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*Research Article*

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# Spectrophotometer Aided Kinetic and Mechanistic Study of Oxidation of Esmolol by Cerium (Iv) in Aqueous Sulphuric Acid Medium

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**Abstract:** The kinetics and mechanism of oxidation of Esmolol by Cerium(IV) in aqueous $H_2SO_4$ at a constant ionic strength of 0.50 mol $dm^{-3}$ was studied spectrophotometrically. The reaction showed first order kinetics in Ce(IV) and fractional order in Esmolol concentrations. Addition of products showed no effect on the rate of the reaction. The main product, methyl-3-(4-(2-hydrox-3-oxopropoxy) phenyl) propanoate, was identified with the aid of IR and LC-MS studies. Stoichiometry with respect to drug substrate and reagent was established as 2:1. Added $HClO_4$ and $SO_4^{2-}$ showed negligible effect on the rate of the reaction. Whereas, added $HSO_4^-$ has considerable influence on the rate of the reaction. $HCe(SO_4)_3^-$ was found to be the predominant reactive species under the experimental conditions. A plausible mechanism was proposed and rate constant, *k* for the proposed slow rate determining step was determined. The activation parameters like activation energy, free energy, enthalpy and entropy of activation were also computed.

**Keywords:** Cerium(IV); Esmolol; Kinetics; Oxidation; Spectrophotometry.

## 1. INTRODUCTION

β- Blockers, also called as β-adrenergic receptor blockers or β-receptor antagonists, are drugs used for treating cardiovascular ailments like arrhythmia and hypertension [1-3]. Esmolol (ESM) is an ultra-short acting $\beta_1$ selective second generation β- blocker with rapid onset. It is used during surgeries, medical emergencies to control rapid heartbeat. ESM loses activity due to enzymatic hydrolysis of its ester group. It has a half life of about 9-10 min [4-6]. Therapeutically ESM is used as its hydrochloride salt. Chemically ESM is (±)-methyl-3-(4-(2-hydroxy-3-(isopropyl amino) propoxy) phenyl) propanoate hydrochloride [7-8].

Literature survey reveals that there have been several determination studies on ESM which include reverse phase high performance liquid chromatography with solid-phase extraction, capillary electrophoresis [9], stereo selective RP-HPLC [10], liquid chromatography-mass spectrometry [11] and spectrophotometrical methods [12].

Cerium is the only rare earth element with a stable +4 oxidation state in addition to +3 states. The coloured Ce (IV) and the colourless Ce(III) in solution form a favourable one electron redox couple in aqueous acidic medium [13]. The redox potential of the $Ce^{4+}/Ce^{3+}$ couple depends on the concentration and type of acid media used. A survey of the literature reveals that the redox potentials of $Ce^{4+}/Ce^{3+}$ couple in 1 M aqueous solutions of HCl, $H_2SO_4$, $HNO_3$, $HClO_4$ are 1.28 v, 1.44 v, 1.61 v and 1.70 v respectively [14 -16]. Ce(IV) in aqueous $H_2SO_4$ is a highly stable oxidant capable of oxidizing both organic and inorganic substances. Generally with most of the organic compounds including drug substrates, Ce(IV) oxidations occur through complex formation. In these reactions, the substrate reversibly forms a complex with Ce(IV) which later decomposes into products in the rate determining step. In majority of these oxidations, evidence for complex formation is provided by Michaelis-Menten plot, which is a plot between 1/rate vs. 1/[substrate] or $1/k_{obs}$ vs. $1/[HSO_4^-]$ giving straight line with positive intercept on the rate axis [17-41].

$$Ce(IV) + \text{substrate} \rightleftharpoons \text{Complex}$$

$$\text{Complex} \rightleftharpoons Ce(III) + \text{Free Radical}$$

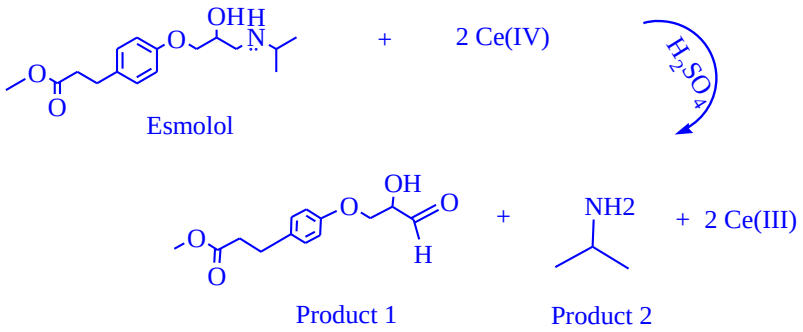
$$Ce(IV) + \text{Free Radical} \rightleftharpoons \text{Products}$$

There have been several studies on the kinetics of Oxidation of many drugs over the past many years, but the detailed investigation on the Kinetics & Mechanism of oxidation of β-blockers has met only a limited attention.The drug ESM has not been explored kinetically, although there are few studies on the oxidations of other β blockers like labetalol, metoprolol, propranolol, atenolol etc. with different oxidants [42-45]. There are fewer studies on the Ce(IV) aided oxidation kinetics of β blockers in acidic medium. Atenolol is the most studied β-blocker in terms of kinetics and mechanism [44-50]. Structurally ESM is similar to atenolol in having a propanoloxy moiety and an isopropyl group attached secondary amine. It differs from atenolol only in having a hydrolysable methyl ester group in the side chain. Hence, an over view of the oxidative degradation products of atenolol along with other kinetic aspects could serve as a background in understanding the kinetics of oxidative degradation of ESM.

Hiremath et al have studied the kinetics of oxidative degradation and deamination of atenolol by permanganate in aqueous alkaline medium and found that reaction is first ordered in [$KMnO_4$], fractional ordered in both [Atenolol] and [alkali] with stoichiometry being 2:1 in substrate and oxidant. 4-carboxy methoxy phenyl acetic acid and N-isopropyl methyl amine are reported as oxidation products [46].

Mulla et al have reported the kinetics of ruthenium (III) catalyzed oxidation of atenolol by permanganate in which the reaction is first ordered in both [$KMnO_4$], [Ru(III)] and fractional ordered in both [Atenolol] and [alkali] with stoichiometry being 1:8 in substrate and oxidant. The products are identified as 4-carboxy methoxy phenyl acetic acid and N-(isopropyl)-amino carboxylic acid [47].

Nandibewoor et al and also Anand et al have independently studied the oxidative deamination of atenolol in aqueous perchloric acid and aqueous sulphuric acid medium respectively. 4-carboxy methoxy phenyl acetic acid and N-isopropyl methyl amine are reported as oxidation products [48-50].




**Scheme 1.** 2:1 stoichiometry of oxidative deamination of ESM by Ce(IV) with the two products and Ce(III), the reduced form of Ce(IV)

A systematic study on the kinetics & mechanism of oxidation of ESM may be helpful not only in understanding the oxidation mechanism of this bio-active compound, but also for the development of physiologically more relevant mimics of its oxidation processes. Metabolically, β blockers undergo glucuronidation, aromatic ring hydroxylation, N-dealkylation etc; whereas they are prone to oxidative de-amination during in vitro analysis. The present work involving the redox reaction between Ce(IV)$SO_4$ and ESM aims at finding the following:

(i) To determine the order and stoichiometry with respect to both oxidant and drug substrate.

(ii) To determine the reactive species involved.

(iii) To develop a plausible mechanism.

## 2. EXPERIMENTAL

### *2.1 Chemicals*

ESM hydrochloride was used as supplied (Gift sample of pure bulk drug, MSN Labs, Hyderabad, India) without further purification. Ce(IV) Sulphate, and all other chemicals (S. R Chemicals, Hyderabad) used were of A.R grade with more than 99.5% purity. Double distilled water was used for the preparation of solutions and for carrying out kinetic runs. A stock solution of 0.1 mol $dm^{-3}$ ESM was prepared by weighing appropriate amount of it. 0.1 mol $dm^{-3}$ Ce (IV) Sulphate solution was prepared and standardized as per the standard procedure [51, 52]. $NaClO_4$ solution, used to maintain the ionic strength during the course of the kinetic run, was prepared by neutralizing $HClO_4$ with NaOH. Commercial grade $HClO_4$ with a specific gravity of 1.35 was used.

### *2.2 Instrumental*

Spectronics double beam spectrophotometer 2203 was used for measuring the absorbance of coloured oxidant solution. Mettler-Toledo electronic balance of 0.1 mg accuracy was used for weighing. A temperature bath was used to maintain constant temperature. All kinetic runs were carried out in the temperature range of 22 to 37 $^{o}$C with an error of ≤ 1%. Regression analysis of experimental data to

obtain the correlation coefficient of points and Standard deviation were performed using M S Excel 2012 Program.

### *2.3 Kinetic study*

Ce (IV) Sulphate in 0.1 M $H_2SO_4$ solution has a molar absorbance coefficient of 5240 mol $dm^{-3}$ $cm^{-1}$. The orange coloured solution undergoes discoloration in the reaction with ESM. The course of the reaction was followed as a measure of decrease in absorbance determined spectrophotometrically at the wave length of 320 nm, which is the wave length of maximum absorbance for Ce(IV)Sulphate solution [53, 54]. The substrate showed negligible absorbance (0.006) at the wave length.

All kinetic runs were carried out under pseudo first order conditions with ESM being nearly 10 times greater than [Ce(IV)] at a constant ionic strength of 0.5 mol $dm^{-3}$. Thermally equilibrated requisite amounts of reactants were mixed in the following order: water, $H_2SO_4$, $NaClO_4$, substrate and then finally oxidant. Stop clock was started when exactly half the volume of oxidant was added to the reaction mixture. The concentration of $H_2SO_4$ was maintained at 0.1 mol $dm^{-3}$ in all the kinetic runs by adding appropriate volumes of $H_2SO_4$ solution to the reaction mixture. The results were reproducible with an error of less than 1%.

The order with respect to coloured reagent is determined from the slope of log Abs v/s time plots by following pseudo first order kinetics employing isolation method. The rate of the reaction in terms of rate law may be given by,

$$r = k_r [ESM] [Ce (IV)]$$

$k_r$ = overall rate constant of the reaction

At pseudo first order conditions,

[ESM] >> [Ce (IV)]

Rate law becomes,

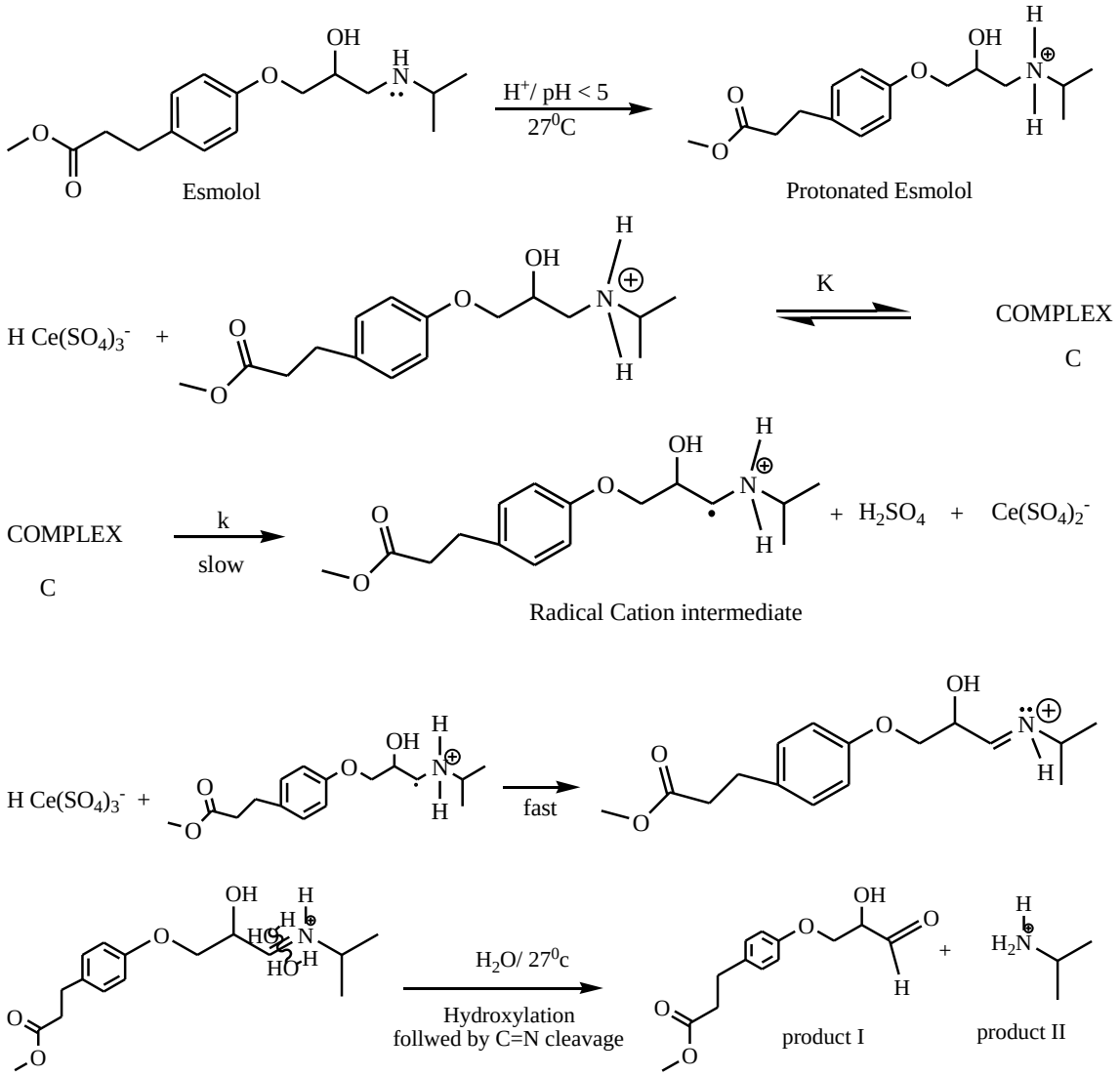
$$r = k_{obs} [Ce (IV)] \quad \text{..... (I)}$$

Where, $k_{obs}$ = pseudo first order rate constant.

## 3. RESULTS & DISCUSSION

### *3.1 Stoichiometry & Reaction Products*

Five reaction mixtures of 10 mL each containing excess Ce(IV) over the drug ESM in 0.1 mol $dm^{-3}$ $H_2SO_4$, maintained at a constant ionic strength of 0.50 mol $dm^{-3}$, were allowed to react for 6 hours at 25 $^{o}$ C. The remaining Ce(IV) was then analyzed spectrophotometrically. The results indicate that two moles of Ce(IV) are consumed by one mole of ESM as depicted in scheme 1.




**Scheme 2.** Mechanism involved in the oxidation reaction of ESM with Ce(IV) in aqueous $H_2SO_4$ medium

The main product is extracted with ether. This is identified as 3-(4-(2-hydroxy-3-oxopropoxy) phenyl) proponoate by its I.R spectrum, which showed a band at 1647 $cm^{-1}$ due to >C=O bond stretching of aldehyde group. The decrease in wave number is probably due to intramolecular hydrogen bonding between >C=O and O-H bonds. This is also confirmed by the formation of a broad band at 3334 $cm^{-1}$ due to O-H stretching vibration. The characteristic fragment ion peak formed at m/z value of 251 amu with good abundance corresponding to $(M–H^{\cdot})^{+}$ ion also confirms aldehyde group of the obtained main product. The extract showed sodium adduct peaks at m/z values of 274 amu, 275 amu corresponding to $(M + Na)^{+}$ and $(M–H^{\cdot} + Na)^{+}$ ions. The molecular ion fragment peak of $M^{+}$ ion is formed at 252 amu. Another product, isopropyl amine is identified by its I.R spectrum in aqueous layer.

The products indicate that ESM undergoes oxidative deamination in the reaction with Ce(IV) in 0.1 mol $dm^{-3}$ $H_2SO_4$ medium.

### *3.2 Order w.r.t. individual reactants*

The Ce(IV) concentration was varied in the range from $5 \times 10^{-5}$ to $2 \times 10^{-4}$ mol $dm^{-3}$. The linearity of the plots of ln Abs versus time up to more than 80% completion of the reaction indicated a reaction order of unity in [Ce(IV)] (Fig. 1). This result was confirmed by varying the [Ce(IV)], which showed no change in the pseudo first order rate constant, $k_{obs}$ **(**Table 1**).** The substrate [ESM] was varied in the range from $5 \times 10^{-4}$ to $2 \times 10^{-3}$ mol $dm^{-3}$ at the temperature range of 22 $^oC$ to 37 $^oC$ while keeping all the other reactant concentrations and reaction conditions constant. The variation of $k_{obs}$ with [ESM] is studied and a graph was plotted between ln $k_{obs}$ and ln [ESM] (Fig. 2). The order w.r.t [ESM], as given by the slope of the above plot, was fractional (0.26). The effect of acid on the reaction is studied by using perchloric acid at constant concentrations of ESM and Ce(IV) and keeping a constant ionic strength of 0.50 mol $dm^{-3}$. A constant amount of sulphuric acid coming from stock solution of Ce(IV) is also present in all cases. The rate constant almost remained constant with increase in [$HClO_4$] as also [$SO_4^{2-}$].

The addition of $HSO_4^-$ has marked influence on the rate of the reaction, although the order with respect to [$HSO_4^-$] is fractional (0.11) (Fig. 3). This was confirmed by the linear plot obtained from $1/k_{obs}$ vs. 1/[$HSO_4^-$]. The *in situ* [$H^+$], [$SO_4^{2-}$] and [$HSO_4^-$] were calculated from the known second ionization constant value of $H_2SO_4$ as shown in Table 2 [55, 56].

$$Ce(IV) + H_2O \underset{}{\overset{K_{OH}}{\rightleftharpoons}} Ce(OH)^{3+} + H^+$$

$$Ce(IV) + HSO_4^- \overset{K_1}{\rightleftharpoons} Ce(SO_4)^{2+} + H^+$$

$$Ce(SO_4)^{2+} + HSO_4^- \overset{K_2}{\rightleftharpoons} Ce(SO_4)_2 + H^+$$

$$Ce(SO_4)_2 + HSO_4^- \overset{K_3}{\rightleftharpoons} Ce(SO_4)_3^{2-} + H^+ \quad (\mathbf{OR}) \quad Ce(SO_4)_2 + HSO_4^- \overset{K_3}{\rightleftharpoons} HCe(SO_4)_3^-$$

$$HCe(SO_4)_3^{2-} + HSO_4^- + H^+ \overset{K_4}{\rightleftharpoons} H_3Ce(SO_4)_4^-$$

**Scheme 3.** Formation of different Ce(IV) complexes in aqueous $H_2SO_4$ medium with $HCe(SO_4)_3^-$ being the predominant species at the specified condition

### *3.3 Ionic Strength*

On adding $NaClO_4$ by an increment of 0.01 mol $dm^{-3}$, raising ionic strength from 0.5 to 0.6 mol $dm^{-3}$, no effect was observed on the rate of reaction. This indicates that neither positive nor negative ions are involved in the slow rate determining step, confirming the formation of uncharged (neutral) complex in fast equilibrium step as depicted in scheme 2.

### *3.4 Determination of Reactive Species & Mechanism*

At 0.1 mol $dm^{-3}$ [$H_2SO_4$], addition of 0.01 mol $dm^{-3}$ increments of $HClO_4$ showed no effect on the rate of reaction, whereas addition of $HSO_4^-$ has marked influence on the rate of reaction. Literary survey

**Table 1** Effect of [Ce(IV)], [ESM], [$HSO_4^-$] on the oxidation reaction in aqueous $H_2SO_4$ medium at 27 $^oC$

| [Ce(IV)] | [ESM] | [$HSO_4^-$] | $k_{obs}$ | $k$ |
|---|---|---|---|---|
| $10^{-4}$ mol $dm^{-3}$ | $10^{-3}$ mol $dm^{-3}$ | mol $dm^{-3}$ | $10^{-3}$ ( $s^{-1}$) | $10^{-3}$ ($s^{-1}$) |
| 1 | 1 | 0.083828 | 1.3971 | - |
| 1.25 | 1 | 0.083828 | 1.3588 | - |
| 1.5 | 1 | 0.083828 | 1.3615 | - |
| 1.75 | 1 | 0.083828 | 1.3611 | - |
| 2 | 1 | 0.083828 | 1.361 | 1.837 |
| 2 | 0.5 | 0.083828 | 1.138 | 1.837 |
| 2 | 0.75 | 0.083828 | 1.261 | 1.837 |
| 2 | 1.25 | 0.083828 | 1.441 | 1.837 |
| 2 | 1.5 | 0.083828 | 1.508 | 1.837 |
| 2 | 1.75 | 0.083828 | 1.575 | 1.837 |
| 2 | 2 | 0.083828 | 1.63 | 1.837 |
| 2 | 1 | 0.089339 | 1.37 | 1.837 |
| 2 | 1 | 0.097234 | 1.383 | 1.837 |
| 2 | 1 | 0.114597 | 1.408 | 1.837 |
| 2 | 1 | 0.123549 | 1.419 | 1.837 |
| 2 | 1 | 0.169512 | 1.469 | 1.837 |

**Table 2.** Effective concentration of $H^+$, $HSO_4^-$, $SO_4^{2-}$ on the addition of $HClO_4$, $HSO_4^-$, $SO_4^{2-}$ to the reaction mixture

| | Concentration (mol $dm^{-3}$) | Effective concentration in reaction mixture (mol $dm^{-3}$) | | | Ionic Strength (mol $dm^{-3}$) |
|---|---|---|---|---|---|
| | [Added Species] | [$H^+$] | [$HSO_4^-$] | [$SO_4^{2-}$] | I |
| Addition of $HClO_4$ | 0.01 | 0.125552 | 0.084448 | 0.015552 | 0.51 |

| | | | | | |
|---|---|---|---|---|---|
| | 0.02 | 0.134975 | 0.085025 | 0.014975 | 0.52 |
| | 0.04 | 0.153935 | 0.086065 | 0.013935 | 0.54 |
| | 0.05 | 0.163465 | 0.086535 | 0.013465 | 0.55 |
| | 0.1 | 0.211508 | 0.088492 | 0.011508 | 0.6 |
| | 0.01 | 0.120869 | 0.089339 | 0.020869 | 0.51 |
| | 0.02 | 0.122766 | 0.097234 | 0.022766 | 0.52 |
| | 0.04 | 0.125403 | 0.114597 | 0.025403 | 0.54 |
| | 0.05 | 0.126451 | 0.123549 | 0.026451 | 0.55 |
| Addition of $HSO_4^-$ | 0.1 | 0.130488 | 0.169512 | 0.030488 | 0.6 |
| | 0.01 | 0.111649 | 0.088351 | 0.021649 | 0.505 |
| | 0.02 | 0.107322 | 0.092678 | 0.027322 | 0.51 |
| | 0.04 | 0.099241 | 0.100759 | 0.039241 | 0.52 |
| | 0.05 | 0.095479 | 0.104522 | 0.045479 | 0.525 |
| Addition of $SO_4^{2-}$ | 0.1 | 0.079227 | 0.120773 | 0.079227 | 0.55 |

reveals that the nature of Ce (IV) species depends on the ratio of $[SO_4^{2-}]$ to $[Ce(IV)]_T$. The complex $CeSO_4^{2+}$ predominates at a ratio of ≤ 50, while $Ce(SO_4)_3^{2-}$ is formed mostly at a ratio ≥ 500 [57, 58]. In the present study, the ratio was more than 500. This confirms $Ce(SO_4)_3^{2-}$ or $HCe(SO_4)_3^-$ or $Ce(SO_4)_2(HSO_4^-)$ as the predominant species formed at the specified conditions. The predominant reactive species is formed in a prior equilibrium (Scheme 3).

The active $Ce(SO_4)_2(HSO_4^-)$ species reacts with protonated form of ESM to give a complex. The complex formation involving bridging between substrate and oxidant supports inner sphere mechanism. The formed complex then decomposes in a slow step to give a radical cation which then reacts with another molecule of active species in a fast step to give an imine. The formed imine is hydrolyzed in another fast step to give the products as proposed in scheme 3. The added product i.e. Ce(III) formed in the reaction, did not show any significant effect on the rate of the reaction. This confirms that the rate determining step is irreversible as the formed Ce(III) is not reverting back to regenerate complex, C. The oxidation of ESM by Ce(IV) is a non-complementary electron transfer reaction, since the oxidant and reductant change their oxidation state by different units [59-61].

The complex is confirmed by the fractional order dependence on [ESM] and also by the positive intercept formed in Michaelis- menten plot drawn between $1/k_{obs}$ vs. 1/[ESM] as shown in Fig.4.

Since the reaction involves kinetic run where an excess substrate was used, oxidant being the limiting reagent, the reactive species completely reacts. Hence, the stepwise formation constant ($K_3$) in the pre-equilibrium step involving reactive species was used for deriving rate equation. The rate equation was developed for the slow rate determining step of the proposed mechanism and rate constant ($k$) was deduced using equation 4 of scheme 4.

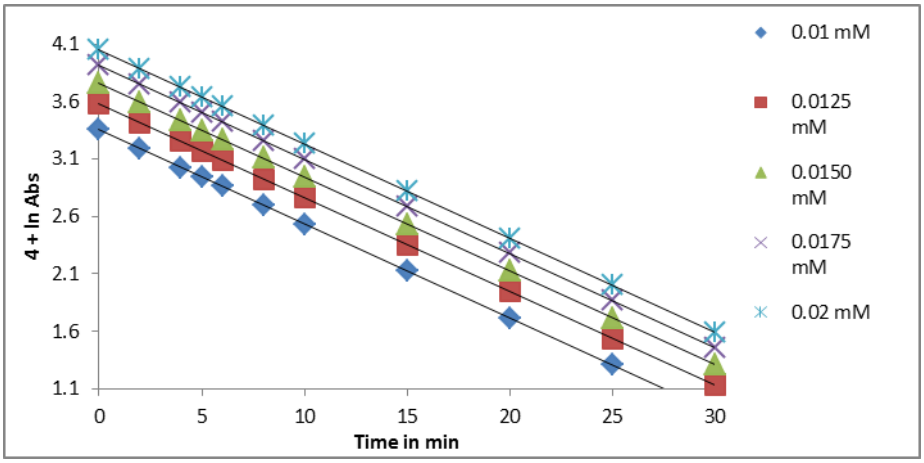



**Figure 1.** Plot of ln Abs vs. Time at [ESM] = $2 \times 10^{-4}$ mol $dm^{-3}$ ; [ $H^+$] = 0.1 mol $dm^{-3}$; I = 0.5 mol $dm^{-3}$

### 3.5 Rate Law Derivation

The rate law was derived based on the kinetic considerations and earlier reported literature [17, 34, 48, 49, 50, 62].

Rate of the reaction based on slow step of the mechanism,

$$r = -dc/dt = k\,[C]$$

$$= k\,K\,[HCe(SO_4)^-_3]\,[ESM]$$

$$= k\,K\,K_3\,[HSO_4^-]\,[Ce(SO_4)_2][ESM]$$

$$-dc/dt = k\,K\,K_3\,[Ce(SO_4)_2][ESM][HSO_4^-]$$

$$[Ce(IV)]_T = [Ce(IV)]_f + [HCe(SO_4)^-_3] + [C]$$

$$=[Ce(IV)]_f + K_3\,[HSO_4^-]\,[Ce(SO_4)_2] + K\,[HCe(SO_4)^-_3][ESM]$$

$$= [Ce(IV)]_f + K_3\,[HSO_4^-][Ce(SO_4)_2] + K\,K_3\,[HSO_4^-]\,[Ce(SO_4)_2]\,[ESM]$$

$$[Ce(IV)]_T = [Ce(IV)]_f\left\{1+K_3\,[HSO_4^-] + K\,K_3\,[HSO_4^-][ESM]\right\}$$

$$[Ce(IV)]_f = \frac{[Ce(IV)]_T}{1+K_3\,[HSO_4^-] + K\,K_3\,[HSO_4^-][ESM]} \longrightarrow (1)$$

Similarly,

$$[HSO_4^-]_T = [HSO_4^-]_f + [HCe(SO_4)_3^-] + [C]$$

$$=[HSO_4^-]_f + K_3\,[HSO_4^-][Ce(IV)]_f + K\,K_3\,[HSO_4^-]\,[Ce(IV)]_f\,[ESM]$$

$$[HSO_4^-]_T = [HSO_4^-]_f \; 1+K_3[Ce(IV)]_f + K K_3 [Ce(IV)]_f [ESM] \}$$

$$[HSO_4^-] = \frac{[HSO_4^-]_T}{1+K_3[Ce(IV)]_f + K K_3 [Ce(IV)]_f [ESM]}$$

$$[Ce(IV)] <<< 1$$

$$[HSO_4^-]_f = [HSO_4^-]_T \longrightarrow (2)$$

Also, $[ESM]_T = [ESM]_f + [C]$

$$= [ESM]_f + K K_3 k [SO_4^{2-}] [Ce(IV)]_f [ESM]_f$$

$$= [ESM]_f \{1 + K K_3 k [SO_4^{2-}] [Ce(IV)]_f\}$$

$$[ESM]_f = \frac{[ESM]_T}{\{1 + K K_3 k [SO_4^{2-}] [Ce(IV)]_f\}}$$

since $[Ce(IV)] <<< 1$

Hence, $[ESM]_f = [ESM]_T \longrightarrow (3)$

$$-dc/dt = k K K_3 [Ce(IV)][ESM] [HSO_4^-]$$

$$\frac{-dc/dt}{[Ce(IV)]_T} = \frac{k K K_3 [HSO_4^-][ESM]}{1+K_3[HSO_4^-] + K K_3 k [HSO_4^-][ESM]}$$

writing the reciprocal,

$$\frac{[Ce(IV)]_T}{-dc/dt} = \frac{1+K_3[HSO_4^-] + K K_3 [HSO_4^-][ESM]}{k K K_3 [HSO_4^-][ESM]}$$

$$\frac{[Ce(IV)]_T}{k_{obs}[Ce(IV)]_T} = \frac{1}{k K K_3 [HSO_4^-][ESM]} + \frac{1}{k K [ESM]} + \frac{1}{k}$$

$$\frac{1}{k_{obs}} = \frac{1}{k K K_3 [HSO_4^-][ESM]} + \frac{1}{k K [ESM]} + \frac{1}{k} \longrightarrow (4)$$

$$K = \frac{1}{i_2 k[Esm] - [Esm]} \longrightarrow (5)$$

$$K_3 = \frac{1}{k K S_2 [Esm]} \longrightarrow (6)$$

Here $i_2$ = intercept; $s_2$ = slope of the plot drawn b/w $1/k_{obs}$ v/s. $1/[HSO_4^-]$

### *3.6 Effect of Temperature*

The $k$ values in the given temperature range were determined from the intercept of the plots of $1/k_{obs}$ versus 1/[ESM].. The $K$, $K_3$ values at the specified temperatures were obtained from the combined equations (Eqn. 5 & 6) developed from the slopes and intercepts of the plots $1/k_{obs}$ versus 1/[ESM] and $1/k_{obs}$ versus $1/[HSO_4^-]$. The values of $k$ determined at 22, 25, 27, 32 and 37 $^oC$ were 0.001138, 0.001263, 0.001359, 0.001441, 0.001508, 0.001575, 0.00163 $s^{-1}$ respectively with a standard deviation in the range of $0.000001 \geq s \leq 0.000002$. The corresponding $K$ values were found to be 6165.093, 6198.763, 6241.361, 6306.27, 6390.553 $dm^3\ mol^{-1}$ ($0.323667 \geq s \leq 3.083647$).

**Table 3.** Thermodynamic activation parameters for the proposed mechanism with regard to complex formation equilibrium step & rate determining dissociation step

| Kinetic /Thermodynamic Parameter | Unit | Temperature in $^0C$ | Value | Standard Deviation (s) for two trials |
|---|---|---|---|---|
| Activation Energy, $E_a$ | KJ/mol | - | 68.15 | ± 0.07 |
| Free Energy Change, $\Delta G^{\neq}$ | KJ/mol | 27 | -21.43 | ± 0.001 |
| Enthalpy Change, $\Delta H^{\neq}$ | KJ/mol | 27 | 65.66 | ± 0.07 |
| Entropy Change, $\Delta S^{\neq}$ | J/K | 27 | -290.3 | ± 0.23 |
| Rate Constant, $k$ | $s^{-1}$ | 27 | 0.001837 | ± 0.000001 |
| Formation Constant, $K$ | $dm^3\ mol^{-1}$ | 27 | 6241.36 | ± 1.2 |
| Pre- Equilibrium Constant, $K_3$ | $dm^3\ mol^{-1}$ | 27 | 9.8 | ± 0.07 |

The activation energy was evaluated from the plot of ln $k$ versus 1/T (Fig. 5). The $\Delta H^{\neq}$ values were evaluated from the relation $\Delta H^{\neq} = E_a$ **- RT**. The $\Delta G^{\neq}$ values were determined from the relation $\Delta G^{\neq} =$ -RT ln $K$. The $\Delta S^{\neq}$ was obtained from the equation, $\Delta G^{\neq} = \Delta H^{\neq}$ **-** $\mathbf{T}\Delta S^{\neq}$. The kinetic and thermodynamic

activation parameters were evaluated for two trials along with their standard deviations and were tabulated (Table 3). The positive enthalpy and negative entropy of activation values are indicative of the more ordered complex formation in the fast equilibrium step. The moderate value of enthalpy and higher values of rate constant of the rate limiting step indicate inner sphere electron transfer [63-64].

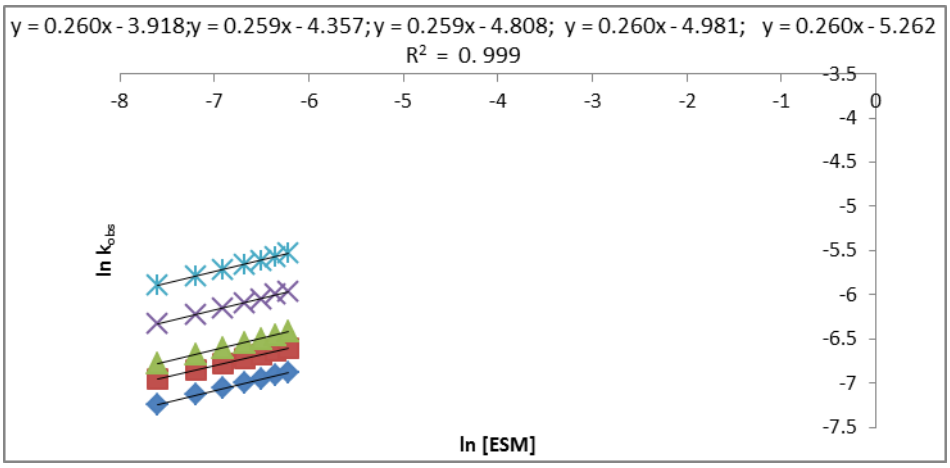



**Figure 2.** Plot of ln [ESM] v/s. ln $k_{obs}$ at 22, 25, 27, 30, 35 $^0$C with slope giving order (0.26) w.r.t [ESM]

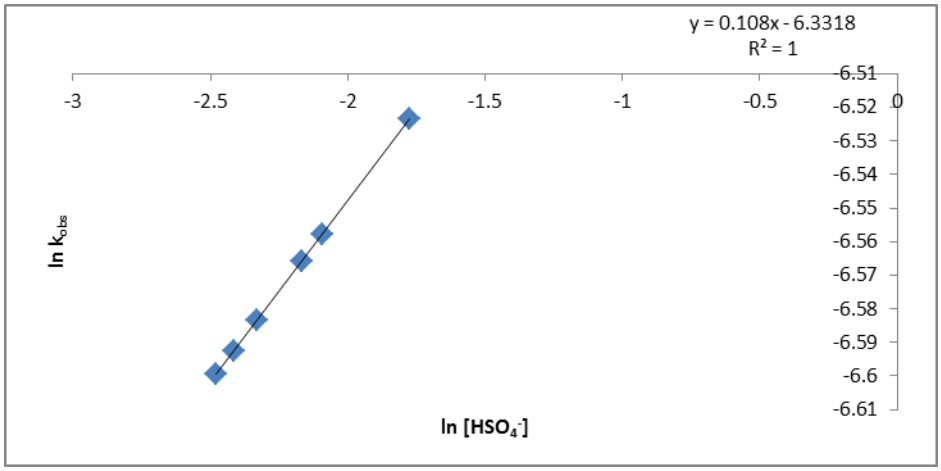



**Figure 3.** Plot of ln [ESM] v/s. ln $k_{obs}$ at 27 $^0$C with slope giving order (0.11) w.r.t. [$HSO_4^-$]

### *3.7 Polymerization study*

The free radical formation is proven by polymerization study. The reaction mixture is added with acrylonitrile and kept for 24 hour. The formation of white precipitate on dilution of the mixture with methanol confirms the presence of free radicals. The blank experiment with Ce(IV) or ESM individually on standing with acrylonitrile did not give precipitate with methanol. Also, initially added acrylonitrile decreased the rate of the reaction. The decrease in rate is due to free radical scavenging by the added acrylonitrile.

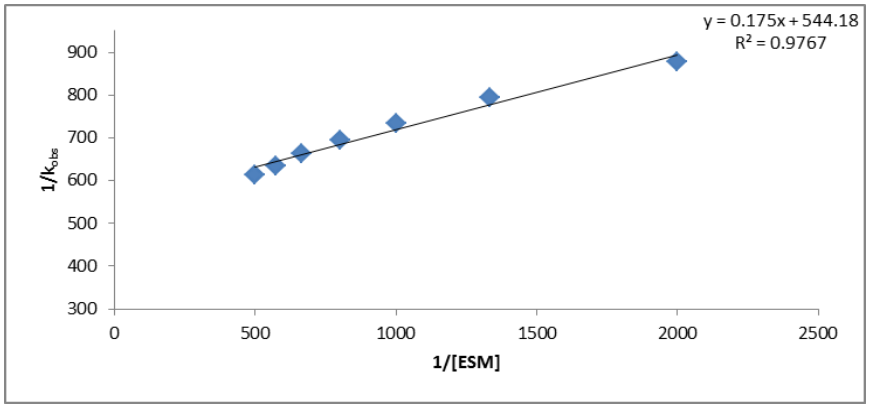



**Figure 4**. Michaelis-Menten plot b/w $1/k_{obs}$ vs. 1/[ESM] at 27 $^{o}$C. [Ce(IV)] = 2 x $10^{-5}$; [$H^{+}$] = 0.1 mol $dm^{-3}$; I = 0.5 mol $dm^{-3}$

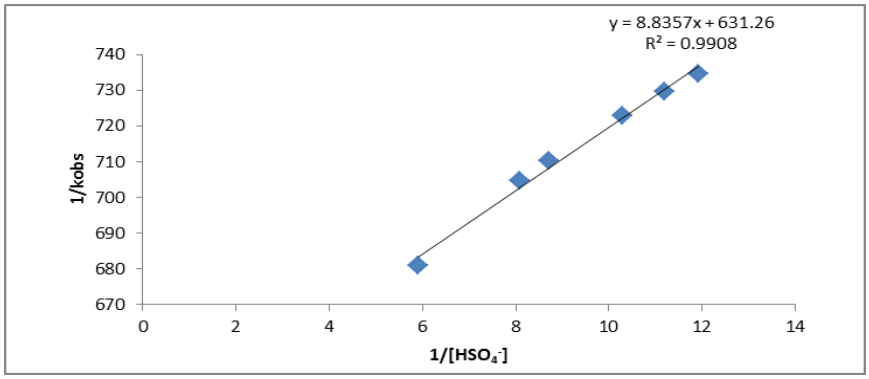



**Figure 5.** Michaelis-Menten plot b/w $1/k_{obs}$ vs. 1/[$HSO_4^{-}$] at 25 $^{o}$C; [Ce(IV)] = 2 x $10^{-5}$; [$H^{+}$] = 0.1 mol $dm^{-3}$; I = 0.5 mol $dm^{-3}$

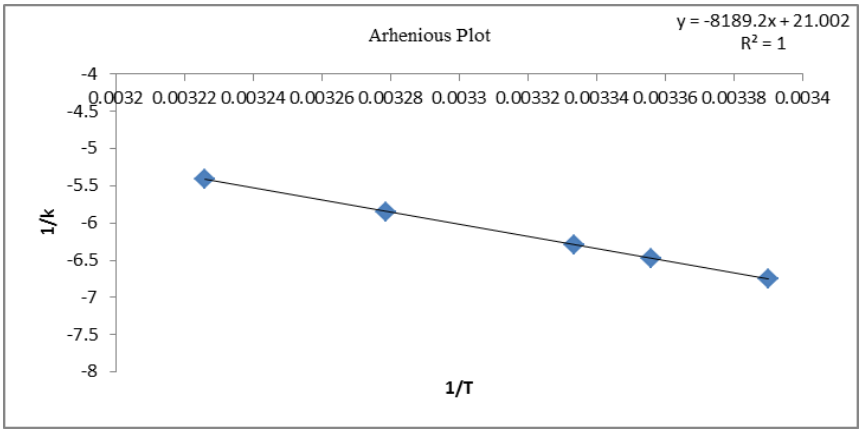



**Figure 6.** ln k = ln A – $E_a$/RT; Plot of ln K v/s. 1/T whose slope gives Activation Energy ($E_a$)

### *3.8 Effect of Hydrolysable Ester Group*

The inherent limitation in the study of oxidation of ESM in aqueous acid medium is in its hydrolysable ester group producing methanol that undergoes oxidation with Ce(IV), thus complicating the kinetic study. The limitation has been overcome by carefully selecting the temperature range below 40 $^{o}$C. The negative test for methanol is done based on the fact that methanol if formed by the hydrolysis of the ester group would get oxidized as formaldehyde, during the course of the reaction, restoring pink colour of Schiff's base or giving violet coloration with chromotropic acid [65]. The reaction mixture gave negative spot test with both Schiff's base and chromotropic acid establishing that methanol was not formed in the selected temperature range. It is to be further noted that the main product, 3-(4-(2-hydroxy-3-oxopropoxy) phenyl) propionate – also having an aldehydic group, did not give colouration with chromotropic acid.

## 4. CONCLUSION

The oxidative deamination of ESM by Cerium(IV) in aqueous sulphuric acid medium gave 3-(4-(2-hydroxy-3-oxopropoxy) phenyl) proponoate as the main product. The kinetics of the reaction was studied spectrophotometrically, a mechanism proposed and rate law was deduced based on the kinetic considerations and products formed. The reaction has a stoichiometry of 1:2 with fractional order dependence on both $HSO_4^-$ and ESM concentrations and first order dependence on Cerium(IV). No effect of the products on rate was found. $HCe(SO_4)_3^-$ was found to be the reactive species. Although beta blockers are being replaced clinically by other potent cardiovascular drugs, they continue to be the lead compounds for the development of new drugs. A systematic study on the kinetics & mechanism of oxidation of ESM has been carried out which may be helpful for the development of physiologically more relevant mimics of its oxidation processes.

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*The authors declare no conflict of interest*