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Oxidation of clindamycin phosphate by chromium(VI) in aqueous sulfuric acid medium—A kinetic and mechanistic study

Amar K. Durgannavar¹, Manjunath D. Meti¹, Sharanappa T. Nandibewoor¹ and Shivamurti A. Chimatadar¹*

Abstract: Kinetics and mechanism of oxidation of clindamycin phosphate by potassium dichromate in aqueous sulfuric acid medium is studied spectrophotometrically at 25°C at a constant ionic strength of 3.60 mol dm⁻³. The stoichiometry of the reaction is determined and it was found that one mole of clindamycin phosphate consumes two moles of chromium(VI) (1:2). The oxidation products are characterized and confirmed by spectral studies such as IR, GC-MS and LC-MS. The reaction is first order each in chromium(VI) and clindamycin phosphate concentrations. An increase in the sulfuric acid concentration causes an increase of the reaction rate. The order with respect to acid concentration is found to be 1.65. From the results of kinetic studies, reaction stoichiometry and product analysis a suitable free radical mechanism is proposed. Based on investigation of the reaction at different temperatures, computation of the activation parameters with respect to the slow step of the proposed mechanism was evaluated.

Subjects: Applied & Industrial Chemistry; Environmental Chemistry; Organic Chemistry; Physical Chemistry

Keywords: kinetics; mechanism; clindamycin phosphate; chromium(VI)

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PUBLIC INTEREST STATEMENT

Over the past few years, pharmaceuticals are considered as an emerging environmental problem due to their continuous input and persistence to the aquatic ecosystem even at low concentrations. In view of effective antibacterial activity, and various susceptible oxidation sites in clindamycin phosphate. The present study deals with the title reaction in order to investigate the redox chemistry of Cr(VI) in acidic medium and to compute the thermodynamic quantities of various steps involved in the mechanism to those derived on the basis of kinetic and spectroscopic results. Such oxidation studies shed light on the mechanism of degradation of these drugs in biological or ecological systems and can be helpful to design advanced oxidation processes which can further be applied to combat environmental issues.
1. Introduction

Chromium(VI) is widely used specifically in organic chemistry, due to its versatile oxidative mechanistic pathways, which makes them inherently interesting. Chromium(VI) has been used for the oxidation of alcohols (Noshiranzadeh, Bikas, Ślepokura, Mayeli, & Lis, 2014), aldehydes (Gupta, Dey, Gupta, Adhikari, & Banerjee, 1990), ketones (Rocek & Riehl, 1967), hydrocarbons (Chen & Sheldon, 1995), sulfides (Liang, Cheng, & Trudell, 2003) to name a few serving as economically viable oxidation processes. Biologically, chromium is essential for proper metabolism of carbohydrates and lipids in mammals, evidently, the mechanism of these actions have proved elusive (Davis, Sumrall, & Vincent, 1996). Among various oxidation states of chromium, Cr(VI) and Cr(III) are stable oxidation states. In acidic medium the reduction potential of Cr(VI)/Cr(III) couple is 1.33 V (Chimatadar, Basavaraj, & Nandibewoor, 2006; Day & Selbin, 1964). Kinetics and oxidation of organic compounds by chromic acid has been the subject of large number of investigators (Das, 2004; Wiberg & Mukherjee, 1974). Description of mechanism in these cases follow either intermediate complex formation or free radical mechanism depending on interpretation of results. Considerably interest has been shown in the chemistry of the intermediate oxidation states, Cr(V) and Cr(IV), due to their observation during the oxidation of organic substrates by Cr(VI) and implication in the mechanism of Cr-induced cancers (Fawzy, Ashour, Musleh, Hassan, & Asghar, in press).

Clindamycin phosphate (clindamycin), methyl 7-chloro-6,7,8-trideoxy-6-[(2S,4R)-1-methyl-4-pyrrolidine-2-carboxamide]-1-thio-1-threo-D-galactoctopyranoside monohydrochloride inhibits protozoans such as toxoplasma and mycoplasma as well as many anaerobic bacteria (Portugal, Lujan, & Murrieta, 2008). Clindamycin has been prescribed to treat serious infectious caused by Staphylococcus aureus strain in children for more than 35 years (Kaplan, 2005). Clindamycin and several macrolide antibiotics are effective for the treatment of AIDS-toxoplasmosis, usually in association with pyrimethamine (Dannemann et al., 1992). These block protein synthesis in bacteria by interacting with peptidyl transferase domain of 23S rRNA. Structural features of clindamycin phosphate include the presence of two secondary alcoholic groups, an amide linkage and a methyl sulfide all of which are susceptible for oxidation. Measurements of rates of oxidation of several cyclic alcohols by chromium(VI) have demonstrated that alcohol with most hindered hydroxyl group is oxidized most rapidly (Kwart & Francis, 1958). While, the oxidation of electron deficient sulfide to sulfone and its kinetic study is crucial to understand cheaper and reliable direct oxidation processes. Moreover, sulfone moieties are useful synthetic intermediates in the preparation and functionalization of bio-chemically potent compounds. Our literature survey reveals that the oxidation of biologically potent organic compounds by different oxidants has received limited attention (Fawzy, Ashour, & Musleh, 2014; Ionita, Sahini, Semenescu, & Ionita, 2000). These mechanisms are interesting because of its complexity resulting out of possibility of a variety of mechanistic pathways, involving reactive intermediates which encounter in chemical reactions. The present investigation is an attempt to gain insight on the role of the oxidizing agent and its selectivity over range of susceptible oxidation sites in clindamycin phosphate, to understand intermediate oxidation states of chromium during oxidation process and to propose the mechanism based on kinetic and spectral data.

2. Experimental

2.1. Materials and reagents

All chemicals used, clindamycin phosphate, sulfuric acid, potassium dichromate, sodium sulfate were of reagent grade. Double distilled water was used throughout our work. The stock solution of clindamycin phosphate (Sigma Aldrich, Bangalore, India) was freshly prepared by dissolving equivalent quantity in double distilled water. The solution of chromium(VI) (s.d. fine-chem., Mumbai, India) was prepared by dissolving potassium dichromate in double distilled water (Jeffery, Bassett, Mendham, & Denny, 1996). The chromium(III) solution was prepared by dissolving chromic potassium sulfate (Cr2(SO4)3.K2SO4.24H2O) (AR) in water. H2SO4 and Na2SO4 were used to maintain the acidity and ionic strength of the reaction system respectively.
2.2. Kinetic measurements and procedure

The kinetic measurements were carried out under pseudo-first order conditions, where clindamycin phosphate concentration was present at least 10 times excess quantity over that of chromic acid concentration at a constant ionic strength of 3.60 mol dm$^{-3}$. The reaction was initiated by mixing thermally equilibrated (at 25.0 ± 0.1°C) solutions of chromium(VI) and clindamycin phosphate which also contained the required quantities of H$_2$SO$_4$ and Na$_2$SO$_4$. The course of reaction was followed by recording the decrease in absorbance of chromium(VI) at 360 nm as a function of time in a 1 cm cell placed in the thermostatted compartment of Varian Cary-50 Bio UV–vis Spectrometer (Varian, Victoria-3170, Australia). It was examined and verified that there was no interference from other reagents at this wavelength. Beer’s Law has been verified between $1.0 \times 10^{-4}$ and $1.0 \times 10^{-3}$ mol dm$^{-3}$ of chromium(VI) at 360 nm under the reaction conditions and the extinction coefficient was found to be 1200 ± 12 dm$^3$ mol$^{-1}$ cm$^{-1}$. The kinetic runs were followed more than 70% completion of reaction and good first order kinetics were observed. The pseudo-first order rate constants, $k_{obs}$, were obtained from the slopes of the plots of log (absorbance) vs. time. The pseudo-first order plots were linear over three half lives (Figure 1). The rate constants $k_{obs}$ were reproducible to within ±5% and are average of at least three independent kinetic runs (Table 1).

2.3. Stoichiometry and product analysis

The stoichiometry of the overall reaction of clindamycin phosphate with excess chromic acid in 1.0 mol dm$^{-3}$ H$_2$SO$_4$ and at 3.60 mol dm$^{-3}$ ionic strength was determined spectrophotometrically. Reaction mixtures containing different initial concentrations of the reactants were equilibrated for about 3 h under nitrogen atmosphere at 25°C. The unreacted chromic acid was estimated spectrophotometrically. The result indicates that one mole of clindamycin phosphate requires two moles of chromium(VI) (1:2) as shown in Equation (1).

\[
\text{Clindamycin phosphate} + 2\text{H}_2\text{CrO}_4 + 4\text{H}_2\text{O} \rightarrow \text{Product (A)} + \text{Product (B)}
\]

The reaction products were identified as chromium(III), 4-{(1-chloroethyl)-hexahydro-7,8-dihydroxy-6-(methylsulfonyl)pyrano[2,3-e][1,3]oxazin-2(3H)-one (A), and 1-methyl-5-propylpyrrolidin-2-ol (B). The product (A) was characterized and confirmed by IR (Figure 2) and LC-MS spectrum (Figure 3). IR spectrum (Nicolet 5700-FT-IR spectrometer) of (A) showed broad OH peak at 3346 cm$^{-1}$, lactone carbonyl at 1759 cm$^{-1}$. The LC-MS spectrum (Agilent Compact 1120 and Thermo Surveyor model for liquid chromatography and Thermo LCQ Deca XP MAX model for Mass Spectrometer) of (A) showed molecular ion peak at m/z 329. Product (B) was isolated from the reaction mixture by extraction using ether.
and evaporated, resulted in white solid and it was confirmed using GC-MS (Figure 4). The GC-MS spectrum of B showed molecular ion peak at m/z 141. GC-MS data was obtained on Shimadzu 17A Gas Chromatograph with a Shimadzu QP-5050A mass spectrometer using EI ionisation technique.

Table 1. Effect of variation of chromium(VI), clindamycin phosphate, sulfuric acid concentrations on the oxidation of clindamycin phosphate by chromium(VI) at $I = 3.60 \text{ mol dm}^{-3}$ and at 25°C

<table>
<thead>
<tr>
<th>$[\text{Cr(VI)}] \times 10^{-4}$ (mol dm$^{-3}$)</th>
<th>$[\text{CP}] \times 10^{-3}$ (mol dm$^{-3}$)</th>
<th>$[\text{H}_2\text{SO}_4]$ (mol dm$^{-3}$)</th>
<th>$k_{\text{obs}} \times 10^{-3}$ (s$^{-1}$)</th>
<th>$k_2 = \frac{k_{\text{obs}}}{[\text{clindamycin}]}$ (dm$^3$ mol$^{-1}$ s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>2.0</td>
<td>1.0</td>
<td>1.12</td>
<td>-</td>
</tr>
<tr>
<td>1.0</td>
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<td>1.0</td>
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<td>-</td>
</tr>
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<td>1.0</td>
<td>1.17</td>
<td>-</td>
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<td>1.0</td>
<td>1.17</td>
<td>-</td>
</tr>
<tr>
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<td>0.30</td>
<td>0.60</td>
</tr>
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<td>0.61</td>
</tr>
<tr>
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<td>1.0</td>
<td>1.17</td>
<td>0.59</td>
</tr>
<tr>
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<td>3.0</td>
<td>1.0</td>
<td>1.78</td>
<td>0.59</td>
</tr>
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<td>2.0</td>
<td>4.0</td>
<td>1.0</td>
<td>2.44</td>
<td>0.61</td>
</tr>
<tr>
<td>2.0</td>
<td>5.0</td>
<td>1.0</td>
<td>3.00</td>
<td>0.60</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>0.2</td>
<td>0.04</td>
<td>-</td>
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<tr>
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<td>2.0</td>
<td>0.4</td>
<td>0.14</td>
<td>-</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>0.6</td>
<td>0.28</td>
<td>-</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>0.8</td>
<td>0.62</td>
<td>-</td>
</tr>
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<td>2.0</td>
<td>2.0</td>
<td>0.9</td>
<td>0.92</td>
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<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
<td>1.23</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure 2. FT-IR Spectra of the product 4-(1-chloroethyl)-hexahydro-7,8-dihydroxy-6-(methylsulfonyl) pyrano [2,3-e] [1,3]oxazin-2(3H)-one obtained after oxidation of clindamycin phosphate.
3. Results

3.1. Reaction orders
The orders were determined from the slopes of log $k_{obs}$ vs. log (concentration) plots by varying the concentrations of clindamycin phosphate and H$_2$SO$_4$, in turn, while keeping all other conditions constant.

3.2. Effect of [chromium(VI)] on rate of oxidation
The concentration of chromium(VI) was varied in the range of 5.0 $\times$ 10$^{-5}$ to 5.0 $\times$ 10$^{-4}$ mol dm$^{-3}$ retaining all other reaction conditions constant. Resultant $k_{obs}$ are nearly constant values (Table 1) indicating order with respect to chromium(VI) concentration is unity. This was further confirmed by the linearity of the plots of log absorbance vs. time over three half lives (Figure 1).

3.3. Effect of [clindamycin phosphate] on rate of oxidation
The effect of clindamycin phosphate concentration on the rate was studied in the range of 5.0 $\times$ 10$^{-4}$ to 5.0 $\times$ 10$^{-3}$ mol dm$^{-3}$ retaining concentrations of all other reaction components constant. It was observed that, increase in concentration of clindamycin phosphate resulted in an increase in rate constants (Table 1). The order with respect to clindamycin phosphate concentration was obtained from the plot of log $k_{obs}$ vs. log [CP] and was found to be unity.
3.4. Effect of [sulfuric acid] on rate of oxidation

Kinetic measurements were performed in \( \text{H}_2\text{SO}_4-\text{Na}_2\text{SO}_4 \) solutions with different hydrogen ion concentrations maintaining constant ionic strength of 3.60 mol dm\(^{-3}\) and temperature 25°C ± 0.1 in order to clarify the influence of acid concentration on the reaction rates. It was found that, as sulfuric acid concentration increases the rate of reaction also increases (Table 1). The order with respect to acid concentration was found to be close to 2 (1.65).

3.5. Effect of variation in ionic strength (I) and dielectric constant (D) on rate of oxidation

To shed some light on the reactive ionic species in the rate-determining step, kinetic runs were performed by varying ionic strength and dielectric constant at constant concentrations of reactants and maintaining other conditions constant. Ionic strength (I) was varied from 3.20 to 5.0 mol dm\(^{-3}\) by varying the concentrations of \( \text{Na}_2\text{SO}_4 \). The values of \( k_{\text{obs}} \) were found to decrease with increasing ionic strength (Table 2). The plot of \( \log k_{\text{obs}} \) vs. \( \sqrt{I} \) is shown in Figure 5. The effect of dielectric constant (D) was studied by varying the acetic acid–water (v/v) content from 0 to 35% in the reaction mixture with all other conditions being maintained constant. Since the dielectric constants of aqueous acetic acid are not available in the literature, they were computed from the values of pure liquids (Lide, 1992). Obtained experimental results showed no significant effect of dielectric constant on the rate of reaction (Table 2).

3.6. Effect of externally added product on rate of oxidation

The effect of added product, chromium(III) was studied in the range of 0.5 × 10\(^{-4}\) mol dm\(^{-3}\) to 5.0 × 10\(^{-4}\) mol dm\(^{-3}\) by keeping all other reaction conditions constant. It was observed that, initially added product, chromium(III) did not have any significant effect on rate of reaction. Thus, from the above experimental results, the rate law is

\[
\text{Rate} = k_{\text{obs}} [\text{Cr(VI)}]^{1.00} [\text{CP}]^{1.00} [\text{H}_2\text{SO}_4]^{1.65}
\]

### Table 2. Effect of variation of ionic strength and dielectric constant on the oxidation of clindamycin phosphate by chromium(VI) in aqueous sulfuric acid medium at 25°C

<table>
<thead>
<tr>
<th>Ionic strength (I) (mol dm(^{-3}))</th>
<th>( k_{\text{obs}} \times 10^{-3} ) (s(^{-1}))</th>
<th>Dielectric constant</th>
<th>( k_{\text{obs}} \times 10^{-3} ) (s(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>1.36</td>
<td>0%</td>
<td>78.50</td>
</tr>
<tr>
<td>3.6</td>
<td>1.17</td>
<td>10%</td>
<td>71.27</td>
</tr>
<tr>
<td>4.0</td>
<td>0.91</td>
<td>15%</td>
<td>67.64</td>
</tr>
<tr>
<td>4.2</td>
<td>0.83</td>
<td>20%</td>
<td>64.03</td>
</tr>
<tr>
<td>4.6</td>
<td>0.60</td>
<td>25%</td>
<td>60.41</td>
</tr>
<tr>
<td>5.0</td>
<td>0.48</td>
<td>35%</td>
<td>53.17</td>
</tr>
</tbody>
</table>

Notes: [Cr(VI)] = 2.0 × 10\(^{-4}\); [CP] = 2.0 × 10\(^{-3}\); [H\(_2\)SO\(_4\)] = 1.0 mol dm\(^{-3}\).

\(^{a}\)Dielectric constant values are taken from Lide (1992).

![Figure 5. Effect of ionic strength on the oxidation of clindamycin phosphate by chromium(VI) in aqueous sulfuric acid medium.](image)
3.7. Test for free radicals (polymerization study)

The oxidation of clindamycin phosphate by chromium is usually assumed to proceed via free radical intermediates. The possible occurrence of free radicals in this reaction was tested by the addition of known quantity of acrylonitrile (scavenger) to the following reaction solutions: (1) 0.01 mol dm$^{-3}$ chromium(VI); (2) 0.01 mol dm$^{-3}$ clindamycin phosphate; (3) 0.01 mol dm$^{-3}$ chromium(VI) + 0.01 mol dm$^{-3}$ clindamycin phosphate; all in 1.0 mol dm$^{-3}$ H$_2$SO$_4$ + 0.2 mol dm$^{-3}$ Na$_2$SO$_4$. To all three solutions known quantities of acrylonitrile (scavenger) was added initially, and were kept in an inert atmosphere for 1 h at room temperature. These solutions were diluted with methanol, it was observed that solution (3) became turbid, whereas solutions 1 and 2 remained perfectly clear, this suggested that there was participation of free radicals in the reaction. And account of which has been undertaken in understanding the mechanism and has been proposed accordingly in Scheme 1.
3.8. Effect of temperature

The influence of temperature on the reaction was studied at 15, 25, 35, and 45°C by varying clindamycin phosphate and H₂SO₄ concentrations. It was found that the rate of reaction increases with an increase in temperature. The rate constant (kₙₐ₅) of the slow step of Scheme 1 were obtained from the intercepts of 1/kₙₐ₅ vs. 1/[H⁺] and 1/kₙₐ₅ vs. 1/[CP] at different temperatures and the values are given in Table 3. The energy of activation for rate determining step was obtained from a plot of log kₙₐ₅ vs. 1/T, from which activation parameters were calculated by using Eyring equation (Lente, Fabian, & Poe, 2005) and are given in Table 3. Thermodynamic quantities of first and second step of Scheme 1 were evaluated from the slope and intercept of the plot of 1/kₙₐ₅ vs. 1/[H⁺]² and 1/kₙₐ₅ vs. 1/[CP] respectively at different temperatures. Van’t Hoff plot was drawn for the variation of K with temperature (log K vs. 1/T). Thermodynamic quantities are provided in Table 3.

4. Discussion

The chromium(VI) oxidation of clindamycin phosphate in acid media has a stoichiometry 2:1. The reaction is first order with respect to chromium(VI) and clindamycin phosphate concentrations. The effect of acid on the rate was studied by varying the sulfuric acid concentration and it was found that, as the acid concentration increases the rate of reaction also increases. These experimental results have been schematically represented in Scheme 1.
It is well known fact that in aqueous acid solutions, chromium(VI) exists in the form of H₂CrO₄⁻ (Chimatadar, Madawale, & Nandibewoor, 2007; Hasan & Rocek, 1975; Saunte, Chaubey, & Mahanti, 2008). In a pre-equilibrium step, CrO₂⁻⁴ reacts with two moles of acid to give H₂CrO₄, which is in accordance with observed order of two in acid concentration. The results indicate that H₂CrO₄ reacts with clindamycin phosphate forming a complex. The formation of complex is evident kinetically by a Michaelis–Menton plot, i.e. a non zero intercept of the plot of 1/kobs vs. 1/[CP] (Figure 6). It is agreed that chromium(VI) undergoes direct two electron reduction during the process of oxidation. In view of this, in the rate determining step complex undergoes decomposition in presence of water to give sulfoxide (1a) and chromium(IV) while H₃PO₄ is eliminated. Further, sulfoxide (1a) formed, undergoes oxidation with one more mole of chromium(VI) in fast step to yield sulfone (1b) and chromium(IV) intermediate species. Chromium(IV) being highly unstable and is responsible for carbon–carbon bond cleavage with the formation of free radical in numerous organic compounds (Rahman & Rocek, 1971). Evidently after conversion of methyl sulfide to methyl sulfone in clindamycin phosphate, the chromium(IV) formed cleaves carbon–carbon bond in sulfone (1b), resulting in free radical(1c), cation (2a) and chromium(III). The free radical (1c) is highly unstable which leads it to attack closest secondary alcohol followed by intramolecular cyclization leading to the formation of 4-(1-chloroethyl)-hexahydro-7,8-dihydroxy-6-(methylsulfonyl)pyrano[2,3-e][1,3]oxazin-2(3H)-one (1d) and chromium(III) which are final product of oxidation. The oxidation of clindamycin phosphate by chromium(VI) occurs through intervention of reactive chromium(IV) species. The intervention of chromium(IV) is evident through the progressive rate decline in the presence of increasing amounts of added manganese(II), the decrease reaching a limit of about one half of the rate found in the absence of manganese(II). Similar results have also been witnessed in chromium(VI) oxidation of 2-propanol in acetic acid (Chimatadar, Koujalagi, & Nandibewoor, 2004). All these experimental results were summarized in the form of Scheme 1.

From Scheme 1 the following rate law (7) can be derived as follows

\[\text{Rate} = k \text{[Complex(C)]}\]

\[
\text{Rate} = \frac{-d[\text{CrO}_4^{2-}]}{dt} = kK_1K_2[\text{CP}]_{f}[\text{CrO}_4^{2-}]_{f}[\text{H}^+]^2
\]

The total concentration of CrO₄²⁻ is given by,

\[
[\text{CrO}_4^{2-}]_{f} = [\text{CrO}_4^{2-}]_{r} + [\text{H}_2\text{CrO}_4] + [\text{Complex (C)}]
\]

\[
= [\text{CrO}_4^{2-}]_{r} + K_1[\text{CrO}_4^{2-}]_{r}[\text{H}^+]^2 + K_1K_2[\text{CP}][\text{CrO}_4^{2-}]_{r}[\text{H}^+]^2
\]

\[
= [\text{CrO}_4^{2-}]_{r}\left\{1 + K_1[H^+]^2 + K_1K_2[CP][H^+]^2\right\}
\]

Therefore,

\[
[\text{CrO}_4^{2-}]_{f} = \frac{[\text{CrO}_4^{2-}]_{r}}{\left\{1 + K_1[H^+]^2 + K_1K_2[CP][H^+]^2\right\}}
\]

where \(t\) and \(f\) stands for total and free concentration of chromium(VI).

Similarly,

\[
[\text{CP}]_{r} = [\text{CP}]_{r} + [\text{Complex (C)}] = [\text{CP}]_{r} + K_1K_2[\text{CrO}_4^{2-}]_{r}[\text{CP}][\text{H}^+]^2
\]

\[
= [\text{CP}]_{r}\left\{1 + K_1K_2[\text{CrO}_4^{2-}]_{r}[\text{H}^+]^2\right\}
\]
In view of the low concentrations of chromium(VI) in the experiment, in Equation (4) the term $K_1K_2[CrO_2^{-4}][H^+]^2$ can be neglected in comparison with unity. Hence,

$$[CP]_f = [CP]_t$$  \hspace{1cm} (5)$$

and

$$[H^+]^2_f = [H^+]^2_t + [H_2CrO_4] + [\text{Complex (C)}] = [H^+]^2_t + K_1[CrO_2^{-4}][H^+]^2 + K_2[H_2CrO_4][CP]$$

$$= [H^+]^2_t + K_1[CrO_2^{-4}][H^+]^2 + K_2[H_2CrO_4][CP]$$

$$= [H^+]^2_t \left( 1 + K_1[CrO_2^{-4}] + K_2[CP][CrO_2^{-4}] \right)$$  \hspace{1cm} (6)$$

Similarly,

$$[H^+]^2_f = [H^+]^2_t$$  \hspace{1cm} (7)$$

Substituting Equations (3), (5), and (6) in Equation (2), and omitting subscripts we get Equation (7), which explains all the experimentally observed orders with respect to different species of reaction.

$$\text{Rate} = -\frac{d[CrO_2^{-4}]}{dt} = \frac{kK_1K_2[CrO_2^{-4}][CP][H^+]^2}{1 + K_1[H^+]^2 + K_1K_2[CP][H^+]^2}$$  \hspace{1cm} (8)$$

or

$$\frac{\text{Rate}}{[CrO_2^{-4}]} = k_{\text{obs}} = \frac{k K_1K_2[CP][H^+]^2}{1 + K_1[H^+]^2 + K_1K_2[CP][H^+]^2}$$  \hspace{1cm} (9)$$

The rate law (7) can be rearranged to Equation (8), which is suitable for verification.

$$\frac{1}{k_{\text{obs}}} = \frac{1}{k K_1K_2[CP][H^+]^2} + \frac{1}{k K_2[CP]} + \frac{1}{k}$$  \hspace{1cm} (10)$$

According to Equation (8), plots of $1/k_{\text{obs}}$ vs. $1/[CP]$ and $1/k_{\text{obs}}$ vs. $1/[H^+]^2$ should be linear and were found to be so (Figure 6). The slopes and intercepts of these plots lead to the values of $K_1$ (2.16 dm$^3$ mol$^{-2}$), $K_2$ (9.71 dm$^3$ mol$^{-1}$) and $k$ ($8.81 \times 10^{-2}$ s$^{-1}$) at 25°C (Table 3). Similarly $k$, $K_1$ and $K_2$ values for other temperatures were calculated and are given in Table 3. Since ions exert electrostatic forces on each other, the kinetics of reaction between ions deviates from such reactions which involve non-electrolytes. The rate constants of ionic reactions depend upon the charges carried by the ions and also upon the ionic strength of the solution. The salt effect on the reaction rates has been well described by the Bronsted–Bjerrum theory. In the present investigations, variation of the ionic strength of the medium by adding Na$_2$SO$_4$ solution decreases the rate constant linearly with negative slope indicating that reactant species involved are oppositely charged as shown in Scheme 1. Hence the observed ionic strength effect is consistent with the Bronsted–Bjerrum concept (Laidler, 1995). Insignificant effect of dielectric constant of solvent on rate of reaction has been resulted may be due to polar and non-polar nature of clindamycin phosphate which is soluble both in highly polar solvent like water and less polar solvent like acetic acid (Badi & Tuwar, in press). The smaller activation energies observed support that the reaction proceeds between ions of opposite charges or an ion and a neutral...
molecule (Zaafarany, Khairou, & Hassan, 2009). Therefore, the electrostatic attraction between the reactants does not need much energy to bring them together in order to form the respective intermediates and oxidation products. The values of $\Delta H^\ne$ and $\Delta S^\ne$ are both favorable for electron transfer processes. The negative value of $\Delta S^\ne$ are within the range of radical reaction and have been ascribed to the nature of electron pairing and unpairing process and to the loss of degree of freedom formerly available to reactants upon the formation of rigid transition state. In view of foregoing experimental observations and kinetic interpretations this reaction mechanism presumably occurs via an inner-sphere mechanism. Thus, with these arguments and the experimental findings, the oxidation of clindamycin phosphate by chromium(VI) illustrated in Scheme 1, representing the oxidation of sulfide to corresponding sulfone.

5. Conclusion

Through kinetics study, we proposed a free radical reaction mechanism for oxidation of clindamycin phosphate by chromium(VI). Among the various competitive oxidation sites in clindamycin phosphate it was evident through our study that methyl sulfide of clindamycin phosphate leads in taking first priority to get oxidized by chromium(VI). The active species of chromium(VI) was found to be H$_2$CrO$_4$. It was apparent, that reaction medium played crucial role during the process of oxidation. The rate constant of the slow step, equilibrium constant involved in the mechanism and activation parameters were evaluated and computed. Oxidation products were identified, while the proposed mechanism is in well agreement with the experimental and spectral interpretations.

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