CHAPTER IV

Kinetic and Mechanistic Study of Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in Aqueous Alkaline Medium

The periodate and tellurate complexes of copper in its trivalent state have been extensively used in the analysis of several organic compounds.\(^1\) The kinetics of self-decomposition of these complexes were studied in some detail.\(^2\) Movius\(^3\) reported the reactivity of some alcohols with diperiodatocuprate(III) (DPC). DPC is a versatile one-electron oxidant for various organic compounds in alkaline medium and its use as an analytical reagent is now well recognized\(^4\) and also used in the analytical determination of amino acids.\(^4\) Copper(III) is shown to be an intermediate in the Cu(II)-catalysed oxidation of amino acids by peroxydisulphate.\(^5\) The use of diperiodatocuprate(III) as an oxidant in alkaline medium is new and restricted to a few cases\(^6\) due to the fact of its limited solubility and stability in aqueous medium. The kinetics and mechanism of oxidation of some organic substrates by DPC have been studied. Moreover, when the copper(III) periodate complex is the oxidant, since multiple equilibria between the different copper(III) the species are involved, it needs to be known which of species is the active oxidant.

Sulfamethoxazole (SMZ), \(\text{[N}^S\text{-methyl-S-iso-xazolyl]sulfanilamide}\) is a well-known antibacterial drug. It mainly finds use\(^7\) in treating urinary tract and lower respiratory tract infections. It readily gets absorbed in the body. A literature
survey reveals that there are a few reports on the kinetics of oxidation of SMZ using different oxidizing agents. The oxidation of SMZ is of interest as the product of oxidation differs with different oxidants and media. In view of multiple equilibria embracing the different copper(III) periodate species and the complexity of the title reaction, a detailed study of the reaction was undertaken in this chapter.

EXPERIMENTAL

Materials
All chemicals used were of reagent grade. Double-distilled water was used throughout the work. A stock solution of sulfamethoxazole (Indian Pharmacopoeia) was prepared by dissolving the appropriate amount of sample in 0.10 mol dm$^{-3}$ NaOH solution. The purity of the sample was checked by TLC and its melting point 167 °C (Literature melting point 167 °C). The copper(III) periodate complex was prepared as follows: 3.54g of Copper sulphate, 6.80g of potassium periodate, 2.20g of potassium persulphate and 9.0g potassium hydroxide were added to about 250 cm$^3$ of water. The order of addition is not important. The mixture was shaken thoroughly and heated on a hot plate. In about 20 minutes, the boiling mixture turned intense red and the boiling was continued for another 20 minutes, more for the completion of the reaction. The mixture was then cooled, filtered through sintered glass crucible (G4) and diluted to 250 cm$^3$. The persulphate used was just sufficient to oxidise copper(II) to copper(III) and was therefore completely removed during boiling. If an excess of persulphate was
used, boiling for a long time was necessary for its complete decomposition. The purity of the complex was checked by its UV-Visible spectrum, which showed broad absorption band at 415 nm. The aqueous solution of copper(III) was standardized by the back titration\textsuperscript{11} method.

The Copper(II) solution was made by dissolving the known amount of copper sulfate (BDH) in distilled water. The periodate solution was prepared by weighing out the required amount of sample in hot water and it was used after keeping for 24 hours. Its concentration was ascertained iodometrically\textsuperscript{12} at neutral pH by a phosphate buffer. Since periodate is present in excess in DPC, the possibility of oxidation of sulfamethoxazole by periodate in alkaline medium at 25 °C was tested. The progress of the reaction was followed iodometrically. However, it was found that there was no significant reaction under the experimental conditions employed compared to the DPC oxidation of sulfamethoxazole. Potassium hydroxide and potassium nitrate were employed to maintain the required alkalinity and ionic strength, respectively, in reaction solutions.

**Kinetic Procedure**

The oxidation of sulfamethoxazole by DPC was followed under pseudo-first order conditions where sulfamethoxazole was in excess over [DPC] at 25 ± 0.1 °C, unless otherwise stated. The reaction was initiated by mixing the required quantities of previously thermostatted solutions of sulfamethoxazole and DPC, which also contained defined quantities of KOH, KNO\textsubscript{3} and IO\textsubscript{4} to maintain the
required alkalinity, ionic strength and periodate. Here, the total concentration of hydroxide ion was calculated considering the KOH in DPC as well as the KOH additionally added. Similarly, the total metaperiodate concentration was calculated by considering metaperiodate present in the solution of DPC and the additionally added amount. The course of reaction was followed by measuring the absorbance of unreacted DPC in the reaction mixture in a 1 cm quartz cell located in the thermostatted compartment of a Peltier Accessory (temperature control) attached Varian CARY 50 Bio UV-Vis spectrophotometer at its maximum absorption wavelength of 415 nm as a function of time. Earlier, it was verified that there is negligible interference from other species present in the reaction mixture at this wavelength. The obedience of Beer’s law by DPC at 415 nm was verified earlier and the molar absorbance coefficient, ‘\( \varepsilon \)’ was found to be 6231 ± 311 dm\(^3\) mol\(^{-1}\) cm\(^{-1}\) at this wavelength as shown in Figure IV (i) (p.105). The first order rate constants, \( k_{obs} \), were obtained from the plots of \( \log(a-x) \) versus time, where \( a \) and \( x \) are the initial concentration and change in concentration of diperiodatocuprate(III) at time \( t \), respectively. The plots were linear up to about 85 % completion of the reaction and the rate constants were reproducible within ± 5 %. The spectral changes during the reaction are shown in Figure IV (ii) (p.106) and it is evident from the figure that the concentration of DPC decreases at 415 nm.

The effect of dissolved oxygen on the rate of reaction was studied by preparing the reaction mixture and following the reaction in an atmosphere of the nitrogen. No significant difference between the results was observed. In view of
Figure IV (i)

Verification of Beer's law for [DPC] at 415 nm in 0.05 mol dm$^{-3}$ alkali.

![Absorbance vs. [DPC] graph](image)
Figure IV (ii)
Spectroscopic changes occurring in the Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) at 25 °C, [DPC] = 1 x 10^{-4}, [SMZ] = 1 x 10^{-3}, [OH^-] = 0.05, [IO_4^-] = 1.2 x 10^{-5} and I = 0.10 / mol dm^{-3} with scanning time interval = 1 min.
ubiquitous contamination of basic solutions by carbonate, the effect of carbonate on the reaction was also studied. Added carbonate had no effect on the reaction rate. However, fresh solutions were used during the experiments.

In view of the modest concentration of alkali used in the reaction medium, attention was also given to the effect of the surface of the reaction vessel on the kinetics. The use of polythene or acrylic ware and quartz or polyacrylate cells gave the same results, indicating that the surface does not have any significant effect on the rate.

Regression analysis of the experimental data to obtain the regression coefficient, ‘r’ and standard deviation, ‘S’ of points from the regression line was performed using a Pentium-IV personal computer.

RESULTS

Stoichiometry and Product Analysis

Different sets of reaction mixtures containing different concentrations of sulfamethoxazole and DPC at constant ionic strength and alkali were kept for ca. 6 hours at 25 ± 0.1 °C in an inert atmosphere and in a closed vessel. When [DPC] was higher than [Sulfamethoxazole], the unreacted DPC was found by measuring the absorbance at 415 nm spectrophotometrically. The results indicated that two moles of DPC consumed one mole of sulfamethoxazole as shown in equation (1) and in Table IV (i) (p.109).
The reaction products were extracted with diethyl ether. The main reaction products were identified as p-aminobenzenesulfonamide (p-ABS) by preparative TLC technique using a mixture of petroleum ether : CHCl₃ : n-butanol (2:2:1 v/v) (p-ABS Rf = 0.70) and butanol : acetic acid : water (4:1:1 v/v) (p-ABS Rf = 0.71) as the eluent and iodine as spray reagent, respectively. p-ABS was identified by a colorimetric technique and further was characterized by IR and ¹H NMR spectroscopy which showed bands at 3476, 3379, 3299 cm⁻¹ (NH of NH₂Ar/SO₂NH₂), 1314, 1366 cm⁻¹ (SO₂). The ¹H NMR spectrum (DMSO-d₆) showed a broad singlet at 4.18 δ due to NH₂ protons, which disappeared on D₂O exchange. The doublets at 6.65 δ (J = 8Hz) and 7.63δ (J = 8Hz) are due to four aromatic protons. 5-Methyl-3-isoxazolone was also identified by its IR spectrum showing a sharp band at 1720 cm⁻¹ (C=O stretching), 3200 cm⁻¹ (N-H stretching) and its ¹H NMR spectrum (CDCl₃) which showed a singlet at 2.36 δ due to methyl protons while another singlet at 6.22 δ due to -CH proton. A broad singlet at 11.22 δ belonged to -NH proton, which vanished on D₂O exchange. The reaction products do not undergo further oxidation under the present kinetic conditions.
Table IV (i)
Stoichiometry of Oxidation of Sulfamethoxazole by DPC in aqueous alkaline medium at 25 °C.

\[ [\text{OH}'] = 0.05; \quad [\text{IO}_4^-] = 1.2 \times 10^{-5}; \quad I = 0.10 \text{ mol dm}^{-3}. \]

<table>
<thead>
<tr>
<th>[DPC] x 10^4 (mol dm⁻³)</th>
<th>[SMZ] x 10^4 (mol dm⁻³)</th>
<th>[DPN] x 10^4 (mol dm⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taken</td>
<td>Taken</td>
<td>Found</td>
</tr>
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</tr>
<tr>
<td>4.0</td>
<td>2.0</td>
<td>0.02</td>
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</table>
Reaction Order

The reaction orders were determined from the slope of log $k_{obs}$ versus log (concentration) by varying the concentrations of reductant and alkali in each while keeping all other concentrations and conditions constant.

Effect of [Diperiodatocuprate(III)]

The concentration of diperiodatocuprate(III) was varied in the range, $2.0 \times 10^{-5}$ to $2.0 \times 10^{-4}$ mol dm$^{-3}$ at fixed [Sulfamethoxazole], [OH$^-$], [IO$_4^-$] and ionic strength.

The non-variation in the pseudo-first order rate constants at various concentrations of DPC indicates the order in [DPC] as unity (Table IV (ii) (p. 111)). This was also confirmed from the linearity of plots of log absorbance versus time ($r \geq 0.9994$, $S \leq 0.026$) up to 80% completion of the reaction (Fig. IV (iii) (p. 112)).

Effect of [Sulfamethoxazole]

The substrate, sulfamethoxazole was varied in the range of $2.0 \times 10^{-4}$ to $2.0 \times 10^{-3}$ mol dm$^{-3}$ at 25 °C keeping all other reactants concentrations constant. The $k_{obs}$ values increased with the increase in concentration of sulfamethoxazole indicating an apparent less than unit order dependence on [Sulfamethoxazole] (Table IV (ii) (p. 111)) (Fig. IV (iv) (p. 115)) ($r \geq 0.9996$, $S \leq 0.0132$).

Effect of [Alkali]

The effect of [Alkali] on the rate of reaction was studied at constant concentrations of sulfamethoxazole, DPC, IO$_4^-$, and ionic strength of 0.10 mol dm$^{-3}$ at 25 °C.

The rate constants increased with increase in [Alkali]. The order in [Alkali] was
Table IV (ii)

Effect of variation of [DPC] and [Sulfamethoxazole] on Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

\[
[\text{IO}_4^-] = 1.2 \times 10^{-5}; \quad [\text{OH}] = 0.05; \\
I = 0.10 \text{ mol dm}^{-3}.
\]

<table>
<thead>
<tr>
<th>[DPC] x 10^4 (mol dm^-3)</th>
<th>[SMZ] x 10^3 (mol dm^-3)</th>
<th>(k_{\text{obs}} \times 10^3 \text{ (s}^{-1}))</th>
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</thead>
<tbody>
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<td>5.73</td>
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</tr>
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<td>6.66</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>7.52</td>
</tr>
</tbody>
</table>
Figure IV (iii)

First order plots of Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

\[ \text{[DPC]} \times 10^4 \ (\text{mol dm}^{-3}) : \]

1. 0.2; 2. 0.5; 3. 1.0; 4. 1.5; 5. 2.0

(Conditions as given in Table IV (ii) (p. 111))
Effect of [Periodate]
The effect of $[\text{IO}_4^-]$ was observed by varying the concentration from $1.2 \times 10^{-3}$ to $1.2 \times 10^{-4}$ mol dm$^{-3}$ at constant concentrations of diperiodatocuprate(III), sulfamethoxazole, alkali and constant ionic strength. It was found that the added periodate retarded the rate, and order in periodate was inverse fractional as shown in Table IV (iii) (p.114) and Figure IV (v) (p.116) ($r \geq 0.9995$, $S \leq 0.0125$).

Effect of Initially Added Products
The initially added products, such as Cu(II) and p-aminobenzenesulfonamide and 5-Methyl-3-isoxazolone did not show any significant effect on the rate of the reaction.

Effect of Ionic Strength
The effect of ionic strength was studied by varying the potassium nitrate concentration in the reaction medium. The ionic strength of the reaction medium was varied from 0.05 to 0.50 mol dm$^{-3}$ at constant [DPC], [Sulfamethoxazole], [IO$_4^-$] and [Alkali]. It was found that the ionic strength has a negligible effect on the rate of the reaction as in Table IV (iv) (p.117).

Effect of Solvent Polarity
The relative permittivity ($\varepsilon_T$) effect was studied by varying the t-butyl alcohol-water content in the reaction mixture with all other conditions being constant. Attempts to measure the relative permittivities of the mixture of t-butyl alcohol-
Table IV (iii)
Effect of variation of \([\text{OH}^-]\) and \([\text{IO}_4^-]\) on Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

\[
[\text{DPN}] = 1.0 \times 10^{-4}, \quad [\text{Sulfamethoxazole}] = 1.0 \times 10^{-3},
\]
\[I = 0.10 / \text{mol dm}^{-3}.
\]

<table>
<thead>
<tr>
<th>[OH(^-)] (mol dm(^{-3}))</th>
<th>[IO(_4^-)] \times 10(^4) (mol dm(^{-3}))</th>
<th>(k_{obs} \times 10^3) (s(^{-1}))</th>
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<td>5.73</td>
<td>5.71</td>
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<td>5.71</td>
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<td>2.0</td>
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<td>4.35</td>
<td></td>
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<td>2.72</td>
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<tr>
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<td>0.74</td>
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Figure IV (iv)

Order in [SMZ] and [OH'] on the Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

(Conditions as in Table IV (ii) (p.111) and IV (iii) (p.114))
Figure IV (v)

Order in [IO₄⁻] on the Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

(Conditions as in Table IV (iii) (p.114))
Table IV (iv)

Effect of Ionic Strength (I) and Relative Permittivity ($\varepsilon_r$) on the Oxidation of Sulfamethoxazole by DPC in an aqueous alkaline medium at 25 °C.

\[
\begin{align*}
[DPC] = 1.0 \times 10^{-4}; & \quad [DPC] = 1.0 \times 10^{-4}; \\
[SMZ] = 1.0 \times 10^{-3}; & \quad [SMZ] = 1.0 \times 10^{-3}; \\
[OH^-] = 0.05; & \quad [OH^-] = 0.05; \\
[IO_4^-] = 1.2 \times 10^{-5}/\text{mol dm}^{-3}. & \quad [IO_4^-] = 1.2 \times 10^{-5}; \\
I = 0.10/\text{mol dm}^{-3}.
\end{align*}
\]

<table>
<thead>
<tr>
<th>I (mol dm$^{-3}$)</th>
<th>$k_{obs} \times 10^3$ (s$^{-1}$)</th>
<th>% of *t-butanol-water</th>
<th>$\varepsilon_r$</th>
<th>$k_{obs} \times 10^3$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
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<td>77.14</td>
<td>5.65</td>
</tr>
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<td>0.10</td>
<td>5.73</td>
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<td>75.12</td>
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<td>5.69</td>
<td>10</td>
<td>71.74</td>
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<td>5.72</td>
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<td>64.98</td>
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</table>

* t-butanol-water (V/V)
water were not successful. However, they were computed from the values of pure liquids. It was also found that there was no reaction of the solvent with the oxidant under the experimental conditions used. The $k_{\text{obs}}$ values decreased with the decrease in the relative permittivity of the medium (Table IV (iv) (p.117)). The plot of $\log k_{\text{obs}}$ versus $1/\varepsilon_T$ was linear (Fig. IV (vi) (p.119) ($r \geq 0.9998$, $S \leq 0.0112$)) with a negative slope.

**Test for Free Radicals**

To test the intervention of free radicals, the reaction mixture was mixed with acrylonitrile monomer and kept for 24 hours under nitrogen atmosphere. On dilution with methanol, a white precipitate of polymer was formed, indicating the presence and intervention of free radicals in the reaction. The blank experiment of either DPC or SMZ in with acrylonitrile alone did not induce polymerization under the same condition as those induced with the reaction mixture. Initially added acrylonitrile decreases the rate indicating free radical intervention, which is also the case in earlier work.¹⁷

**Effect of Temperature**

The rate of reaction was measured at different temperatures under varying sulfamethoxazole concentration, keeping other conditions constant. The rate of reaction increased with the increase of temperature. The rate constants, $k$ of the slow step of the Scheme 1 were obtained from intercepts of the plots of $1/k_{\text{obs}}$ versus $1/[\text{Sulfamethoxazole}]$ ($r \geq 0.9998$, $S \leq 0.0152$) at different temperatures. The data are subjected to least square analysis as in chapter II (p.50) and were
Figure IV (vi)

Effect of Relative Permittivity ($\varepsilon_r$) on the Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

(Conditions as in Table IV (iv) (p.117)
tabulated in Table IV (v a) (p.121). The energy of activation corresponding to these constants was evaluated from the plot \((Y^* ca) \log k \) versus \(1/T\) (Fig. IV (vii) (p.122) \((r \geq 0.9989, S \leq 0.0135)\)) and other activation parameters are obtained as in chapter II (p.50) and are tabulated in Table IV (v b) (p.121).

**DISCUSSION**

The water-soluble Copper(III) periodate complex is reported \(^6,18\) to be \([\text{Cu} (\text{HIO}_6)_2(\text{OH})_2]^7\). However, in an aqueous alkaline medium and at a high pH range, as employed in the study, periodate is unlikely to exist as \(\text{HIO}_6^+(\text{as present in the complex})\) as is evident from its involvement in the multiple equalibria \(^19\) (2) to (4) depending on the pH of the solution.

\[
\begin{align*}
\text{H}_5\text{IO}_6 & \rightleftharpoons K_1 \quad \text{H}_4\text{IO}_6^- + \text{H}^+ \quad K_1 = 5 \times 10^{-4} \quad (2) \\
\text{H}_4\text{IO}_6^- & \rightleftharpoons K_2 \quad \text{H}_3\text{IO}_6^{2-} + \text{H}^+ \quad K_2 = 4.9 \times 10^{-9} \quad (3) \\
\text{H}_3\text{IO}_6^{2-} & \rightleftharpoons K_3 \quad \text{H}_2\text{IO}_6^{3-} + \text{H}^+ \quad K_3 = 2.5 \times 10^{-12} \quad (4)
\end{align*}
\]

Periodic acid (\(\text{H}_3\text{IO}_6\)) exists in acid medium and also as \(\text{H}_4\text{IO}_6^-\) at pH 7. Thus, under alkaline conditions, the main species are expected to be \(\text{H}_3\text{IO}_6^{2-}\) and \(\text{H}_2\text{IO}_6^{3-}\). At higher concentrations, periodate also tends to dimerise.\(^{20}\) Hence, at the pH employed in this study, the soluble copper(III) periodate complex exists as diperiodatocuprate(III), \([\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)_2]^{3-}\) in aqueous alkaline medium, a conclusion also supported by earlier work.\(^6\)

The results of rate increase with increase in alkalinity and the rate decrease with increase in [Periodate] (Table IV (iii) (p.114)) suggest that equilibria of
Table IV (v)

(a) Effect of temperature on the slow step of the mechanism of Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in an aqueous alkaline medium.

\[
\begin{align*}
[DPC] &= 1.0 \times 10^{-4}, \\
[OH^-] &= 0.05; \\
[I0_4] &= 1.2 \times 10^{-4}; \\
I &= 0.10 / \text{mol dm}^{-3}.
\end{align*}
\]

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>(k \times 10^2) (s(^{-1}))</th>
<th>(\log k) (Y)</th>
<th>(1/T \times 10^3) (X)</th>
<th>(Y_{\text{calc}})</th>
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<td>-1.6314</td>
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</table>

*Calculated

(b) Activation Parameters with respect to slow step of Scheme 1.

<table>
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<th>Activation Parameters</th>
<th>Values</th>
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<td>(E_a) (kJ mol(^{-1}))</td>
<td>30 ± 1.6</td>
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<tr>
<td>(\log A)</td>
<td>3.3 ± 0.2</td>
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<tr>
<td>(\Delta H^#) (kJ mol(^{-1}))</td>
<td>27 ± 1</td>
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<td>(\Delta S^#) (JK(^{-1}) mol(^{-1}))</td>
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<td>(\Delta G^#) (kJ mol(^{-1}))</td>
<td>88 ± 4</td>
</tr>
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</table>
Figure IV (vii)

Effect of temperature on the Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium.

(Conditions as in Table IV (v) (p.121))

\[ \frac{1}{T} \times 10^3 \text{ (K)} \]

\begin{array}{cccccccc}
3.08 & 3.13 & 3.18 & 3.23 & 3.28 & 3.33 & 3.38 \\
\end{array}

\[ \log k \text{ (Y*cai)} \]

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{figure}
\end{figure}
different Cu(III) periodate complexes as in equation (5) and (6) are possible.

\[
\begin{align*}
[Cu(OH)_2(H_3IO_6)_2]^{3+} + [OH^-] & \xrightleftharpoons{K_4} [Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4+} + H_2O \quad (5) \\
[Cu(OH)_2(H_3IO_6)(H_2IO_6)]^{4+} + [OH^-] & \xrightleftharpoons{K_5} [Cu(OH)_2(H_3IO_6)]^{5+} + H_2IO_6^{3-} \quad (6)
\end{align*}
\]

It may be expected that monoperiodatocuprate(III) (MPC) is more important in the reaction than the diperiodatocuprate(III) (DPC). The inverse fractional order in \([IO_4^-]\) might also be due to this reason. Added acrylonitrile monomer undergoes polymerization under inert atmosphere indicating the presence of free radical formation in the mixture.

The reaction between sulfamethoxazole and diperiodatocuprate(III) complex in alkaline medium has a 1 : 2 stoichiometry. The reaction exhibits first order dependence on \([DPC]\), apparent less than unit order in \([OH^-]\) and \([\text{Sulfamethoxazole}]\) and inverse fractional order in \([IO_4^-]\). The less than unit order in \([\text{Sulfamethoxazole}]\) presumably results from a complex (C) formation between the oxidant and substrate prior to the formation of the products. \(K_6\) is the composite equilibrium constant comprising the equilibrium to bind sulfamethoxazole to monoperiodatocuprate(III) (MPC) species to form a complex (C). Then this complex (C) reacts in a slow step to form an intermediate free radical species of sulfamethoxazole. This intermediate species further reacts with another molecule of MPC species in a fast step to yield the products. All the results indicate a mechanism as given in the Scheme 1.
\[
\begin{align*}
\text{Cu(II)HL}_2 + [\text{OH}^-] \quad &\xrightarrow{K_4} \quad \text{CuLHL} + \text{H}_2\text{O} \\
\text{CuLHL} \quad &\xrightarrow{K_5} \quad \text{Cu(II)HL} + \text{L} \\
\text{Cu(II)HL} + \text{S} \quad &\xrightarrow{K_6} \quad \text{Complex (C)} \\
\text{Complex (C)} \quad &\xrightarrow{k_{\text{slow}}} \quad \text{S}^- + \text{Cu(II)} \\
\text{S}^- + \text{Cu(IIHL)} \quad &\xrightarrow{\text{fast}} \quad \text{Product} + \text{Cu(II)}
\end{align*}
\]

Scheme 1. General Mechanistic Scheme for the Sulfamethoxazole Oxidation by Diperiodatocuprate(III).

\[
\begin{align*}
[\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)_2]^{3-} + [\text{OH}^-] \quad &\xrightarrow{K_4} \quad [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^{4+} + \text{H}_2\text{O} \\
[\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^{4+} \quad &\xrightarrow{K_5} \quad [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)]^{3+} + \text{H}_2\text{IO}_6^{3-} \\
[\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)]^{3+} + \text{H}_2\text{N}-\text{SO}_2-\text{NH}-\text{N} &\xrightarrow{K_6} \quad \text{Complex (C)} \\
\text{Complex (C)} \quad &\xrightarrow{k_{\text{slow}}} \quad \text{H}_2\text{N}-\text{SO}_2-\text{NH}-\text{N} + \text{Cu}^{2+} + \text{H}_2\text{IO}_6^{3-} + \text{H}_2\text{O}
\end{align*}
\]
Scheme 1. A Detailed Mechanistic Scheme for the Sulfamethoxazole Oxidation by Diperiodatocuprate(III).

The probable structure of complex (C) is

The spectral evidence for the complex (C) formation between oxidant and substrate was obtained from UV-Vis spectra of the oxidant and mixtures of substrate and oxidant. A bathochromic shift of about 5 nm from 257 to 262 nm is observed, and hyperchromicity is also observed at $\lambda_{\text{max}}$ of about 257 nm. Analogous effects upon complex (C) formation between a substrate and an oxidant
The formation of complex (C) is proved kinetically by the non-zero intercept of the plot of \(1/k_{obs} \) versus \(1/[\text{SMZ}]\) (\(r \geq 0.9998, S \leq 0.0152\)). The observed modest enthalpy of activation and a relatively low value of the entropy of activation as well as a higher rate constant of the slow step indicate that the oxidation presumably occurs via inner-sphere mechanism. This conclusion is supported by earlier observations. Since the Scheme 1 is in accordance with the generally well-accepted principle of non-complementary oxidations taking place in sequence of one-electron steps, the reaction between the substrate and oxidant would afford a radical intermediate. A free radical scavenging experiment revealed such a possibility. This type of radical intermediate has also been observed in earlier work.

Scheme 1 leads to the rate law (16) as follows

\[
\text{Rate} = k [C] \quad (7)
\]

From third step of Scheme 1, we have

\[
K_6 = \frac{[C]}{[\text{Cu(OH)}_2(H_3\text{IO}_6)][\text{SMZ}]} \]

\[
[C] = K_6 [\text{Cu(OH)}_2(H_3\text{IO}_6)][\text{SMZ}] \quad (8)
\]

From equation (7) and (8) we have

\[
\text{Rate} = k K_6 [\text{Cu(OH)}_2(H_3\text{IO}_6)][\text{SMZ}] \quad (9)
\]

\[
[\text{Cu(OH)}_2(H_3\text{IO}_6)] = \frac{K_2 [\text{Cu(OH)}_2(H_3\text{IO}_6)(\text{H}_2\text{IO}_6)^+] [\text{H}_2\text{IO}_6^2]}{[\text{H}_2\text{IO}_6^2]} \quad (10)
\]
But,

\[ [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^+ = K_4 [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)_2]^+ [\text{OH}^-] \]  

Substituting the values of equations (10) and (11) in equation (9)

\[
\text{Rate} = \frac{k K_4 K_5 K_6 [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)_2]^+ [\text{OH}^-] [\text{SMZ}]_T [\text{H}_2\text{IO}_6^3]}{[\text{H}_2\text{IO}_6^3]} 
\]

The total \([\text{DPC}], [\text{DPC}]_T\), is given by equation (13), (where the subscripts \(T\) and \(F\) stand for total and free respectively)

\[
[\text{DPC}]_T = [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)_2]^+ + [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^4 + [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)]^3 + [\text{C}] 
\]

Therefore

\[
[\text{SMZ}]_T = [\text{SMZ}]_F + [\text{C}] 
\]

Similarly

\[
[\text{SMZ}]_F = \frac{[\text{SMZ}]_T [\text{H}_2\text{IO}_6^3]}{[\text{H}_2\text{IO}_6^3] + K_4 K_5 K_6 [\text{OH}^-] [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)_2]^3} 
\]

In the view of low \([\text{DPC}]\) used, the term \(K_4 K_5 K_6 [\text{OH}^-] [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)_2]^3\) compared to \([\text{H}_2\text{IO}_6^3]\) can be neglected.

Hence,

\[
[\text{SMZ}]_T = [\text{SMZ}]_F 
\]

Similarly

\[
[\text{OH}^-]_T = [\text{OH}^-]_F + [\text{Cu(OH)}_2(\text{H}_3\text{IO}_6)(\text{H}_2\text{IO}_6)]^4 
\]
\[ [\text{OH}^-]_f = \frac{[\text{OH}^-]_i}{1 + K_4 [\text{Cu(OH)}_2 (\text{H}_3\text{I}_0_6)_2]^3} \]

Since,

\[ K_4 [\text{Cu(OH)}_2 (\text{H}_3\text{I}_0_6)_2]^3 \] is too small compared to unity,

\[ [\text{OH}^-]_t = [\text{OH}^-]_f \]

Substituting the values of \([\text{DPC}]_f\), \([\text{SMZ}]_f\) and \([\text{OH}^-]_f\) in equation (12), the rate law (16) results. On omitting subscripts \(t\) and \(f\).

\[
\text{Rate} = \frac{d [\text{DPC}]}{dt} = \frac{k K_4 K_5 K_6 [\text{DPC}] [\text{SMZ}] [\text{OH}^-]}{[\text{H}_2\text{I}_0_6^3^-] + K_4 [\text{OH}^-] [\text{H}_2\text{I}_0_6^3^-] + K_4 K_5 [\text{OH}^-] + K_4 K_5 K_6 [\text{SMZ}] [\text{OH}^-]} \tag{15}
\]

\[
\frac{\text{Rate}}{[\text{DPC}]} = \frac{k K_4 K_5 K_6 [\text{SMZ}] [\text{OH}^-]}{[\text{H}_2\text{I}_0_6^3^-] + K_4 [\text{OH}^-] [\text{H}_2\text{I}_0_6^3^-] + K_4 K_5 [\text{OH}^-] + K_4 K_5 K_6 [\text{SMZ}] [\text{OH}^-]} \tag{16}
\]

The rate law (16) may be verified by rearranging it in the form of equation (17)

\[
\frac{1}{k_{\text{obs}}} = \frac{[\text{H}_2\text{I}_0_6^3^-]}{k K_4 K_5 K_6 [\text{OH}^-] [\text{SMZ}]} + \frac{[\text{H}_2\text{I}_0_6^3^-]}{k K_5 K_6 [\text{SMZ}]} + \frac{1}{k K_6 [\text{SMZ}]} + \frac{1}{k} \tag{17}
\]

According to equation (17), the plots of \(1/k_{\text{obs}}\) versus \(1/[\text{SMZ}]\) \((r \geq 0.9998, S \leq 0.0152)\), \(1/[\text{OH}^-]\) \((r \geq 0.9989, S \leq 0.0121)\), \([\text{H}_2\text{I}_0_6^2^-]\) \((r \geq 0.9978, S \leq 0.0186)\) should be linear as shown in Figure IV (viii a) (p.129) and Figure IV (viii b) (p.130)). From the slopes and intercepts, the values of \(K_4, K_5, K_6\) and \(k\) could be derived as \(1.15 \pm 0.06 \text{ dm}^3 \text{ mol}^{-1}\), \((5.13 \pm 0.25) \times 10^6 \text{ mol dm}^{-3}\), \((4.87 \pm 0.24) \times 10^4\)

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Figure IV (viii a)

Verification of rate law (16) in the form of (17) on Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

(Conditions as in Table IV (ii) (p. 111) and Table IV (iii) (p. 114))
Verification of rate law (16) in the form of (17) on Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium at 25 °C.

(Conditions as in Table IV (iii) (p.114))
The value of $K_4$ is in agreement with the literature value. Using these constants, the rate constants were calculated over different experimental conditions and there is a reasonable agreement between the calculated and experimental values (Table IV (ii) (p.111) and Table IV (iii) (p.114)), which verifies the proposed mechanism.

The negligibly small effect of ionic strength on the reaction is presumably due to the fact that the reaction takes place between a neutral and charged species (Scheme 1). The effect of solvent on the reaction rate is described elsewhere. This effect was studied by varying the t-butyl alcohol-water content in the reaction mixture with all other conditions being constant. Increasing the content of t-butanol in the reaction medium leads to a decrease in the rate of reaction. The plot of $\log k_{\text{obs}}$ versus $1/\epsilon_T$ ($r \geq 0.9998$, $S \leq 0.0112$) is expected to be linear with a negative slope for a reaction between a negative ion and neutral molecule, whereas positive slope results for a positive ion and neutral molecule. In the present study, a plot of $\log k_{\text{obs}}$ versus $1/\epsilon_T$ ($r \geq 0.9998$, $S \leq 0.0112$) is linear with a negative slope (Fig. IV (vi) (p.119)) which supports the involvement of negative ions as given in Scheme 1.

The thermodynamic quantities for the first equilibrium step in the scheme 1 may be evaluated as follows. The [SMZ], hydroxide ion concentration and $H_3IO_6^{2-}$ ion concentration (Table IV (ii) (p.111) and Table IV (iii) (p.114)) was varied at five different temperatures. The plots of $1/k_{\text{obs}}$ versus $1/[\text{SMZ}]$ ($r \geq 0.9998$, $S \leq 0.0152$), $1/[\text{OH}^-]$ ($r \geq 0.9989$, $S \leq 0.0121$), $[H_3IO_6^{2-}]$ ($r \geq 0.9978$, $S \leq 0.0186$)
should be linear as shown in Figure IV (viii a) (p.129) and Figure IV (viii b) (p.130)). From the slopes and intercepts, the values of $K_4$, $K_5$, and $K_6$ were calculated at different temperatures and these values are given in Table IV (vi a) (p.133). A van't Hoff plot was made for the variation of $K_4$ with temperature i.e., $\log K_4$ versus $1/T$ ($r \geq 0.9999$, $S \leq 0.0108$) Figure IV (ix) (p. 134) and the values of the enthalpy of reaction, $\Delta H$, entropy of reaction, $\Delta S$, and free energy of reaction, $\Delta G$, were calculated for $K_4$. These values are given in Table IV (vi b) (p. 133). A comparison of the latter values with those obtained for the slow step of the reaction shows that these values mainly refer to the rate-limiting step, supporting the fact that the reaction before the rate-determining step is fairly slow and involves a high activation energy.\textsuperscript{26}

The moderate values of $\Delta H^*$ and $\Delta S^*$ were both favorable for electron transfer processes. The negative value of $\Delta S^*$ indicates that the complex(C) is more ordered than the reactants.\textsuperscript{27}

**IMPORTANCE OF CHAPTER IV**

Among various species of DPC in alkaline medium, monoperiodatocuprate (MPC) is considered as the active species for the title reaction. It becomes apparent that in carrying out this reaction, the role of pH in the reaction medium is crucial. The rate constant of the slow step and other equilibrium constants involved in the mechanism evaluated and activation parameters with respect to the slow step of the reaction were computed. The overall mechanistic sequence described here is consistent with product studies, mechanistic studies and kinetic studies.
Table IV (vi)

(a) Effect of temperature to calculate $K_4$, $K_5$, and $K_6$ for the Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in alkaline medium.

\[
\begin{align*}
[DPC] &= 1.0 \times 10^{-4}, \\
[OH^-] &= 0.05; \\
[I] &= 0.10 / \text{mol dm}^3.
\end{align*}
\]

\[
\begin{array}{cccc}
\text{Temperature (K)} & K_4 (\text{dm}^3 \text{mol}^{-1}) & K_5 \times 10^6 (\text{mol dm}^3) & K_6 \times 10^4 (\text{dm}^3 \text{mol}^{-1}) \\
298 & 1.14 & 5.13 & 4.87 \\
303 & 2.17 & 5.01 & 3.62 \\
308 & 3.66 & 4.88 & 2.65 \\
313 & 6.10 & 4.77 & 1.65 \\
318 & 9.72 & 4.64 & 0.84 \\
\end{array}
\]

(b) Thermodynamic quantities using $K_4$ values

\[
\begin{array}{ll}
\text{Thermodynamic quantities} & \text{Values} \\
\Delta H (\text{kJ mol}^{-1}) & 83.6 \pm 4.2 \\
\Delta S (\text{JK}^{-1} \text{mol}^{-1}) & 282 \pm 10 \\
\Delta G (\text{kJ mol}^{-1}) & -4.6 \pm 0.2 \\
\end{array}
\]
Figure IV (ix)

Effect of temperature on the Oxidation of Sulfamethoxazole by Diperiodatocuprate(III) in aqueous alkaline medium.

(Conditions as in Table IV (vi) (p.133))
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