



Mechanistic Investigation of Oxidation of Rizatriptan Benzoate by Chloramine-B: A Kinetic Spectrophotometric Study

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ABSTRACT

The kinetics of Rizatriptan benzoate oxidation by chloramine-B in HCl medium at 298 K has been studied using UV-spectrophotometry as an analytical tool. The progress of the oxidation was monitored at 279nm. The reaction follows first order dependence on [oxidant] and fractional order each in [substrate] and [HCl]. The rate of the reaction was found to increase with decrease in dielectric constant of the medium. Variation of ionic strength and added reaction products had no significant effect on the rate of the reaction. The reaction was studied at different temperatures and the values of thermodynamic parameters were deduced. The oxidation products were identified by spectral analysis and suitable mechanism is suggested.

Keywords: Kinetics, oxidation, Chloramine-B, spectrophotometric.

INTRODUCTION

Aromatic sulfonyl haloamines (N-haloamines) are known to be a class of versatile oxidising agents as it acts as a good source of haloamine cations and N-anions.¹ The prominent member of this class is chloramine-B (CAB) which is used as an oxidant for kinetic oxidation of various organic substrates in both acidic and alkaline media.²⁻⁵

Sufficient reports are available about oxidation of antibiotics⁶ and dyes⁷ by Chloramine-B. A review of the literature reveals that there are no reports on oxidative kinetics of anti-migraine drugs by CAB.

Rizatriptan benzoate (RTB) is a serotonin 5-HT₁ receptor agonist triptan drug indicated for the acute treatment of migraine. It is used in the activation of 5-HT_{1β} receptor leading to selective vasoconstriction of certain cranial extra cerebral blood vessel segments. RTB is chemically described as N,N-dimethyl-5-(1H-1,2,4-triazol-1-yl methyl)-1H-indole-3-ethanamine monobenzoate. The metabolism, disposition and in vitro pharmacokinetics of RTB in laboratory animals has been investigated.⁸ It has been reported that metabolic pathway of rizatriptan included oxidative deamination, aromatic hydroxylation followed by N-oxidation in presence of air. However, there is hardly any reference to the in vitro kinetics of oxidation of this drug in the literature. Therefore understanding the mechanism of oxidative degradation of RTB is of importance in medicinal and redox chemistry.

MATERIALS AND METHODS

Materials

Solutions were prepared by using AR chemicals and double distilled water.

Chloramine-B was obtained by Merck, India and was purified by the method of Verger and Perlin.⁹ The purity of the sample was checked by iodometric determination of active chlorine. An aqueous solution of CAB was prepared, standardised iodometrically and preserved in a brown bottles to prevent its photochemical deterioration.

The substrate RTB was of acceptable grade of purity received by Apotex India Ltd as a gift sample and was used without further purification. Aqueous solution of desired strength was prepared before use.

Kinetic procedure

Kinetic measurements were performed on Shimadzu UV 2401 PC UV-vis spectrophotometer. RTB exhibited two peaks at 226 and 279 nm. The progress of the reaction was followed spectrophotometrically at 279 nm by monitoring the decrease in absorbance of RTB.

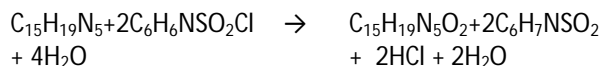
The kinetics was followed under pseudo-first order condition where [oxidant] >> [substrate] at constant concentration of HCl and NaClO₄ (to maintain a constant ionic strength) at 298K. Reactions were carried out in glass stoppered pyrex boiling tubes whose outer surfaces were coated black to prevent photochemical effects.

The reaction was initiated by rapid addition of a measured amount of oxidant to the stirred reaction mixture. Immediately, 4mL of the solution was pipette in to a cuvette placed in the spectrophotometer. Absorbance measurements were made for two half lives. The pseudo-first order rate constant 'K_{obs}' were determined from the log (absorbance) versus time plots. The course of the reaction was studied up to 75% completion. The pseudo-first order rate constant were evaluated and were reproducible with ±3%.



Reaction Stoichiometry

Different sets of reaction mixtures containing varying ratios of CAB to RTB in presence of constant amount of H⁺ were equilibrated at 298 K for 24 hours. Iodometric titrations of unreacted CAB showed that one mole of RTB consumed two moles of CAB, confirming the following stoichiometry.



The RTB-CAB reaction was allowed to progress for 24 hours under stirred conditions in presence of acid. After completion of the reaction, water insoluble and water soluble products were observed.

The water insoluble product was filtered, dried and the purity was checked using TLC technique with 1:1 benzene and ethanol as eluting solvent.

The HR-MS data of the product was obtained by electron impact ionisation technique using Q-TOF Micro mass spectrometer. The mass spectra showed a molecular ion peak at 301 amu (Fig 1). The molecular weight of RTB being 269 amu clearly indicates the oxidised product.

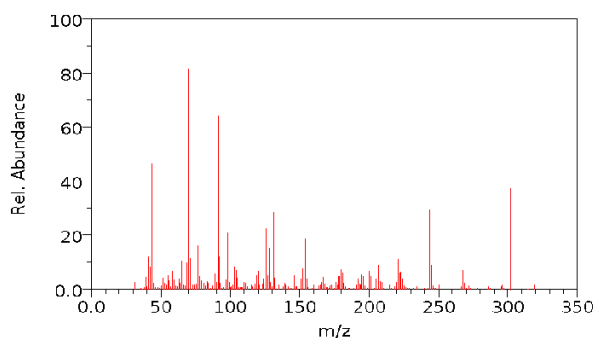


Figure 1: Mass spectrum of oxidised product

The product was further characterised by the following spectroscopic data.

IR(KBr): cm⁻¹, using Nicolet 6700

3398 (N-H)

3122 (aromatic secondary N-H)

1734 (Imide in-phase), 1616 (Imide out of -phase)

1274 (aliphatic amine)

¹H NMR (DMSO) δ/ppm: using NMR Bruker 500 MHz

2.00 -2.35 [m, 4H, -CH₂]

4.80 [s, 6H, -N(CH₃)₂]

7.40 - 7.65 [m, 4H, Aromatic H]

8.35 - 8.42 [s, 2H, Heterocyclic H]

8.89 [s, 1H, N-H]

The reduction product was extracted using ethyl acetate and was identified as Benzenesulfonamide (PhSO₂NH₂), by TLC¹⁰ using a mixture of Petroleum-ether, CHCl₃ and n-

butanol (2:2:1 v/v)) as eluting solvent and iodine as spray reagent (R_f = 0.88). Further the mass spectra showed a molecular ion peak at 157 amu confirms benzenesulfonamide (Figure 2)

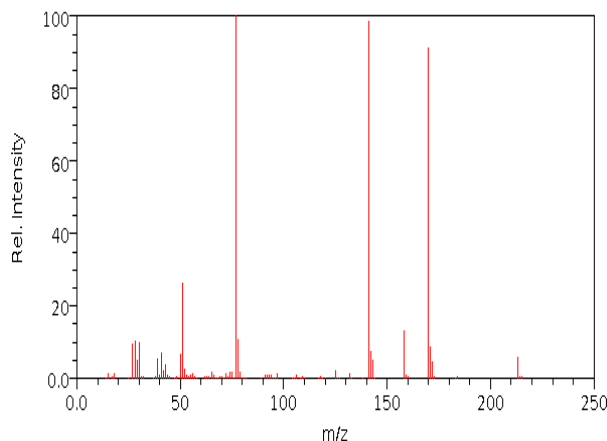


Figure 2: Mass spectrum of benzenesulfonamide

RESULTS AND DISCUSSION

The kinetics of oxidation of RTB by CAB was investigated at 298 K in presence of known concentration of HCl. The reaction orders, rate law and other experimental data were obtained.

Effect of varying oxidising agent on the rate

Kinetics of oxidation of RTB by CAB was studied at various initial concentrations [0.2 x 10⁻³ – 2 x 10⁻³] of CAB at 298K keeping the concentration of RTB [1 x 10⁻⁴ M] and HCl [1 x 10⁻⁴ M] as constant. Plots of log[CAB] versus time was linear indicating a first order dependence of rate on CAB. The constant values of K_{obs} at different concentrations of oxidant evaluated from integrated first order rate equation. Table-1 is a further evidence for pseudo-first order dependence of rate on [oxidant].

The order of the reaction with respect to CAB was found to be 1.33±0.03.

Table 1: Effect of varying concentrations of reactants on the reaction rate at 298 K

10 ³ [CAB] (M)	10 ⁴ [HCl] (M)	10 ⁴ [RTB] (M)	10 ³ k' (s ⁻¹)
1.00	1.00	0.20	5.10
1.00	1.00	0.50	5.30
1.00	1.00	1.00	5.80
1.00	1.00	2.00	5.90
0.20	1.00	1.00	3.62
0.50	1.00	1.00	4.70
1.00	1.00	1.00	5.80
2.00	1.00	1.00	5.98
1.00	0.20	1.00	2.01
1.00	0.50	1.00	3.11
1.00	1.00	1.00	5.80
1.00	2.00	1.00	5.92

Effect of varying RTB on the rate

The oxidation was carried out with various concentrations of RTB [0.2×10^{-4} – 2×10^{-4} M] by using [1×10^{-3} M] of CAB and [1×10^{-4}] of HCl. The rate of the reaction increased with increasing [RTB]. Plots of $\log K_{\text{obs}}$ versus [RTB] was linear with a slope of 0.6, indicating a fractional order dependence of [RTB].

Effect of varying HCl on the rate

The reaction was also carried out with [1×10^{-3} M] oxidant and [1×10^{-4} M] of RTB, by varying HCl [0.2×10^{-4} – 2×10^{-4} M]. The rate increased with increase in [HCl] (table 1). A plot of $\log K$ versus $\log [\text{HCl}]$ was linear with a slope of 0.5, indicating a fractional order dependence of [RTB].

Effect of varying $[\text{H}^+]$ and $[\text{Cl}^-]$ on the rate

In order to determine the order of the reaction with respect to each of the $[\text{H}^+]$ and $[\text{Cl}^-]$, the reaction was also studied by varying the concentration of one ion while keeping the concentration of the other constant. The reaction was fractional order with respect to each of the ions (0.42 to H^+ ion and 0.08 to Cl^- ions).

At fixed $[\text{H}^+]$, addition of NaCl did not affect the rate significantly. Hence the dependence of rate on [HCl] reflected the effect of $[\text{H}^+]$ only and the rate of the reaction is directly proportional to $[\text{H}^+]$.

Effect of solvent polarity and dielectric medium

The reaction of RTB [1×10^{-4} M] and CAB [1×10^{-3} M] was carried out in the mixture of methanol and water of various concentrations (% v/v) containing HCl [1×10^{-4} M] at 298 K. Reaction rate increased with increase in methanol content in the medium. (Table 2)

Table 2: Effect of solvent composition on the reaction rate

MeOH (%)	D	$10^3 k' (\text{s}^{-1})$
0	76.73	5.02
5	74.55	5.86
10	72.37	5.94
20	67.48	6.02

Effect of added reaction product

Addition of the reaction product benzenesulphonamide had no effect on the rate of oxidation

Effect of ionic strength

The ionic strength of medium was varied by adding NaClO_4 [1×10^{-4} – 1×10^{-3} M] but had no significant effect on rate of the reaction. Hence, no attempt was made to keep it constant for kinetic runs.

Effect of temperature

The reaction rates were studied at different temperatures (298-305 K). From the linear Arrhenius plot of $\log k'$

versus $1/T$ (Fig 3), the activation parameters E_a , ΔH^\ddagger , ΔS^\ddagger , ΔG^\ddagger and $\log A$ were computed. (Table 3)

Table 3: Rate constants at varying temperatures and activation parameters

Temperature (K)	$10^3 k' (\text{s}^{-1})$	Activation parameter
298	5.20	$E_a (\text{kJ mol}^{-1})$ 77.92
300	7.44	$\Delta H^\ddagger (\text{kJ mol}^{-1})$ 17.67
303	9.88	$\Delta G^\ddagger (\text{kJ mol}^{-1})$ 461.262
306	14.50	$\Delta S^\ddagger (\text{J.K}^{-1} \text{mol}^{-1})$ -14.64
309	25.64	$\log A$ 2.62

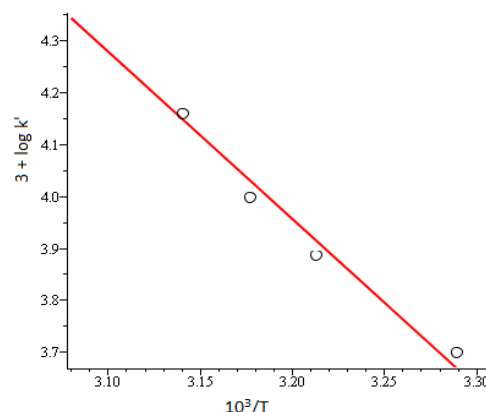


Figure 3: Plot of $3 + \log k'$ versus $10^3/T$

Variation of the concentrations of each of the oxidant (CAB), substrate (RTB) and acid while keeping the others fixed, showed that the reaction exhibits first order in oxidant, less than unit order in substrate and acid concentration.

Bishop and Jennings¹¹, Hardy and Johnston¹², Morris et al¹³ and Pryde and Soper¹⁴ have formulated that in acidic solutions probable oxidising species of CAB are PhSO_2NHCl , $\text{PhSO}_2\text{NCl}_2$ and HOCl .

If $\text{PhSO}_2\text{NCl}_2$ were to be the oxidising species, then the rate law predicts second order dependence on [CAB], which is not shown by the present experimental results.

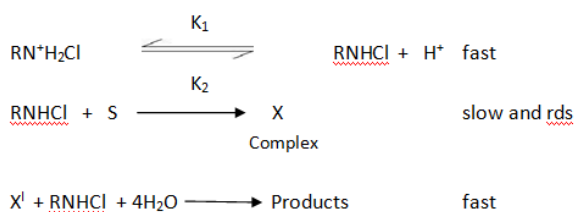
If HOCl were to be the oxidising species, a first order retardation of rate on adding benzenesulphonamide was expected, but such effects were not observed. Hence PhSO_2NHCl is the oxidising agent.

It is also known that RNHCl undergoes further protonation in slightly higher acidic conditions ($\text{pH} < 2$)

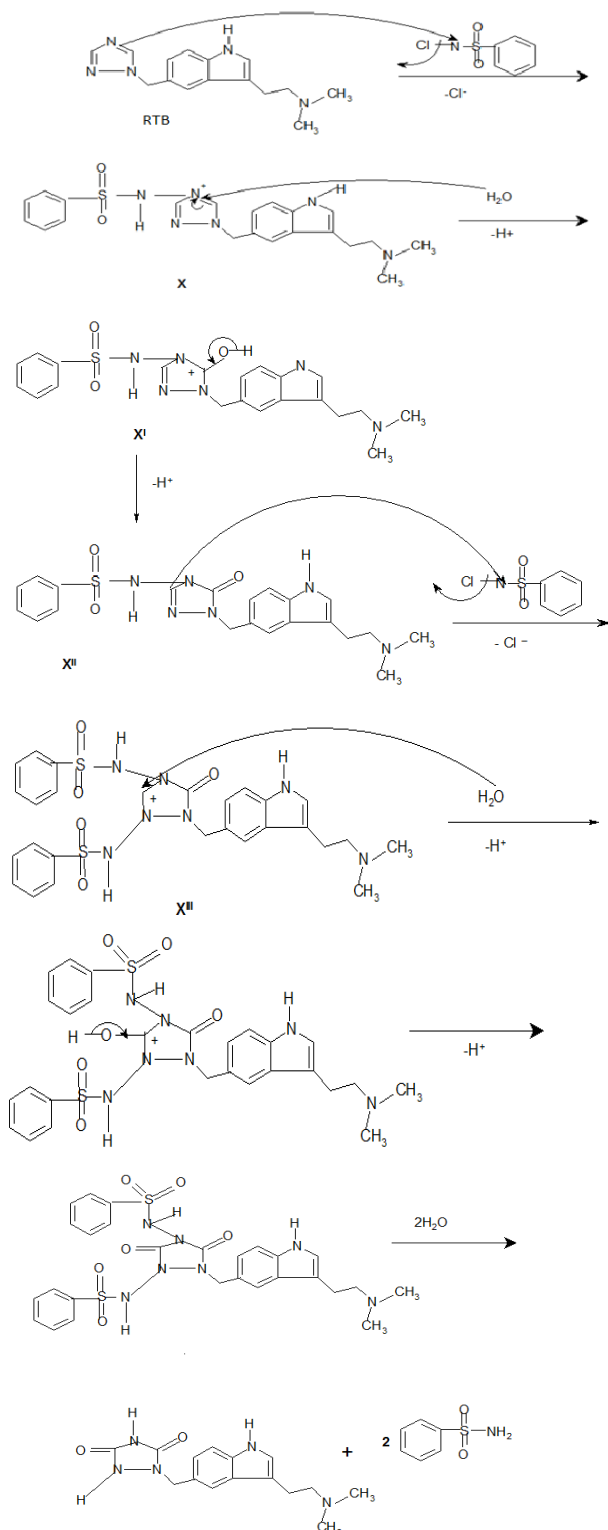


Since the present observations are carried on at $\text{pH} > 3$, it may be concluded that PhSO_2NHCl is the oxidising agent.

The oxidation of RTB by CAB in acid medium shows a fractional order dependence of the reaction rate on concentration of RTB indirectly suggests the involvement of the substrate and also clearly indicates complex formation between substrate and oxidant in the fast pre-equilibrium prior to the rate determining step as in the Michaelis-Menten type of kinetics.¹⁵



Based on these facts, the mechanism of the reaction could be explained by the following scheme 1.



Scheme II

If $[\text{CAB}]_t$, represents the total effective concentration of CAB, then

$$[\text{CAB}]_t = [\text{RN}^+\text{H}_2\text{Cl}] + [\text{RNHCl}] \quad (\text{i})$$

$$K_1 = \frac{[\text{RNHCl}][\text{H}^+]}{[\text{RN}^+\text{H}_2\text{Cl}]}$$

$$[\text{RN}^+\text{H}_2\text{Cl}] = \frac{[\text{RNHCl}][\text{H}^+]}{K_1}$$

$$\text{Equation (i) becomes } [\text{CAB}]_t = \frac{[\text{RNHCl}][\text{H}^+] + [\text{RNHCl}]}{K_1}$$

$$[\text{CAB}]_t = \frac{[\text{RNHCl}][\text{H}^+] + K_1[\text{RNHCl}]}{K_1}$$

$$[\text{CAB}]_t = \frac{[\text{RNHCl}]([\text{H}^+] + K_1)}{K_1}$$

$$[\text{RNHCl}] = \frac{K_1[\text{CAB}]}{([\text{H}^+] + K_1)} \quad (\text{ii})$$

$$\text{Since Rate} = K_2 [\text{RNHCl}] [\text{S}]$$

$$\text{From (ii) Rate} = \frac{K_2 K_1 [\text{CAB}] [\text{S}]}{([\text{H}^+] + K_1)}$$

$$\text{Since Rate} = K^1 [\text{CAB}]_t$$

$$K^1 = \frac{K_2 K_1 [\text{S}]}{([\text{H}^+] + K_1)}$$

The above rate expression is in agreement with the experimental results.

A detailed mode of oxidation of RTB by CAB is shown in scheme 2.

RNHCl reacts with the substrate in the equilibrium step to give the intermediate X.

The intermediate X undergoes hydrolysis to give X^1 . Deprotonation followed by oxidation of X^1 leads to the formation of X^{II} . Further, repeated hydrolysis of X^{II} leads to the formation of oxidised product N,N-dimethyl-5-(1H-1,2,4-triazol-3,5-dione-1-yl)methyl-1H-indole-3-ethanamine and benzenesulphonamide as the byproduct.

The change in the ionic strength of the medium does not alter the reaction rate, which suggests the non involvement of ions of opposite sign in the rate determining step.

The dielectric permittivity of the medium was varied by adding different proportions of methanol to the reaction mixture. Increase in content of methanol in the reaction mixture leads to increase in the rate of the reaction.

For the limiting case of zero angle of approach between two dipoles or an ion-dipole system, Amis¹⁶ has shown that a plot of $\log K^1$ versus $1/D$ gives a straight line with negative slope for reaction between two dipoles and positive slope for a reaction between positive ion and a dipole.

The positive dielectric effect in the present study, seems to agree with the expected interaction between the cationic form of the substrate and dipolar water in the rate determining step of the proposed mechanism.

The proposed mechanism is also supported by moderate values of energy of activation. The high value of positive free energy and a modest positive value of enthalpy indicate that the transition state is highly solvated. The negative entropy of activation suggests the formation of a compact activated complex.

CONCLUSION

Oxidative cleavage of RTB with CAB in hydrochloric acid medium has been studied. The stoichiometry of the reaction was found to be 1:2 and the oxidation products were identified by spectral studies and activation parameters were computed. The observed results are supported by suggested mechanism and the predicted rate law.

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