



OXIDATION OF PROPRANOLOL USING CHLORAMINE – T IN HClO₄ MEDIUM: A KINETIC AND MECHANISTIC STUDY

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ABSTRACT:

Kinetics and oxidation of Propranolol (PPL) ((*RS*)-1-(1-methylethylamino)-3-(1-naphthoxy)propan-2-ol) by sodium - N- chloro - p- toluenesulphonamide (Chloramine - T or CAT) in HClO₄ medium at 298K have been studied. The rate was first order in [CAT]₀, fractional order in [PPL] and zero order in [H⁺]. Addition of p-toluenesulphonamide, NaCl and NaBr did not affect the rate of the reaction. Variation in ionic strength did not affect the rate of the reaction indicating that non - ionic species are involved in the rate limiting step. The dielectric effect of the medium was positive. Rate increased with increase in temperature from 288K to 318K. From the linear Arrhenius plot, activation parameters were computed. Addition of reaction mixture to aqueous acrylonitrile solution did not initiate polymerization, showing the absence of free radicals species. Oxidation products were identified. TsNCINa, the reactive species, oxidizes the substrate. Based on kinetic results, reaction stoichiometry and oxidation products, a suitable mechanism have been proposed.

KEYWORDS: Propranolol, Oxidation, mechanism, Chloramine - T, kinetics, p-toluene sulphonamide.

INTRODUCTION:

Redox reactions have been the subject of detailed mechanistic and kinetic studies as they are most commonly encountered in chemical analysis. Investigation reveals that oxidation of compounds using other oxidants have been carried out¹⁻⁸. Organic haloamines resemble hypohalites in their oxidative behaviour, but are more stable than hypohalites and are developing rapidly as oxidants, disinfectants and antiseptics. Diverse nature of chemistry of haloamines is the consequence of their ability to act as oxidizing and halogenating agents in acidic and alkaline media. They react surprisingly with a wide range of industrially and biologically important functional groups affecting an array of molecular transformations. Halo amines furnish halonium cations in the +1 oxidation state and are generally known to undergo a two electron change in its reaction.

Chloramine-T(sodium-N-chloro-p-toluenesulfonamide or CAT;p- CH₃C₆H₄ClSO₂· Na) a prominent member of the series of haloamines. Literature survey shows that lot of work have been carried out using CAT as oxidant⁹⁻¹⁴.

Propranolol is a sympatholytic non-selective beta blocker. Sympatholytics are used to treat hypertension, anxiety and panic^{15,16}. It was the first successful beta blocker developed. It is used for treating high blood pressure, heart pain (angina), abnormal rhythms of the heart and some neurologic conditions. It also reduces the force of contraction of heart muscle and thereby lowers blood pressure. Literature survey revealed no information in the kinetics of oxidation mechanism of this drug by any other oxidants. Since the reaction was very fast when bromamine - T reacted with PPL, therefore kinetics of oxidation of PPL(*RS*)-1-(1-methylethylamino)-3-(1-naphthoxy)propan-2-ol) by CAT in HClO₄ medium at 298K have been studied.

MATERIAL AND METHODS:

Propranolol (Biocon, Bangalore, India) and Chloramine - T (E.Merck) was used without further purification. An aqueous solution of CAT was standardized iodometrically and preserved in brown bottles to prevent photochemical degradation. All other chemicals used were of analytical

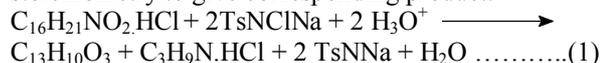
grade. Double distilled water was used in preparing all aqueous solutions. Permittivity(Dielectric constant D) of the reaction medium was altered by addition of methanol in varying proportions (v/v) and values of permittivity of methanol - water mixtures reported in literature were employed¹⁷.

Kinetic procedure

All reactions were performed under pseudo-first order conditions ([PPL]₀ >> [CAT]₀) at 298K, in a glass stoppered borosil boiling tubes coated black on outside to prevent photochemical effects. For each run, requisite amounts of solution of PPL, HClO₄ and H₂O (total volume kept constant) were introduced into the tube and thermally equilibrated at 298 ±1K. Reaction was initiated by rapid addition of measured amount of CAT solution to the above mixture and was shaken intermittently. Progress of the reaction was monitored by iodometric determination of unreacted CAT in a measured (5 cm³) aliquot of the reaction mixture at different time intervals. Reaction was studied for more than two half-lives. Pseudo-first order rate constants (k'), calculated from the linear plots of log [CAT] versus time were reproducible to ± 4%.

Stoichiometry

Reaction mixtures containing a known excess of [CAT] over [PPL] were kept in the presence of HClO₄ at 298K for 72 hours. Estimation of unreacted CAT showed showed 1:2 stoichiometry to give corresponding product.



Product analysis

Reduction product of the oxidant, p-toluenesulphonamide was detected by thin layer chromatography using light petroleum-chloroform-butan-1-ol (2:2:1v/v/v) as solvent and iodine as reducing agent (R_f=0.88). The reported R_f value is consistent with that given in the literature¹⁸. Further it was confirmed by its melting point 150-151°C (melting point: 149-151°C) and IR spectra. Oxidation product 3-(naphthalene-1-yloxy)-2-oxopropanal and Isopropylamine was detected by spot tests¹⁹ ie. 2, 4- dinitrophenyl hydrazine test and sodium nitroprusside test and was confirmed by IR

spectroscopy. Strong peak for -CHO group was observed at 1725cm⁻¹.

RESULTS

Effect of Reactants on the reaction rate

With substrate in excess, at constant [PPL], [H⁺] and temperature, plots of log [CAT] vs time were linear indicating a first order dependence of rate on [CAT]₀. The rate constant k' was not affected by a change in [CAT]₀ (Table 1) confirming first order dependence on [CAT]₀. Under identical experimental conditions, an increase in [PPL] lead to increase in k' (Table 1) and a plot of log k' vs log [PPL] was linear (Figure 1) with a positive slope of 0.846 indicating a fractional order dependence on [PPL]. The rate of the reaction was unaffected with increase in [HClO₄] (Table 1). Plot of log k' vs log [HClO₄] showed a zero order dependence on [H⁺].

Effect of halide ions and p-toluenesulphonamide(PTS)

At constant [H⁺], addition of NaCl or NaBr did not affect the reaction rate (Table 2). It reflected that the rate of the reaction depends only on [H⁺].

Addition of the reduction product of the oxidant, PTS did not affect the rate (Table 2) which indicates its non – involvement in pre equilibrium step with the oxidant.

Effect of ionic strength and dielectric constant

Variation in ionic strength using NaClO₄ solution did not affect the rate of the reaction (Table 2) indicating that non – ionic species are involved in the rate limiting step.

Dielectric constant (D) of the medium was varied by adding methanol to the reaction mixture. Addition of methanol resulted in increase in the rate of the reaction. Plot of (10²/D) vs log k' (Table 3) was found to be linear with a positive slope 2.0 (Figure 2). Blank experiments showed that MeOH was oxidized slowly (~3%) by the oxidants under the experimental conditions. This was corrected for the calculations in the net reaction for the rate constant.

Effect of temperature on the reaction rate

Reaction was studied over a range of temperature 288K to 318K (Table 4) by varying the [PPL] and keeping the other experimental conditions constant. It was found that the rate increased with increase in temperature (Figure 3).

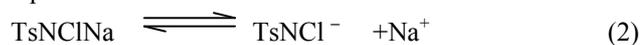
From the linear Arrhenius plot of log k' vs 1/T (Figure 4), activation parameters were computed (Table 5).

Test for free radicals

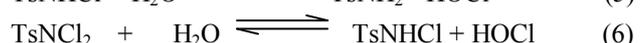
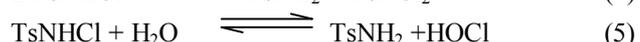
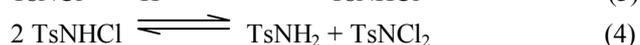
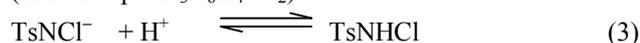
Addition of reaction mixture to aqueous acrylonitrile solution did not initiate polymerization, showing the absence of free radicals species.

DISCUSSION

Investigations by Pryde and Soper²⁰, Morris et.al²¹ and Bishop and Jinnings²² on sodium-N-haloarenesulfonamides have shown that Chloramine-T behave as strong electrolyte in aqueous solution forming different species as shown in equations.

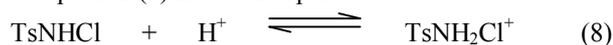


(Here Ts=p-CH₃C₆H₄SO₂)



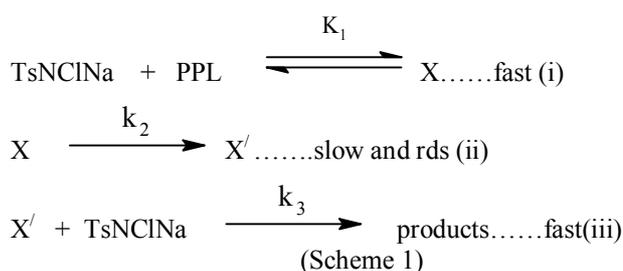
The possible oxidizing species in acid medium are TsNHCl, TsNCl₂ and HOCl. If TsNCl₂ were to be the reactive species,

the rate law predicts a second order dependence of rate on [CAT] which is contrary to the experimental observations. If HOCl is primarily involved, a first order retardation of the rate by the added p-toluenesulphonamide is expected. Since no such effect is noticed, HOCl can be ruled out as the oxidizing species. Hardy and Johnston²³ who have studied the pH dependent relative concentrations of the species present in acidified haloamine solutions of comparable molarities have shown that TsNHCl is the likely oxidizing species in acid medium. Further protonation of TsNHCl at pH < 2 according to equation (8) has been reported^{24,25}.



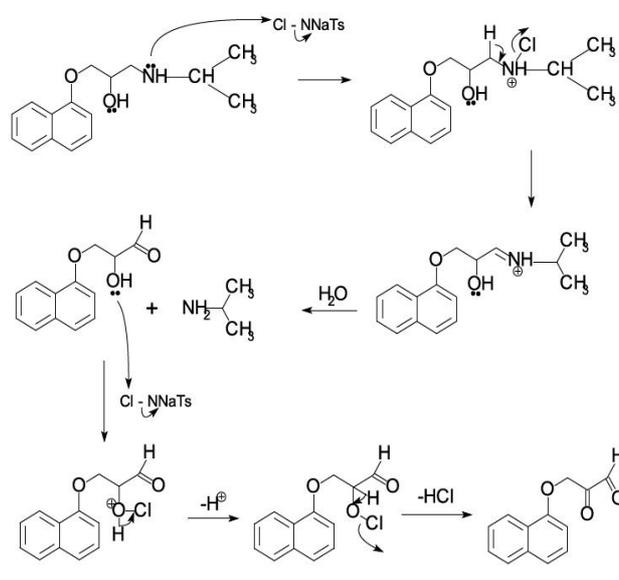
Since the rate of the reaction is independent of [HClO₄], TsNH₂Cl⁺ cannot be the oxidizing species. Hence CAT (TsNCINa) itself can oxidize the propranolol under the conditions employed.

Based on the preceding discussion and observed kinetic results, a mechanism (Scheme 1) is proposed for the oxidation of PPL by CAT in acidic medium.



In Scheme 1, X and X' represents the intermediate species, whose structures are shown in Scheme 2 in which a detailed mechanistic interpretation of PPL oxidation by CAT in acid medium is proposed. In this, the oxidant species TsNCINa reacts with the substrate in a fast equilibrium step to form complex (X). X decomposes to intermediate X' in rate limiting step. X' reacts with another mole of TsNCINa to form products. Two moles of the oxidant are consumed to yield the products.

SCHEME 2 Mechanism of Oxidation of [PPL] with [CAT]



From step (i), (ii) and (iii) of Scheme 1, we have

$$\text{Rate} = \frac{k_1 k_2 [\text{CAT}]_i [\text{PPL}]}{k_{-1}} \quad \dots\dots (9)$$

Rate law Equation (9) is in agreement with the experimental results.

Variation in ionic strength of the medium did not alter the rate indicating the involvement of non-ionic species in the rate limiting step. Addition of halide ions had no effect on the rate indicating that no interhalogen or free chlorine is formed. The positive dielectric effect observed in present case supports the positive ion – dipole interactions in the rate limiting step. Proposed mechanism is further supported by the moderate values of energy of activation and other activation parameters. Fairly high positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the large negative entropy of activation suggests the formation of the compact activated complex with less degrees of freedom.

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TABLE 1: EFFECT OF [CAT], [PPL] AND [HClO₄] ON THE REACTION RATE

10 ⁴ [CAT] ₀ mol dm ⁻³	10 ³ [PPL] ₀ mol dm ⁻³	10 ⁵ [HClO ₄] mol dm ⁻³	10 ³ k s ⁻¹
6.0	10.0	20.0	1.112
10.0	10.0	20.0	1.228
20.0	10.0	20.0	1.110
10.0	5.0	20.0	0.734
10.0	10.0	20.0	1.228
10.0	15.0	20.0	1.783
10.0	20.0	20.0	2.300
10.0	10.0	1.0	1.310
10.0	10.0	20.0	1.228
10.0	10.0	60.0	1.032
10.0	10.0	100.0	1.350

TABLE 2: EFFECT OF HALIDE IONS, PTS, NaClO₄ ON THE REACTION RATE

10 ⁴ [conc] mol dm ³	PTS 10 ³ k(s ⁻¹)	NaCl 10 ³ k(s ⁻¹)	NaClO ₄ 10 ³ k(s ⁻¹)	NaBr 10 ³ k(s ⁻¹)
0.0	1.228	1.228	1.228	1.228
10.0	1.730	1.140	1.310	1.102
50.0	1.350	1.025	1.012	1.234
100.0	1.210	1.230	1.210	1.200

TABLE 3: EFFECT OF DIELECTRIC CONSTANT ON THE REACTION RATE

MeOH (% v/v)	D	10 ⁷ /D	10 ³ k(s ⁻¹)
0	76.93	1.30	1.228
10	72.37	1.38	1.750
20	67.38	1.48	2.990
30	62.71	1.60	4.910

TABLE 4: EFFECT OF [PPL] AT DIFFERENT TEMPERATURES

10 ³ [PPL] mol dm ³	10 ³ k(s ⁻¹)		
	288K	298K	308K
5.0	0.398	0.734	1.258
10.0	0.794	1.228	2.990
15.0	1.230	1.783	2.691
20.0	1.584	2.300	3.162

TABLE 5: EFFECT OF TEMPERATURE ON THE RATE OF THE REACTION

Temperature(K)	$10^3 k (s^{-1})$	Activation parameters
288	0.310	$E_a = 78.07 \text{ kJ mol}^{-1}$
298	1.228	$\Delta H^\ddagger = 75.983 \text{ kJ mol}^{-1}$
308	2.990	$\Delta G^\ddagger = 21.472 \text{ kJ mol}^{-1}$
318	7.600	$\Delta S^\ddagger = -179.90 \text{ JK}^{-1} \text{ mol}^{-1}$
		$\log A = 10.786$

Figure 1: Effect of [PPL] on the reaction rate

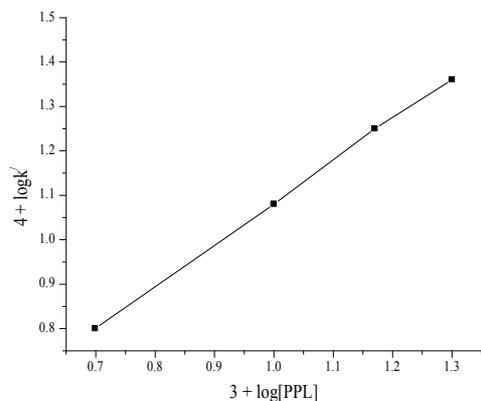


Figure 2: Effect of Dielectric constant of the medium on the reaction rate

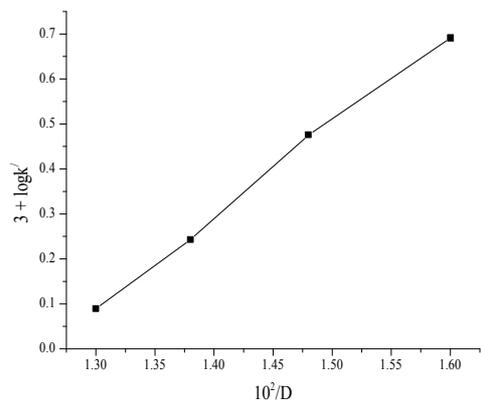


Figure 3: Effect of [PPL] at different temperatures in acid medium

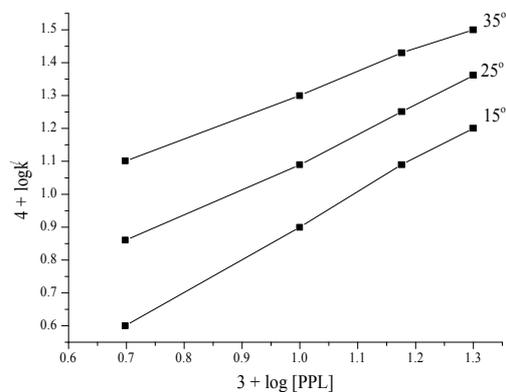
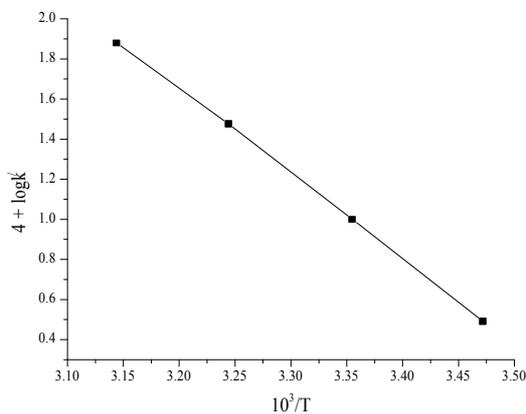


Figure 4: Effect of temperature on the rate of the reaction



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