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Oxidation of clindamycin phosphate by cerium(IV) in perchloric acid medium – A kinetic and mechanistic approach



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KEYWORDS

Ce(IV);
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Abstract Methyl 7-chloro-6,7,8-trideoxy-6-[(2S,4R)-1-methyl-4-propylpyrrolidine-2-carboxamido]-1-thio-1-threo-D-galactooctapyranoside monohydrochloride, commonly called clindamycin phosphate (CYN-P) used largely as an antibiotic for the treatment of serious infections caused by susceptible Gram-positive bacteria and anaerobic bacteria was oxidized by using Ceric ammonium sulphate (Ce(IV)) in perchloric acid medium. Progress of the reaction was followed by measuring the decrease in absorbance of ceric ammonium sulphate at 360 nm. The reaction was found to be first order each in [CYN-P] and [Ce(IV)]. Order in [HClO₄] was calculated as 0.8. The reactive species of Ce(IV) appears to be H₃Ce(SO₄)₄⁻. Stoichiometry of the reaction was found to be 2:1 of [Ce(IV)]:[CYN-P]. Initially added product did not alter the rate of reaction. A free radical mechanism was proposed, and rate law was derived and verified. The activation parameters, ΔH^\ddagger , ΔS^\ddagger , ΔG^\ddagger and $\log A$ were found to be 54.7 kJ mol⁻¹, -117 J K⁻¹ mol⁻¹, 103 kJ mol⁻¹ and 7, respectively. © 2013 Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

1. Introduction

Cerium(IV) is a strong one electron oxidant used as an analytical reagent especially in acid media (Richardson, 1965). It is also used in kinetic studies on oxidation of different substrates in perchloric acid medium (Domagala et al., 1998). The mechanism of 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 ceric hydroxide ion, whereas in sulphuric acid medium its active forms were reported to be H₃[Ce(SO₄)₄]⁻ or H[Ce(SO₄)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 catalysed 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-galactooctapyranoside monohydro chloride

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Table 1 Effect of variation of [Ce(IV)] and [CYN-P] on oxidation of clindamycin phosphate by Ce (IV) in aqueous acid medium at 25 °C.

[Ce(IV)] × 10 ⁴ (mol dm ⁻³)	[CYN-P] × 10 ³ (mol dm ⁻³)	$k \times 10^4 \text{ s}^{-1}$	
		Experimental ^a	Calculated ^b
0.3	1.0	9.51	—
0.5	1.0	9.56	—
0.7	1.0	9.55	—
0.9	1.0	9.55	—
1.1	1.0	9.56	—
1.3	1.0	9.56	—
1.5	1.0	9.55	—
1.7	1.0	9.56	—
2.0	1.0	9.56	—
1.3	0.2	1.68	1.92
1.3	0.4	2.92	3.83
1.3	0.6	4.66	5.75
1.3	0.8	7.05	7.60
1.3	1.0	9.56	9.59
1.3	1.2	11.6	11.5
1.3	1.4	13.4	13.4
1.3	1.6	15.4	15.3
1.3	1.8	16.3	17.3
1.3	2.0	18.1	19.2

[H₂SO₄] = 0.05 mol dm⁻³; [H⁺] = 0.46 mol dm⁻³; I = 0.5 mol dm⁻³.

^a Experimental.

^b Calculated: k_{obs} were calculated by using $k_1 = 0.9583 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$, $k_2 = 2582990 \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ from rate law (9) and (11), respectively.

(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 (Mazur et al., 1999). CYN-P and several macrolide antibiotics have proven effective for the treatment of AIDS- toxoplasmosis, usually in combination with pyrimethamine (Dannemann et al., 1992; Katlama, 1991; Luft et al., 1993). These compounds are known to block protein synthesis in bacteria by interacting with peptidyl transferase domain of 23S rRNA (Cundliffe, 1990).

2. Experimental

2.1. Materials

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 melting point and TLC. Aging of aqueous solution of CYN-P was tested by performing the kinetics of oxidation at different intervals of time from hours to days. It was observed that its kinetics of oxidation stands remain identical. However, stock solutions are prepared afresh 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 H₂SO₄ and kept for over night. 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 exposed to sunlight.

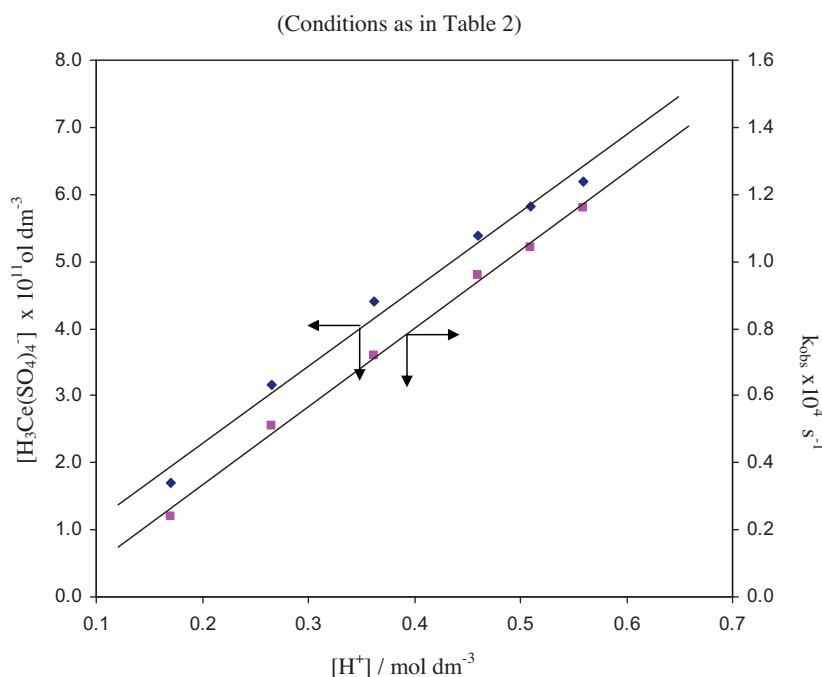


Figure 1 Variation of concentration of Ce(IV) species at various [H⁺] along with k_{obs} values in the oxidation of clindamycin phosphate by Ce(IV) in aqueous acid medium.

Table 2 Effect of $[H^+]$ on cerium (IV) species and on k_{obs} of oxidation of clindamycin phosphate by Ce (IV) in aqueous acid medium at 25 °C.

HClO ₄	$[H^+]$	$[SO_4^{2-}]$	$[HSO_4]$	α_o	α_{OH}	α_1	α_2	α_3	α_4	k_{obs}	k_{cal}^*
		$\times 10^2$	$\times 10^2$	$\times 10^2$	$\times 10^1$	$\times 10^2$	$\times 10^4$	$\times 10^5$	$\times 10^7$	$\times 10^4$	$\times 10^4$
0.1	0.17055	2.055	2.945	1.032	9.074	8.156	7.387	1.298	1.311	2.68	3.39
0.2	0.26548	1.548	3.452	1.572	8.898	9.377	6.396	1.124	2.428	5.13	6.27
0.3	0.36236	1.236	3.764	2.120	8.774	10.080	5.492	1.233	3.383	7.64	8.73
0.4	0.46027	1.027	3.973	2.663	8.677	10.517	4.760	1.129	4.149	9.56	10.70
0.45	0.50947	0.947	4.053	2.933	8.634	10.681	4.457	1.078	4.477	10.70	11.61
0.5	0.55878	0.878	4.122	3.548	8.594	10.812	4.183	1.029	4.766	11.51	12.32

α_o , α_1 , α_2 , α_3 and α_4 are the fractions of total cerium(IV) of the species Ce^{4+} , $Ce(OH)^{3+}$, $CeSO_4^{2+}$, $Ce(SO_4)_2$, $HCe(SO_4)_3^-$ and $H_3Ce(SO_4)_4^-$, respectively.

$[Ce(IV)] = 1.3 \times 10^{-4} \text{ mol dm}^{-3}$; $I = 0.5 \text{ mol dm}^{-3}$; $[CYN-P] = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$; $H_2SO_4 = 0.05 \text{ mol dm}^{-3}$.

* k_{cal} are the rate constants regenerated by using the values of K_{OH} , β_1 , β_2 , β_3 , β_4 and k_2 .

Ce(III) solution was prepared by dissolving cerium(III) acetate in water. The $[H^+]$ was maintained by adding requisite concentration of HClO₄ by subtracting the $[H^+]$ added due to H₂SO₄ present in Ce(IV) stock solution. Similarly ionic strength was maintained by using aqueous solution of NaClO₄ after deducting the concentration of SO₄²⁻ due to H₂SO₄ 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 HClO₄ and NaClO₄. 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 25 ± 0.1 °C 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 λ , 360 nm as a function of time. The obedience to Beer's law of absorption of Ce(IV) at 360 nm in the concentration range of 1.0 × 10⁻⁵ to 3.0 × 10⁻⁴ mol dm⁻³ under the reaction conditions has been tested earlier ($\epsilon = 3585 \pm 10 \text{ dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$). First order plot of log abs. *versus* time was found to be linear up to 90% completion of reaction. 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 ± 3%.

3. Results

The reaction orders were determined from the slopes of log k_{obs} *versus* log concentration plots by varying the concentration of reductant and acid in turn while keeping others constant.

3.1. Effect of [CYN-P]

The substrate effect on rate of reaction was studied by varying [CYN-P] in the range of 2.0 × 10⁻⁴ to 2.0 × 10⁻³ mol dm⁻³, keeping all other reactant concentrations constant. The k_{obs} values were increased with an increase in concentration of CYN-P (Table 1). From the plot of log k_{obs} *versus* log [CYN-P], order in [CYN-P] was also found to be unity.

3.2. Effect of [Ce(IV)]

The effect of [Ce(IV)] on rate of reaction was studied by varying its concentration in the range of 1.0 × 10⁻⁵ to 2.0 × 10⁻⁴ mol dm⁻³ at fixed [CYN-P], $[H^+]$ and ionic strength. The first order plots were found to be linear and non-variation of k_{obs} values at various [Ce(IV)] indicated the order in [Ce(IV)] as unity (Table 1).

3.3. Effect of acidity

The effect of acid concentration on rate of reaction was studied by using perchloric acid at constant concentrations of CYN-P

Table 3 Effect of ionic strength and dielectric constant of the medium on oxidation of clindamycin phosphate by Ce (IV) in aqueous acid medium at 25 °C.

I	\sqrt{I}	$k_{obs} \times 10^3 (s^{-1})$	% of acetic acid in water(v/v)	D	$k_{obs} \times 10^3 (s^{-1})$
$D = 78$			$I = 0.5$		
0.4	0.63	0.78	0	78.5	0.96
0.5	0.71	0.96	1	74.9	0.43
0.6	0.77	1.10	2	71.3	0.41
0.7	0.84	1.31	3	67.6	0.48
0.8	0.89	1.48	4	64.0	0.48
0.9	0.99	1.67	5	60.4	0.46
1.0	1.00	1.94	–	–	–

$[Ce(IV)] = 1.3 \times 10^{-4} \text{ mol dm}^{-3}$; $[H^+] = 0.46 \text{ mol dm}^{-3}$; $[CYN-P] = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$; $H_2SO_4 = 0.05 \text{ mol dm}^{-3}$.

Table 4a Effect of temperature on oxidation of clindamycin phosphate by Ce(IV) in aqueous acid medium.

Temp (K)	$k_{\text{obs}} \times 10^3 \text{ (s}^{-1}\text{)}$
298	0.95
303	1.02
308	1.73
313	2.47
318	3.88
323	5.33
328	6.47

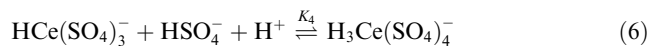
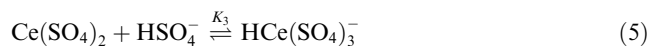
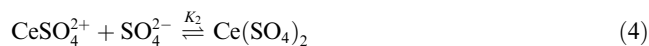
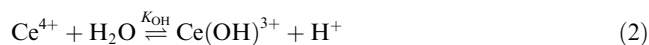
$[\text{Ce(IV)}] = 1.3 \times 10^{-4} \text{ mol dm}^{-3}$; $[\text{CYN-P}] = 1.0 \times 10^{-3} \text{ mol dm}^{-3}$;
 $[\text{H}^+] = 0.46 \text{ mol dm}^{-3}$; $[\text{H}_2\text{SO}_4] = 0.05 \text{ mol dm}^{-3}$;
 $I = 0.5 \text{ mol dm}^{-3}$.

Table 4b Activation parameters.

Activation parameters	Values
$E_a \text{ (kJ mol}^{-1}\text{)}$	57.23 ± 1.0
$\Delta H^\ddagger \text{ (kJ mol}^{-1}\text{)}$	54.75 ± 1.0
$\Delta S^\ddagger \text{ (JK}^{-1} \text{ mol}^{-1}\text{)}$	-116.9 ± 1.5
$\Delta G^\ddagger \text{ (kJ mol}^{-1}\text{)}$	102.9 ± 2
$\text{Log } A$	6.7 ± 0.1

and Ce(IV) and keeping a constant ionic strength of 0.5 mol dm^{-3} at 25°C . A constant amount of sulphuric acid coming from the stock solution of Ce(IV) is also present in all the cases. The *in situ* $[\text{H}^+]$ concentration in sulphuric acid-sulphate media was calculated by using known ionization constant (Vogel, 1973). The rate constants increased with an increase in [acid] (Table 1) and order was found to be 1.2. 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+} , $\text{Ce(SO}_4)_2$, $\text{HCe(SO}_4)_3^-$ and $\text{H}_3\text{Ce(SO}_4)_4^-$ as shown in Eqs. (2)–(6).



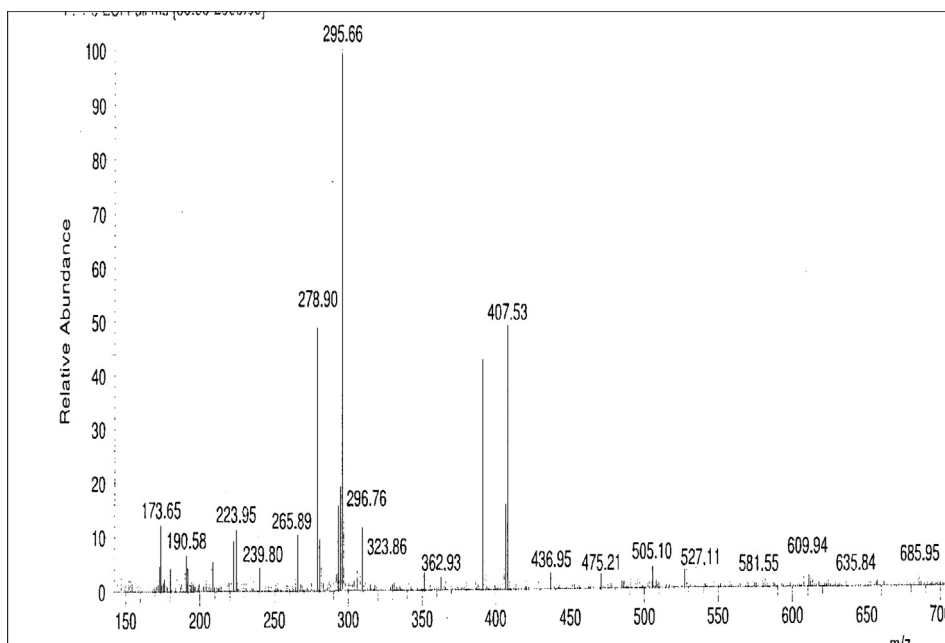
Since, total cerium(IV) is distributed between different species with the equilibrium constants, $K_{\text{OH}} = 15$, $\beta_1(K_1) = 384.62$, $\beta_2(K_1K_2) = 169.49$, $\beta_3(K_1K_2K_3) = 101.17$ and $\beta_4(K_1K_2K_3K_4) = 203.4$ characterizing of such species may be calculated from Eq. (7).

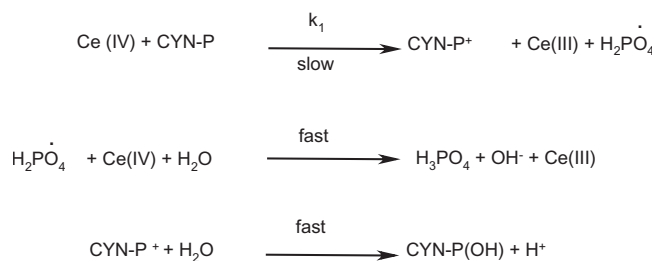
$$[\text{Ce(IV)}]_T = [\text{Ce}^{4+}] \left[1 + \frac{K_{\text{OH}}}{[\text{H}^+]} + \beta_1[\text{SO}_4^{2-}] + \beta_2[\text{SO}_4^{2-}]^2 + \beta_3[\text{SO}_4^{2-}]^2[\text{HSO}_4^-] + \beta_4[\text{SO}_4^{2-}]^2[\text{HSO}_4^-]^2[\text{H}^+] \right] \quad (7)$$

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 2 and are used to draw Fig. 1. It is seen that, among the different species of Ce(IV), $\text{H}_3\text{Ce(SO}_4)_4^-$ is an active species which shows parallelism with variation of k_{obs} with acidity.

3.4. Effect of dielectric constant and Ionic strength

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 3)

**Figure 2** LC-MS spectra of clindamycin hydroxide.



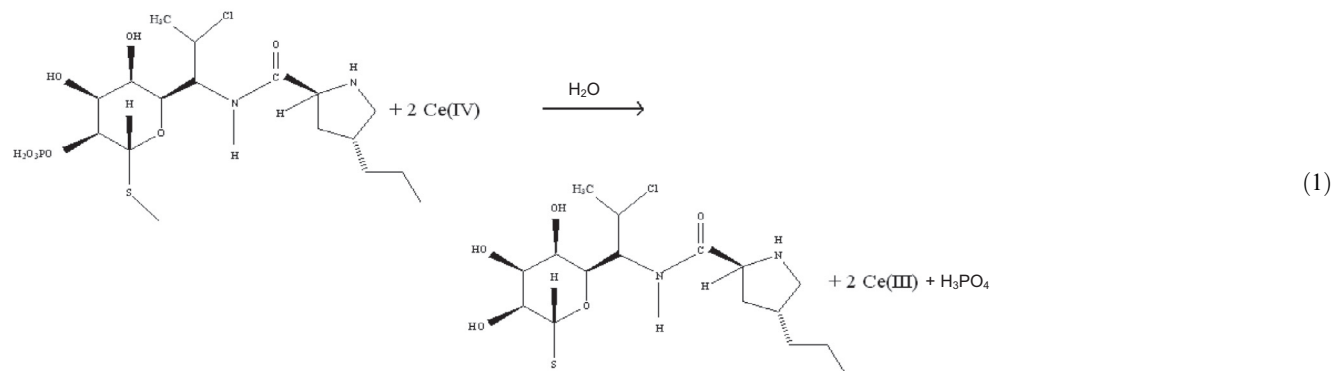
Scheme 1

(acetic acid + water). The dielectric constants of their different compositions were calculated by considering their D in pure form using equation:

$$D = D_1 V_1 + D_2 V_2$$

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 25 °C, respectively. Earlier, it 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 SO₄²⁻ from H₂SO₄ 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 [NaClO₄] (Table 3) and a plot of log k_{obs} versus \sqrt{I} leads a positive slope.



3.5. Effect of initially added product

The influence of initially added products, Ce(III) and clindamycin hydroxide on rate of reaction was studied in their concentration range, 5.0×10^{-5} to 5.0×10^{-3} 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.

3.6. Test for free radical intermediates

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 h 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 (Kolthoff et al., 1953).

3.7. Effect of temperature

The kinetics was also studied at different temperatures at a constant concentration of reactants and other conditions being constant. k_{obs} values were increased with an increase in temperature. Hence, k_{obs} at various temperatures are calculated and tabulated (Tables 4a and 4b). From the Arrhenius plot of log k_{obs} versus $1/T$, activation energy, E_a and other activation parameters ΔH^\ddagger , ΔS^\ddagger , ΔG^\ddagger and log A are calculated (Tables 4a and 4b).

3.8. 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 HClO₄ adjusted to a constant ionic strength of 0.5 mol dm⁻³ was kept for over 24 h at 25 °C in a closed vessel for completion of reaction. Unreacted Ce(IV) was then analysed spectrophotometrically and also titrimetrically. The results showed that 2 mol of Ce(IV) was required to oxidize 1 mol of CYN-P according to reaction (1).

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 Clindamycin hydroxide and the product was analysed by LC-MS, the molecular ion peak (Fig. 2) shows at 407.5 which was expected for the molecular mass of clindamycin hydroxide. An aqueous solution of the above reaction mixture was also tested for the presence of free PO₄³⁻ ion by adding ammonium molybdate solution and conc. HNO₃, after cooling the mixture a canary yellow precipitate was obtained which confirms the presence of PO₄³⁻ ion in the reaction mixture. Hence, it is concluded that the oxidative products of CYN-P were clindamycin hydroxide and phosphoric acid.

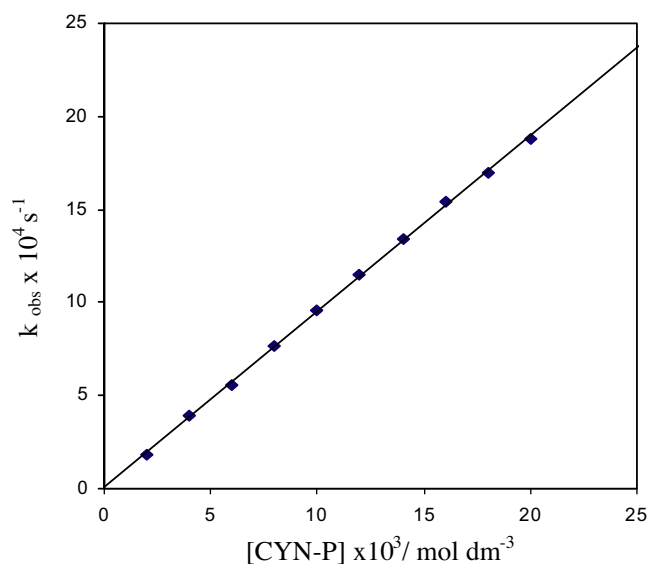


Figure 3 Verification of rate law (9) on oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 25 °C.

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.

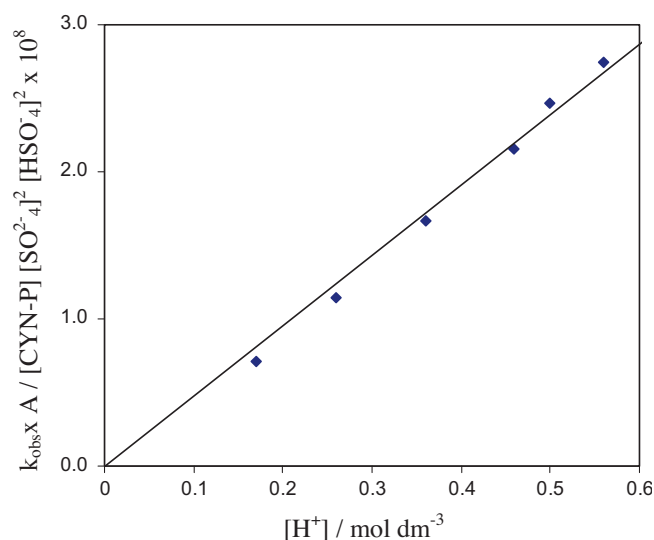
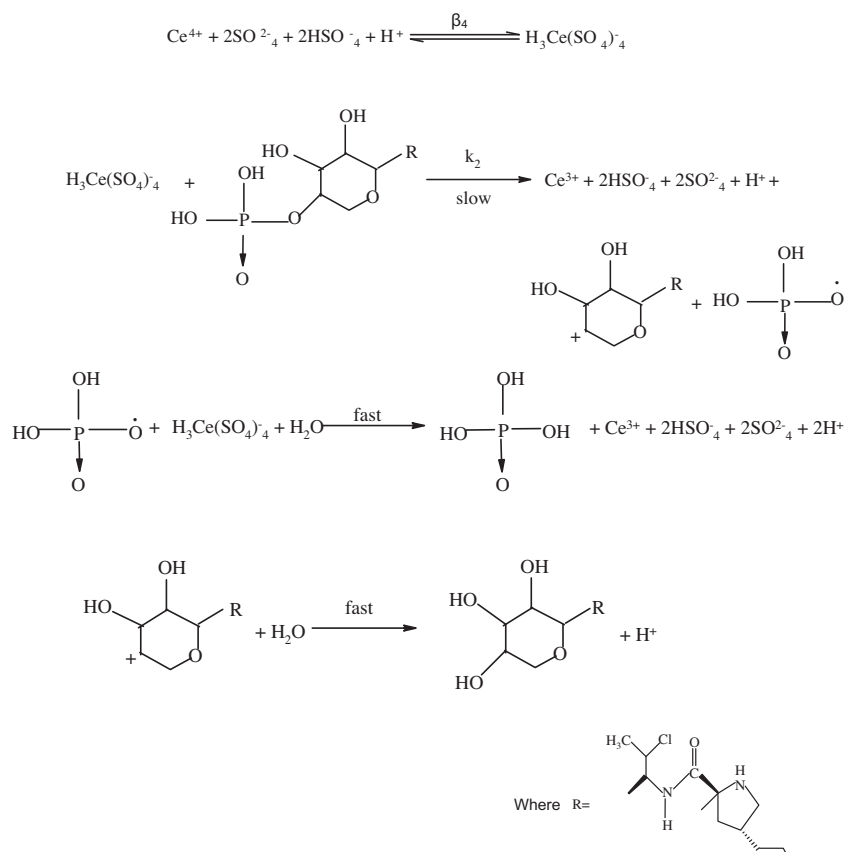


Figure 4 Verification of rate law (12) on oxidation of clindamycin phosphate by cerium(IV) in aqueous acid medium at 25 °C.

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 a fast step to give H_3PO_4 and



Scheme 2

Ce(III), and clindamycin cation undergoes hydrolysis to give product, clindamycin hydroxide.

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 (Tuwar et al., 1991) on oxidation of various organic substrates by Ce(IV) in acidic medium. The orders in [Ce(IV)] and [CYN-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 $1/k_{\text{obs}}$ versus $1/[\text{CYN-P}]$ without intercept as against the non-zero intercept of Michaelis-Menton 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)].

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

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

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

According to Eq. (9), plot of k_{obs} versus [CYN-P] should be linear and is verified as in Fig. 3. The slope of such plot leads to the value of k_1 as $0.958(\pm 0.04) \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$. Using this value in Eq. (9), rate constants were calculated over a range of different concentrations for all the variations of [CYN-P] and compared with experimental values (Table 1). 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 [Ce(IV)] and [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 $\text{H}_3\text{Ce}(\text{SO}_4)_4^-$ with increasing acidity, are compared and it is seen that a good parallelism between the two is obtained (Table 2, Fig. 1). $\text{H}_3\text{Ce}(\text{SO}_4)_4^-$ is considered to be the most active species of Ce(IV) in acid - sulphate media as the plot of reaction rate versus $[\text{H}^+]$ is linear (Fig. 1). Hence, effect of increase in [acid] on rate of reaction is well accommodated by the formation of species $\text{H}_3\text{Ce}(\text{SO}_4)_4^-$. The mechanism of reaction involving species, $\text{H}_3\text{Ce}(\text{SO}_4)_4^-$ 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. Scheme 2 explains a unit fractional order in $[\text{H}^+]$ and free radical intervention. The rate law for Scheme 2 can be derived as

$$\text{Rate} = k_2[\text{H}_3\text{Ce}(\text{SO}_4)_4^-]_f[\text{CYN-P}]_f \quad (10)$$

However, $[\text{Ce(IV)}]_T$ is a sum of all the various [Ce(IV)] sulphate species, CeSO_4^{2+} , $\text{Ce}(\text{SO}_4)_2$, $\text{HCe}(\text{SO}_4)_3^-$ and $\text{H}_3\text{Ce}(\text{SO}_4)_4^-$, and hydroxide species, $\text{Ce}(\text{OH})^{3+}$. They are computed from their equilibrium steps (2)–(6). On incorporating such species of [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.

$$\text{rate} = \frac{k_2\beta_4[\text{Ce}^{4+}][\text{SO}_4^{2-}]^2[\text{HSO}_4^-]^2[\text{H}^+][\text{CYN-P}]}{\left[1 + \frac{k_{\text{OH}}}{[\text{H}^+]} + \beta_1[\text{SO}_4^{2-}] + \beta_2[\text{SO}_4^{2-}]^2 + \beta_3[\text{SO}_4^{2-}]^2[\text{HSO}_4^-] + \beta_4[\text{SO}_4^{2-}]^2[\text{HSO}_4^-]^2[\text{H}^+]\right]} \quad (11)$$

$$\text{rate}/[\text{Ce(IV)}] = k_{\text{obs}} = \text{RHS}$$

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

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

$$\text{where } A = \left[1 + \frac{k_{\text{OH}}}{[\text{H}^+]} + \beta_1[\text{SO}_4^{2-}] + \beta_2[\text{SO}_4^{2-}]^2 + \beta_3[\text{SO}_4^{2-}]^2[\text{HSO}_4^-] + \beta_4[\text{SO}_4^{2-}]^2[\text{HSO}_4^-]^2[\text{H}^+]\right]$$

The plot of LHS versus RHS of Eq. (12) at various $[\text{H}^+]$ at a constant [CYN-P] leads a linear plot (Fig. 4). 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 Eq. (11), k_{cal} values are regenerated which are in close agreement with k_{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 $E_a = 57.2 \text{ kJ mol}^{-1}$. The $\Delta S^\ddagger = -103 \text{ JK}^{-1} \text{ mol}^{-1}$ indicates that the activated complex is more rigid than its reactants. $\log A = 6.7$ emphasizes that the reaction is inner sphere type.

5. Conclusion

The oxidation of CYN-P in aqueous acid medium by Ce(IV) follows a second order kinetics with an inner sphere mechanism which is evidenced by a unit order each in oxidant and reductant. The oxidation occurs through the formation of free radical in a slow step. The more than unit order in $[\text{H}^+]$ indicates the protonated Ce(IV) sulphate complex involved in the rate determining step. Among the various forms of protonated Ce(IV) sulphate complexes, $\text{H}_3\text{Ce}(\text{SO}_4)_4^-$ was likely to be the active species.

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