OXIDATION OF TRICYCLIC ANTIDEPRESSANTS: AN INTRODUCTION

Tricyclic antidepressants (TCAs) are heterocyclic chemical compounds and are used chiefly as antidepressants [89]. The TCAs were first discovered in the early 1950s. They contain three rings of atoms and are named after their chemical structure. In recent times, the TCAs have been largely replaced in clinical use in most parts of the world by newer antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which usually have minimal side-effects. However, TCAs are still important for a division of people who don’t respond to other types of antidepressants [89]. They are primarily used in the medical treatment of mood disorders such as major depressive disorder, dysthymia, and treatment-resistant variants. TCA’s also show efficiency in the clinical treatment of a number of different types of chronic pain particularly neuropathic pain and fibromyalgia. They are highly metabolised by the cytochrome P450 hepatic enzymes. The majority of the TCAs act mainly as serotonin-norepinephrine reuptake inhibitors (SNRIs) by blocking the serotonin transporter (SERT) and the norepinephrine transporter (NET), respectively. This results in an increase of the synaptic concentrations of these neurotransmitters which sequentially enhances the neurotransmission [90, 91]. Notably, the TCAs have insignificant affinity for the dopamine transporter and therefore have no efficacy as dopamine reuptake inhibitors.

Imipramine hydrochloride [IMP; (10,11-Dihydro-5-(3-(dimethylamino)propyl)-5H-dibenz[b,f]azepine hydrochloride] and Clomipramine hydrochloride [CLM; (3-(3-Chloro-10,11-dihydro-5H-dibenz[b,f]azepin-5-yl)propyldimethylamine hydrochloride] are important compounds of this group of drugs. The main function of these drugs is to block the reuptake of the neurotransmitters in the central nervous system and is widely used for the treatment of psychiatric patients suffering from clinical depression. Owing to the pharmaceutical applications of these drugs, various methods such as spectrophotometry [92, 93] and high pressure liquid chromatography [94] have been employed for its determination. Except for the work of Joanna Wisniewska et al [95], so far no other kinetic and mechanistic data are
available on the oxidation of IMP. Moreover, to the best of our knowledge there are no reports available in literature about the oxidation of CLM by any oxidants in respect of its kinetic and mechanistic studies. The work carried about by Wisniewska et al [95] has been cited here. The kinetics of oxidation of imipramine and opipramol using peroxydisulfate salts in the presence of a large excess of dibenzoazepine derivative in acidic sulfate media was studied by using UV–vis spectroscopy. The reaction between imipramine and S₂O₈²⁻ proceeds via the formation of two intermediates: a free organic radical and a dimeric dication. The rate constants were determined by numerical analysis based on ordinary differential equations. Reaction schemes were proposed and discussed.

In light of the above information and also the sparse comprehensive studies on the solution behaviour of IMP and CLM especially on their oxidation-kinetics and mechanisms it was, therefore, found to be a subject of interest and important to investigate the detailed mechanism of oxidation of these drugs with halogen +1 oxidant kinetically. In view of this, we describe herein the investigations carried out on the oxidation-kinetics of IMP and CLM with CAT in perchloric acid medium to explore the mechanistic aspects of these redox systems. Such a study may be beneficial to the kineticists who are working on the mechanistic chemistry of these two drugs in biological systems.
OXIDATION-KINETICS AND MECHANISM OF TRICYCLIC ANTIDEPRESSANTS WITH CHLORAMINE-T IN PERCHLORIC ACID MEDIUM

This chapter describes the results obtained on the kinetics and mechanism of oxidation of two tricyclic antidepressants viz., imipramine hydrochloride and clomipramine hydrochloride with CAT in perchloric medium at 300 K. The details regarding the preparation of reagents and the experimental procedures are similar to those reported in section 1.5 of Chapter 1.

Stoichiometry: Reaction mixtures containing varying proportions of CAT and substrates were equilibrated at 300 K in presence of 2.9 x 10⁻³ mol dm⁻³ HClO₄ for 24 h. An iodometric determination of the residual oxidant showed that one mole of CAT consumed per mole of the substrate, in both cases, confirming the following stoichiometry:

$$
\begin{align*}
\text{R} - \text{H}_{2}\text{N-N}=\text{CH}_{2}-\text{CH}_{2}-\text{CH}_{2}-\text{N}=\text{CH}_{3} + \text{TsNHClO}_{3} + \text{HClO}_{4} \rightarrow \\
\text{R} - \text{H}_{2}\text{N-N}=\text{CH}_{2}-\text{CH}_{2}-\text{CH}_{2-N}=\text{CH}_{3} + \text{TsNH}_{2} + \text{Na}^+ + \text{Cl}^- + \text{ClO}_{4}^- \\
(2.1)
\end{align*}
$$

Here R = -Cl for CLM and R= -H for IMP, and Ts= -C₆H₅SO₂⁻.

Product analysis: The reaction mixtures (1 mole of substrate and 1 mole of CAT in the presence of 2.9 x 10⁻³ mol dm⁻³ HClO₄) were allowed to progress for 6 – 8 h under stirred condition at 300 K. After completion of the reaction (monitored by TLC), the reaction products were neutralized with NaOH and then extracted with ether. The organic products were subjected to spot tests and chromatographic analysis (TLC technique), which revealed the formation of imipramine-5-N-oxide and clomipramine-5-N-oxide as the oxidation products of imipramine and clomipramine, respectively. The oxidation products were
separated by column chromatography. The products were confirmed by GC-MS analysis. The mass spectrum was obtained using the electron impact ionization technique. The mass spectra showed a molecular ion peak at 296 and 330 amu, clearly confirming imipramine-5-N-oxide and clomipramine-5-N-oxide, respectively (Figures 2.1 and 2.2). It was also observed that there was no further oxidation of these products under present kinetic conditions. The reduction product of CAT, p-toluenesulfonamide (PTS or TsNH₂), was extracted with ethyl acetate and detected by paper chromatography [96]. Benzyl alcohol saturated with water was used as the solvent with 0.5% vanillin in 1% HCl solution (in ethanol) as spray reagent (Rf = 0.905). It was further confirmed by GC MS analysis (Figure 2.3). All other peaks observed in GC-MS can be interpreted in accordance with the observed structure. Further, these 5-N-oxides also find clinical applications as antidepressants. Consequently, the present redox system developed was found to be an efficient method and the involvement of cost effective reagents makes the reaction simple and expedient for scaling this method for the industrial operation to synthesize imipramine-5-N-oxide and clomipramine-5-N-oxide with suitable modifications. Hence, this protocol for the synthesis of imipramine-5-oxide and clomipramine-5-oxide will be a valuable addition to the existing methods.

**Kinetic results:** Under pseudo-first-order conditions of [TCA]₀ >> [CAT]₀ at constant [TCA]₀, [HClO₄] and temperature, plots of log [CAT] versus time were linear (R² > 0.9927), indicating a first-order dependence of the rate on [CAT]₀. The values of pseudo-first-order rate constants (k' s⁻¹) are given in Table 2.1. The values of k' remain unaffected with a change in [CAT]₀, confirming the first-order dependence on [CAT]₀. The rate increased with increase in [TCA]₀ (Table 2.1). Plots of log k' versus log [TCA] were linear (Figure 2.4; R² > 0.9978) with slopes of 0.84 and 0.78 for IMP and CLM, respectively, indicating a fractional-order dependence of rate on [TCA]₀. The fractional order with respect to the substrate, presumably results from a complex formation between oxidant and substrate prior to the formation of products. Indeed, in the present case, it is to be noted that the plots of 1 / k' versus 1 / [TCA] were linear (Figure 2.5; R² > 0.9994) having a y-intercept which is in agreement with such a complex formation. This establishes the fractional-order dependence on [TCA]₀. The reaction rates are enhanced with increase in [HClO₄] (Table 2.1). Plots of log k' versus log [HClO₄]
were linear (Figure 2.6; \( R^2 > 0.9959 \)) with slopes equal to 0.38 and 0.47 for IMP and CLM respectively, showing a fractional-order dependence of rate on [HClO₄].

Addition of p-toluenesulfonamide (PTS or TsNH₂; 2.0 \( \times 10^{-3} - 8.0 \times 10^{-3} \) mol dm\(^{-3} \)), the reduction product of CAT, retards the rate of the reaction in both cases (Table 2.2). Further, log-log plots of \( k' \) versus [PTS] were linear (Figure 2.7; \( R^2 > 0.9994 \)) with negatives slopes of 0.36 and 0.31 for IMP and CLM respectively, indicating a negative fractional-order dependence of the rate on [PTS]. It also indicates that PTS is involved in a fast pre-equilibrium to the rate-determining step (rds) in the proposed reaction scheme (Scheme 2.1). In order to find out the nature of the reactive species, the dielectric constant (D) of the medium was varied by adding MeOH (0 - 30% v/v) to the reaction mixture by keeping all other experimental conditions constant. An increase in the rate was noticed with increase in MeOH content in both cases. Plots of log \( k' \) versus 1/ D were linear (Figure 2.8; \( R^2 > 0.9920 \)) with positive slopes. The results are reported in Table 2.3. The values of dielectric constant of MeOH-H\(_2\)O mixtures of different compositions are available in the literature [97-98]. Controlled experiments with MeOH indicated that its oxidation by CAT was negligible (< 2 %) under the present set of experimental conditions. However, the rate constants were corrected to present only the oxidation of IMP and CLM.

Effect of ionic strength of the reaction system on the rate of the reaction was studied by adding 0.3 mol dm\(^{-3} \) NaClO₄ solution to the reaction mixture. It was noticed that there was no remarkable change on the rate of the reaction. Hence, no attempt was made to keep the ionic strength of the system constant for kinetic runs. The rate remained constant with the addition of Cl\(^-\) or Br\(^-\) ions in the form of NaCl or NaBr (2.0 \( \times 10^{-2} \) mol dm\(^{-3} \)), indicating that no inter halogen compound or free chlorine was formed. As a dependence of the rate on hydrogen ion concentration was noticed, solvent isotope studies were made using D\(_2\)O for both the drugs. Studies of the reaction rate in D\(_2\)O medium for IMP and CLM revealed that \( k' \) (H\(_2\)O) was equal to 7.54 \( \times 10^{-4} \) s\(^{-1} \) and 4.80 \( \times 10^{-4} \) s\(^{-1} \), and \( k' \) (D\(_2\)O) was 9.20 \( \times 10^{-4} \) s\(^{-1} \) and 6.38 \( \times 10^{-4} \) s\(^{-1} \) respectively. The solvent isotope effect \( k' \) (H\(_2\)O) / \( k' \) (D\(_2\)O) was found to be 0.82 and 0.75 for IMP and CLM. The reaction rates were determined at different temperatures.
(290 - 310 K), keeping the other experimental conditions the same. Based on the Arrhenius plots of log $k'$ versus 1 / $T$ (Figure 2.9; $R^2 > 0.9908$), activation energy and other thermodynamic parameters were computed for the overall reaction. All these results are summarized in Table 2.4. The oxidation reaction fails to induce the polymerization of the added acrylonitrile, indicating the absence of the formation of any free radical during the reaction sequence.

**Discussion:** Chloramine-T (TsNClNa) is a mild and effective oxidizing agent in both acid and base due to its versatile behaviour [1]. In general, CAT undergoes a two electron change in its reactions forming the reduction products, PTS and sodium chloride [9]. The oxidation potential of CAT-PTS redox couple is pH dependant and it decreases with increase in pH of the medium. Chloramine-T behaves as a strong electrolyte in aqueous solutions [8] and depending on the pH of the medium, it furnishes following equilibria in aqueous solutions [8, 10-13]:

$$\text{TsNClNa} \rightleftharpoons \text{TsN-Cl} + \text{Na}^+ \quad (2.2)$$

$$\text{TsN-Cl} + \text{H}^+ \rightleftharpoons \text{TsNHCl} \quad (2.3)$$

$$2 \text{TsNHCl} \rightleftharpoons \text{TsNH}_2 + \text{TsNCl}_2 \quad (2.4)$$

$$\text{TsNHCl} + \text{H}_2\text{O} \rightleftharpoons \text{TsNH}_2 + \text{HOCl} \quad (2.5)$$

$$\text{TsNCl}_2 + \text{H}_2\text{O} \rightleftharpoons \text{TsNHCl} + \text{HOCl} \quad (2.6)$$

$$\text{TsNHCl} + \text{H}^+ \rightleftharpoons \text{TsN}^+\text{H}_2\text{Cl} \quad (2.7)$$

$$\text{TsN}^+\text{H}_2\text{Cl} + \text{H}_2\text{O} \rightleftharpoons \text{TsNH}_2 + \text{H}_2\text{O}^+\text{Cl} \quad (2.8)$$

$$\text{HOCl} \rightleftharpoons \text{H}^+ + \text{O Cl} \quad (2.9)$$

$$\text{HOCl} + \text{H}^+ \rightleftharpoons \text{H}_2\text{O}^+\text{Cl} \quad (2.10)$$

Therefore, the possible oxidizing species in acidified CAT solutions are TsNHCl, TsNCl$_2$, HOCl and possibly H$_2$O$^+\text{Cl}$ and in alkaline solutions they are TsNHCl, HOCl, TsN$^-\text{Cl}$ and O$^-\text{Cl}$. Further, formation of species of the type TsN$^+\text{H}_2\text{Cl}$ has been reported [99-100] with CAT in acid medium and the protonation constant for the reaction TsNHCl + H$^+ \rightleftharpoons \text{TsN}^+\text{H}_2\text{Cl}$ is found to be 1.02 x 10$^2$ at 298 K. If dichloramine-T (TsNCl$_2$) were to
be the reactive species, then the rate law predicts a second-order dependence of rate on [CAT]₀ (Eq. (2.4)), which is contrary to the experimental observations. In the present study, the rate of the reaction increases with increase in [H⁺] but it is retarded by the added p-toluenesulfonamide (TsNH₂). Further, chloramine-T contains a polar N-Cl bond as the source of positive chlorine Cl⁺ species, which forms the conjugate acid TsNHCl, in acidic solutions. This conjugate acid with N-Cl bond intact interacts with H₂O⁺ to form the reactive oxidant species, H₂O⁺Cl, and the p-toluenesulfonamide (TsNH₂) as shown in Scheme 2.1.

The pKa of substrates IMP and CLM were reported as 9.5 and hence these drugs are basic in nature [101]. Consequently, they get readily protonated in acidic pH. The present redox system was studied around pH 3, which is less than pKa of the drugs and hence form B of the substrate is considered as the reactive species. The protonation of these drugs is as shown below:

Free drug (Form A)  
\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} & \quad \text{CH}_3
\end{align*}
\]

Ionized drug (Form B)  
\[
\begin{align*}
\text{R} & \quad \text{N} \\
\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{N} & \quad \text{CH}_3
\end{align*}
\]

Based on the preceding discussion and experimental observations, a tentative mechanism (Scheme 2.1) for the oxidation of IMP and CLM with CAT in acid medium has been proposed:
Scheme 2.1 A detailed reaction scheme for the oxidation of TCA-CAT redox system in acid medium

In a fast pre-equilibrium (step (i) of Scheme 2.1), the protonation and subsequent hydrolysis of TsNHCl yields the reactive oxidizing species H$_2$O$^+$Cl, with the elimination of TsNH$_2$. In the next fast equilibrium step, (step (ii)), lone pair of electrons on the nitrogen atom of the substrate reacts with positive chlorine of the oxidizing species to form an intermediate complex (X). Further, in the next slow and rate-determining step, (step (iii)), X undergoes a nucleophilic attack of water molecule to yield the final products 5-N oxides with the elimination of a molecule of HCl.
If $[\text{CAT}]_0$ represents the total concentration of $[\text{CAT}]$, then

$$[\text{CAT}]_0 = [\text{TsNHCl}] + [\text{H}_2\text{O}^+\text{Cl}] + [X]$$  \hspace{1cm} (2.11)

From steps (i) and (ii) of Scheme 2.1,

$$[\text{TsNHCl}] = \frac{[\text{TsNH}_2][X]}{K_1K_2[H_2O^+][\text{TCA}]}$$  \hspace{1cm} (2.12)

$$[\text{H}_2\text{O}^+\text{Cl}] = \frac{[X]}{K_2[\text{TCA}]}$$  \hspace{1cm} (2.13)

By substituting for $[\text{TsNHCl}]$ and $[\text{H}_2\text{O}^+\text{Cl}]$ from Eq. (2.12) and Eq. (2.13) respectively into Eq. (2.11) and solving for $X$, we get

$$[X] = \frac{K_1K_2[\text{CAT}]_0[\text{TCA}][H_2O^+]}{[\text{TsNH}_2]+K_1[H_2O^+]+K_1K_2[\text{TCA}][H_2O^+]}$$  \hspace{1cm} (2.14)

From the slow and rate-determining step (step(iii)) of Scheme 2.1,

Rate $= k_3[X]$  \hspace{1cm} (2.15)

By substituting for $[X]$, from Eq. (2.14) into Eq. (2.15), the following rate law is obtained:

Rate $= \frac{K_1K_2k_3[\text{CAT}]_0[\text{TCA}][H_2O^+]}{[\text{TsNH}_2]+K_1[H_2O^+]+K_1K_2[\text{TCA}][H_2O^+]}$  \hspace{1cm} (2.16)

Rate law (2.16) is in good agreement with the experimental results, wherein a first-order dependence of rate on $[\text{CAT}]_0$, fractional-order dependence each on $[\text{TCA}]_0$ and $[\text{H}^+]$, and an inverse-fractional order on $[\text{TsNH}_2]$ was observed.

Since Rate $= k' [\text{CAT}]_0$, under pseudo-first order conditions of $[\text{CAT}]_0 \ll [\text{TCA}]_0$, Eq. (2.16) can be transformed as Eq. (2.17), Eq. (2.18) and Eq. (2.19):

$$k' = \frac{K_1K_2k_3[\text{TCA}][H_2O^+]}{[\text{TsNH}_2]+K_1[H_2O^+]+K_1K_2[\text{TCA}][H_2O^+]}$$  \hspace{1cm} (2.17)

$$\frac{1}{k'} = \frac{[\text{TsNH}_2]}{K_1K_2k_3[\text{TCA}][H_2O^+]} + \frac{1}{K_2k_3[\text{TCA}]} + \frac{1}{k_3}$$  \hspace{1cm} (2.18)

$$\frac{1}{k'} = \frac{1}{[\text{TCA}]} \left\{ \frac{[\text{TsNH}_2]}{K_1K_2k_3[H_2O^+]} + \frac{1}{K_2k_3} \right\} + \frac{1}{k_3}$$  \hspace{1cm} (2.19)
According to Eq. (2.18) and Eq. (2.19), in order to deduce equilibrium and decomposition constants, the reaction has been studied in presence of $2.0 \times 10^{-3}$ mol dm$^{-3}$ p-toluenesulfonamide (TsNH$_2$) by varying the concentrations of TCA and HClO$_4$ in the range given in Table 2.1.

From Eq. (2.18), plot of $1 / k'$ versus $1 / \left[ \text{H}^+ \right]$ at constant [TCA] and [TsNH$_2$] were linear (Figure 2.10; $R^2 > 0.9907$) with

\[
\text{slope} = \frac{[\text{TsNH}_2]}{K_j \cdot k_j \cdot \left[ \text{TCA} \right]} \quad \text{and intercept} = \frac{1}{K_j \cdot k_j \cdot \left[ \text{TCA} \right]} + \frac{1}{k_3}.
\]

From Eq. (2.19) plots of $1 / k'$ versus $\left[ \text{TCA} \right]$ at constant $\left[ \text{H}^+ \right]$ and $[\text{TsNH}_2]$ were linear (Figure 2.13; $R^2 = 0.9910$) with

\[
\text{slope} = \frac{[\text{TsNH}_2]}{K_j \cdot k_j \cdot \left[ \text{H}_3\text{O}^+ \right]} + \frac{1}{K_j \cdot k_j \cdot \left[ \text{H}_3\text{O}^+ \right]} \quad \text{and intercept} = \frac{1}{k_3}.
\]

From the slopes and the intercepts of the above plots, the values of equilibrium constants $K_j$ and $K_2$, and the decomposition constant $k_3$ were found to be 0.6 and 0.5, 84 and 151 mol dm$^{-3}$ and $5.0 \times 10^{-3}$ and $1.66 \times 10^{-3}$ s$^{-1}$ for IMP and CLM, respectively. This proves the validity of rate law (2.16) and hence the proposed reaction scheme 2.1. The proposed scheme and the derived rate law are also supported by the experimental observations discussed below.

Since the rate was fractional-order in [TCA]$_0$, Michaelis-Menten kinetics [102] were adopted. In order to evaluate thermodynamic parameters for the rate-determining step, the $k_3$ values were determined by varying the concentration of both the drugs in the range given in Table 2.1 at different temperatures (290 – 310 K) at constant $[\text{TsNH}_2] = 2.0 \times 10^{-3}$ moldm$^{-3}$. The activation parameters for the rate-determining step were evaluated using Arrhenius plots of log $k_3$ versus $1 / T$ (Figure 2.12; $R^2 > 0.9959$). All these results are compiled in Table 2.4. The proposed mechanism and the derived rate law are supported by the following experimental findings:
As expected for a H\(^+\) catalyzed reaction, the rate of the reaction increased in D\(_2\)O medium and hence the proposed mechanism is supported by this observation. For a reaction involving a fast equilibrium H\(^+\) or OH\(^-\) ion transfer, the rate increases in D\(_2\)O since D\(_3\)O\(^+\) and OD\(^-\) which are stronger acid and stronger base (~2–3 times greater), respectively, than H\(_3\)O\(^+\) and OH\(^-\) ions [64,65]. The increase of reaction rate with D\(_2\)O observed in the present studies and the solvent isotope effect which is \(k'\) (H\(_2\)O) / \(k'\) (D\(_2\)O) < 1 conform to the above theory. However, the magnitude of acceleration in D\(_2\)O is small compared to the expected value, which can be attributed to the fractional order dependence of rate on [H\(^+\)].

A change in the solvent composition by varying the methanol content in methanol-water affects the reaction rate. The effect of solvent on the reaction kinetics has been described in detail in the well-known monographs of Laidler and Eyring [103], Benson [104], Frost and Pearson [78], Laidler and Landskroener [60], Amis and Jaffe [58], and Entelis and Tiger [63]. For the limiting case of zero angle of approach between two dipoles or an ion dipole system, Amis and Jaffe [58] has shown that a plot of log \(k'\) versus 1 / D gives a straight line, with a negative slope for a reaction between a negative ion and a dipole or between the dipoles, while a positive slope results for a positive ion-dipole interaction (Eq. (1.25)). In the present observations, plots of log \(k'\) versus 1 / D were linear with positive slopes (Figure 2.8) and hence the later concept agrees where a positive ion and a dipole are involved in the rate-determining step of the proposed scheme (Scheme 2.1).

The proposed reaction mechanism is also evinced by the observed effect of ionic strength on the rate of the reaction. The primary salt effect on the reaction rates has been described by Bronsted and Bjerrum [54] theory. According to this concept, the effect of ionic strength (\(\mu\)) on the rate of a reaction involving two ions is given by Eq. (1.23). This equation (1.23) shows that a plot of log \(k'\) versus \(\mu^{1/2}\) would be linear. In the present case, the slope of such a plot is zero. It implies that a positive charge and a neutral molecule is involved in the rate-determining step (step (iii) of Scheme 2.1). Hence, variation of the ionic strength of the medium does not alter the rate in both the cases clearly conform to the above theory.
The relative reaction rates and activation energies indicate that the IMP oxidation is faster when compared to CLM. Since chlorine is present at the meta position, the electron-withdrawing inductive effect dominates and thus it deactivates the ring which makes the nitrogen atom of the ring less reactive towards the reactive oxidant species. Hence, the rate of oxidation of CLM is comparatively slower than IMP. The proposed mechanism and the related rate law are supported by the moderate values of energy of activation and other activation parameters. The fairly high positive values of $\Delta G^\ddagger$ and $\Delta H^\ddagger$ indicate that the transition state is highly solvated, while the high negative $\Delta S^\ddagger$ suggests the formation of a rigid associative transition state with a reduction in the degrees of freedom of molecules in both the drugs. The values of $\Delta G^\ddagger$ are almost the same in both the cases suggesting that the oxidation of IMP and CLM with CAT proceeds by a similar mechanism.

**Conclusion:** Based on the present research work, the following conclusive remarks are drawn:

- The oxidation reaction follows similar kinetic patterns for both the drugs.
- The reaction obeys the experimental rate law: $\text{rate} = k^I [\text{CAT}]_0 [\text{TCA}]^x [\text{HClO}_4]^y [\text{PTS}]^z$, where $x,y,z < 1$.
- The rate of oxidation of IMP is faster than CLM.
- The thermodynamic parameters and reaction constants were evaluated.
- Reaction mechanism and the rigorous kinetic modeling proposed fitting well with the experimental data.
- In the course of this research, optimum conditions for the facile oxidative conversion of IMP and CLM to the corresponding 5-N oxides were established.
Table 2.1 Effect of variation of [CAT]₀, [TCA]₀ and [HClO₄] on the reaction rate at 300 K.

<table>
<thead>
<tr>
<th>10⁴ [CAT]₀ (moldm⁻³)</th>
<th>10³ [TCA]₀ (mol dm⁻³)</th>
<th>10³ [HClO₄] (mol dm⁻³)</th>
<th>10⁴ k' (s⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IMP</td>
</tr>
<tr>
<td>1.0</td>
<td>4.0</td>
<td>2.9</td>
<td>7.62</td>
</tr>
<tr>
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<td>4.0</td>
<td>2.9</td>
<td>7.54</td>
</tr>
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<td>4.0</td>
<td>2.9</td>
<td>7.65</td>
</tr>
<tr>
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<td>15.0</td>
<td>13.7</td>
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**Table 2.2** Effect of variation of p-toluenesulfonamide (PTS) concentration on the reaction rate at 300 K.

<table>
<thead>
<tr>
<th>$10^3$ [PTS] (mol dm$^{-3}$)</th>
<th>$10^4 k'$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMP</td>
</tr>
<tr>
<td>0.00</td>
<td>7.54</td>
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<tr>
<td>2.00</td>
<td>7.24</td>
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<td>4.00</td>
<td>5.24</td>
</tr>
<tr>
<td>5.00</td>
<td>4.79</td>
</tr>
<tr>
<td>8.00</td>
<td>3.98</td>
</tr>
</tbody>
</table>

Experimental conditions: $[\text{CAT}]_o = 2.0 \times 10^{-4}$ mol dm$^{-3}$; $[\text{TCA}]_o = 4.0 \times 10^{-3}$ mol dm$^{-3}$; $[\text{HClO}_4] = 2.9 \times 10^{-3}$ mol dm$^{-3}$.

**Table 2.3** Effect of variation of dielectric constant of the medium on the reaction rate at 300K.

<table>
<thead>
<tr>
<th>% [MeOH] (v/v)</th>
<th>D</th>
<th>$10^4 k'$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IMP</td>
</tr>
<tr>
<td>0.0</td>
<td>76.73</td>
<td>7.54</td>
</tr>
<tr>
<td>10.0</td>
<td>72.37</td>
<td>8.48</td>
</tr>
<tr>
<td>20.0</td>
<td>67.48</td>
<td>9.32</td>
</tr>
<tr>
<td>30.0</td>
<td>62.71</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Experimental conditions: $[\text{CAT}]_o = 2.0 \times 10^{-4}$ mol dm$^{-3}$; $[\text{TCA}]_o = 4.0 \times 10^{-3}$ mol dm$^{-3}$; $[\text{HClO}_4] = 2.9 \times 10^{-3}$ mol dm$^{-3}$.
Table 2.4 Effect of variation of temperature on the reaction rate and values of activation parameters.

<table>
<thead>
<tr>
<th>Temperature (K)</th>
<th>10^4 k_1 (s^{-1})</th>
<th>10^3 k_2 (s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>290</td>
<td>3.90 (1.66)</td>
<td>2.58 (1.11)</td>
</tr>
<tr>
<td>295</td>
<td>4.86 ( --- )</td>
<td>3.36 ( --- )</td>
</tr>
<tr>
<td>300</td>
<td>7.54 (2.50)</td>
<td>4.80 (1.43)</td>
</tr>
<tr>
<td>305</td>
<td>9.98 (3.30)</td>
<td>5.92 (2.0)</td>
</tr>
<tr>
<td>310</td>
<td>15.8 (4.0)</td>
<td>9.40 (2.64)</td>
</tr>
<tr>
<td>Ea (kJ mol^{-1})</td>
<td>38.3 (32.6)</td>
<td>46.7 (38.5)</td>
</tr>
<tr>
<td>ΔH^o (kJ mol^{-1})</td>
<td>35.8 (30.1)±0.01</td>
<td>44.2 (35.8)±0.01</td>
</tr>
<tr>
<td>ΔG^o (kJ mol^{-1})</td>
<td>91.5 (88.6)±0.09</td>
<td>92.7 (90.0)±0.002</td>
</tr>
<tr>
<td>ΔS^o (JK-1 mol^{-1})</td>
<td>-185 (-194)±0.03</td>
<td>-161 (-180)±0.08</td>
</tr>
<tr>
<td>Log A</td>
<td>6.94±0.06</td>
<td>8.56±0.24</td>
</tr>
</tbody>
</table>

Values in the parentheses refer to the rate-determining step.

Experimental conditions: [CAT]_o = 2.0 x 10^{-4} mol dm^{-3}; [TCA]_o = 4.0 x 10^{-3} mol dm^{-3}; [HClO_4] = 2.9 x 10^{-3} mol dm^{-3}.  

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Figure 2.1 GC-Mass spectrum of imipramine-5-N-oxide with a molecular ion peak at 296 amu.

Figure 2.2 GC-Mass spectrum of clomipramine-5-N-oxide with a molecular ion peak at 330 amu.
Figure 2.3 GC-Mass spectrum of p-toluenesulfonamide with a molecular ion peak at 171 amu.

Figure 2.4 Plots of log $k'$ versus log [TCA]
Figure 2.5 Plots of $1/k'$ versus $1/[TCA]$.

Figure 2.6 Plots of $\log k'$ versus $\log [\text{HClO}_4]$.
Figure 2.7 Plots of log $k'$ versus log [PTS]

Figure 2.8 Plots of log $k'$ versus $1/D$
Figure 2.9 Plots of log k' versus 1 / T

Figure 2.10 Double reciprocal plots of 1 / k' versus 1 / [H+]
Figure 2.11 Double reciprocal plots of $1/k'$ versus $1/[\text{TCA}]$

Figure 2.12 Plots of $\log k_3$ versus $1/T$