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KINETICS OF OXIDATION OF PHARMACEUTICAL DRUG DOXYCYCLINE HYDROCHLORIDE BY CHLORAMINE-T IN NaOH MEDIUM. A MECHANISTIC STUDY

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ABSTRACT

The kinetics of oxidation of doxycycline hydrochloride(DOX) by chloramine-T (CAT) has been investigated in NaOH medium at 303 K. The Stoichiometry of the reaction was found to be 1:1 and the oxidation product of DOX, 1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,4,11-trioxotetracene-2-carboxamide is identified by the spot tests and further by LC-MS spectral analysis. The reaction followed first-order kinetics with respect to $[CAT]_0$, $[DOX]_0$ and fractional-order with $[OH^-]_0$. The effect of added halide ions, reduction product, p-toluene sulfonamide (PTS), ionic strength ($NaClO_4$) and dielectric constant of the medium was studied on the rate of reaction. A mechanism was proposed on the basis of experimental results. The activation parameters with respect to the slow step of the mechanism were evaluated, and the thermodynamic parameters was also determined and discussed.

KEYWORDS: Kinetics, Doxycycline hydrochloride, oxidation, chloramine-T, mechanism.

1. INTRODUCTION

Doxycycline hydrochloride hemiethanolate (DOX), was 2-(Amino-hydroxy-methylidene)-4-dimethylamino-5,10,11,12a-tetrahydroxy-6-methyl-4a,5,5a,6-tetrahydro-4H-tetracene-1,3,12-trione hydrochloride hemiethanolate .

It was a tetracycline derivative used as an antibiotic, inhibits the growth of microorganisms that cause infections. It was used in the treatment of Lyme disease, respiratory tract infections, genito-urinary tract infections, severe acne, rickettsial diseases, and eye infections (including chlamydial conjunctivitis). It was also used for treatment of traveler's diarrhea and other microorganisms sensitive to tetracycline. [1-5]

DOX may having possible side effects of skin rash or mouth sores, rectal itching or soreness, vaginal itching or discharge, or diarrhea occur also make sensitive to sunlight, sensation of nausea, vomiting, loss of appetite, dizziness, headaches or difficulty in swallowing.By the available literature, there was no information available on the oxidation kinetics of DOX with CAT. There was a need for understanding the oxidation mechanism of this compound so that the study could throw some light on the fate of the drug in biological system and also the behavior of CAT towards DOX in the presence of NaOH. Therefore the present chapter reports the kinetics of oxidation of DOX with CAT in NaOH medium at 303 K.

2. MATERIALS AND METHODS

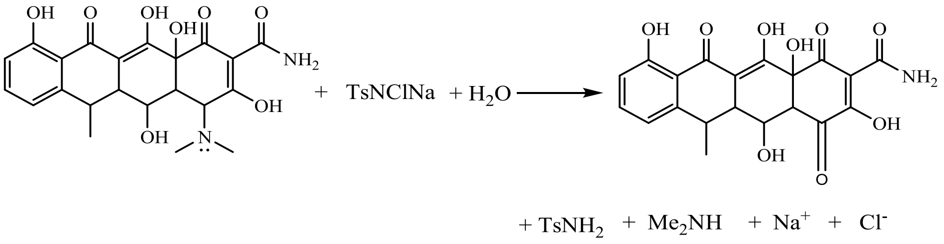
Chloramine-T (sodium N-chloro-p-toluenesulfonamide; CAT) is one of the most important organic haloamine behaves as oxidizing agent in both acidic and alkaline media. Mechanistic aspects of many of its reaction have been studied [6–12]. However, literature survey revealed that, there are sparse efforts made from the kinetic and mechanistic view points on the oxidation of pharmaceutical drug Doxycycline hydrochloride by CAT.

Reactions were carried out under pseudo first-order conditions with a known excess of $[\text{substrate}]_0$ over $[\text{oxidant}]_0$ at constant temperature 303 K in glass stopperd Pyrex boiling tubes coated black from outside to eliminate any photochemical deterioration. A Raaga digital proportional temperature controller (CH-61) was used to maintain the desired temperature with an accuracy of ± 0.1°C. Requisite amounts of solutions of substrate, NaOH and enough water to keep the total volume constant (50 ml) for all kinetic runs were equilibriated at 303K for about 30 min. A measured amount of CAT solution, also equilibriated at the same temperature was rapidly added to the reaction mixture which was periodically shaken for uniform concentration. The progress of the reaction was monitored by withdrawing measured aliquots (5 ml each) from the reaction mixture at regular time intervals and determined the unreacted CAT eudiometrically. The course of the reaction was studied more than two half-lives. The pseudo first-order rate constants (k/ s^{-1}) calculated from the linear plots of log CAT] versus time were reproducible within ±5%.

3. RESULT AND DISCUSSION

3.1 Stoichiometry and Product Analysis

Reaction mixtures containing varying ratios of CAT to DOX in the presence of NaOH, were equilibrated at 303 K for 24 hours. The results of estimation of unreacted Chloramine -T indicated 1:1 stoichiometry that is one mole of Doxycycline hydrochloride consumed one mole of Chloramine -T.



...(1)

The oxidation product of DOX, 1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,4,11-trioxotetracene-2-carboxamide is identified by the spot tests.[13] Further the oxidation product was confirmed by LC-MS spectral analysis. The mass spectrum showed a molecular ion peak at m/z = 415 [Fig.1].

The reduction product of the oxidant, p-Toluene sulfonamide was detected [14] by thin layer chromatography using light petroleum-chloroform-1-butanol (2: 2: 1) as the solvent and iodine as the spray reagent. Further confirmed by GC-MS analysis. The mass spectrum showed a molecular ion peak at m/z = 171. Finally it was confirmed by its MP 138 - 139°C (lit. mp 137° C– 140°C).

3.2 Kinetic Results of Oxidation Reaction

The oxidation of DOX by CAT in the presence of NaOH medium, carried out in a measurable rate. The reaction orders have been determined from the slopes of log $k^{/}$ versus respective logarithemic concentration of DOX, NaOH and MeOH except [CAT], by keeping the others concentrations are constant.

3.3 Effect of Reactants on the Reaction Rate

The kinetics of oxidation of DOX by CAT was investigated at several initial concentrations of reactants in basic medium. The experiments conducted under pseudo-first order conditions of [DOX] >> [CAT] at constant [DOX], [NaOH] and temperature. The plots of log $[CAT]_0$ vs. time, were made and found to be linear. The rate constant did not change with

$[CAT]_0$which was varied in the range of 5×10^{-4} to 30×10^{-4}mol dm^{-3}, confirming the first order dependence on the reaction rate of $[CAT]_0$ (Table .1).Under identical experimental conditions, an increase in the [DOX] in the range 5×10^{-3} to 30×10^{-3} mol dm^{-3} leads to an increase in the $k^{/}$ values [Table.1 and Fig.2]. The plots at constant $[CAT]_0$, $[NaOH]_0$ and temperature showed a first-order (+1.12) dependence of the rate on [DOX]. The plots of log $k^{/}$ vs. log [DOX] were linear with unit slopes showing first-order dependence of the rate on the [DOX].The effect of the medium NaOH concentration was studied in the range of 5×10^{-2} to 30×10^{-2}mol dm^{-3}, keeping DOX, CAT concentration and temperature at constant values. The rate constants decreased with increase in the concentration of NaOH. The plots of log $k^{/}$vs [NaOH] were linear with positive slope (0.464) [Table.1 and Fig.3] indicating a fractional-order dependence in [NaOH].

Table.1 Effect of Varying [Cat], [Dox] and Naoh] on the Reaction Rate At 303 K

10^4[CAT]/M	**10^3[DOX]/M**	**10^2[NaOH]/M**	**$k^{/}$ ($\times 10^4$ s^{-1})**
05	10	10	2.20
10	10	10	2.14
20	10	10	2.31
30	10	10	2.30
10	05	10	1.45
10	10	10	2.14
10	20	10	6.38
10	30	10	12.0
10	10	05	0.96
10	10	10	2.14
10	10	20	2.47
10	10	30	3.08

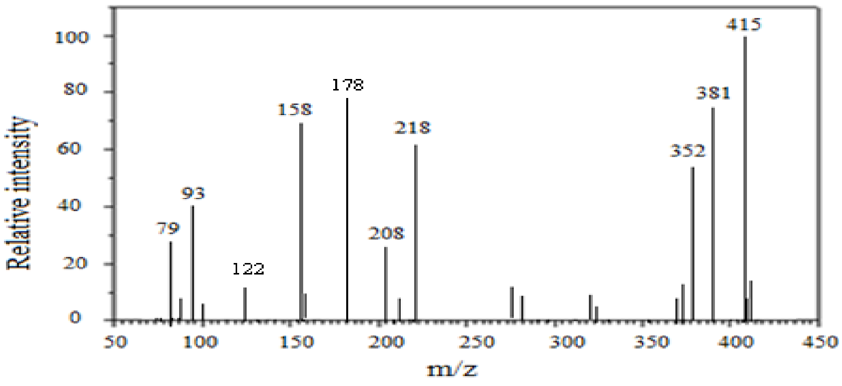


Fig.1 Mass spectrum of 1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,4,11-trioxotetracene-2-carboxamide with its molecular ion peak at 415 amu

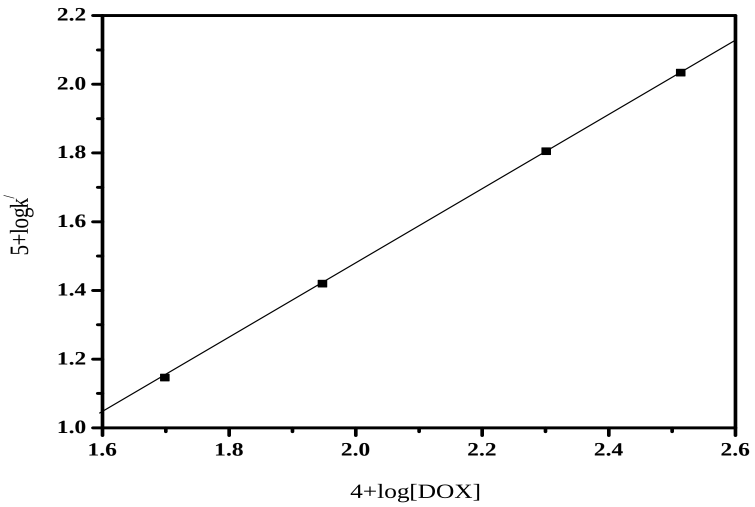


Fig.2 Effect of Variation of Concentration of [DOX] on the Oxidation of DOX by CAT in Naoh At 303 K (Conditions as in Table.1)

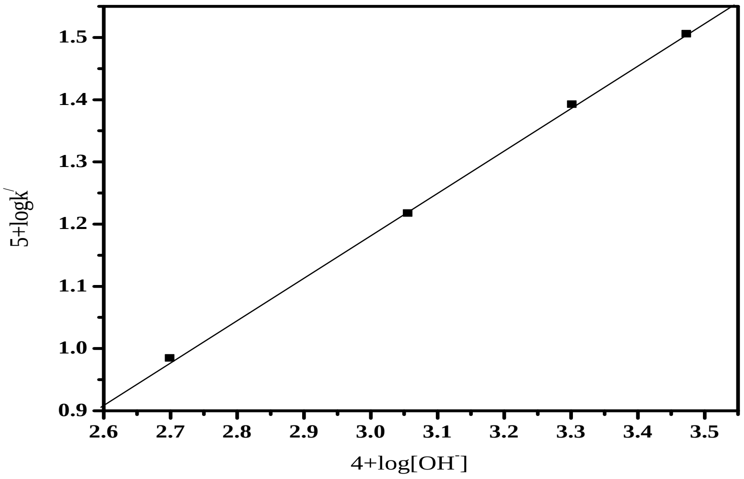


Fig. 3 Effect of Medium [Naoh] on the Oxidation of DOX by CAT At 303 K (Conditions as In Table.1)

3.4 Effect of Pts, Halide Ions and Ionic Strength on the Rate of Reaction

Addition of p-toluene sulfonamide (PTS, 5×10^{-4} to 20×10^{-4}mol dm^{-3}), the reduction product of CAT, to the reaction mixture did not affect the rate significantly [Table.2]. This indicates that PTS is not involved in any step prior to the rate determining step in the scheme proposed. Similarly addition of Cl^- or Br^- ions as NaCl or NaBr (1×10^{-2} to 10×10^{-2}mol dm^{-3}) had no effect on the rate [Table.2] suggesting that no interhalogen or free halogen is formed in the reaction sequence.

The effect of ionic strength of the medium on the rate of reaction was carried out using $NaClO_4$ (5×10^{-3} to 20×10^{-3}mol dm^{-3}) solution with all other experimental conditions held constant. It was found that ionic strength had negligible effect on the reaction rate suggesting no ionic species are involved in the rate determining step. Subsequently, the ionic strength of the reaction mixture was not kept constant for kinetic runs are rate constants are shown in Table.2.

Table.2 Effect of Varying [Nacl], [Nabr], [PTS] And Naclo$_4$on The Reaction Rate.

10^2[NaCl] / [NaBr] / M	**$k^/$ ($\times 10^4$ s^{-1})**
01	2.83 (2.30)
05	3.10 (2.69)
10	2.90 (2.53)
10^4 [PTS]/M	
05	1.90
10	2.22
20	1.92
10^3 [$NaClO_4$]/M	
05	2.29
10	1.97
20	2.14

Values in parenthesis refers to the rate constants with NaBr

[CAT] = 10×10^{-4}mol dm^{-3}; [DOX] =10×10^{-3}mol dm^{-3};

[NaOH] = 10×10^{-2}mol dm$^{-3;}$ T =303 K

3.5 Effect of Dielectric Constant of Medium on the Rate of Reaction

The dielectric constant (D) of the medium was studied by the addition of methanol to the reaction medium. Addition of methanol resulted in decrease in reaction rate supporting the rate limiting step with no charge dispersal [Table.3]. Plots of dielectric constant [D] vs. log $k^/$ are shown in [Fig.4] was linear with negative slope of 0.391.

Table 3. Effect of Varying Dielectric Constant of Medium on the Reaction Rate.

[MeOH] (%v/v)	**D**	**10^2/D**	**$k^/$($\times 10^4$ s^{-1})**
00	76.73	1.3032	2.14
10	72.37	1.3817	1.87
20	67.48	1.4819	1.80
30	62.71	1.5946	1.77

[CAT] = 10×10^{-4} mol dm^{-3} ; [DOX] = 10×10^{-3}mol dm^{-3} ;

[NaOH] = 10×10^{-2} mol dm^{-3};T = 303K

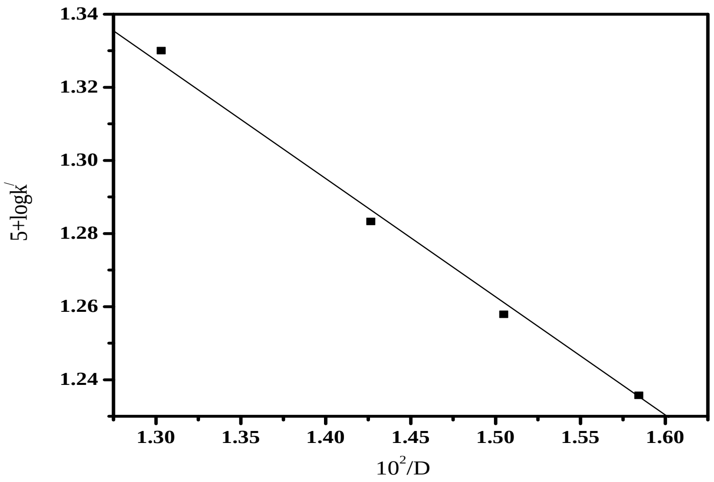


Fig. 4 Effect of Dielectric Constant (Meoh) on the Oxidation of DOX ByCAT in Naoh At 303K (Conditions As In Table.3)

3.6 Effect of Temperature

The rate constant for the oxidation of DOX with CAT at different temperature ranges (293-313 K) was measured by keeping the other experimental conditions constant. It was observed that the rate constant of the reaction increases with increase in temperature for given concentration of DOX. Further the rate constant increases with increasing the concentration of DOX for a given temperature [Table.4 and Fig.5]. From the Arrhenius plot of log $k^{/}$ vs.1/T activation parameters were computed [Table.5 and Fig.6].

Table4. Effect of Varying Doxycycline Concentrations on the Reaction Rate at Different Temperatures

10^3 [DOX]/M	$k^{/}(\times 10^4\ s^{-1})$		
	293K	303K	313K
05	0.91	1.45	2.02
10	1.42	2.14	3.33
20	3.14	6.38	11.25

[CAT] = 10 × 10^{-4} mol dm^{-3} ; [NaOH] = 10 ×10^{-2} mol dm^{-3}

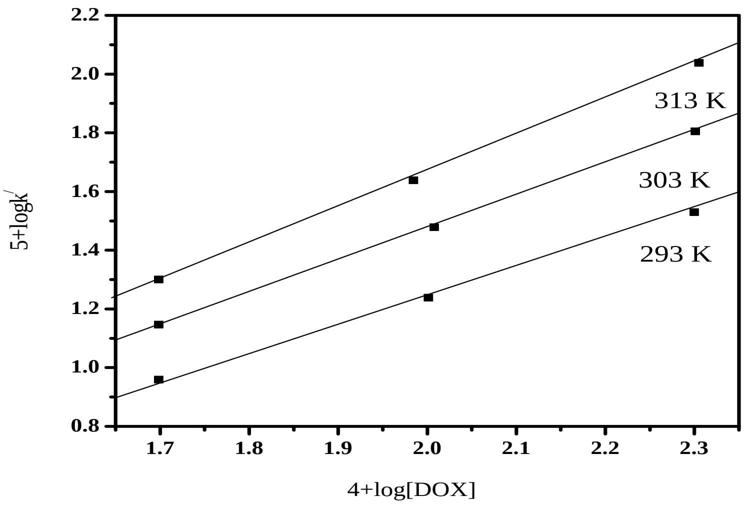


Fig. 5- Effect of Variation of Concentration of the DOX at Different Temperature on the Oxidation of DOX byCAT in Naoh.Onditions as In Table.4)

Table.5 Effect of Varying Temperature and the Values of Activation Parameters For The Composite Reaction Between CAT And DOX

Temperature (K)	$k^{/}(\times 10^{4}\ s^{-1})$	Activation parameter
293	1.42	$Ea = 33.76\ kJmol^{-1}$
303	2.14	$\Delta H^{\#} = 31.21\ kJmol^{-1}$
313	3.33	$\Delta S^{\#} = -213.4\ JK^{-1}\ mol^{-1}$
		$\Delta G^{\#} = 95.85\ kJmol^{-1}$
		log A = 2.136

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

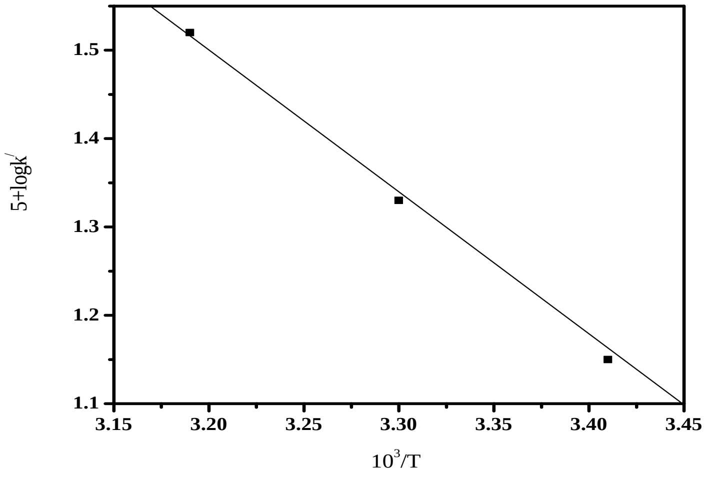


Fig. 6 Effect of Temperature on the Oxidation of DOX by CAT In Naoh. (Conditions as In Table 5)

3.7 Test For Free Radicals

The negative test for polymerization of the monomer of aqueous acrylamide solution shows the absence of free radicals generation in situ in the reaction mixture.

DISCUSSION

Chloramine-T behaves as an oxidizing agent in both acidic and alkaline media [14-29]. It is a strng electrolyte and depending upon the pH of the medium, it furnishes different types of reactive species. The possible oxidizing species in acidified CAT solutions are the conjugate acid TsNHCl, the dichloramine $TsNCl_2$, the hypochlorous acid HOCl and possibley the protonated hypochlorous acid H_2O^+Cl.

$TsNClNa \rightleftharpoons TsNCl^- + Na^+$ … (1)

$TsNCl^- + H^+ \rightleftharpoons TsNHCl$ … (2)

$TsNHCl \rightleftharpoons TsNH_2 + TsNCl_2$ … (3)

$TsNHCl + H_2O \rightleftharpoons TsNH_2 + HOCl$ … (4)

$TsNCl_2 + H_2O \rightleftharpoons TsNHCl + HOCl$ … (5)

$HOCl \rightleftharpoons H^+ + OCl^-$ ... (6)

(Here $Ts = p\text{-}CH_3C_6H_4SO_2^-$)

In alkaline solution of CAT, $TsNCl_2$ does not exist, and the predominant species are $TsNCl^-$, OCl^-, TsNHCl and HOCl. Bishop and Jennings [16] have calculated the concentration of various species of CAT present at different pH. Under the present experimental conditions, the concentration of OCl^- ion is small and it does not make any significant contribution to the oxidation of DOX. Hence, at the pH employed in the present studies, the dominant oxidizing species are TsNHCl, $TsNCl^-$ and HOCl. Hardy and Johnson [17] have reported the following equilibrium in alkaline solution of CAT.

$TsNClNa + H_2O \rightleftharpoons TsNHCl + NaOH$ …(8)

For the alkali accelerating step eq. 8 can be written as

$TsNHCl + OH^- \rightleftharpoons TsNCl^- + H_2O$ … (9)

In present case, the rate of the reaction is accelerated with respect to $[OH^-]$, indicates that the anion $TsNCl^-$ is the most likely oxidizing species.

$$\text{TsNHCl} + \text{OH}^- \underset{}{\overset{K_1}{\rightleftharpoons}} \text{TsNCl}^- + \text{H}_2\text{O} \qquad \text{(i) fast}$$

$$\text{TsNCl}^- + \text{DOX} \xrightarrow{k_2} \text{X (Complex)} \qquad \text{(ii) slow \& r d s}$$

$$\text{X (Complex)} \longrightarrow \text{Products} \qquad \text{(ii) slow}$$

Scheme 1

The total concentration of CAT is $[\text{CAT}]_t$, then

$$[\text{CAT}]_t = [\text{TsNHCl}] + [\text{TsNCl}^-] \qquad ...(10)$$

By substituting for [TsNHCl] from equilibrium (1) of Scheme 1 in Eq. (1) and solving for $[\text{TsNCl}^-]$, one obtains,

$$[\text{TsNCl}^-] = \frac{K\ [\text{CAT}]_t\ [\text{OH}^-]}{[\text{H}_2\text{O}] + K\ [\text{OH}^-]} \qquad ...(11)$$

From the slow step (ii) of Scheme 1,

$$\text{Rate} = k\ [\text{TsNCl}^-]\ [\text{DOX}] \qquad ....(12)$$

By substituting for $[\text{TsNCl}^-]$ from Eq. (11) in to Eq. (12), the following rate law is obtained

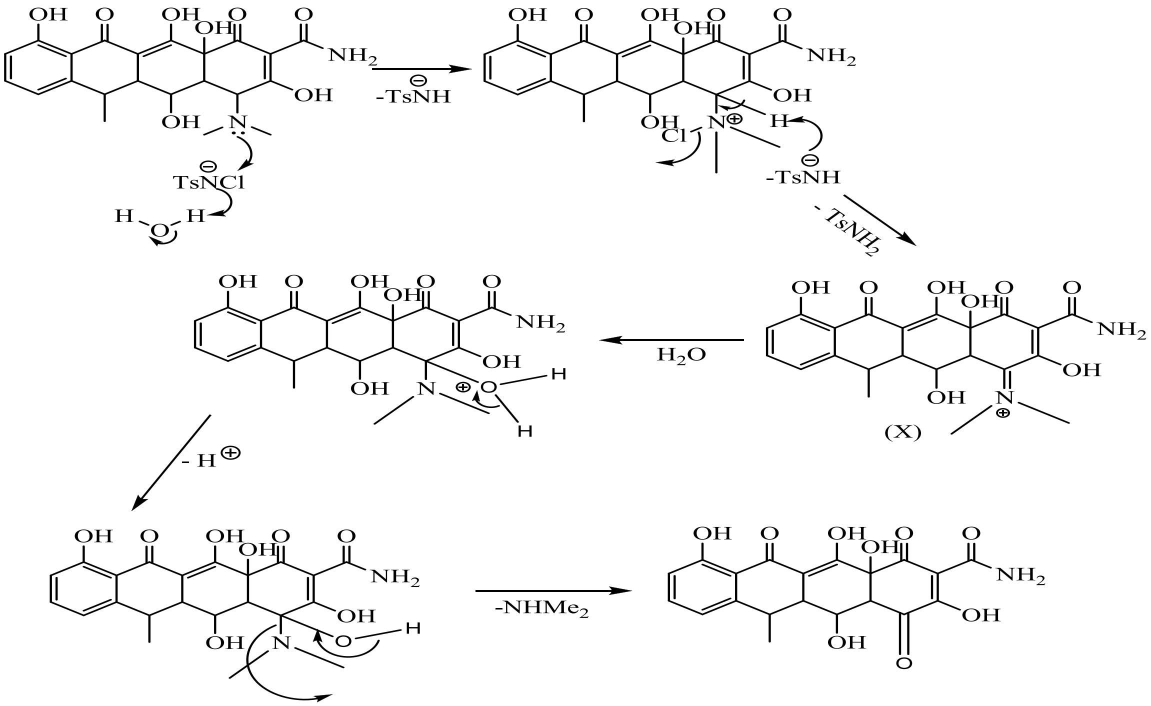
$$\text{Rate} = \frac{K\ k\ [\text{CAT}]_t\ [\text{DOX}]\ [\text{OH}^-]}{[\text{H}_2\text{O}] + K\ [\text{OH}^-]} \qquad ...(13)$$

The rate law (13) is in agreement with the experimetal data, including a first order dependance of rate each on $[\text{CAT}]_t$ and [DOX] and a fractional order dependance on $[\text{OH}^-]$.

In the present investigation, variation of dielectric constant of the medium showed negative effect. The effect of varying dielectric constant on the rate of reaction has been described in several studies [20-29]. For limiting case of zero angle of approach between two dipoles or ion-dipole system, Amis [21] 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 two dipoles, where a positive slope results for a positive ion-dipole interaction. The absence of the effect of varying dielectric constant on the rate cannot be explained by the Amis theory [21]. Applying the Born equation, Laidler [25] has prposed the following equation for a dipole-dipole interaction:

$$\ln k' = \ln k_0 + 3 / 8kT\ (2/D-1)\ [\mu^2_A / r^3_A + \mu^2_B / r^3_B - \mu^2_\# / r^3_\#] \qquad \dots (14)$$

Where k_0 is the rate constant in a medium of infinite dielectric constant, μ represents the dipole moment and r refers to the radii of the reactant and activated complex. It can be seen from equation [14] that the rates should be greater in a medium of lower dielectric constant when $r^3_{\#} = r^3_A + r^3_B$ indicating that the extent of charge dispersal in the transition state is different. In the present investigation, suggesting that ion dipole interaction in the rate limiting step.



Scheme -2

4. CONCLUSIONS

The kinetics of oxidation of Doxycycline hydrochloride by Chloramine-T in NaOH medium has been investigated at 303 K. Reaction stoichiometry was found to be 1:1 and the oxidation product was identified as 1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,4,11-trioxotetracene-2-carboxamide and confirmed by LC-MS spectral analysis. The activation parameters have been calculated. The scheme proposed and the derived rate law has been correlated with the observed kinetics.

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