CHAPTER III

KINETICS AND MECHANISM OF OXIDATION
OF METOCHLOPRAMIDE BY

CHLORAMINE-T IN HClO₄ MEDIUM
Section 3.1

OXIDATION OF METOCLOPRAMIDE: A REVIEW

Metochlopramide (MCP) is a frequently prescribed drug in adults and children as an anti-emetic activity with limited local anesthetic properties. Metochlopramide was found to possess central dopamine antagonist properties, and subsequently has been shown to be antipsychotic and for preventing vomiting induced by antineoplastic drugs. In addition, it has been widely used as gastrointestinal prokinetic drug for gastro esophageal reflux disease, dyspepsia, and diabetic gastoparesis.

Teng L et al. have reported the Metochlopramide metabolism and determination by high-pressure liquid chromatography. Here oxidative metabolite of metoclopramide was identified, where MCP is predominantly N-dealkylated to monodeethylmetoclopramide.

Kinetic study of the Maillard reaction between metoclopramide hydrochloride and lactose has reported by Zhihui Qiu et al.

Spectrophotometric determination metoclopramide has reported by Elazazy, Marwa S. et al. The method is based on the formation of tris (o-phenanthroline) iron (II) complex (Ferroin) upon the reaction of the cited drugs with iron (III)-o- phenanthroline mixture. Optimization of the experimental conditions was described.

Anodic stripping voltammetric determination of metoclopramide has reported by Farghaly, O. A. et al. Different parameters such as medium, supporting electrolyte, pH, accumulation potential, scan rate, accumulation time and ionic strength, were tested to optimize the conditions for the determination of MCP.

Antiemetic drug metoclopramide is a Substrate and Inhibitor of Cytochrome P450 2D6, a gastroprokinetic study has been reported by Z. Desta et al. Metochlopramide was predominantly N-dealkylated to monodeethylmetoclopramide, a metabolite that has not so far been described in humans. Formation rate of this metabolite followed Michaelis-Menten kinetics.
A review of the literature shows that kinetics of oxidation of MCP with CAT has not been reported. Hence it was found interesting to investigate the title reaction. Therefore in the present communication we report an investigation of the kinetic and mechanistic aspects of the oxidation of MCP with chloramine-T in HClO₄ at 313K.

Section 3.2

KINETICS OF OXIDATION OF METOCLOPRAMIDE BY CHLORAMINE-T IN HClO₄ MEDIUM

This section presents the kinetics and mechanism of oxidation of MCP by CAT in the presence of HClO₄ at 313K.

The details regarding the preparation of reagents and the experimental procedures are given in Section 1.8 of Chapter 1.

Stoichiometry

Reaction mixtures containing varying ratios of CAT to MCP in the presence of HClO₄ were equilibrated at 313K for 48 hours. Estimation of un-reacted CAT showed that one mole of MCP consumed two moles of oxidant, confirming the following stoichiometry

\[
C_{14}H_{22}O_{2}N_{3}Cl + 2RNClNa + 2H_{2}O \rightarrow C_{10}H_{11}O_{4}N_{2} Cl + N(C_{2}H_{5})_{2}H + 2RNH_{2} + 2Cl^{-} + 2Na^{+} \quad (3.1)
\]

Where R = CH₃C₆H₄SO₂.

Product analysis

The oxidation product 2-(4-amino-5-chloro-2-methoxybenzamido) acetic acid is identified by the spot tests. Further the product is confirmed by IR and GC-MS spectral analysis. IR spectral bands of the product observed are 3445 cm⁻¹ (N-H stretch); 3190 cm⁻¹ (CONH₂); 2810 cm⁻¹ (CH₂); 1693 cm⁻¹ (C=O); 3468 cm⁻¹ (-OH), and 3366 cm⁻¹ and 3234 cm⁻¹ (-NH₂); Aromatic C-H stretch, 3070, 3030 cm⁻¹. Where the mass spectrum (obtained using electron impact ionization technique) showed a molecular ion peak at 257 amu clearly confirms the identity of the product. The other oxidation product diethyl amine is identified
by spot tests. It was also observed that there was no further oxidation of these products under the present kinetic conditions.

*p*-toluenesulfonamide (CH₃C₆H₄NH₂), the reduction product of CAT was also extracted with ethyl acetate and identified by TLC⁴ using petroleum ether-chloroform-1-butanol (2:2:1 v/v) as the solvent system and iodine as spray reagent (Rᵣ = 0.84). Further, the molecular ion peak of 171amu clearly confirms p-toluene sulfonamide (PTS). All other peaks observed in GC-MS spectra are to be interpreted in accordance with the observed structure.

RESULTS

The oxidation of MCP by CAT in perchloric acid medium has been kinetically investigated at different initial concentrations of the reactants in the presence of HClO₄ at 313K.

Effect of reactants

With the substrate in excess ([MCP] >> [CAT]), at constant [HClO₄], [NaClO₄] and temperature, the [CAT]₀ was varied. Plots of log [CAT] versus time were linear (r > 0.986) indicating a first-order dependence of the rate on [CAT]₀. The pseudo first-order rate constants (k') calculated from the slopes are given in Table 3.1. Under similar experimental conditions, an increase in [MCP]₀ increased the k' values (Table 3.1). Plots of log k' versus log [MCP] was linear (Fig.3.1; r = 0.998) with a slope of 0.42 indicating a fractional-order dependence on [MCP]₀.

Effect of varying [HClO₄]

The [H⁺] was varied using HClO₄. The rate decreased with increase in [HClO₄] (Table 3.1). A plot of log k' versus log [HClO₄] was linear (Fig.3.1; r = 0.998) with a negative slope of 0.47 indicating an inverse fractional-order dependence of rate on [H⁺].

Effect of added p-toluene sulfonamide and halide ions

The addition of reduced product of oxidant, p-toluene sulfonamide (1x10⁻³-8x10⁻³ mol dm⁻³) had no significant effect on the rate indicating that, it is not involved in pre-
equilibrium step (Table 3.2). At constant $[\text{H}^+]$, addition of Cl$^-$ in the form of NaCl ($1 \times 10^{-3}$ - $8 \times 10^{-3}$ mol dm$^{-3}$), had no significant effect on the rate of reaction (Table 3.2).

**Effect of varying ionic strength and dielectric constant**

The reaction rate remained unaffected upon varying ionic strength of the medium by the addition of NaClO$_4$ (0.1 - 0.8 mol dm$^{-3}$). The dielectric permittivity of the medium was varied by adding different proportions (0 - 40 %, v/v) of methanol to the reaction mixture. The rate decreased with decrease in dielectric permittivity of the reaction mixture (Table 3.2). The plot of log $k'$ versus $1/D$ (Fig. 3.2), where $D$ is the dielectric permittivity of the medium ($D$ values are taken from the literature$^{11}$, gave a straight line with a negative slope. Blank experiments showed that methanol was not oxidized by CAT under the experimental conditions employed.

**Effect of solvent isotope effect**

Solvent isotope studies were performed in D$_2$O medium at 313K. Values of $k'(\text{D}_2\text{O})$ and $k'(\text{H}_2\text{O})$ were found to be $3.05 \times 10^{-4}$ s$^{-1}$ and $5.1 \times 10^{-4}$ s$^{-1}$, respectively, leading to a solvent isotope effect $k'(\text{H}_2\text{O})/k'(\text{D}_2\text{O}) = 1.67$.

**Effect of temperature**

The reaction was studied at different temperatures (313 – 323 K) keeping other experimental conditions constant (Table 3.3). From the linear Arrhenius plot of log $k'$ versus $1/T$ (Fig. 3.3; $r = 0.994$), the activation energy and other thermodynamic parameters for the composite reaction were computed. These are given in Table 3.3.

**Test for free radicals**

The addition of aqueous acrylonitrile solution to the reaction mixture in an inert atmosphere did not initiate polymerization, indicating the absence of free radical species in the reaction sequence.
Table 3.1

Effect of varying concentrations of oxidant, substrate and acid on the reaction rate constant.

<table>
<thead>
<tr>
<th>$10^4$[CAT] (mol dm$^{-3}$)</th>
<th>$10^3$ [MCP] (mol dm$^{-3}$)</th>
<th>$10^3$[HClO$_4$] (mol dm$^{-3}$)</th>
<th>$k \cdot 10^4$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
<td>5.10</td>
</tr>
<tr>
<td>4.0</td>
<td>2.0</td>
<td>1.0</td>
<td>5.15</td>
</tr>
<tr>
<td>6.0</td>
<td>2.0</td>
<td>1.0</td>
<td>5.11</td>
</tr>
<tr>
<td>8.0</td>
<td>2.0</td>
<td>1.0</td>
<td>5.08</td>
</tr>
<tr>
<td>2.0</td>
<td>0.4</td>
<td>1.0</td>
<td>2.52</td>
</tr>
<tr>
<td>2.0</td>
<td>0.8</td>
<td>1.0</td>
<td>3.20</td>
</tr>
<tr>
<td>2.0</td>
<td>4.0</td>
<td>1.0</td>
<td>6.31</td>
</tr>
<tr>
<td>2.0</td>
<td>5.0</td>
<td>1.0</td>
<td>6.90</td>
</tr>
<tr>
<td>2.0</td>
<td>10.0</td>
<td>1.0</td>
<td>9.40</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>0.3</td>
<td>8.80</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>0.5</td>
<td>7.00</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>3.70</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>5.0</td>
<td>2.22</td>
</tr>
<tr>
<td>2.0</td>
<td>2.0</td>
<td>10.0</td>
<td>1.60</td>
</tr>
</tbody>
</table>

$\mu = 0.5$ mol dm$^{-3}$; $T = 313$K.

Table 3.2

Effect of Variations of PTS, NaCl, NaClO$_4$ and MeOH on the reaction rate

<table>
<thead>
<tr>
<th>[PTS]$\times 10^3$ (mol dm$^{-3}$)</th>
<th>$10^4$ k (s$^{-1}$)</th>
<th>[NaCl]$\times 10^3$ (mol dm$^{-3}$)</th>
<th>$10^4$ k (s$^{-1}$)</th>
<th>[NaClO$_4$] (mol dm$^{-3}$)</th>
<th>$10^4$ k (s$^{-1}$)</th>
<th>CH$_3$OH (%, v/v)</th>
<th>$10^4$ k (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0</td>
<td>5.10</td>
<td>0.0</td>
<td>5.10</td>
<td>0.1</td>
<td>5.10</td>
<td>0.0</td>
<td>5.10</td>
</tr>
<tr>
<td>1.0</td>
<td>4.88</td>
<td>1.0</td>
<td>5.16</td>
<td>0.2</td>
<td>5.18</td>
<td>10.0</td>
<td>4.00</td>
</tr>
<tr>
<td>2.0</td>
<td>5.13</td>
<td>2.0</td>
<td>5.08</td>
<td>0.4</td>
<td>5.14</td>
<td>20.0</td>
<td>3.30</td>
</tr>
<tr>
<td>5.0</td>
<td>5.07</td>
<td>5.0</td>
<td>5.15</td>
<td>0.6</td>
<td>5.09</td>
<td>30.0</td>
<td>2.35</td>
</tr>
<tr>
<td>8.0</td>
<td>5.00</td>
<td>8.0</td>
<td>5.11</td>
<td>0.8</td>
<td>5.13</td>
<td>40.0</td>
<td>1.40</td>
</tr>
</tbody>
</table>

$[\text{CAT}] = 2 \times 10^{-4}$ mol dm$^{-3}$; $[\text{MCP}] = 2 \times 10^{-3}$ mol dm$^{-3}$;

$[\text{HClO}_4] = 1 \times 10^{-3}$ mol dm$^{-3}$; $\mu = 0.5$ mol dm$^{-3}$, $T = 313$K.
### Table 3.3

Effect of varying Metochlopramide concentrations at different temperature

<table>
<thead>
<tr>
<th>[MCP]x10³ mol dm⁻³</th>
<th>10⁴ k' (s⁻¹)</th>
<th>303K</th>
<th>308K</th>
<th>313K</th>
<th>318K</th>
<th>323K</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.4</td>
<td>1.45</td>
<td>1.90</td>
<td>2.52</td>
<td>3.85</td>
<td>6.00</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>2.10</td>
<td>2.80</td>
<td>3.60</td>
<td>5.40</td>
<td>8.90</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>2.60</td>
<td>3.74</td>
<td>5.10</td>
<td>7.60</td>
<td>10.4</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>3.30</td>
<td>5.00</td>
<td>6.31</td>
<td>11.9</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>3.60</td>
<td>5.70</td>
<td>6.90</td>
<td>12.8</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td>4.80</td>
<td>8.00</td>
<td>9.40</td>
<td>16.8</td>
<td>21.1</td>
<td></td>
</tr>
</tbody>
</table>

[CAT] = 2 x 10⁻⁴ mol dm⁻³; [HClO₄] = 1 x 10⁻³ mol dm⁻³; μ = 0.5 mol dm⁻³

### Table 3.4

Effect of Temperature on the reaction rate and Activation Parameters

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>10⁴ k' (s⁻¹)</th>
<th>10⁴k₃ (s⁻¹)</th>
<th>Activation Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>303</td>
<td>2.60</td>
<td>(4.84)</td>
<td>Eₐ (kJ mol⁻¹) 55.65 (46.10)</td>
</tr>
<tr>
<td>308</td>
<td>3.74</td>
<td>(6.90)</td>
<td>ΔH° (kJ mol⁻¹) 53.00 (43.68)</td>
</tr>
<tr>
<td>313</td>
<td>5.10</td>
<td>(9.69)</td>
<td>ΔS° (JK⁻¹mol⁻¹) -140.0 (134.5)</td>
</tr>
<tr>
<td>318</td>
<td>7.60</td>
<td>(16.70)</td>
<td>ΔG# (kJ mol⁻¹) 96.82 (92.20)</td>
</tr>
<tr>
<td>323</td>
<td>10.4</td>
<td>(19.20)</td>
<td>-                     -</td>
</tr>
</tbody>
</table>

[CAT] = 2 x 10⁻⁴ mol dm⁻³; [MCP] = 2 x 10⁻³ mol dm⁻³; [HClO₄] = 1 x 10⁻³ mol dm⁻³; μ = 0.5 mol dm⁻³

**Note:** Values in parenthesis are the decomposition constants and activation parameters for the rate-limiting step.
Fig 3.1 Plot of log(k') versus (a) log[MCP]; (b) log[HClO₄]

Fig 3.2 Plot of log(k') versus 1/D $10^2/D$
Fig. 3.3 Plot of log$k'$ versus $1/T$

Fig. 3.4 Plot of $1/k'$ versus (a)[MCP]^{-3}; (b)[H^+]x10^2
Fig. 3.5 Plot of $1/k'$ versus $1/[\text{MCP}]$.

Fig. 3.6 Plot of $\log k_3$ versus $1/T$. $10^3/T$. 

75
DISCUSSION

The oxidation potential of CAT-PTS red-ox couple varies with pH of the medium 1.139V at pH 0.65, 0.778V at pH 7.0 and 0.614V at pH 9.7. Bishop and Jennings, Hardy and Johnston, Morris et al and Pryde and Soper have formulated the following equilibria in aqueous acidic medium of CAT solutions:

\[
\begin{align*}
\text{RNCINa} & \rightleftharpoons \text{RNCI}^- + \text{Na}^+ \\
\text{RNCI}^- + \text{H}^+ & \rightleftharpoons \text{RNHCl} \\
2\text{RNHCl} & \rightleftharpoons \text{RNH}_2 + \text{RNCI}_2 \\
\text{RNCI}_2 + \text{H}_2\text{O} & \rightleftharpoons \text{RNHCl} + \text{HOCl} \\
\text{RNHCl} + \text{H}_2\text{O} & \rightleftharpoons \text{RNH}_2 + \text{HOCl} \\
\text{HOCl} & \rightleftharpoons \text{H}^+ + \text{OCl}^-
\end{align*}
\]

Where \( R = \text{CH}_3\text{C}_6\text{H}_4\text{S}0_2^- \).

The possible oxidizing species in acidified CAT solutions are therefore RNHCl, RNCI\(_2\) and HOCl. If RNCI\(_2\) were to be the reactive species then from (3.4) the rate law should predict a second order dependence of rate on [CAT]\(_0\), which is not observed at the present experimental conditions. Further (3.6) indicates that hydrolysis is slight and if HOCl is primarily involved a first order retardation of the rate by the added \( p \)-toluenesulfonamide is expected. However no such effect was noticed. It is therefore, probable that RNHCl is the reactive species. Further protonation of RNHCl at pH< 2 according to equation (3.8) has been reported.

\[
\text{RNHCl} + \text{H}^+ \rightleftharpoons \text{RNH}_2\text{Cl}^+
\]

Where, when \( R = p- \text{CH}_3\text{C}_6\text{H}_4\text{S}0_2^- \), \( K = 1.02 \times 10^2 \) at 298K, while with \( R = \text{C}_6\text{H}_5\text{S}0_2^- \), \( K = 61 \pm 5 \) at 298K.

In the present investigations, the retardation of rate by \( \text{H}^+ \) ion indicates that the unprotonated oxidant (RNHCl) is the active oxidizing species. Based on the preceding discussion the following scheme 3.1 is proposed to account the observed kinetics for the oxidation of MCP by CAT in acid medium:

76
\[
\begin{align*}
\text{RNH}_2\text{Cl}^+ & \xrightleftharpoons[k_1]{k_3} \text{RNHCl} + H^+ & \text{fast (i)} \\
\text{RNHCl} + \text{MCP} & \xrightarrow[k_2]{k_3} \text{X} & \text{fast (ii)} \\
\text{X} & \xrightarrow[k_3]{k_4} \text{X}^\cdot & \text{slow and r. d. s (iii)} \\
\text{X}^\cdot + \text{RNHCl} & \xrightarrow[k_4]{k_5} \text{products} & \text{fast (iv)}
\end{align*}
\]

**Scheme 3.1**

In scheme 3.1, MCP represent the substrate, X and \(X^\cdot\) represents the complex intermediate species whose structures are shown in Scheme 3.2, where a detailed plausible mechanism of oxidation of MCP with CAT in HClO₄ medium is illustrated.

From the slow step of Scheme 3.1,

\[
\text{rate} = -\frac{d[\text{CAT}]}{dt} = k_3[X]
\]

(3.9)

If \([\text{CAT}]_t\) represents the total effective concentration of CAT, then

\[
[\text{CAT}]_t = [\text{RNH}_2\text{Cl}^+] + [\text{RNHCl}] + [X]
\]

(3.10)

From which, solving for [X], one obtains

\[
X = \frac{K_1K_2[\text{CAT}]_t[\text{MCP}]}{[H^+] + K_1(1 + K_2[\text{MCP}])}
\]

(3.11)

Substituting equation (3.11) in equation (3.9), the following rate law can be obtained:

\[
\text{rate} = -\frac{d[\text{CAT}]}{dt} = \frac{K_1K_2k_3[\text{CAT}]_t[\text{MCP}]}{[H^+] + K_1(1 + K_2[\text{MCP}])}
\]

(3.12)

Rate law (3.12) is in agreement with the experimental results, where a first order dependence of rate on [CAT], a fractional order on [MCP] and an inverse fractional order in \([H^+]\) have been noted.

Since rate \(= k'[\text{CAT}]_t\), equation (3.12) can be transformed into equations \{(3.13)-(3.15)\}
Based on equations (3.14) and (3.15), plots of \(1/k'\) versus \(1/\text{[MCP]}\) and \(1/k'\) versus \([H^+]\) were found to be linear (Fig. 3.4). From the slopes and intercepts of these plots, values of formation constants \(K_1\) and \(K_2\) and decomposition constant \(k_3\) were calculated and found to be \(K_1 = 3.06 \times 10^{-4}\) mol dm\(^{-3}\); \(K_2 = 3.1 \times 10^3\) dm\(^3\) mol\(^{-1}\) and \(k_3 = 9.69 \times 10^{-4}\) s\(^{-1}\) respectively.

Since the rate was fractional in \([\text{MCP}]_0\), the Michaelis-Menten kinetics\(^{18}\) was adopted to study the effect of \([\text{MCP}]_0\) on rate at different temperatures (Table 3.3). By plotting \(1/k'\) versus \(1/[\text{MCP}]_0\) and using the calculated \(k_3\) values, activation parameters for the rate-limiting step were computed from the linear Arrhenius plot of log \(k_3\) versus \(1/T\) (Fig. 3.6, \(r=0.996\)). These data are presented in Table 3.4. On comparing the activation parameters for the composite reaction shows that the values largely refer to the rate limiting step supporting the fact that reaction before the rate limiting step is fast, involving low activation energy.

The effect of solvent on the reaction kinetics has been described by Laidler\(^{18}\) and Amis\(^{19}\). In the present investigation, a plot of log \(k'\) versus \(1/D\) was linear with a negative slope. This observation indicates the ion-dipole nature of the rate determining step in the reaction sequence and also points to extending of charge to the transition state.

The rate of the reaction is unaltered by the added PTS showing that it is not involved in a pre-equilibrium. The variation of ionic strength of the medium does not alter the rate indicating the involvement of the non-ionic species in the rate limiting step. Solvent isotope studies in D\(_2\)O medium show a retardation of the rate. It is well known that D\(_3\)O\(^+\) is a stronger acid than hydronium ion\(^{20}\) and, hence, this observation supports the proposed

\[
k' = \frac{K_1K_2k_1[MCP]}{[H^+] + K_1(1 + K_2[MCP])}
\]

(3.13)

\[
\frac{1}{k'} = \frac{1}{K_2k_3[MCP]} \left( \frac{[H^+]}{K_1} + 1 \right) + \frac{1}{k_3}
\]

(3.14)

\[
\frac{1}{k'} = \frac{[H^+]}{K_1K_2k_3[MCP]} + \frac{1}{K_2k_3[MCP]} + \frac{1}{k_3}
\]

(3.15)
mechanism. Addition of halide ions had no effect on the rate indicating that no interhalogen or free bromine is formed. All these results are in agreement with the proposed mechanism.

The proposed mechanism is also supported by the moderate values of energy of activation and other thermodynamic parameters (Table 3.4). The moderate value of $\Delta H^\#$ and the high negative value of $\Delta S^\#$ indicate that, the transition state is more ordered than the reactants.
Scheme 3.2
REFERENCE


