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A kinetic and mechanistic study of oxidative degradation of ciprofloxacin in aqueous acidicmedium

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Abstract:

The kinetics and mechanism of Ciprofloxacin [CIP] oxidation in $HClO_4$ medium with sodium N- chloro-p-toluene sulfonamide or chloramine-T (CAT) was investigated at 303 K. The rate of reaction was followed by first-order kinetics on [CAT] and [CIP] and inversely proportional to [H+] concentration. Activation parameters were assessed and the reaction was examined at various temperatures. P-toluene sulfonamide addition slows down the rate of reaction. 7-amino fluoroquinolone and p-toluene sulfonamide were the oxidation products detected, and the reaction's stoichiometry was found to be 1: 2. A mechanism and rate law have been proposed to account for the observed results.

Keywords – stoichiometry, mechanism**,** kinetics**,** Activation parameters.

INTRODUCTION:

Environmental problems are raised by the fate of antibiotic parent and metabolite chemicals that enter environmental ecosystems through several mechanisms. The possibility is antibiotics released into the aquatic environment could contaminate drinking water is a serious concern, Worldwide. As a result, the use of significant doses of antibiotics, hormones, analgesics,sedatives, medications, and various disinfectant preparations, as well as the difficulty in completely inactivating them in water treatment, has been a serious issue[1]. The use of pollutedwater contaminated with pharmaceutical residues and their metabolites disrupts body equilibrium and increases harmful drug resistance, causing major difficulties for human health [2].

There have been several studies of FQ contamination in surface water, ground water, discharge of waste sample, and other aquatic forms reported. The current study is therefore oxidative in nature, as drug modifications in their natural habitat are most likely to follow anoxidation path. The goal of the current study was to calculate the reaction kinetics and elucidate the reaction pathways involved in oxidative degradation of the environmentally relevant antibacterial drugs in an acidic/alkaline aqueous media.

Ciprofloxacin(1-cyclopropyl-l–6–fluoro-1,4-dihydro-4-oxo-7-(piperazinyl)–quinolone-3 - carboxylic acid) (CIP) is one of the most commonly used fluoroquinolones in hospitals, where they find their way into the various environmental compartments because there is no regulation of concentration limits for such compounds. **(Fig.1)** depicts the structure of (CIP), which contains piperazine and pyridone moieties. Several investigators have demonstrated CIP oxidation by various oxidants [3-7].

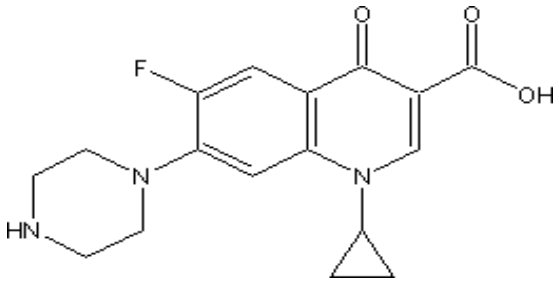


Fig. 1: Structure of Ciprofloxacin

The Sodium N-chloro p-toluene sulfonamide or chloramine–T (p- $CH_3C_6H_4SO_2NClNa.3H_2O$) or (CAT) is a prominent member of the classof N-haloaryl sulfonamides. Chloramine-T species are pH-dependent, and differentiating them in acid media is more difficult due to an interaction of such species governed by several types of equilibrium (8,9).

In general, CAT undergoes at two-electron hang in its reactions, yielding p- toluene Sulfonamide or PTS (p - $CH_3C_6H_4SO_2NH_2$) and sodium chloride asreduction products. Because hypochlorite and CAT can operate as chlorine

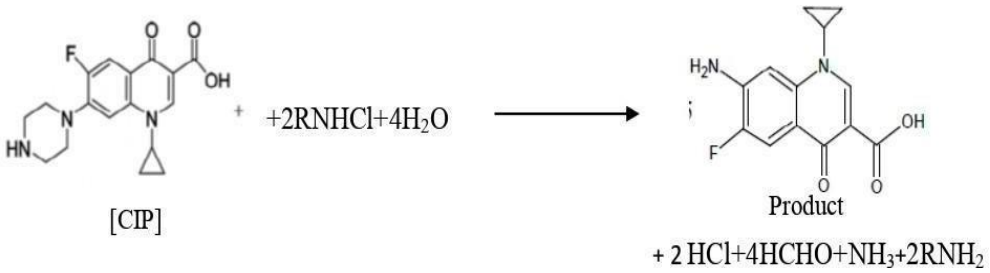
sources, they are used in the disinfection of drinking water [10,11]. Chloramine-T (CAT) is well-known for its versatility & its oxidative activity that affects a wide range of characteristic groups to generate molecular changes [12]. Here, oxidative degradation of CIP by Chloramine-T in $HClO_4$ medium is studied. To characterizethe degradation products, UV and IR studies were used as supplementary and confirmatory approaches.

EXPERIMENTAL:

All chemicals used were of analytical grade. N- Chloro P-Toluene Sulphonamide [CAT] was taken as its Sodium salt (E-Merck). An aqueous solution of chloramines–T [CAT] was prepared and stored in brown bottles to prevent photochemical degradation. Chloramine–T solution was a standardized iodometrically

The process of reaction was followed by measuring the absorbance of unreacted CIP, in the reaction mixture by UV–Visible 3000^{+} (LABINDIA) spectrophotometer at λmax=278nm as there is no interference of other reagents at this wavelength. After 3-4min. retardation of reaction rates is seen due to one of the reaction products PTS (p–Toluene Sulfonamide) so initial rates are calculated. Calibration curves were plotted to verify Beer's law and the absorptivity values calculated at the respective wavelength is ε=9.083 $x10^{3}dm^{3}mol^{-1}cm^{-1}$ [13]. Initial rates were calculated employing the plane-mirror method. The pseudo-first-order plots were made wherever reaction conditions permitted. The stoichiometry of the reaction was resolved by taking excess CIP over CAT which revealed that the oxidation of each mole of CIP requires for oxidation of two moles of CAT.

The final product 7-amino fluoroquinolone was obtained from dealkylation anddeamination of piperazine moiety and identified by FTIR results[14] **[Fig.(2)]**.



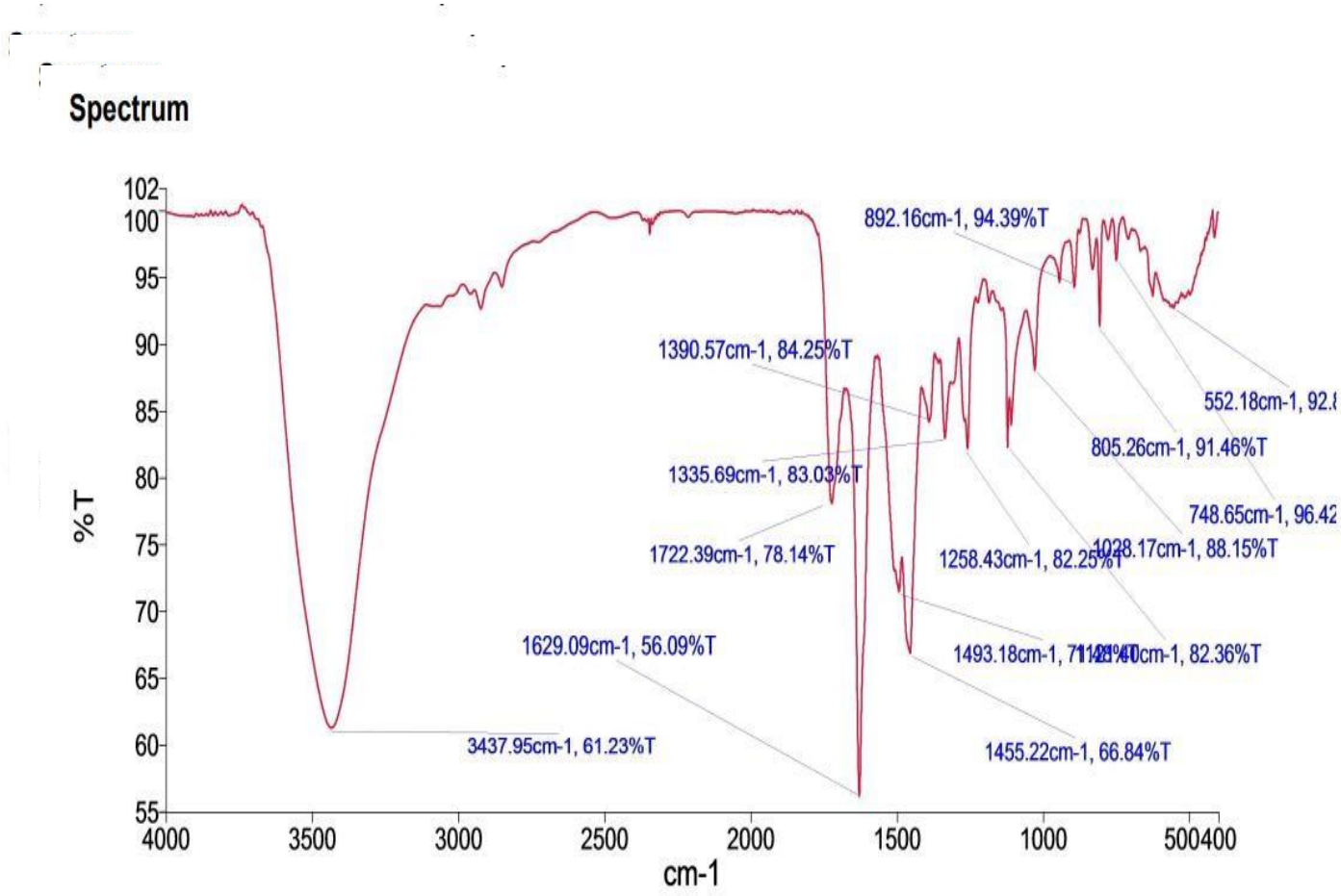


Fig.2 FTIR Spectra of Oxidation Product of CIP & CAT

RESULTS:

a. Dependence on ciprofloxacin

The plots of initial rates versus time were prepared that yielded straight lines indicating first-order dependence of rate concerning the drug. Second-order plots were also prepared by plotting log $[CIP]_t$ /$[CAT]_t$ versus time. Second- order rate constants have good agreement calculated from initial rates as wellas second-order plots.

b. Chloramine –T Dependence

The plots of initial rates (k_i, mol $dm^{-3}s^{-1}$) against the concentrations of [CAT] were prepared, which show straight lines passing through the origin these plots confirm first-order dependence of rates concerning oxidant [CAT]**.** Second-order plots were also prepared by plotting log $[CAT]_t$ /$[CIP]_t$ versus time. The second-order rate constant calculated from initial rates has good agreement with those obtained from second-order plots.

c. Hydrogen ion Dependence

The rate of reaction was found to be decreased with increasing concentrationsof $[H^+]$ ion. The plots of initial rates (k_i, mol dm^{-3} s^{-1}) against the concentrations of $[H^+]$ ion at three different temperatures were prepared. Theinitial rates are high at low $[H^+]$ ion concentrations but low at middle $[H^+]$ ion concentrations and almost steady at much lower at low$[H^+]$ ion concentrations.

d. Ionic Strength Dependence

At constant concentrations of reactants and other conditions, the ionic strength wasvaried. The rate of reaction is negligibly affected by ionic strength.

e. Effect of added product

The concentration of PTS is varied at three different concentrations of [HClO4] The rate of reaction decreases with an increase in concentrations of PTS**,** which is regarded to the fact that PTS is involved with hydrolysis of chloramines-T as an equilibrium step, and due to PTS addition reverse step is increased and inhibits the rates of reaction [15]. Basically, due to this reason ki, the initial rates are taken into account for kinetic studies.

DISCUSSION:

a. Mechanism

Since the studies show that the rate of reaction is decreased by the PTS, whichis a side product of the reaction, it seems that there is an equilibrium between CAT and PTS as well HOCl appears to be the reactive species of CAT. Retardation of rate which is associated with $[H^+]$ also shows that it is involvedin a different equilibrium step. As stoichiometric studies show that two moles of CAT react with one mole of CIP, while the order of reaction for both reactants is one, the following mechanism can be suggested for the above- discussed reaction.

$$RNHCl + H_2O \underset{}{\overset{K_1}{\rightleftharpoons}} RNH_2 + HOCl \quad (2)$$

$$[CIP] + HOCl \overset{K_2}{\rightleftharpoons} [C] + [H^+] \quad (3)$$

$$[C] \overset{k'}{\underset{(slow)}{\rightleftharpoons}} [C'] + Products \quad (4)$$

$$[C'] + HOCl \xrightarrow[(fast)]{} [Product] \quad (5)$$

(SCHEME: I)

Here, RNHCl refers to N- Chloro p- Toluene Sulphonamide (CAT), and RNH_2 refers to p-Toluene Sulphonamide i.e. PTS.

4.2 Rate law:

Based on the above mechanism and all the observed studies the rate law can be given below

The above equation can be further reduced as below (9),

$$-\frac{d[RNHCl]}{dt} \Big/ [RNHCl][CIP] = k = \frac{2k' K_1 K_2}{[H^+]([RNH_2] + K_1)} \quad (9)$$

where 'k' is introduced as observed second-order rate constant

Finally, the reciprocal of equation (9) can lead to the rate law as below equation (10),

$$\frac{1}{k} = \frac{[RNH_2][H^+]}{2k' K_1 K} + \frac{[H^+]}{2k' K_2} \quad (10)$$

When 1/k is plotted against $[RNH_2]$ $[H^+]$, it yielded a straight line with non-zero intercept). It also confirms the rate law presented as equation (10). The slope and intercept calculated can be given by equations (11), and (12) respectively

$$S = \frac{1}{2k' K_1K_2} \quad .(11)$$

$$I = \frac{[H^+]}{2\,k' K_2} \quad (12)$$

$$\frac{S}{I} = \frac{2k' K_1K_2}{2\,k' K_2\,[H^+]} = \frac{K_1}{[H^+]} \quad (13)$$

(SCHEME II)

When the plot of intercept 'I' versus $[H^+]$ was prepared at 30°C and ionic strength I = 2.0 $x10^{-4}$ mol dm^{-3} it yielded a straight line passing through the origin. The slope calculated from this plot gives the 1 / 2 k' K2 value. The values of k', $K_{1,\text{ and}}$ K_2 calculated from equations (11) and (12) were further employed in equation (9), which were in full agreement with observed values.This also confirms the above rate law. Activation parameters and thermodynamic parameters are also calculated.

CONCLUSION:

The kinetic and mechanistic study of the oxidation of ciprofloxacin by chloramine–T in an acidic medium was investigated. The final product obtained by dealkylation of piperazine moiety of ciprofloxacin which has antimicrobial activity as having fluoroquinolone ring structure intact and hence can play an important role in wastewater treatment. The reaction does not follow the free radical pathway. The present investigation widens the knowledge about the applicability of CAT for oxidative treatment processes of various compounds. The importance of this study is to develop a sensitive and cost effective technique for employing the kinetic colorimetric degradation of fluoroquinolone drugs in quality control laboratories.

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