_2]/d[H^+]^2$ . The value of second derivative is found to be positive showing the plot of  $1/k_2$  versus  $[H^+]$  to pass through a minimum. Thus, on setting  $d[1/k_2]/d[H^+]$  equal to zero for obtaining hydrogen ion concentration at which the  $1/k_2$  vs  $[H^+]$  profile will pass through minimum, we obtain,  $[H^+]_{\min.} = (K_2 K_w / K_b)^{1/2}$ .

On substituting the values of  $K_2$ ,  $K_w$  and  $K_b$ , we get

$$[H^+]_{\min.} = 0.52 \times 10^{-6} \text{ mol dm}^{-3}$$

It is gratifying to note that the calculated value of  $[H^+]_{\min.}$  is in excellent agreement with the experimental value of  $[H^+]_{\min}$  of  $1.0 \times 10^{-5} \text{ mol dm}^{-3}$  obtained from  $1/k_2$  versus  $[H^+]$  plot (Fig. 2).

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