CATALYTIC OXIDATION OF ATORVASTATIN BY Th(IV) USING CHLORAMINE-T: A COMPREHENSIVE KINETIC AND MECHANISTIC STUDY

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ABSTRACT:

The kinetics of the oxidation of atorvastatin (ATV) by chloramine-T (CAT) in a hydrochloric acid solution both uncatalysed and catalysed by Th (IV), have been investigated at 303K. The reaction stoichiometry was established and the oxidation products were identified. In both catalysed and uncatalysed reactions, the reaction exhibited first order with respect to [CAT], while exhibiting fractional order with regard to [ATV], [HCl], and Catalyst Th (IV). The reaction's rate is not significantly impacted by its products. In both catalysed and uncatalysed processes, the dielectric constant has a marginally unfavourable impact. Reaction rate was not significantly impacted by ionic strength, suggesting that non-ionic species were involved in both situations. Thermodynamic parameters were computed by performing the kinetic runs at different temperatures (293K-313K) and mechanism was proposed on the basis of product analysis. Rate law was derived from the experimental data.

Keywords: Th (IV) Catalysed, Kinetics, Chloramine-T, Atorvastatin, Oxidation, Mechanism

Introduction:

The chemical names for atorvastatin (ATV) are βR and δR.1-methyl-lethyl-2-(4-fluorophenyl)-β,δ-dihydroxy-5-3-phenyl-4-[carbonyl (phenylamino)]The acid -1H-pyrrole-1-heptanoic is a synthetic inhibitor of HMG-CoA reductase[1-2]. By preventing endogenous cholesterol synthesis, it reduces plasma cholesterol levels. It is a statin of the second generation. Clinical investigations have shown that this synthetic HMG-CoA reductase inhibitor significantly lowers plasma triglycerides, low density lipoprotein cholesterol, and total cholesterol[3–4]. Its non-lipid-lowering properties include enhancing endothelial function, inhibiting smooth muscle proliferation, and decreasing platelet aggregation. Atorvastatin's impact is dose dependent; it first reduces low density lipoprotein by 39% at 10 mg[5], reaching a maximum reduction of 60% at 80 mg.

Because N-haloamines can function as sources of halonium ions, hypochlorites, and N-anions, which function as bases and nucleophiles[6], their chemistry is incredibly diverse. They undergo a wide range of transformations[7] when they react with different functional groups. A well-known member of the N-haloamines family, sodium-N-chloro-4-methyl benzene sulphonamide, also referred to as chloramine-T (CAT), acts as an oxidising agent in both acidic and alkaline environments. This oxidant is affordable, non-toxic, stable, effective, and moderate[8]. Chloramine-T has been used to study the oxidation reactions of numerous medications[9-16].

Because of their varying valencies, transition and inner transition elements exhibited catalytic behaviour. Osmium, Ruthenium, Cerium, Thorium, Nickel, and other common transition and inner transition elements function as catalysts. It is employed as a catalyst. According to preliminary experimental findings, ATV and CAT undergo an oxidation reaction in a hydrochloric acid media.

Information regarding the spectrophotometric analysis of ATV drug[17] is provided via a survey of the literature. There is no published kinetic analysis of the catalysed oxidation of ATV with the oxidant chloramine-T. Comparative kinetic, mechanistic, and thermodynamic studies of Th (IV) catalysed and uncatalysed oxidation of ATV by Chloramine-T in a hydrochloric acid media is presented in the current articles.

Experimental:

Materials and Methods:

A solution of ATV was freshly prepared each time by dissolving appropriate amount in methanol. An aqueous solution of CAT (E. Merck) was prepared using doubly distilled water, standardised by iodometric method and stored in brown bottle in dark in order to avoid any photochemical deterioration. Th (IV) Nitrate was prepared using double distilled water. Other reagents used were of analytical grade and their solutions were freshly prepared using double distilled water. Acetic acid was added to alter the dielectric constant of the medium. Solution of Hydrochloric acid used to study the effect of acid concentration. Sodium chloride solution was added to study the effect of halide concentration. Ionic strength was adjusted and maintained using sodium perchlorate solution.

Kinetic measurements:

The kinetics of oxidation of ATV by Chloramine-T was followed under pseudo first order conditions of $[ATV]_0 >> [CAT]_0$ in both catalysed and uncatalysed reactions. The progress of the Th (IV) catalysed and Uncatalysed oxidation was studied by measuring decrease in the absorbance maximum for CAT (λ_{max}=260nm). All the absorbance values were recorded on a coputer-controlled Thermos scientific spectrophotometer; instrument model GENESYS 150 (Fig.1).

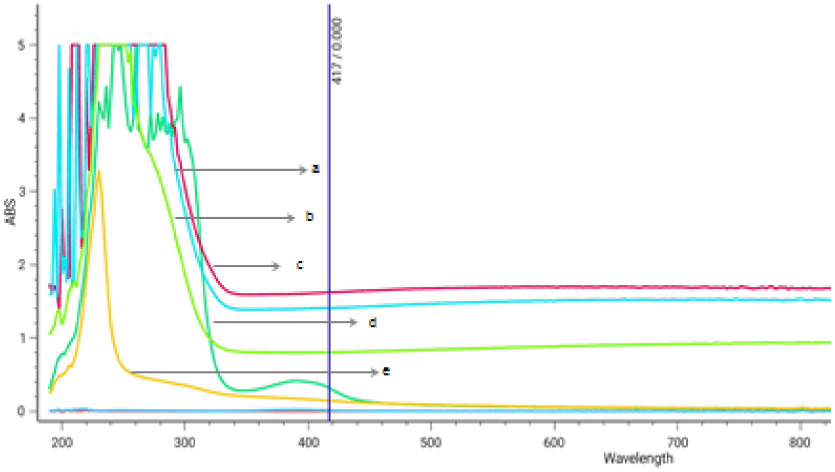


Fig.1: UV-visible spectra for the different reaction mixtures.

a) [CAT] = 10×10^{-5} mol dm^{-3}.

b) [CAT] = 10×10^{-5} mol dm^{-3}, [Th (IV)] = 10×10^{-6} mol dm^{-3}, [ATV] = 10×10^{-4} mol dm^{-3}, [Cl^-] = 10×10^{-4} mol dm^{-3}, [H^+] = 10×10^{-4} mol dm^{-3}

c) [CAT] = 10×10^{-5} mol dm^{-3}, [Th (IV)] = 10×10^{-6} mol dm^{-3}, [ATV] = 10×10^{-4} mol dm^{-3}, [Cl^-] = 10×10^{-4} mol dm^{-3}, [H^+] = 10×10^{-4} mol dm^{-3}.

d) [ATV] = 10×10^{-4} mol dm^{-3}.

e) [Th (IV)] = 10×10^{-6} mol dm^{-3}.

The kinetic runs were studied within 30±0.1°C. The reaction mixture, containing the required amounts of solutions of ATV, HCl and NaCl along with water to maintain a constant volume (100ml) for all kinetic runs was thermostated at 303K. An equilibrated solution of requisite volume of CAT was added to the reaction mixture and shaken periodically for uniform concentration. The reaction progress was monitored by withdrawing aliquots (5ml) of the reaction mixture at regular intervals of time by estimating unreacted CAT iodometrically for uncatalysed reaction. The catalysed reaction was initiated by mixing CAT to ATV which contains HCl, NaCl and Th(IV). The course of the reaction was studied at different time intervals. The pseudo first order rate constants for catalysed (k_C) and uncatalysed (k_U) reactions calculated from linear plots of log [CAT] versus time were reproducible within ±3%.

Stoichiometry and Product analysis:

The reaction mixture containing one mole of ATV and one mole of CAT in presence of HCl, NaCl in uncatalysed reaction and Th(IV) in catalysed reaction were equilibirated under stirred condition at 303K for about 24hrs. Unreacted CAT was estimated iodometrically using starch as indicator. This confirm the following stoichiometry as one mole of ATV consumed one mole of CAT as follows,

$$C_{33}H_{35}FN_2O_5 + PTSO_2NClNa + CH_3OH \xrightarrow{Th\ (IV)} C_{34}H_{37}FN_2O_5 + PTSO_2NH_2 + H_2O + Na^+ + Cl^-$$

Where PT = $CH_3C_6H_4$ …….(1)

After the completion of reaction, reaction products were extracted with ether. From ether layer the oxidation product of ATV, Methyl- (βR,δR)-2-(4-Fluorophenyl)-β,δ-dihydroxy-5-(1-methyl-lethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoate were extracted with aqueous sodium hydroxide solution and identified by spot test and confirmed by ferric hydroxamate test. The reduction product of oxidant CAT, P-toluenesulfonamide was extracted with ethyl acetate and confirmed by TLC using the system of solvent petroleum ether-chloroform-1-butanol (2:2:1 v/v) and developing reagent iodine (R_f = 0.839).

Results and Discussion:

Effect of reactants concentration on rate of a reaction:

Under pseudo-first order conditions, [ATV] >> [CAT] by varied CAT at constant [ATV], [HCl], [NaCl], Th (IV) and temperature. Plots of log [CAT] versus time indicate a first order condition dependence of the reaction rate on [CAT] in both catalysed and uncatalysed reactions. The pseudo first order rate constants (k_c and k_u) were calculated from the slopes (table-1). The unchanged k_C / k_U values on varying oxidant concentration further confirm the first order dependence of the rate on [CAT]. Under similar experimental conditions by varying the concentration of ATV, the rate constants for both catalysed and uncatalysed reactions increases by increasing concentration of ATV (table-1). The linear plot of log k_C / log k_U versus log [ATV] (figure-2) with a slope of 0.13 for uncatalysed reaction indicate fractional-order dependence on [ATV] and the slope of 0.74 for catalysed reaction indicate fractional order dependence on [ATV]. The rate constants k_C / k_U were calculated and listed in Table-1.

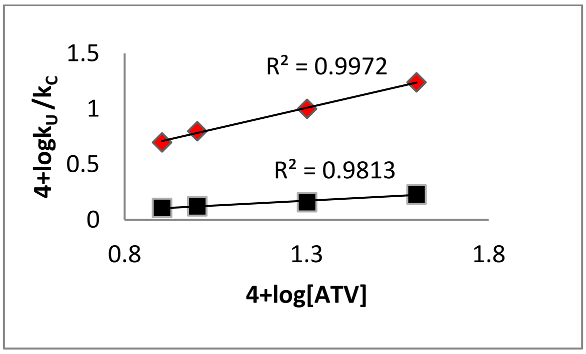


Figure-2: plots of log k $_U$ / k $_C$ versus log [AT].

Effect of variation of [ATV] on rate at 303K, [CAT] = 10×10^{-5}mol dm^{-3}, [ATV] = 0.8-40×10^{-4} mol dm^{-3}, [Th (IV)] = 10×10^{-6} mol dm^{-3}, [H$^+$] = 10×10^{-4} mol dm^{-3} and [Cl$^-$] = 10×10^{-4} mol dm^{-3}.

Effect of acid concentration on rate of a reaction:

The reaction was studied with varying [HCl] with all other reaction conditions kept constant. The rate of reaction increased with increase in the concentration of HCl (Table-1) for both catalysed and un-catalysed reaction. Plot of log k $_C$ / log k $_U$ v/s log [H$^+$] (figure-3) was linear with a positive slope of 0.18 and 0.75 for uncatalysed and catalysed reactions respectively shows fractional order dependence of rate on [H$^+$].

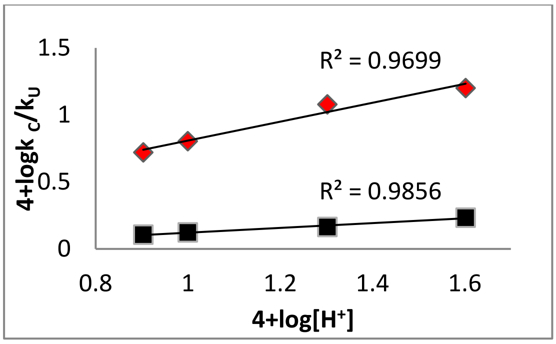


Figure-3: plots of log k$_u$ / k $_c$ versus log [H$^+$].

Table-1:

Effect of [AT], [CAT], [H$^+$], [Cl$^-$] and [Th(IV)] on reaction rate at 303K for catalysed oxidation of ATV with Chloramine-T in Hydrochloric acid medium.

$10^5\times$[CAT] Mol dm^{-3}	$10^4\times$[ATV] Mol dm^{-3}	$10^4\times$[H$^+$] Mol dm^{-3}	$10^4\times$[Cl$^-$] Mol dm^{-3}	$10^6\times$[Th(IV)] Mol dm^{-3}	$10^4\times$ k$_U$ Sec^{-1}	$10^3\times$ k$_C$ Found	Calculated
8	10	10	10	10	1.33	0.640	0.641
10	10	10	10	10	1.32	0.636	0.634
20	10	10	10	10	1.33	0.638	0.639
40	10	10	10	10	1.33	0.645	0.647
10	**8**	10	10	10	1.23	0.510	0.509
10	**10**	10	10	10	1.32	0.636	0.634
10	**20**	10	10	10	1.45	1.000	1.001
10	**40**	10	10	10	2.67	1.740	1.742
10	10	**8**	10	10	1.28	0.525	0.527
10	10	**10**	10	10	1.32	0.636	0.634

10	10	**20**	10	10	1.48	1.197	1.198
10	10	**40**	10	10	1.71	1.590	1.591
10	10	10	**8**	10	1.28	0.501	0.502
10	10	10	**10**	10	1.32	0.636	0.634
10	10	10	**20**	10	1.67	1.280	1.282
10	10	10	**40**	10	2.16	2.001	2.003
10	10	10	10	**8**	-	0.551	0.553
10	10	10	10	**10**	-	0.636	0.634
10	10	10	10	**20**	-	1.030	1.032
10	10	10	10	**40**	-	1.428	1.429
10	10	10	10	**60**	-	2.560	2.562

T = 303K, $10^2/D = 1.27$

Effect of halide ions on rate of a reaction:

The effect of [Cl$^-$] on the rate of reaction for both cases was studied by varying the amount of NaCl at constant [CAT]$_0$, [ATV], HCl, Th (IV) and temperature. The rate of both catalysed and uncatalysed reactions increased with the increasing concentration of NaCl (Table-1). Plot of log k_C / log k_u versus log [Cl$^-$] (Figure-4) was linear with a slope 0.34 and 0.84 for uncatalysed and catalysed reactions respectively confirming fractional order dependence on [Cl$^-$]. The rate constants of oxidation of ATV by CAT does not depend on halide ions concentration, hence halide ions showed no effect on the rate of the reaction.

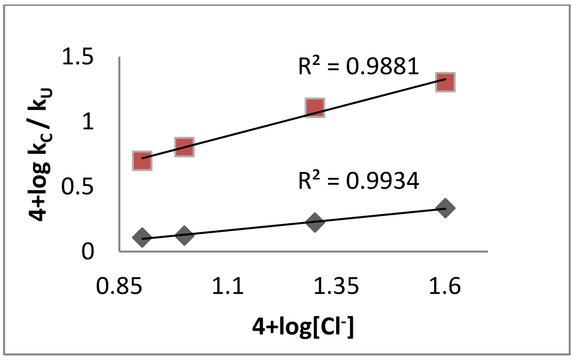


Figure-4: plots of log k$_U$ / k$_C$ versus log [Cl$^-$].

Effect of variation of concentration of [Cl$^-$] on reaction rate at 303K for oxidation of AT with Chloramine-T in hydrochloric acid medium, [CAT]=10×10^{-5}mol dm^{-3}, [ATV] =10×10^{-4} mol dm^{-3}, [Th(IV)] = 10×10^{-6} mol dm^{-3}, [H$^+$] = 10×10^{-4} mol dm^{-3} and [Cl$^-$] =0.8-40×10^{-4} mol dm^{-3}.

Effect of ionic strength on rate of a reaction:

The ionic strength of the medium was varied by adding $NaClO_4$ (0.1-1.0 mol dm^{-3}). The unchanged rate of reaction confirmed the involvement of non-ionic species in the rate determining step both in Th (IV) catalysed and uncatalysed reactions.

Effect of dielectric constant on rate of a reaction:

The dielectric permittivity of the medium was studied by varying different proportions of acetic acid(0-30%, v/v). Increase in dielectric permittivity (D) of the medium decreased the rate of reaction(table-2) in case of both catalysed and uncatalysed reaction. The plot of log k_C / log k_U versus 1/D (D is dielectric permittivity) is linear with a negative slope (Figure-5).

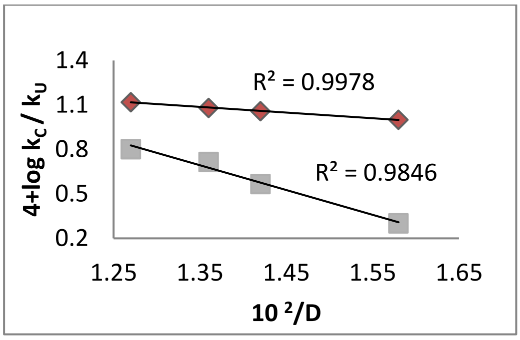


Fig-5: Plot of log k_C / k_U versus 10 ^{2}/D

Table-2: Effect of dielectric constant of the medium:

% CH_3COOH (v/v)	D	10^2/D	$K_U \times 10^4$ (sec^{-1})	$K_C \times 10^4$ (sec^{-1})
0	78.2	1.27	1.32	6.36
5	73.2	1.36	1.22	5.22
10	70.2	1.42	1.16	3.71
20	62.9	1.58	1.10	2.01

Effect of the product PTS concentration on the rate:

The addition of product PTS (1×10^{-3} -10×10^{-3} mol dm^{-3}), the reduced product of oxidant CAT had no significant effect on the rate. This indicates the non-involvement of it in pre-equilibrium step both in catalysed and uncatalysed reactions.

Effect of varying catalyst concentration on rate of a reaction:

As the concentration of Th(IV) was varied in the reaction mixture at constant [ATV], [HCl], [CAT], [Cl^-] and temperature, the rate was found to be increased with increase in concentration of Th(IV) from 8×10^{-6} to 40×10^{-6}. The order with respect to catalyst found to be fractional order with a positive slope of 0.63 from linearity plot of log k_C versus log [Th(IV)] (Figure-6).

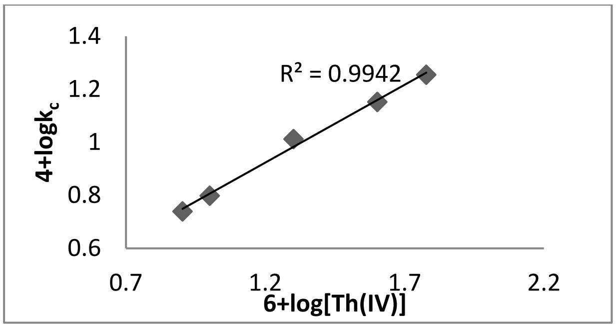


Figure-6: plots of log k$_C$ versus log [Th(IV)].

Effect of variation of concentration of catalyst on reaction rate at 303K for oxidation of ATV with Chloramine-T in hydrochloric acid medium, [CAT]=10×10^{-5}mol dm^{-3}, [ATV] =10×10^{-4} mol dm^{-3}, [Th(IV)] =8-40×10^{-4} mol dm^{-3}, [H$^+$] = 8×10^{-4} mol dm^{-3} and [Cl$^-$] = 10×10^{-4} mol dm^{-3}.

Effect of temperature on rate of a reaction:

Effect of temperature on the reaction rate was studied by performing kinetic runs at different temperatures (293K-313K) keeping other experimental conditions constant (table-3). It was observed that the rate constant of the reaction increases with increase in temperature for both Th(IV) catalysed and uncatalysed reaction. The activation parameters of the reaction were computed from linear Arrhenius plot of log k$_C$ / log k$_U$ versus 1/T (figure-7).

Table-3: Effect of varying temperature on reaction rate and activation parameters.

Temperature in K	**k$_c$ × 10^4 sec^{-1}**	**k$_u$×10^4 sec^{-1}**	**Activation parameters**	**catalysed**	**Uncatalysed**
293	4.16	0.85	E$_a$ (kJ mol^{-1})	58.70	65.10
298	6.36	1.28	$\Delta H^{\neq}$ (kJ mol^{-1})	56.18	62.58
303	10.66	2.00	$\Delta S^{\neq}$ (JK^{-1} mol^{-1})	-116.55	-90.22
308	13.29	3.83	$\Delta G^{\neq}$ (kJ mol^{-1})	91.50	122.55
313	19.80	4.69	log A	7.13	8.5

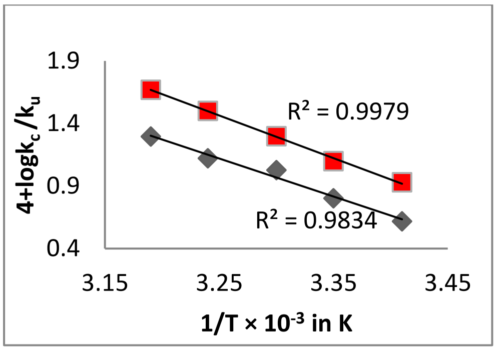


Figure-7: Plot of log k_C / k_U versus 1/T

Test for free radicals:

The reaction mixture fails to initiate the polymerization when added to aqueous acrylamide. This indicates the absence of free radical species in both catalysed and uncatalysed course of the reaction.

Thermodynamic Parameters:

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 $\Delta G^{\neq}$ and $\Delta H^{\neq}$ indicate that the transition state is highly solvated, while the high negative value of $\Delta S^{\neq}$ suggests the formation of rigid associative transition state in both catalysed and uncatalysed reaction (Table-3).

TABLE-4: Values of Catalytic constant (K_C) at different temperatures and activation parameters calculated using K_C values.

Temperature (K)	$K_C \times 10^2$	Activation parameters	Values
293	2.58	E_a (kJ mol^{-1})	53.61
298	3.96	$\Delta H^{\neq}$ (kJ mol^{-1})	48.65
303	6.76	$\Delta S^{\neq}$ (JK^{-1} mol^{-1})	-29.73
308	7.39	$\Delta G^{\neq}$ (kJ mol^{-1})	60.18
313	11.80	log A	11.65

Deduction of rate law and mechanism:

Mechanism for uncatalysed reaction:

Chloramine-T acts as mild oxidant in both acid and alkali solutions with a two electron change to give reduced products. In aqueous solution it behaves as a strong electrolyte. In aqueous acidic medium it exhibit following equilibria furnishing different ionic species as follows[18-21].

$PTSO_2NClNa \rightleftharpoons PTSO_2NCl^- + Na^+$ (2)

$PTSO_2NCl^- + H^+ \rightleftharpoons PTSO_2NHCl$ (3)

$2PTSO2NHCl \rightleftharpoons PTSO_2NH_2 + PTSO_2NCl_2$ (4)

$PTSO_2NCl_2 + H_2O \rightleftharpoons PTSO_2NHCl + HOCl$ (5)

$PTSO_2NHCl + H_2O \rightleftharpoons PTSO_2NH_2 + HOCl$ (6)

Where, PT = $CH_3C_6H_4$

Hence the possible oxidizing species of CAT in aqueous acid mixture are $PTSO_2NHCl$, $PTSO_2NCl_2$ and HOCl. The possibility of $PTSO_2NCl_2$ as reactive species was ruled out as the rate is not second order with respect to [CAT] (equation-4). Further the rate does not show first order retardation by the added p-toluenesulfonamide. Hence HOCl is not primarily involved in oxidation. Thus $PTSO_2NHCl$ is considered as the active oxidising species. In acid medium (pH < 2) $PTSO_2NHCl$ is accepts proton to give $PTSO_2NH_2Cl^+$ [22-23].

$PTSO_2NHCl + H^+ \rightleftharpoons PTSO_2NH_2Cl^+$ (7)

The protonation constant for (7) at 298K is 1.02 $x10^2$. The rate is retarded by added H^+ ions confirming the deprotonation of $PTSO2NH2Cl^+$ leading to the formation of unprotonated active oxidizing species PTSO2NHCl.

To account for the experimental results of ATV oxidation by CAT the following scheme-1is proposed. Let $PTSO_2NHCl$ represent the active oxidant, ATV represent substrate and X represent the intermediate complex species. The reaction is initiated through the formation of $PTSO_2NH_2Cl^+$ which attacks the substrate to give an intermediate complex X which on reaction with methanol give product. The detailed plausible reaction mechanism is illustrated in scheme-2.

$$PTSO_2NHCl + H^+ \xrightleftharpoons{k_1} PTSO_2NH_2Cl^+ \qquad \text{(i) fast}$$

$$PTSO_2NH_2Cl^+ + ATV \xrightleftharpoons{k_2} x \qquad \text{(ii) fast}$$

$$x \xrightleftharpoons{k_3} x^I \qquad \text{(iii) slow and r. d. s}$$

$$x^{\mathbf{I}} + CH_3OH \xrightleftharpoons{k_4} \text{Products} \qquad \text{(iv) fast}$$

Scheme-1

Here, X and $X^{'}$ are complex intermediate species whose structures are illustrated in scheme-2. Let $[CAT]_t$ is the total effective concentration of CAT, then

$$[CAT]_t = [PTSO_2NH_2Cl^+] + [PTSO_2NHCl] + [X] \qquad (1.1)$$

From steps (i) and (ii) of scheme-1,

$$[PTSO_2NH_2Cl^+] = \frac{[X]}{k_2[AT]} \qquad (1.2)$$

$$[PTSO_2NHCl] = \frac{[X]}{k_1k_2[ATV][H^+]} \qquad (1.3)$$

On substituting equation (1.2) and (1.3) in equation (1.1) and solving for [X], we get

$$[X] = \frac{k_1k_2[H^+][ATV][CAT]_t}{1+k_1[H^+]+ k_1k_2[H^+][ATV]} \qquad (1.4)$$

From slow step of scheme-1,

$$\text{Rate} = k_3\,[x] \qquad (1.5)$$

By substituting for [X], from equation (1.5) to equation (1.4), we get

$$\text{Rate} = \frac{k_1k_2k_3[H^+][ATV][CAT]_t}{1+k_1[H^+]+k_1k_2[H^+][ATV]} \qquad (1.6)$$

The deduced rate law agrees with the experimental results that a first and fractional order dependence of reaction rate on [CAT] and [ATV], $[H^+]$ respectively.

Since, Rate = $k_u\,[CAT]_t$, equation (1.6) can be transformed into,

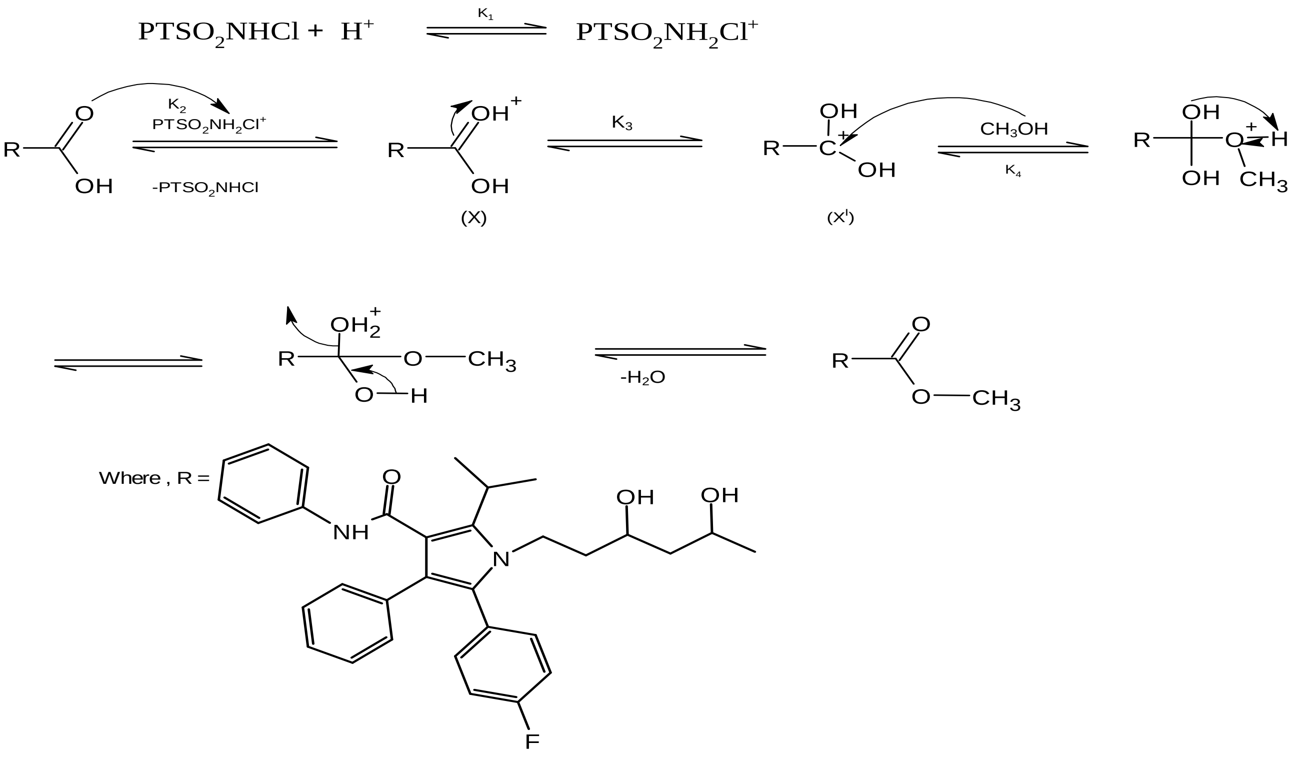
$$k_u = \frac{k_1k_2k_3[H^+][ATV]}{1+k_1[H^+]+k_1k_2[H^+][ATV]} \qquad (1.7)$$

On rearranging equation (1.7) we get,

$$\frac{1}{k_u} = \frac{1}{k_2k_3[ATV]}\left\{\frac{1}{k_1[H^+]}+1\right\}+\frac{1}{k_3} \qquad (1.8)$$

From equation (1.7) and (1.8), double reciprocal plot of $1/k_u$ versus 1/[ATV] gives straight lines. From the slope and intercepts values of k_1, k_2 and k_3 were calculated.

Dielectric constant of the medium was varied by adding different proportion of acetic acid (0- 40%, v/v). Plot of log k' versus 1/D has negative effect reveals the presence of dipole-dipole interaction in the reaction [24-26]. The reduction product PTS (p-Toulenesulphonamide) fails to change the rate indicating its non-involvement in pre-equilibrium. The changing ionic strength of the medium fails to influence the rate indicating the involvement of non-ionic species in the rate limiting step. Halide ion has slightly positive effect on reaction rate. The computed thermodynamic parameters support the proposed mechanism. The free energy of activation and enthalpy of activation have moderate positive value and a large negative value of entropy of activation indicate the formation of properly ordered compact transition state complex with lesser degrees of freedom in uncatalysed oxidation of ATV with chloramine-T in Hydrochloric acid medium at 303K.



Scheme-2

Deduction of rate law and mechanism for catalysed reaction:

Th (IV) catalysed oxidation of ATV by chloramine-T in Hydrochloric acid medium is similar to uncatalysed reaction with respect to stoichiometry. The reaction is first order with respect to CAT. The rate of a reaction follows fractional order with respect to substrate and HCl. As the concentration of catalyst increases the rate of reaction also increases this indicates order of reaction with respect to catalyst is fractional order. The dielectric constant of the reaction is studied by varying concentration of CH_3COOH. The dielectric constant has slightly negative effect. $NaClO_4$ is added to study the effect of ionic strength. Ionic strength had no significant effect on reaction rate indicating the involvement of non-ionic species in the reaction. In Th(IV) catalysed oxidation of ATV requires one mole of CAT to oxidise one mole of ATV, confirms that 1:1 stochiometry.

On the basis of preceding discussion the following scheme-3 has been proposed.

$$PTSO_2NHCl + H^+ \overset{k_5}{\rightleftharpoons} PTSO_2NH_2Cl^+ \qquad \text{(i) fast}$$

$$PTSO_2NH_2Cl^+ + Th\,(IV) \overset{k_6}{\rightleftharpoons} X^{II} \qquad \text{(ii) fast}$$

$$x'' + ATV \overset{k_7}{\rightleftharpoons} x''' \qquad \text{(iii) slow and r. d. s}$$

$$x''' + CH_3OH \overset{k_8}{\rightleftharpoons} \text{Products} \qquad \text{(iv) fast}$$

Scheme-3

Here,

X'' and X''' are complex intermediate species whose structures are illustrated in scheme-4.

Let $[CAT]_t$ is the total effective concentration of CAT, then

$$[CAT]_t = [PTSO_2NH_2Cl^+] + [PTSO_2NHCl] + [X''] \qquad (3.1)$$

From steps (i) and (ii) of scheme-3,

$$[PTSO_2NH_2Cl^+] = \frac{X''}{k_6[Th(IV)]} \qquad (3.2)$$

$$[PTSO_2NHCl] = \frac{[X'']}{k_5k_6[Th(IV)][H^+]} \qquad (3.3)$$

On substituting equation (3.2) and (3.3) in equation (3.1) and solving for $[X'']$, we get

$$[X''] = \frac{k_5k_6[H^+][Th(IV)][CAT]_t}{1+k_5[H^+]+k_5k_6[H^+][Th(IV)]} \qquad (3.4)$$

From slow step of scheme-3,

$$\text{Rate} = k_7\,[x''] \tag{3.5}$$

By substituting for $[X'']$, from equation (3.5) to equation (3.4), we get

$$\text{Rate} = \frac{k_5k_6k_7[H^+][Th(IV)][CAT]_t}{1+k_5[H^+]+k_5k_6[H^+][Th(IV)]} \tag{3.6}$$

The deduced rate law agrees with the experimental results that a first and fractional order dependence of reaction rate on [CAT] and [ATV], $[H^+]$, [Th (IV)] respectively.

Since, Rate = $k_C[CAT]_t$, equation (3.6) can be transformed into,

$$k_c = \frac{k_5k_6k_7[H^+][Th(IV)]}{1+k_5[H^+]+k_5k_6[H^+][Th(IV)]} \tag{3.7}$$

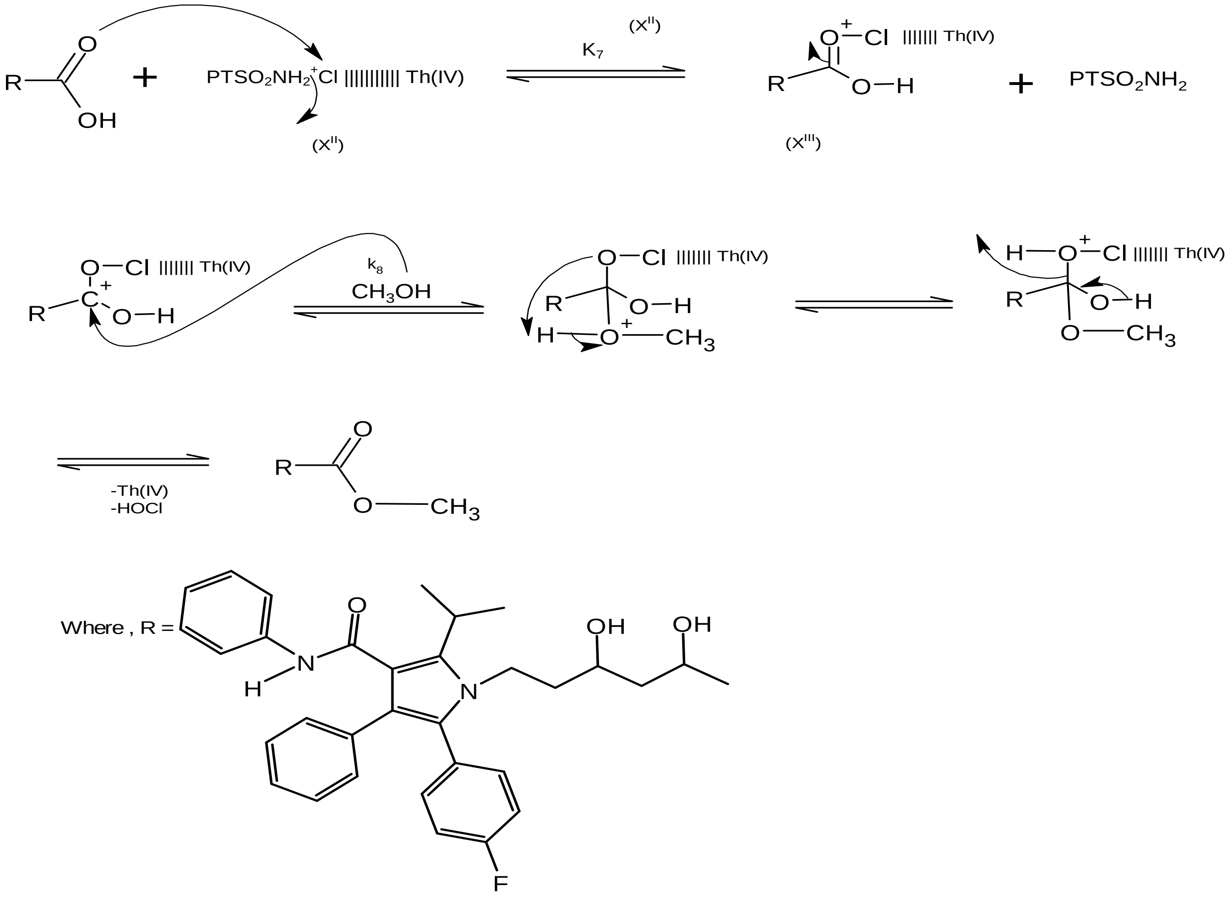
On rearranging equation (3.7) we get,

$$\frac{1}{k_c} = \frac{1}{k_7}\left\{\frac{1}{k_6[Th(IV)]}\left(\frac{1}{k_5[H^+]} + 1\right) + 1\right\} \tag{3.8}$$

From equation (3.7) and (3.8), double reciprocal plot of $1/k_c$ versus 1/[ATV] gives straight lines. From the slope and intercepts values of k_1, k_2 and k_3 were calculated.

$$PTSO_2NHCl + H^+ \overset{K_5}{\rightleftharpoons} PTSO_2NH_2Cl^+$$

$$PTSO_2NH_2Cl^+ + Th\,(IV) \overset{K_6}{\rightleftharpoons} PTSO_2NH_2^{+}Cl \;||||||||||\; Th(IV)$$



Scheme-4

Dielectric constant of the medium was varied by adding different proportion of acetic acid (0- 40%, v/v). Plot of log k' versus 1/D has negative effect reveals the presence of dipole-dipole interaction in the reaction [24]. The reduction product PTS fails to change the rate indicating its non-involvement in pre-equilibrium. The changing ionic strength of the medium fails to influence the rate indicating the involvement of non-ionic species in the rate limiting step. Halide ion has slightly positive effect on reaction rate. The computed thermodynamic parameters support the proposed mechanism. The free energy of activation and enthalpy of activation have moderate positive value and a large negative value of entropy of activation indicate the formation of properly ordered compact transition state complex with lesser degrees of freedom in Th(IV) catalysed oxidation of ATV with Chloramine-T in Hydrochloric acid medium.

Catalytic activity:

In presence of a catalyst, both the catalysed and uncatalysed reactions occurs concurrently, with the catalyst increasing the rate of reaction by providing a more energetically favorable pathways, as proposed by Moelwyn- Hughes[25],

So that, $k_c = k_u + K_C\,[Th(IV)]^x$, …….(8)

Here k_c is the rate constant for catalysed reaction, k_u is the rate constant for uncatalysed reaction, K_C is the catalytic activity with respect to the catalyst Th (IV) and x is the order of the reaction with respect to catalyst Th(IV).

The values of K_C were determined using equation (8) at different temperatures and are summarized in Table-4. The activation parameters were determined by constructing an Arrhenius plot of log k_c / k_u versus 1/T, allowing for the calculation of K_C values. The variation in activation parameters between the catalysed and uncatalysed reactions clearly elucidates the significant impact of the Th(IV) on the reaction. The formation of complex between thorium catalyst and Atorvastatin indicates that the catalyst thorium exhibits a more reducing character than the Atrovastatin itself, thereby enabling the Th(IV) to alter the reaction pathway by lowering its activation energy.

Comparison of catalysed and uncatalysed reactions:

In the present work, the activation parameters tabulated in Table-3 shows that the Thorium catalysed oxidation of Atorvastatin is faster than the uncatalysed reaction. The significant increase in atorvastatin oxidation rate upon addition of the catalyst highlights the crucial role of the catalyst in facilitating the reaction. The presence of catalyst lowers the activation energy. The proposed mechanism is further supported by the moderate values of activation energy and other thermodynamic parameters.

Conclusion:

In HCl medium, the oxidation of the CAT-ATV redox process has been carried out both catalysed and uncatalysed by thorium. In both catalysed and uncatalysed situations, the ATV oxidation by CAT has been found to have a 1:1 (equation 1) reaction stoichiometry. Methyl-(βR,δR)-2-(4-Fluorophenyl)-β,δ-dihydroxy-5-(1-methyl-lethyl)-3-phenyl-4 [(phenylamino)carbonyl] is the oxidation product.Peptanoate-1H-pyrrole. The effects of halide ions, acid concentration, catalyst, oxidant, substrate atorvastatin, ionic strength, temperature, and dielectric constant were all examined in relation to the rate. The measured parameters have been used to estimate the thermodynamic parameters Ea, ΔH≠, ΔG≠, and ΔS≠ from the Arrhenius plots. A rate law was obtained and a consistent method was proposed.

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