1. INTRODUCTION

Cerium(IV) is a strong one electron oxidant used as an analytical reagent especially in acid media [1]. It is also used in kinetic studies on oxidation of different substrates in perchloric acid medium [2-6]. The mechanism of cerium(IV) (Ce(IV)) oxidations of various substrates is found to follow different mechanisms, depending upon acid media used. In perchloric acid medium the active form of Ce(IV) was found to be either free Ce(IV) or Cerric hydroxide ion, where as in sulphuric acid medium its active forms were reported to be $H_3[Ce(SO_4)_4]^-$ or $H[Ce(SO_4)_3]^-$ . In both the media, Ce(IV) oxidizes the substrates either forming a complex with substrates or it oxidizes to form a free radical. In some of Ce(IV) oxidations, the product, Ce(III) was found to have retarded the rate of reaction, particularly in catalyzed reactions. Thus, the oxidation of substrates by Ce(IV) is interesting to understand the different pathways of the reactions and its active form.

Clindamycin Phosphate, methyl 7-chloro-6, 7, 8-trideoxy-6-[(2S, 4R)-1-methyl-4-propylpyrrolidine-2-carboxamide]-1-thio- 1 -threo-D-galacto - octa pyranoside monohydrochloride (CYN-P) is a semi synthetic antibiotic which is a derivative of lincomycin. It is a useful drug against gram-positive cocci and also helpful against protozoan such as toxoplasma and mycoplasma as well as many anaerobic bacteria [7]. CYN-P and several macrolide antibiotics have proven effective for the treatment of AIDS- toxoplasmosis, usually in combination with pyrimethamine [8-10]. These compounds are known to block

2. EXPERIMENTAL SECTION

2.1. Materials and Reagents

All chemicals used, clindamycin phosphate, sulphuric acid, ceric ammonium sulphate, perchloric acid and sodium perchlorate were of reagent grade. Double distilled water was used throughout the study. A stock solution of CYN-P was prepared by dissolving the appropriate amount of a sample in double distilled water. The purity of CYN-P was further ensured by determining its m. p and TLC. Aging of aqueous solution of CYN-P was tested by performing the kinetics of oxidation at different interval of time from hours to days. It was observed that its kinetics of oxidation stands remain identical. However, stock solutions are prepared a fresh as and when the solution is required for kinetics.

The stock solution of Ce(IV) was prepared by dissolving ceric ammonium sulphate in double distilled water in the presence of 1.0 mol dm\(^{-3}\) H\(_2\)SO\(_4\) and kept for overnight. Concentration of Ce(IV) was ascertained by titrating against standard ferrous ammonium sulphate solution using ferroin as an internal indicator. Concentration of Ce(IV) was found to be fairly stable for more than 6 months provided it is not expose to sunlight.

Ce(III) solution was prepared by dissolving cerium(III) acetate in water. The \([\text{H}^+]\) was maintained by adding requisite concentration of HClO\(_4\) by subtracting the \([\text{H}^+]\) added due to H\(_2\)SO\(_4\) present in the Ce(IV) stock solution. Similarly ionic strength was maintained by using aqueous solution of NaClO\(_4\)
after deducting the concentration of $\text{SO}_4^{2-}$ due to $\text{H}_2\text{SO}_4$ from Ce(IV) stock solution.

2.2. Kinetic Measurements

The reaction was initiated by the addition of Ce(IV) solution to CYN-P solution containing required amounts of $\text{HClO}_4$ and $\text{NaClO}_4$. The reaction was followed under pseudo-first order conditions with CYN-P in at least 10-fold excess over Ce(IV) at a constant ionic strength of 0.5 mol dm$^{-3}$ at $298 \pm 1$ K unless otherwise stated. The course of reaction was followed by monitoring the decrease in absorbance of Ce(IV) in a 1 cm quartz cell of thermostated compartment of Hitachi-U3310 spectrophotometer at its $\lambda_{\text{max}}= 360$ nm as a function of time (Figure II (a-1), p. 54) at which other species in the reaction system are not interfering due to their absorbance and tungsten lamp can be used as a source of light instead of deuterium lamp. The spectral changes of Ce(IV) is given in Figure II (a-2), (p.54). The obedience to Beer’s law of absorption of Ce(IV) at 360 nm (Figure II (b), p. 55) in the concentration range of $1.0 \times 10^{-5}$ to $3.0 \times 10^{-4}$ mol dm$^{-3}$ under the reaction conditions has been tested earlier ($\varepsilon = 3585 \pm 10$ dm$^3$ mol$^{-1}$ cm$^{-1}$). First order plot of log absorbance versus time was found to be linear up to 90% completion of reaction (Table II (a), p.56 and Figure II (c), p. 55). Hence, rate constants are used to determine the order with respect to various reactive species which are obtained from the slopes of plots of log[Ce(IV)] versus time. The results were reproducible within $\pm 3\%$. 

Figure II (a-1): Spectra at 298K of
(i) \([\text{Ceric ammonium sulphate}]=1.3 \times 10^{-4}\),
(ii) \([\text{Clindamycin phosphate}]= 1.0 \times 10^{-3} \text{ mol dm}^{-3}\).
\([\text{HClO}_4]= 0.4; \quad [\text{H}_2\text{SO}_4]= 0.05; \quad I = 0.50 / \text{mol dm}^{-3}\)

Figure II (a-2): Spectral changes of Ce(IV) due to oxidation of clindamycin phosphate by cerium (IV) in aqueous acidic medium at 298K.
(time interval = 1 min)
\([\text{Ce(IV)}]= 1.3 \times 10^{-4}; \quad [\text{CYN-P}]= 1.0 \times 10^{-3};
[\text{HClO}_4]= 0.4; \quad [\text{H}_2\text{SO}_4]= 0.05; \quad I = 0.50 / \text{mol dm}^{-3}\)
Figure II (b)

Verification of Beer’s law at 360 nm for freshly prepared ceric ammonium sulphate in aqueous acidic medium at 298K.

\[ [\text{HClO}_4] = 0.4; \quad [\text{H}_2\text{SO}_4] = 0.05; \quad I = 0.50 / \text{mol dm}^{-3} \]

![Graph showing Beer's law](image)

Figure II (c)

Example run for the oxidation of clindamycin phosphate by cerium (IV) in aqueous acidic medium at 298K.

(Conditions as in Table II (a), p. 56)

![Graph showing oxidation](image)
Table II (a)

Example run for the oxidation of clindamycin phosphate by cerium (IV) in aqueous acidic medium at 298K.

\[ [\text{Ce(IV)}] = 1.3 \times 10^{-4}; \quad [\text{CYN-P}] = 1.0 \times 10^{-3}; \]
\[ [\text{HClO}_4] = 0.4; \quad [\text{H}_2\text{SO}_4] = 0.05; \]
\[ I = 0.50 / \text{mol dm}^{-3} \]

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Absorbance (360 nm)</th>
<th>(10^4 \times \text{Ce(IV)}) (mol dm(^{-3}))</th>
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<tbody>
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3. RESULTS
3.1. Stoichiometry and Product Analysis

The reaction mixture containing various ratios of Ce(IV) to CYN-P in the presence of 0.4 mol dm$^{-3}$ HClO$_4$ adjusted to a constant ionic strength of 0.5 mol dm$^{-3}$ was kept for over 24 hrs. at 298K in a closed vessel for completion of reaction (Table II (b), p. 58). Unreacted Ce(IV) was then analyzed spectrophotometrically at 360 nm, and also titrimetrically by titrating with standard ferrous ammonium sulphate solution using ferroin as an internal indicator. The results showed that 2 mol of Ce(IV) was required to oxidize 1 mol of CYN-P according to eqn. (1).

\[ \text{H}_3\text{PO}_4 + \text{O}_3\text{S} \text{N}_3\text{HC Cl} + \text{HO} \text{HO} \text{HO} \text{H} \rightarrow + 2 \text{Ce(III)} + 2 \text{Ce(IV)} \]

The oxidative product of CYN-P was identified as follows: aqueous solution was subjected to TLC for separation of constituents, the iodine spray showed a single spot. The compound was identified as hydroxy form of clindamycin (N-(2-chloro-1-(tetrahydro -3,4,5- trihydroxy -6- (methylthio) -2H- pyran -2- yl) propyl) -4-propylpyrrolidine-2-carboxamide) and the product was analyzed by LC-MS, the molecular ion peak (Figure II (d), p. 59) shows at 407.5 which was expected for the molecular mass of hydroxy form of clindamycin.
Table II (b)

Stoichiometry for the oxidation of clindamycin phosphate by cerium(IV) in aqueous acidic medium at 298K.

\[
[HClO_4] = 0.4; \quad [H_2SO_4] = 0.05; \quad I= 0.5 /\text{mol dm}^{-3}
\]

<table>
<thead>
<tr>
<th>Taken (10^4 \times [\text{Ce(IV)}]) (mol dm(^{-3}))</th>
<th>Unreacted (10^4 \times [\text{CYN-P}]) (mol dm(^{-3}))</th>
<th>Reacted (10^4 \times [\text{Ce(IV)}]) (mol dm(^{-3}))</th>
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Figure II (d)

LC-MS spectrum of oxidative product, hydroxy form of clindamycin due to oxidation of clindamycin phosphate by cerium(IV) in aqueous acidic medium at 298K.
An aqueous solution of the above reaction mixture was also tested for the presence of free PO$_4^{3-}$ ion by adding ammonium molybdate solution and conc. HNO$_3$, after cooling the mixture a canary yellow precipitate was obtained which confirms the presence of PO$_4^{3-}$ ion in the reaction mixture. Hence, it is concluded that the oxidative products of CYN-P were hydroxy form of clindamycin and phosphoric acid.

3.2. Reaction Order

The reaction orders with respect to [CYN-P], and [H$^+$] were determined from the plots of slopes of log $k_{obs}$ versus log concentration; these orders were obtained by varying concentration of reductant and acid intern while others keeping constant. Since, the first order plots were linear up to 90% completion of the reaction the initial rate method was not used to determine the order of such reactants.

3.2.1. Effect of [Ce(IV)]

The effect of [Ce(IV)] on rate of reaction was studied by varying its concentration in the range of 3.0 x 10$^{-5}$ to 2.0 x 10$^{-4}$ mol dm$^{-3}$ at fixed [CYN-P], [H$^+$] and ionic strength. The first order plots were found to be linear (Figure II (e), p. 63) and non-variation of $k_{obs}$ values at various [Ce(IV)] indicated the order in [Ce(IV)] as unity (Table II (c), p. 62).

3.2.2. Effect of [CYN-P]

The substrate effect on rate of reaction was studied by varying [CYN-P] in the range of 2.0 x 10$^{-4}$ to 2.0 x10$^{-3}$ mol dm$^{-3}$, keeping all other reactant concentrations constant. The $k_{obs}$ values were increased with an increase in
concentration of CYN-P (Table II (c), p. 62). From the plot of log $k_{obs}$ versus log [CYN-P], order in [CYN-P] was also found to be unity (Figure II (f), p. 64).

3.2.3. Effect of Acidity

The effect of acid concentration on rate of reaction was studied by using perchloric acid at constant concentrations of CYN-P and Ce(IV) and keeping a constant ionic strength of 0.5 mol dm$^{-3}$ at 298K. A constant amount of sulphuric acid coming from the stock solution of Ce(IV) is also present in all the cases. The in situ $[H^+]$ concentration in sulphuric acid- sulphate media was calculated by using known ionization constant [12] as follows;

\[ \begin{align*}
H_2SO_4 & \rightarrow HSO_4^- + H^+ \quad (i) \\
HSO_4^- & \leftrightarrow H^+ + SO_4^{2-} \quad (ii) \\
H^+ + SO_4^{2-} & \leftrightarrow HSO_4^- \quad (iii) \\
(a-x) & \quad (b-x) \quad (x)
\end{align*} \]

where, ‘a’ is total molar concentration of $H_2SO_4$ and $HClO_4$,

‘b’ is total molar concentration of $SO_4^{2-}$ ion obtained in the step (ii) and added to maintain constant ionic strength,

‘x’ is concentration of $HSO_4^-$.  

The $[HSO_4^-]$ was calculated from the equilibrium (iii)

\[ K = \frac{[HSO_4^-]}{[H^+][SO_4^{2-}]} \]

\[ K = \frac{x}{(a-x) (b-x)} \]

\[ 8.4 = \frac{x}{(a-x) (b-x)} \quad \therefore \quad K = 8.4 \]
Table II (c)

Effect of variation of [Ce(IV)], [CYN-P] and H⁺ on oxidation of clindamycin phosphate by cerium (IV) in aqueous acid medium at 298K.

\[ \text{I}= 0.5 \text{ /mol dm}^{-3} \]

<table>
<thead>
<tr>
<th>(10^3 \times [\text{Ce(IV)}]) (mol dm(^{-3}))</th>
<th>(10^3 \times [\text{CYN-P}]) (mol dm(^{-3}))</th>
<th>([\text{H}^+]) (mol dm(^{-3}))</th>
<th>(10^3 \times k_{\text{obs}} \text{(s}^{-1}))</th>
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<tbody>
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<td>9.51</td>
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<tr>
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</tr>
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<td>9.56</td>
</tr>
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<td>1.0</td>
<td>0.55</td>
<td>11.5</td>
</tr>
</tbody>
</table>

a. Experimental value

b. Calculated values: \( k_{\text{cal}} \) were calculated by using \( k_1=0.958 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \) for \([\text{CYN-P}]\) variations and for \([\text{H}^+]\) variation, \( k_1 \) is used along with \( k_2 = 2.6 \times 10^6 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1} \) from rate law (9) and (12), respectively.
Figure II (e)

First order plots of various concentrations of cerium(IV) on oxidation of clindamycin phosphate by cerium (IV) in aqueous acid medium at 298K.

\[ [\text{Ce(IV)}] = (1) \ 1.1 \times 10^{-4} \ (2) \ 1.3 \times 10^{-4} \ (3) \ 1.5 \times 10^{-4} \ (4) \ 1.7 \times 10^{-4} \ (5) \ 2.0 \times 10^{-4} \ / \ \text{mol dm}^{-3} \]

(Conditions as in Table II (c), p. 62)
Figure II (f)

Order plot of [CYN-P] and [H⁺] on oxidation of clindamycin phosphate by cerium (IV) in aqueous acid medium at 298K.
8.4x^2 - 26.2x + 16.8 = 0

Using following quadratic equation, [HSO_4^-] was calculated.

\[ x = \frac{-b\pm\sqrt{b^2-4ac}}{2a} \]

The rate constants increased with increase in [acid] (Table II (c), p. 62) and order was found to be 1.2 (Figure II (f), p. 64). The constant H_2SO_4 present in the Ce(IV) solution apart from HClO_4, enables formation of various sulphate complexes of Cerium(IV) such as Ce(OH)^3+, CeSO_4^{2+}, Ce(SO_4)_2, HCe(SO_4)_3^- and H_3Ce(SO_4)_4^- as shown in eqn. (2) to (6).

\[
\begin{align*}
\text{Ce}^{4+} + \text{H}_2\text{O} & \rightleftharpoons K_{OH} \text{Ce(OH)}^{3+} + \text{H}^+ \quad (2) \\
\text{Ce}^{4+} + \text{SO}_4^{2-} & \rightleftharpoons K_1 \text{Ce(SO}_4)^{2+} \quad (3) \\
\text{CeSO}_4^{2+} + \text{SO}_4^{2-} & \rightleftharpoons K_2 \text{Ce(SO}_4)_2 \quad (4) \\
\text{Ce(SO}_4)_2 + \text{HSO}_4^- & \rightleftharpoons K_3 \text{HCe(SO}_4)_3^- \quad (5) \\
\text{HCE(SO}_4)_3^- + \text{HSO}_4^- + \text{H}^+ & \rightleftharpoons K_4 \text{H}_{3}\text{Ce(SO}_4)_4^- \quad (6)
\end{align*}
\]

Since, total cerium(IV) is distributed between different species with the equilibrium constants, \( K_{OH} = 15 \), \( \beta_1(K_1) = 384.62 \), \( \beta_2 (K_1K_2) = 169.49 \), \( \beta_3 (K_1K_2K_3) = 101.17 \) and \( \beta_4 (K_1K_2K_3K_4) = 203.4 \) characterizing of such species may be calculated form eqn. (7).

\[
[\text{Ce(IV)}]_T = [\text{Ce}^{4+}]_t + \frac{K_{OH}}{[\text{H}^+]^1} + \beta_1[\text{SO}_4^{2-}] + \beta_2[\text{SO}_4^{2-}]^2 + \beta_3[\text{SO}_4^{2-}]^3[\text{H}^+] + \beta_4[\text{SO}_4^{2-}]^2[\text{HSO}_4^-]^2[\text{H}^+] \quad (7)
\]
The formation of Ce(OH)$_2^{2+}$ occurs to a much smaller concentration in comparison with the above species. Hence, it is neglected. The results of such calculations are given in Table II (d), (p. 67) and are used to draw Figure II (g), (p. 68). It is seen that, among the different species of Ce(IV), H$_3$Ce(SO$_4$)$_4$ is an active species which shows parallelism with variation of $k_{obs}$ with acidity.

3.2.4. Effect of Initially Added Product

The influence of initially added products, Ce(III) and N-(2-chloro-1-(tetrahydro-3,4,5-trihydroxy-6-(methylthio)-2H-pyran-2-yl)propyl)-4-propylpyrrolidine-2-carboxamide on rate of reaction was studied in their concentration range, $7.0 \times 10^{-5}$ to $2.3 \times 10^{-4}$ by keeping all other reactants, acidity and ionic strength constant. It is observed that both the added products initially, did not influence the rate of reaction (Table II (e), p. 69).

3.2.5. Effect of Ionic Strength and Dielectric Constant of the medium

The effect of change in dielectric constant of the medium on reaction rate was studied by using different compositions (v/v) of acetic acid and water. The $k_{obs}$ values were found to vary little with a decrease in dielectric constant of the medium (Table II (f), p. 70) (acetic acid + water). The dielectric constants of their different compositions were calculated by considering their D in pure form using the equation:

$$D = D_1V_1 + D_2V_2$$  

Where, $V_1$ and $V_2$ are volume fractions and $D_1$ and $D_2$ are dielectric constants of water and acetic acid as 78.5 and 6.15 at 298K, respectively. Earlier, it
Table II (d)

Effect of [H+] on cerium (IV) species and on $k_{obs}$ of oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 298K.

$$[\text{Ce(IV)}] = 1.3 \times 10^{-4}; \quad [\text{CYN-P}] = 1.0 \times 10^{-3};$$

$$\text{H}_2\text{SO}_4 = 0.05; \quad \text{I} = 0.5 / \text{mol dm}^{-3}$$

<table>
<thead>
<tr>
<th>HClO₄</th>
<th>[H⁺]</th>
<th>[SO₄²⁻] x10²</th>
<th>[HSO₄⁻] x10²</th>
<th>$\dot{a}_0$ x10²</th>
<th>$\dot{a}_\text{OH}$ x10¹</th>
<th>$\dot{a}_1$ x10⁴</th>
<th>$\dot{a}_2$ x10⁷</th>
<th>$\dot{a}_3$ x10⁷</th>
<th>$\dot{a}_4$ x10⁷</th>
<th>$k_{obs}$ x10⁴ (s⁻¹)</th>
<th>*$k_{cal}$ x10⁴ (s⁻¹)</th>
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</tr>
<tr>
<td>0.40</td>
<td>0.460</td>
<td>1.027</td>
<td>3.973</td>
<td>2.663</td>
<td>8.677</td>
<td>10.52</td>
<td>4.760</td>
<td>1.129</td>
<td>4.149</td>
<td>9.56</td>
<td>10.7</td>
</tr>
<tr>
<td>0.45</td>
<td>0.509</td>
<td>0.947</td>
<td>4.053</td>
<td>2.933</td>
<td>8.634</td>
<td>10.68</td>
<td>4.457</td>
<td>1.078</td>
<td>4.477</td>
<td>10.7</td>
<td>11.6</td>
</tr>
<tr>
<td>0.50</td>
<td>0.558</td>
<td>0.878</td>
<td>4.122</td>
<td>3.548</td>
<td>8.594</td>
<td>10.81</td>
<td>4.183</td>
<td>1.029</td>
<td>4.766</td>
<td>11.5</td>
<td>12.3</td>
</tr>
</tbody>
</table>

$\dot{a}_0$, $\dot{a}_\text{OH}$, $\dot{a}_1$, $\dot{a}_2$, $\dot{a}_3$ and $\dot{a}_4$ are the fractions of total cerium(IV) of the species Ce⁴⁺, Ce(OH)³⁺, CeSO₄²⁺, Ce(SO₄)₂, HCe(SO₄)₃⁻ and H₃Ce(SO₄)₄⁻ respectively.

*$k_{cal}$ are the rate constants regenerated by using the values of K_OH, β₁, β₂, β₃, β₄ and $k_2= 2.6 \times 10^{6}$ dm³ mol⁻¹ s⁻¹ from rate law (12).
Figure II (g)

Variation of concentration of cerium(IV) species at various [H\(^+\)] along with \(k_{\text{obs}}\) values in the oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 298K.

(Conditions as in Table II (d), p. 67)
Table II (e)

Effect of variation of concentrations of product, Ce(III) on the oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 298K.

\[
\begin{align*}
[\text{Ce(IV)}] &= 1.3 \times 10^{-4}; \\
[\text{CYN-P}] &= 1.0 \times 10^{-3}; \\
[\text{HClO}_4] &= 0.4; \\
[\text{H}_2\text{SO}_4] &= 0.05; \\
I &= 0.50 / \text{mol dm}^{-3}
\end{align*}
\]

<table>
<thead>
<tr>
<th>(10^4 \times [\text{Ce(III)}] \text{ mol dm}^{-3})</th>
<th>(10^5 \times k_{\text{obs}} \text{ (s}^{-1}\text{)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.7</td>
<td>9.02</td>
</tr>
<tr>
<td>0.9</td>
<td>9.21</td>
</tr>
<tr>
<td>1.1</td>
<td>9.59</td>
</tr>
<tr>
<td>1.3</td>
<td>9.15</td>
</tr>
<tr>
<td>1.5</td>
<td>9.15</td>
</tr>
<tr>
<td>1.7</td>
<td>9.21</td>
</tr>
<tr>
<td>1.9</td>
<td>9.40</td>
</tr>
<tr>
<td>2.1</td>
<td>9.21</td>
</tr>
<tr>
<td>2.3</td>
<td>9.15</td>
</tr>
</tbody>
</table>
Table II (f)

Effect of Ionic strength (I) and Dielectric constant (D) of the medium on oxidation of clindamycin phosphate by cerium (IV) in aqueous acid medium at 298K.

\[ [\text{Ce(IV)}] = 1.3 \times 10^{-4}; \quad [\text{CYN-P}] = 1.0 \times 10^{-3}; \]
\[ [\text{HClO}_4] = 0.4; \quad \text{H}_2\text{SO}_4 = 0.05 \text{ mol dm}^{-3} \]

<table>
<thead>
<tr>
<th>Ionic strength (D = 78.5)</th>
<th>Dielectric constant (I = 0.5 mol dm$^{-3}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (mol dm$^{-3}$)</td>
<td>√I</td>
</tr>
<tr>
<td>0.4</td>
<td>0.63</td>
</tr>
<tr>
<td>0.5</td>
<td>0.71</td>
</tr>
<tr>
<td>0.6</td>
<td>0.77</td>
</tr>
<tr>
<td>0.7</td>
<td>0.84</td>
</tr>
<tr>
<td>0.8</td>
<td>0.89</td>
</tr>
<tr>
<td>0.9</td>
<td>0.99</td>
</tr>
<tr>
<td>1.0</td>
<td>1.00</td>
</tr>
</tbody>
</table>
was verified that there was no reaction of the solvent with oxidant under experimental conditions used.

Effect of ionic strength was studied by varying sodium perchlorate concentration in the reaction medium. Ionic strength of the reaction medium was varied from 0.4 to 1.0 mol dm\(^{-3}\) by considering a contribution of SO\(_4^{2-}\) from H\(_2\)SO\(_4\) in the stock solution of Ce(IV) at constant concentrations of Ce (IV), CYN-P and perchloric acid. It was found that the rate constants were increased with an increase in [NaClO\(_4\)] (Table II (f), p. 70) and a plot of log \(k_{\text{obs}}\) versus \(\sqrt{I}\) leads a positive slope (1.0) (Figure II (h), p. 72).

3.2.6. Effect of Temperature

The kinetics was also studied at different temperatures at a constant concentration of reactants and other conditions being constant. \(k_{\text{obs}}\) values were increased with an increase in temperature. Hence, \(k_{\text{obs}}\) at various temperatures are calculated (Table II (g), p. 73). From the Arrhenius plot of log \(k_{\text{obs}}\) versus \(1/T\) (Figure II (i), p. 72), activation energy, \(E_a\) and other activation parameters \(\Delta H^\ddagger, \Delta S^\ddagger, \Delta G^\ddagger\) and log \(A\) are calculated (Table II (h), p. 73).

The activation parameters for the reaction were studied by using linear regression analysis (also known as method of least square). In generalized notation, the formula for the straight line is \(y = ax + b\). The most tractable form of linear regression analysis assumes that values of the independent variables ‘\(x\)’ are known without error and that experimental error is manifested only in values of the dependent variable ‘\(y\)’. Most sets of kinetic data approximate this situation, in as much as times of observation are more accurately measurable
Figure II (h)

Effect of Ionic strength of the medium on oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 298K.

(Conditions as in Table II (f), p. 70)

![Graph showing effect of ionic strength on oxidation](image)

Figure II (i)

Arrhenius plot of oxidation of clindamycin phosphate by cerium(IV) in aqueous acid media.

(Conditions as in Table II (g), p. 73)

![Arrhenius plot](image)
Table II (g)

Effect of temperature on oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium.

\[ [\text{Ce(IV)}] = 1.3 \times 10^{-4}; \quad [\text{CYN-P}] = 1.0 \times 10^{-3}; \]
\[ [\text{HClO}_4] = 0.4 \text{ mol dm}^{-3}; \quad [\text{H}_2\text{SO}_4] = 0.05; \]
\[ I = 0.5/ \text{ mol dm}^{-3} \]

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>(10^3 \times k_{\text{obs}} \text{ (s}^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>298</td>
<td>0.95</td>
</tr>
<tr>
<td>303</td>
<td>1.02</td>
</tr>
<tr>
<td>308</td>
<td>1.73</td>
</tr>
<tr>
<td>313</td>
<td>2.47</td>
</tr>
<tr>
<td>318</td>
<td>3.88</td>
</tr>
<tr>
<td>323</td>
<td>5.33</td>
</tr>
<tr>
<td>328</td>
<td>6.47</td>
</tr>
</tbody>
</table>

Table II (h)

Activation parameters for the oxidation of clindamycin phosphate by cerium(IV) in aqueous acid media.

<table>
<thead>
<tr>
<th>Activation parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E_a \text{ (kJ mol}^{-1})</td>
<td>57 ± 2</td>
</tr>
<tr>
<td>(\Delta H^# \text{ (kJ mol}^{-1})</td>
<td>54.5 ± 2</td>
</tr>
<tr>
<td>(\Delta S^# \text{ (J K}^{-1} \text{ mol}^{-1})</td>
<td>-117 ± 4</td>
</tr>
<tr>
<td>(\Delta G^# \text{ (kJ mol}^{-1})</td>
<td>103 ± 3</td>
</tr>
<tr>
<td>(\log A)</td>
<td>6.7 ± 0.2</td>
</tr>
</tbody>
</table>
than the chemical or physical quantities related to reactant concentrations. The straight line selected by the common linear regression analysis is that which minimizes the sum of the squares of the derivations of the ‘y’ variable from the line. The slope ‘a’ and intercept ‘b’ parameters for the above equation can be calculated by linear regression analysis by any of several mathematically equivalent but different looking experiments.

Most familiar are

\[
\text{Slope: } a = \frac{n\Sigma xy - \Sigma x \Sigma y}{n\Sigma x^2 - (\Sigma x)^2}
\]

\[
\text{Intercept: } b = \frac{\Sigma y \Sigma x^2 - \Sigma x \Sigma xy}{n\Sigma x^2 - (\Sigma x)^2}
\]

where ‘n’ is the number of data points and summation are for all data points in the set. These data were subjected to least square analysis and verified with experimental values. The activation energy was evaluated from the slope of plot of \( \log k_{\text{obs}} \) versus \( \frac{1}{T} \) as shown in Figure II (i), (p. 72).

\[E_a = - 2.303 \times R \times \text{slope}\]

The other activation parameters were calculated as follows.

The Arrhenius factor ‘A’ was calculated by,

\[
\log A = \log k_{\text{obs}} + \frac{E_a}{2.303RT}
\]

The entropy of activation was calculated by using the equation,

\[
\log k_{\text{obs}} = \left( \frac{kT}{h} \right) e^{\Delta S^o/R} e^{-E_a/RT}
\]

\[
2.303 \log k_{\text{obs}} = 2.303 \log \left( \frac{kT}{h} \right) + \frac{\Delta S^o}{R} - \frac{E_a}{RT}
\]
CHAPTER II

On substituting the universal gas constant ‘R’ as 8.314 J K\(^{-1}\) mol\(^{-1}\), the Boltzmann constant (k) = 1.3807 \times 10\(^{-23}\) J K\(^{-1}\) and the Planck’s constant (h) = 6.63 \times 10\(^{-34}\) J s.

\[
\frac{\Delta S^\#}{2.303 R} = \log k_{obs} - \log \frac{k}{h} - \log T + \frac{E_a}{2.303 RT}
\]

The \(k_{obs}\) should be in s\(^{-1}\), the temperature in Kelvin, \(E_a\) results in J mol\(^{-1}\); then \(\Delta S^\#\) J K\(^{-1}\) mol\(^{-1}\). The enthalpy of activation was calculated by,

\[
\Delta H^\# = E_a - RT \text{ and the free energy of activation was from } \Delta G^\# = \Delta H^\# - T \Delta S^\#.
\]

3.2.7. Polymerization Study

Ce(IV) is a single equivalent oxidant. Hence, intervention of free radical, generated from organic compound is expected. In view of this, acrylonitrile was used as a free radical scavenger and tested in the reaction mixture as follows. The reaction mixture was mixed with acrylonitrile monomer and kept for 24 hrs. under inert atmosphere. On dilution with methanol, a white
precipitate of polymer was formed, indicating the intervention of free radicals in the reaction. The experiment of either Ce(IV) or CYN-P with acrylonitrile alone did not induce the polymerization under similar condition as those induced with reaction mixture. Initially added acrylonitrile also decreases the rate indicating a free radical intervention [13].

4. DISCUSSION

The reaction between clindamycin phosphate and cerium(IV) in aqueous perchloric acid medium has a stoichiometry of 1:2 with unit order each in cerium(IV) and clindamycin phosphate. No effect of initially added product was observed. These experimental results can be accommodated in Scheme 1. In Scheme 1, it is suggested that clindamycin phosphate first reacts with Ce(IV) to lead a clindamycin cation and a free radical, in a slow step. This free radical further reacts with another molecule of Ce (IV) in fast step to give H₃PO₄ and Ce(III), and clindamycin cation under goes hydrolysis to give product, hydroxy form of clindamycin.

\[
\begin{align*}
\text{Ce (IV)} + \text{CYN-P} & \xrightarrow[k_1]{\text{slow}} \text{CYN}^+ + \text{Ce(III)} + \text{H}_2\text{PO}_4^- \\
\text{H}_2\text{PO}_4^- + \text{Ce(IV)} + \text{H}_2\text{O} & \xrightarrow[\text{fast}]{\text{fast}} \text{H}_3\text{PO}_4 + \text{OH}^- + \text{Ce(III)} \\
\text{CYN}^+ + \text{H}_2\text{O} & \xrightarrow[\text{fast}]{\text{fast}} \text{CYN(OH)} + \text{H}^+ \\
\end{align*}
\]

Scheme 1

Since scheme 1 is in accordance with the generally well accepted principle of non- complementary oxidations taking place in a sequence of one
electron step, the reaction between the substrate and oxidant should yield a radical intermediate. A free radical scavenging experiment revealed such a possibility. This type of radical intermediate has also been observed in earlier work [14] on oxidation of various organic substrates by Ce(IV) in acidic medium. The orders in [Ce(IV)] and [CNY-P] suggest that reaction follows with an outer sphere mechanism, and formation of complex between Ce(IV) is ruled out which is evidenced by the linear plot of $1/k_{obs}$ versus $1/[CYN-P]$ without intercept as against the non-zero intercept of Michalis- Menten plot for the complex between the oxidant and reductant.

Scheme 1 leads to the following rate law, which explains the observed unit order each in [CYN-P] and [Ce(IV)].

$$\text{Rate} = k_1 [\text{Ce(IV)}] [\text{CYN-P}]$$

$$\frac{\text{Rate}}{[\text{Ce(IV)}]} = k_1 [\text{CYN-P}] \quad (8)$$

$$k_{obs} = k_1 [\text{CYN-P}] \quad (9)$$

According to eqn. (9), plot of $k_{obs}$ versus [CYN-P] should be linear and is verified as in Figure II (j), (p. 78). The slope of such plot leads to the value of $k_1$ as 0.958 (± 0.04) dm³ mol⁻¹ s⁻¹. Using this value in eqn. (9), rate constants were calculated over a range of different concentrations for all the variations of [CYN-P] and compared with experimental values (Table II (c), p. 62).
**Figure II (j)**

Verification of rate law (9) on oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 298K.

(Conditions as in Table II (c), p. 62)
There is a reasonable agreement between calculated and experimental rate constants, supporting the proposed mechanism of Scheme 1.

Nevertheless, Scheme 1 explains, free radical path and unit order each in \([\text{Ce(IV)}]\) and \([\text{CYN-P}]\) but will not account the effect of \([\text{H}^+]\) on rate of reaction, having the order of 1.2 on it. Its effect can be explained by considering the various species of Ce(IV) in sulphuric acid - sulphate media as in equilibria (2 - 6). The active species involved in the mechanism can be understood as follows: the variation of rate constant, and the concentration of \(\text{H}_3\text{Ce(SO}_4\text{)}_4^-\) with increasing acidity, are compared and it is seen that a good parallelism between the two is obtained (Table II (d), p. 67 and Figure II (g), p. 68). \(\text{H}_3\text{Ce(SO}_4\text{)}_4^-\) is considered to be the most active species of Ce(IV) in acid - sulphate media as the plot of \(k_{\text{obs}}\) versus \([\text{H}^+]\) is linear (Figure II (g), p. 68). Hence, effect of increase in [acid] on reaction is well accommodated by the formation of species \(\text{H}_3\text{Ce(SO}_4\text{)}_4^-\). The mechanism of reaction involving species, \(\text{H}_3\text{Ce(SO}_4\text{)}_4^-\) and CYN-P may be shown in detail as in Scheme 2. The above species formed in a prior equilibrium, which oxidizes Clindamycin phosphate in a slow step yielding a cation and a free radical.

\[
\begin{align*}
\text{Ce}^{4+} + 2\text{SO}_2^- + 2\text{HSO}_4^- + \text{H}^+ & \overset{\beta_4}{\longrightarrow} \text{H}_3\text{Ce(SO}_4\text{)}_4^- \\
\text{H}_3\text{Ce(SO}_4\text{)}_4^- & \overset{k_2\text{ slow}}{\longrightarrow} \text{Ce}^{3+} + 2\text{HSO}_4^- + 2\text{SO}_2^- + \text{H}^+ \\
\end{align*}
\]
Scheme 2 explains a unit fractional order in $[H^+]$ and free radical intervention.

The rate law for Scheme 2 can be derived as

\[
\text{Rate} = k_2 [H_3\text{Ce}(\text{SO}_4)_4]_f [\text{CYN-P}]_f \tag{10}
\]

However, $[\text{Ce(IV)}]_T$ is a sum of all the various $[\text{Ce(IV)}]$ sulphate species, $\text{CeSO}_4^{2+}$, $\text{Ce(SO}_4)_2$, $\text{HCe(SO}_4)_3^-$ and $\text{H}_3\text{Ce(SO}_4)_4^-$, and hydroxide species, $\text{Ce(OH)}^{3+}$. They are computed from their equilibrium steps (2 - 6).

Using eqn. (7), $[\text{Ce(IV)}]_T$ was calculated. On incorporating such species of $[\text{Ce(IV)}]$ for $[\text{Ce(IV)}]_f$ as $[\text{Ce(IV)}]_T$ in the rate law (10) and $[\text{CYN-P}]_f$ is considered as $[\text{CYN-P}]_T$ the following rate law (11) is obtained.

\[
\text{rate} = \frac{k_2 \beta_4 [\text{Ce}^{4+}] [\text{SO}_4^{2-}]^2 [\text{HSO}_4^-]^2 [H^+] [\text{CYN-P}]}{1 + \frac{K_{\text{OH}}}{[H^+]} + \frac{\beta_1 [\text{SO}_4^{2-}] + \beta_2 [\text{SO}_4^{2-}]^2 + \beta_3 [\text{SO}_4^{2-}]^2 [\text{HSO}_4^-] + \beta_4 [\text{SO}_4^{2-}]^2 [\text{HSO}_4^-]^2 [H^+]}{[H^+]}}
\]
rate /[Ce(IV)] = \( k_{\text{obs}} = \text{RHS} \) \hspace{1cm} (11)

The above rate law is verified by rearranging the above equation in the following form

\[
\frac{k_{\text{obs}} \times A}{[\text{SO}_4^{2-}] \times [\text{HSO}_4^-]^2 \times [\text{CYN-P}]} = k_2 \beta_4 [\text{H}^+] \hspace{1cm} (12)
\]

Where, \( A = \left( 1 + \frac{K_{\text{OH}}}{[\text{H}^+]} + \beta_1 \times [\text{SO}_4^{2-}] + \beta_2 \times [\text{SO}_4^{2-}]^2 + \beta_3 \times [\text{SO}_4^{2-}]^2 \times [\text{HSO}_4^-] + \beta_4 \times [\text{SO}_4^{2-}]^2 \times [\text{HSO}_4^-]^2 \times [\text{H}^+] \right) \)

The plot of LHS versus RHS of eqn. (12) at various [H\(^+\)] at a constant [CYN-P] leads a linear plot (Figure II (k), p. 82). Slope of such a plot leads the value of \( k_2 \beta_4 \) by which \( k_2 \) was evaluated as \( 2.6 \times 10^6 \ (\pm \ 10^2) \ \text{dm}^3 \ \text{mol}^{-1} \ \text{s}^{-1} \). Using this value in eqn. (11), \( k_{\text{cal}} \) values are regenerated which are in close agreement with the \( k_{\text{obs}} \) values at various experimental conditions, fortifies Scheme 2. Increase in rate constants with an increase in ionic strength may be due to involvement of one ionic species of Ce(IV) and a polar molecule of CYN-P in rate determining step. Non-influence of dielectric constant of solvent on rate of reaction may be due to polar and non-polar nature of CYN-P which may be soluble both in highly polar solvent like water and less polar solvent like acetic acid thereby its activated complex also.

The small value of \( k_1 = 0.958 \ \text{dm}^3 \ \text{mol}^{-1} \ \text{s}^{-1} \) clearly supports the moderately higher value of \( \Delta E_a = 57 \ \text{kJ mol}^{-1} \) obtained experimentally. The \( \Delta S^e = -103 \ \text{J K}^{-1} \ \text{mol}^{-1} \) indicates that the activated complex is more rigid than its reactants. Log A = 6.7 emphasizes that the oxidation of CYN-P by Ce(IV) occurs through outer sphere mechanism.
Figure II (k)

Verification of rate law (11) on oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 298K.

(Conditions as in Table II (c), p. 62)
5. CONCLUSION

The oxidation of CYN-P in aqueous acid medium by Ce(IV) follows a second order kinetics with outer sphere mechanism which is evidenced by a unit order each in oxidant and reductant. The oxidation occurs through the formation of free radical by abstracting electron in a slow step. The more than unit order in $[H^+]$ indicates the protonated Ce(IV) sulphate complex involved in the rate determining step. Among the various forms of protonated Ce(IV) sulphate complexes, $H_3Ce(SO_4)_4^-$ was likely to be the active species.
6. REFERENCES


