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# OXIDATION OF ROSUVASTATIN CALCIUM WITH CHLORAMINE-T IN BASIC MEDIUM A KINETIC AND MECHANISTIC APPROACH

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## ABSTRACT

Rosuvastatin Calcium is seventh drug in the class of statins, was approved by the United States Food and Drug Administration (USFDA) marketed under the trade name "Crestor" used for the treatment of high cholesterol and related conditions . The aim of the current investigation was kinetic study of oxidation of Rosuvastatin Calcium with sodium-*N*-chloro-*p*-tolunesulfonamide or chloramine-T (CAT) in NaOH medium at 308 K. the results revealed that reaction followed identical kinetics, first order dependence on $[CAT]_0$,fractional order dependence on $[substrate]_0$, and $[OH^-]$ ion concentration. Variation of ionic strength and addition of toluene sulfonamide have no significant effect on the rate. The reaction was studied at five different temperature; however, the thermodynamic parameters have been assessed from the Arrhenius plots. The stoichiometry of the reaction has been established to be 1:1 and oxidationproduct3*R*,5*S*,E)-methyl7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido) pyrimidin-5-yl)-3,5dihydroxyhept-6-enoate,was predicted by spectroscopic and chromatographic analysis. The observed results were supported by probable mechanism and the related rate law has been deduced.

**KEYWORDS:** Rosuvastatin Calcium, Oxidation Kinetics, Chloramine-T, Alkaline medium.

## INTRODUCTION

Rosuvastatin Calcium (RSV), molecular formula $C_{22}H_{28}FN_3O_6S$ and its molecular weight is 481.39 (chemically [4-(4-flurophenyl)-6-isopropyl 2-[methyl (methyl (methyl sulphonyl) amino] pyrimidin-5-yl] (3*R*,5*S*,)-3, 5-dihydroxyhepta-6-enoic acid] calcium salt is a yellow colored solid powder freely soluble in water, acetonitrile, slightly soluble in chloroform, insoluble in hexane.[1]

Rosuvastatin Calcium an oral medication belongs to class of drugs called statins used for the treatment of high cholesterol and related conditions, and prevent the cardiovascular disease. It is a lipid lowering drug inhibits the enzyme -3 hydroxy3-methyl glutaryl coenzyme A (HMG-CoA) reductase.[2-4] Rousvastatin was approved marketing in USA in 2003 and is therefore newest of the statins studies here; however various muscle related side effects were reported, rhabdomyolysis, a combined category of myalgia ,myopathy and myositis , nausea also occured.[5]

The diverse nature of chemistry of *n*-halo-aryl sulfonamide generally known as *N*-haloamines is of interest due to the ability to act as halonium cations, hypohalites and *N*-anions which act as bases, nucleophiles. As a result, these compounds react with wide range of functional groups and affect variety of molecular changes.[6-9] The prominent member of this class of compounds is sodium *N*-chloro-*p*-tolunesulfonamide or Chloramine-T (*p*-$CH_3C_6S_4SO_2NClNa.3H_2O$ and abbreviated as (CAT) and other member is Chloramine-B (sodium *N*-chlorobenzenesulfonamide) or (CAB).

The *N-Cl* bond in CAT and CAB is highly polar hence these two compounds are fairly strong electrophiles. CAT has been used for the variety of organic and inorganic substances and their oxidation mechanism kinetically well studied.[10-14]

Rosuvastatin Calcium is one of the important drug for reduction of cholesterol in patients with hypercholesterolemia. The review of literature support that there is no information available on oxidation kinetics of Rosuvastatin Calcium with Chloramine –T or any oxidants in alkaline media; so the present study was under taken to study the same.

## EXPERIMENTAL

Chloramine-T ACS reagent (>98.0% purity) obtained from Sigma Aldrich Co,Ltd,India. Rosuvastatin Calcium (purity >98.0% checked by HPLC Fig-1) was received from Jubilant

Bioscience, Ltd, India. The desired strength of drug is taken whenever required, analytical grade chemicals and double distilled water were used throughout the experiment. All calculations was performed using *fx*-991 MS scientific calculator, regression coefficient r was made using MS –Excel program Shimadzu LC-2010 used for HPLC analysis as per in house method Biocon Ltd india. Hypersil BDS, $C_{18,}$100 mm× 4.6 mm, 5*µm* column used. Mass spectrometer Waters Synapt Q-TOF and FT-IR Perkin Elmer KBR pellet were used for analysis.

**Kinetic procedure:** The reactions were carried out in pseudo first order conditions for kinetic runs. $[substrate]_0 > [Oxidant]_0$ required amount of Rosuvastatin Calcium, NaOH, were mixed in a stoppered brown colored bottle to prevent the photochemical reaction. Measured amount of water added to maintain a constant total volume. The tube thermo stated (Techno-ST-405, India) was used maintain the desired temperature in a water bath at 308 K for 30 min. The reaction was initiated by adding a measured amount of pre equilibrated CAT to the mixture, progress of the reaction monitored by iodometric titration of unreacted CAT in measured aliquot (5.0 mL) of mixture at different time intervals. The course of reaction was studied more than two half-lives, the rate constant ($k^{'}$ $s^{-1}$) was calculated from the linear plots.

**Stoichiometry and product analysis** : Various ratios of CAT to RSV were equilibrated at 308 K for 24 h. in the presence of aqueous alkali medium, the residual oxidant determined by iodometry and analysis shows that one mole of RSV consumed by one mole of CAT.

$C_{22}H_{28}FN_3O_6S$ + TsNClNa ⟶ (3*R*,5*S*,E)-methyl 7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoate +$TsNH_2$+ NaCl

The reaction mixture in stoichiometric ratio in presence of base media under stirred condition was allowed to progress for 24 h, at 308 K. After completion, the reaction was monitored by thin layer chromatography (TLC; Ethylacetate:Tolune:Methanol 6:2:2).[15] The reaction product was neutralized by NaOH, extracted with ether the organic product was identified by TLC and HPLC.

Further confirmed by LC-MS it showed molecular ion peak with *m/z* 494 amu (Fig-2) FT –IR analysis shows small peak of *C=O* stretching frequency at 1714 $cm^{-1}$ it with noticeable overtone at 3420 $cm^{-1}$ that confirm the formation of ester namely 3*R*,5*S*,E)-methyl 7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl)-3,5dihydroxyhept-6-enoate.

## RESULTS AND DISCUSSION

**Table 1: Effect of varying oxidant, substrate, and NaOH concentrations on the rate of reaction at 308 K.**

| $10^4$ [CAT] (Mol $dm^{-3}$) | $10^3$ [RSV] (Mol $dm^{-3}$) | $10^2$ [NaOH] (Mol $dm^{-3}$) | $10^4$ $k'$ ($s^{-1}$) |
|---|---|---|---|
| 2.0 | 9.0 | 2.0 | 4.15 |
| 4.0 | 9.0 | 2.0 | 4.10 |
| 6.0 | 9.0 | 2.0 | 4.04 |
| 8.0 | 9.0 | 2.0 | 3.96 |
| 6.0 | 5.0 | 2.0 | 3.37 |
| 6.0 | 7.0 | 2.0 | 3.83 |
| 6.0 | 11.0 | 2.0 | 4.38 |
| 6.0 | 13.0 | 2.0 | 4.79 |
| 6.0 | 9.0 | 0.7 | 2.30 |
| 6.0 | 9.0 | 0.9 | 3.58 |
| 6.0 | 9.0 | 4.0 | 4.36 |
| 6.0 | 9.0 | 6.0 | 4.79 |
| 6.0* | 9.0 | 2.0 | 4.04 |
| 6.0** | 9.0 | 2.0 | 4.26 |

* In presence of tolunesulfonamide

** At ionic strength 0.2 mol/dm $^{-3}$

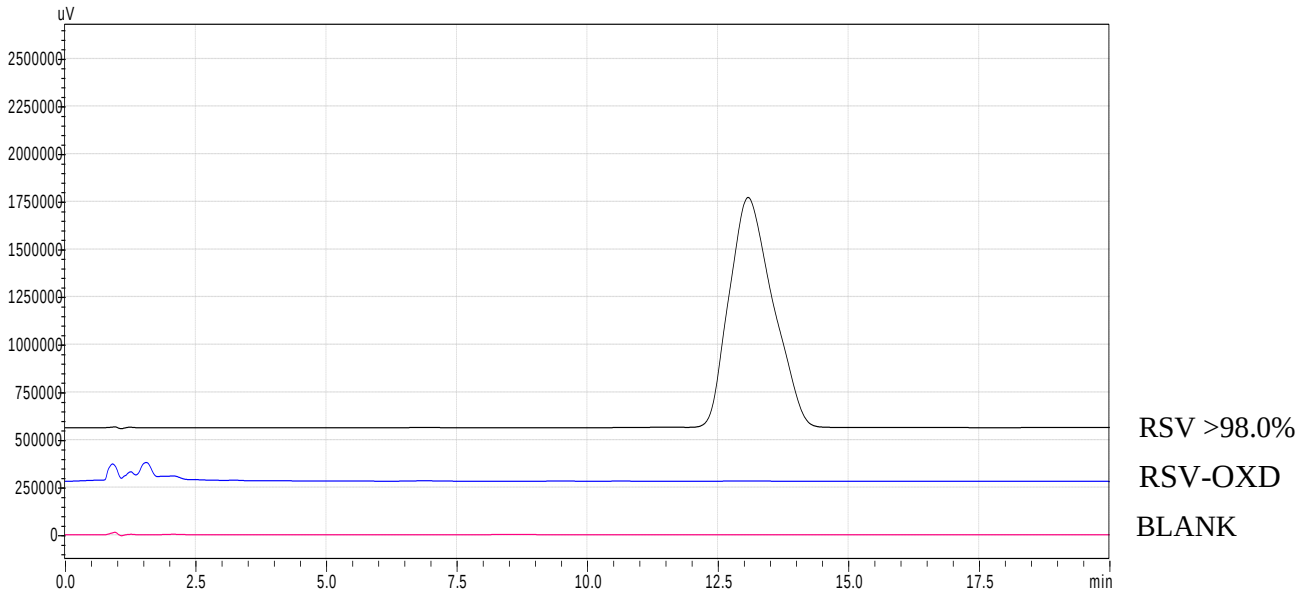



**Figure 1: HPLC comparision of substrate and oxidation product.**

The above HPLC chromatogram Fig-1 RSV shows the sharp peak at RT at 13.08 min (purity > 98.0% by area normalization) in the same method and the oxidation product of RSV it does not shows any peak that clearly indicates RSV completely oxidized and converted to ester type of oxidation product.

**Chromatographic Conditions**

Solutions should be prepared freshly.

Column : Hypersil BDS $C_{18,}$ 4.6 mm X 10 cm 5$\mu$

Wavelength : 248 nm

Flow rate : 1.0 mL/min

Mobile Phase : Acetate Buffer: Acetonitrile: water (50:25:25)

Column Temp : 40 $^0$C

Injection Volume : 20 µL

Retention Time : About 13.08 min

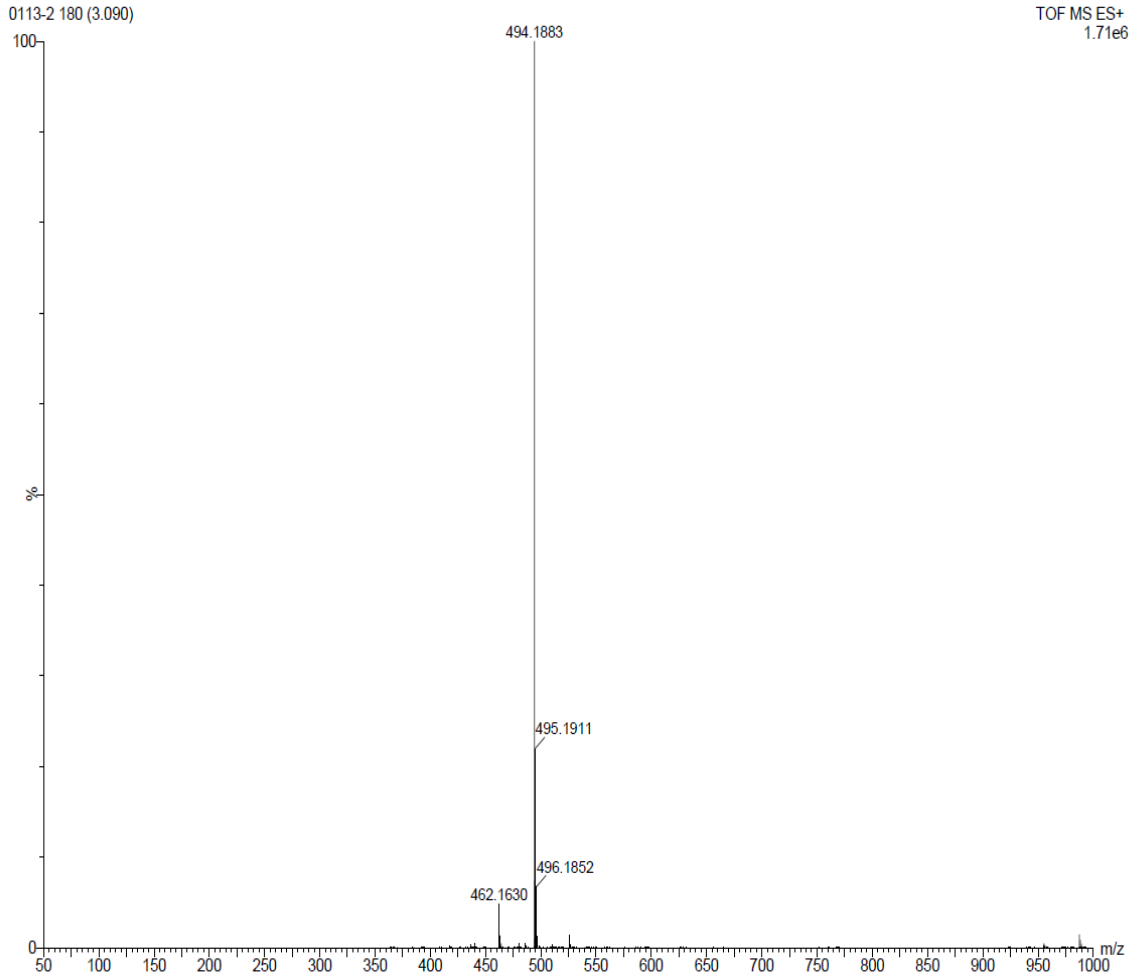



**Figure 2: LC-MS Spectrum of (3*R*,5*S*,E)-methyl 7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoate with its molecular ion peak at 494 amu.**

The kinetic oxidation of RSV by CAT was investigated under pseudo first order conditions. $[CAT]_0 >> [RSV]_0$ at various concentrations of the reactants in basic solutions at 308K.When $[CAT]_0$ was varied, keeping all other reaction conditions constant plot log $[CAT]_0$ versus time were linear (R=0.9933) indicating first order dependence of the reaction rate on $[CAT]_0$.The values of pseudo first order rate constant(k') were unaltered with variation in $[CAT]_0$ (Table-1).

The rate increases with increase in $[RSV]_0$ and plot of log k' versus log $[RSV]_0$ was linear (R=0.9497) with fractional slope 0.16, indicating fractional order on $[RSV]_0$.(Table-1, Fig-3). The rate of reaction increases with increases in $[NaOH]_0$. and plot log k' versus log $[OH^-]$ was linear(R=0.9424) with fractional slope 0.36,indicating the fractional order dependence of rate on $[OH^-]$. (Table-1, Fig-4).

The reaction rate remains unaffected by varying the ionic strength of the medium through an addition of sodium perchlorate (0.1-0.2 mol $dm^{-3}$), indicates non ionic species involved in the rate determining step, The dielectric permittivity of the medium was varied at different proportions of acetonitrile (0-20 %) but there is no significant change in the rate observed (Table 2).

Addition of reactant product *p*-toluene sulfonamide ($2.0\times10^{-4}$ - $8.0\times10^{-4}$ mol $dm^{-3}$) had no pronounced effect on the rate. The reaction was studied at different temperature (298-318K) at Arrhenius plot log k' versus 1/T (R=0.9737) (Fig-5) values of activation parameters namely energy of activation Ea , enthalpy of formation $\Delta H^{\#}$,Gibbs free energy $\Delta G^{\#}$ and entropy $\Delta S^{\#}$, log A, were computed. (Table 3).

**Table 2: Effect of varying dielectric constant of the medium.**

| % of $CH_3CN$ | $10^{-4}$ K ($k's^{-1}$) | D |
|---|---|---|
| 0 | 4.04 | 70.08 |
| 5 | 4.67 | 69.0 |
| 10 | 4.79 | 67.3 |
| 15 | 4.72 | 65.7 |
| 20 | 4.69 | 64.2 |

$[CAT]_0 = 6.0\times10^{-4}$ mol $dm^{-3}$ $[RSV]_0 = 9.0\times10^{-3}$ mol $dm^{-3}$ $[NaOH]_0 = 2.0\times10^{-2}$ mol $dm^{-3}$

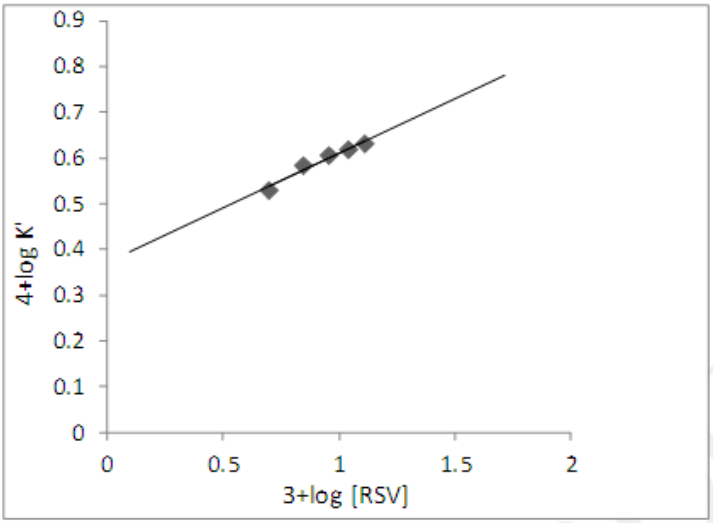



**Figure 3: plot of 4+log k' vs 3+log [RSV].**

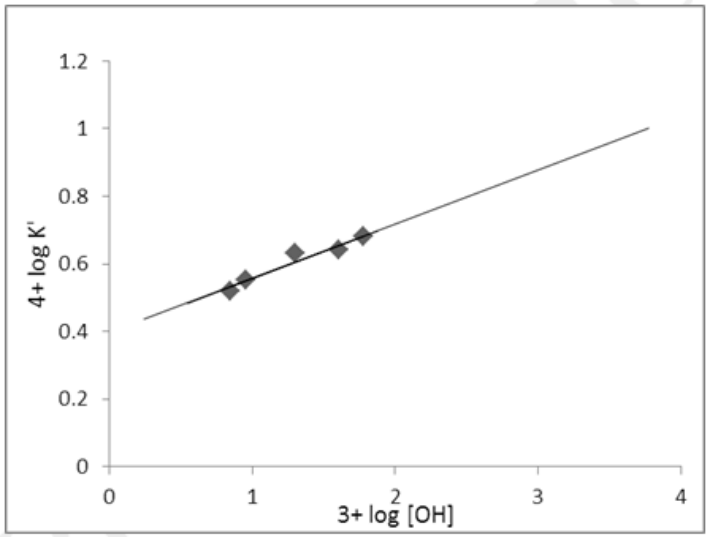



**Figure 4: plot of 4+log k' vs 3+log [$OH^-$].**

**Table 3: Effect of varying temperature on the rate of reaction & activation parameters for oxidation of RSV by CAT in alkaline medium.**

| Temp (K) | $10^4$ k' ($s^{-1}$) |
|---|---|
| 298 | 2.74 |
| 303 | 3.67 |
| 308 | 4.04 |
| 313 | 4.91 |
| 318 | 6.02 |
| $E_a$ $kJ/mol^{-1}$ | 27.84 |
| $\Delta H^{\#}$ $kJ/mol^{-1}$ | 25.37 |
| $\Delta G^{\#}$ $kJ/mol^{-1}$ | 90.94 |
| $\Delta S^{\#}$ $Jk^{-1}/mol^{-1}$ | -214.89 |
| Log A | 3.57 |

$[CAT]_0 = 6.0\times10^{-4}$ mol $dm^{-3}$ $[RSV]_0 = 9.0\times10^{-3}$ mol $dm^{-3}$ $[NaOH]_0 = 2.0\times10^{-2}$ mol $dm^{-3}$

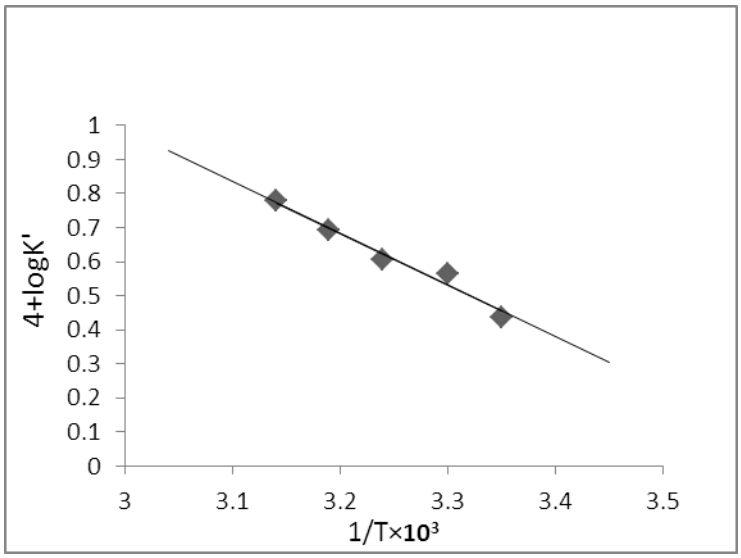



**Figure 5: plot of 4+lok k' vs $1/T\times10^3$.**

**Reactive species of Chloramine-T**

CAT (TsNClNa) act as oxidizing agent in both acidic and alkaline solutions CAT behaves as strong electrolytes in aqueous solution forming different species,[16-17] ( Equations 1,6,8 ).

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

$TsNCl^- + H^+ \rightleftharpoons TsNHCl$ …….. 2

$TsNHCl + H_2O \rightleftharpoons TsNH_2 + HOCl$ …….. 3

$2TsNHCl \rightleftharpoons TsNH_2 + TsNCl_2$ ..... 4

$HOCl + H^+ \rightleftharpoons H_2OCl^+$ ..... 5

$HOCl^+ \rightleftharpoons H^+ + OCl^-$ ……6

In acidic solution of CAT probable oxidizing species were free acids (TsNHCl) dichloramine T ($TsNHCl_2$),HOCl and $H_2OCl^+$. in alkaline solution of CAT $TsNCl_2$ and $H_2OCl^+$ do not exist.Therefore the expected reactive species in basic medium are HOCl, TsNHCl and $TsNCl^-$. the possible species $TsNCl^-$ , $OCl^-$ could be transformed into more oxidizing species TsNHCl and HOCl through reaction 7-9.

$TsNCl^- + H_2O \rightleftharpoons TsNHCl + OH^-$ ……7

$TsNCl^- + H_2O \rightleftharpoons TsNH_2 + OCl^-$ ……. 8

$OCl^- + H_2O \rightleftharpoons HOCl + OH^-$ …….9

If TsNHCl and HOCl are consider to be reactive oxidizing species then the retardation of rate by adding $TsNH_2$ (*p*-tolune sulfonamide) and $OH^-$ would be expected, However no such effect were observed in present case. Hence can these species can ruled out as reactive oxidizing species $TsNCl^-$ is most likely to oxidizing species in alkali which accelerating the reaction with substrate.

**Reaction Scheme-1**

$$TsNHCl + OH^- \underset{}{\overset{k_1}{\rightleftharpoons}} TsNCl^- + H_2O \text{ fast}$$

$$TsNCl^- + RSV \xrightarrow{k_2} X_{(complex)} \text{ slow/rds}$$

$$X + H_2O \xrightarrow{k_3} \text{Products fast}$$

In general reaction scheme-1 RSV represents the substrate, and X is the intermediate species with an initial equilibrium in involves the formation of active oxidizing species of the oxidant.In the next step $TsNCl^-$ attack to substrate to form a intermediate Complex (X). This step is rate determining step. Finally the intermediate step hydrolysis to give end product where detailed plausible mechanism of oxidation of RSV with CAT in basic medium. (scheme -2).

**Kinetic rate law**

The total effective concentration of CAT is $[CAT]_t$ then

$[CAT]_t = [TsNHCl] + [TsNCl^-] + [X]$ …….10

By substituting [TsNHCl] and $[TsNCl^-]$ from equilibrium steps of scheme 1 in equation 10 gets

$$[X] = \frac{K_1 K_2 [CAT]_t [RSV] [OH^-]}{[H_2O] + K_1[OH^-] + K_1 K_2 [RSV][OH^-]} \quad \ldots\ldots 11$$

From the slow step of scheme 1

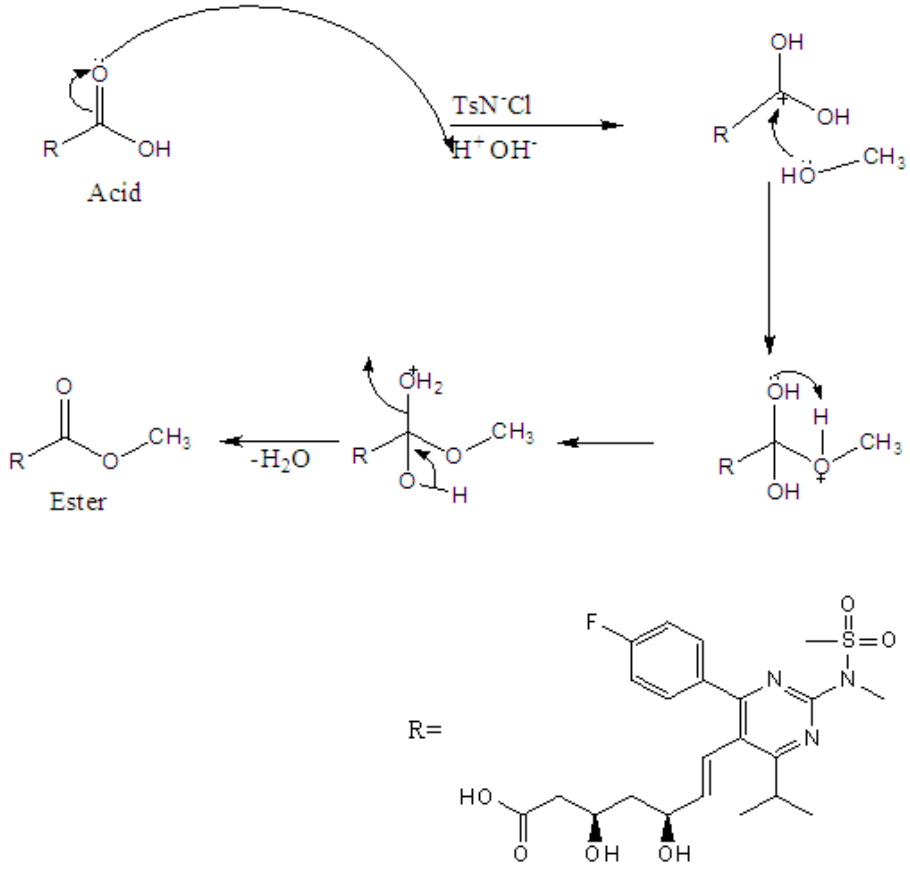
Rate = $k_3$ [X] …..12

By substituting [X] from 11 in to equation 12

$$Rate = \frac{K_1 K_2 k_3 [CAT]_t [RSV] [OH^-]}{[H_2O] + K_1[OH^-] + K_1 K_2 [RSV][OH^-]} \quad \ldots..13$$

The above rate expression (equation13) is good agreement with experimental results,the detailed mode of oxidation of RSV by Chloramine T in scheme-2. The proposed mechanism is supported by observed activation parameters. Further the high positive energy values of Gibbs free energy of activation and enthalpy of activation shows transition state with highly solvated while high negative value of entropy indicates for the formation of compact transition state in which several degree of freedom were lost. [18]

**Mechanism**




**Scheme 2: Detailed Mechanistic elucidations for oxidation of RSV by CAT in Basic medium, ester type of oxidation product is formed namely (3*R*,5*S*,E)-methyl 7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enoate.**

## CONCLUSION

Oxidation of Rosuvastatin Calcium by CAT in alkaline medium has been studied at 308 K. The stoichiometry of the reaction was found to be 1:1; oxidation products were characterized and thermodynamic parameters were computed by Arrhenius plot. The observed results have been supported by plausible mechanism. However, related rate law has been predicted.

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