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Oxidative Cleavage of Propranolol Hydrochloride with Potential Oxidant 1-Chlorobenzotriazole in Acidic and Alkaline Medium: A Kinetic, Mechanistic and Spectrophotometric Approach

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ABSTRACT

Today one of the greatest difficulties in oxidation reactions of drugs is the determination of in vivo oxidative stresses. In the present study, LMSP-UV1200 spectrophotometer is used to monitor the kinetics of oxidation of Propranolol hydrochloride (PPL) with 1-Chlorobenzotriazole (CBT) both in basic and in acidic medium. The PPL-CBT reaction progress has been monitored spectrophotometrically at λ_{max}=314 nm (after using the excitation wavelength of PPL is 289 nm) over the temperature range 299-315 K. The redox reaction follows a rate law - $d[CBT]/dt=K[PPL]^a[CBT]^b[H_2O]$. Where, a and b are one and two respectively. The oxidation of PPL with CBT is zero order with respect to acid and base. Variations of the ionic strength and the solvent dielectric constant have insignificant effect on the rate. An addition of the reduction product of CBT is BTA, to the reaction mixture also has no influence on the rate. A plausible reaction mechanism consistent with the observed kinetic data and thermodynamic parameters has been proposed in basic and acidic solutions.

Keywords: Propranolol hydrochloride, Oxidation reactions, Kinetics, Redox reaction

INTRODUCTION

Propranolol hydrochloride (PPL) is an adrenergic blockers utilized for the treatment of hypertension, angina pectoris and arrhythmia. Chemically is 1-(1-methylethyl)amino-3-naphthalenyloxy-2-propranol. The molecular formula is $C_{16}H_{21}NO_2$.HCl and molecular weight is 295.81. It is white or almost white crystalline powder, freely soluble in water and in alcohol. PPL has been determined titrimetry [1], calorimetry [2-4], spectrophotometrically [5-7], atomic spectrophotometrically [8-10], quantitative Thin Layer Chromatography (TLC) [11], High Performance Liquid Chromatography (HPLC) [12-13] and Gas Chromatography (GC) [14]. Propranolol is a widely used non-cardio selective beta-adrenergic antagonist. Although propranolol is used for myocardial infarction; arrhythmia; angina pectoris; hypertension; hyperthyroidism; migraine; pheochromocytoma and anxiety but adverse effects instigate replacement by newer drugs.

Propranolol was the primary fruitful beta blocker developed by British scientist James W. Black in the 1960 [15] and he was awarded the Nobel Prize in Medicine for the same discovery. Propranolol was inspired by the early β-adrenergic antagonist's dichloro isoprenaline and pronethalol. About 1-3 h after ingestion propranolol is totally absorbed, with peak plasma levels. Co-administration with food seems to improve bio availability [16]. Despite total absorption, propranolol has a variable bioavailability due to extensive first-pass metabolism. Hepatic impairment accordingly expands its bioavailability. The principal metabolite 4-hydroxypropranolol, with a longer half-life (5.2-7.5 h) than the parent compound (3-4 h), is likewise pharmacologically dynamic. Propranolol is an exceptionally lipophilic drug accomplishing high concentrations in the cerebrum. The length of action of a single oral dose is longer than the half-life and might be up to 12 h, if the single dose is sufficiently high (e.g., 80 mg). Effective plasma concentrations are in the vicinity of 10 and 100 mg/l. Toxic levels are related with plasma concentrations over 2000 mg/l.

Propranolol is being examined as a potential treatment for Post-Traumatic Stress Disorder (PTSD) [17,18]. Propranolol attempts to hinder the activities of norepinephrine, a neurotransmitter that enhances memory consolidation. Individuals given promptly after injury experienced less anxiety related side effects and lower rates of PTSD than individual control bunches who did not get the drug [19]. Due to the way that recollections and their enthusiastic substance are reconsolidated in the hour after they are reviewed/re-experienced, propranolol can likewise reduce the passionate effect of officially framed recollections; thus, it is additionally being contemplated in the treatment of treatment of specific phobias, such as arachnophobia, dental fear, and social phobia Figure 1 [20].

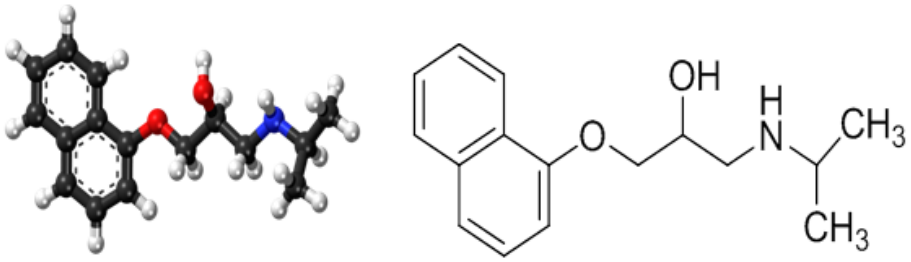


Figure 1: Molecular structure of propranolol hydrochloride with 3D model

1-Chlorobenzotriazole (CBT) is a flexible oxidizing agent and its solution chemistry is sensibly surely knew [21]. 1-CBT can be utilized as a reagent for oxidation and chlorination reactions. Now a days, 1-CBT, has attracted the attention of scientist as a novel potential oxidant because of its reactivity towards various functional groups [22]. There are just couple of reports on the kinetics of oxidation of organic compounds and drugs by 1-CBT [23-27]. The kinetics of oxidation of PPL with CAT was reported by R. Ramachandrappa and others [28,29]. But there were no reports on kinetics of oxidation of PPL with 1-CBT. With this establishment, we report here results identifying with the kinetics of oxidation of PPL using potential oxidant 1-CBT.

EXPERIMENTAL SECTION

Materials and methods

Propranolol (Yarrow Chem Products, Mumbai, India) was utilized without further purification and a freshly prepared aqueous solution of CBT 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 employed [30].

Kinetic procedure

Active runs were set up under pseudo-first kinetics of [PPL] >> [CBT] at 303 K. Essential measures of PPL was taken for each run in a Pyrex glass tube whose external surface was covered dark to dispense with photochemical impacts. A required amount of $HClO_4$/NaOH and distilled water was added to keep up a steady volume in all runs. The tube was thermally equilibrated at a given temperature. The reaction was started by including a deliberate measure of prequilibrated CBT solution and shaken intermittently for uniform fixation. The progress of the reaction was monitored using UV Spectrophotometer LMSP-UV1200. The absorbance of the reaction decreases with increasing time and the absorbance values measured at the λ_{max}=314 nm (λ_{max} of PPL is 289 nm but the λ_{max} of the intermediate X(PPL-CBT) is 314 nm) at regular intervals of three half-lives. The pseudo-first-order rate constants k, calculated. Regression analysis of the experimental data was computed on a Windows 2007 Intel core i5 PC to get the regression coefficient, R^2.

RESULTS

The kinetics of oxidation of PPL by CBT was investigated spectrophotometrically, under pseudo first-order conditions of $[PPL]_0 > [CBT]_0$ at constant temperature 303 K. The λ_{max} of PPL is 289 nm but the mixture of PPL and CBT forming the intermediate (X=PPL-CBT) and its λ_{max} is 314 nm. The absorbance of PPL-CBT intermediate was measured at λ_{max} 314 nm for each 5 min. The kinetics of oxidation of PPL with CBT at constant temperature 303 K requires 180 min, the absorbance of PPL-CBT intermediate with regular intervals of time as shown in Table 1.

Table 1: The absorbance of Propranolol hydrochloride, 1-chlorobenzotriazole intermediate with regular intervals of time

Time (Min)	Absorbance
0	1.1455
5	1.1376
10	1.0855
15	1.0495
20	1.0159
25	0.979
30	0.9553
35	0.9338
40	0.9105
45	0.8911
50	0.8707
55	0.861
60	0.8463

[PPL]=2×10^{-3} M; [CBT]=4×10^{-4} M; Temperature=303 K; λ_{max}=314 nm

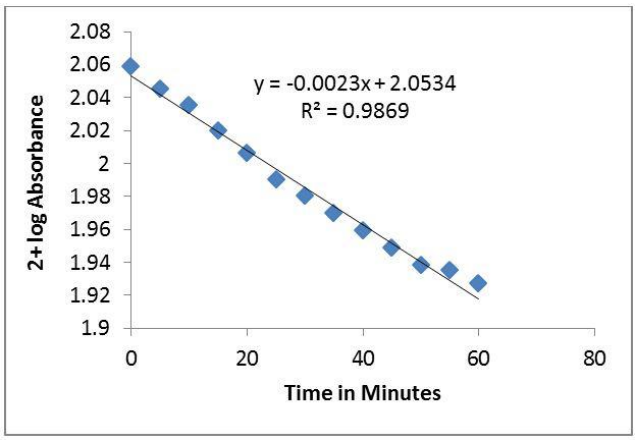


Figure 2: First order dependence of the reaction rate of [PPL], Time *vs.* 2+log absorbance

Effect of reactants [PPL],[CBT]and [NaOH]/ [$HClO_4$] on the reaction rate

Under pseudo-first order conditions of $[PPL]_0 > [CBT]_0$, in a known concentration of $HClO_4$ and NaOH the plots of 2+log absorbance *versus* time were linear indicating a first order dependence of the reaction rate of [PPL] (Figure 2). The pseudo first order rate constant k obtained at 303 K are independent of $[PPL]_0$. This nature indicated a first-order dependence of the rate on [PPL]. Effect of CBT concentration on the rate when $[CBT]_0$ was varied keeping all other reaction conditions constant. Furthermore a figure of log k *versus* log $[CBT]_0$ was straight line with a positive slope 1.85 in basic medium and 1.88 in acidic medium showing second order dependence on [CBT] in both basic and acidic medium. (Table 2, Figure 3a, R^2=0.997 and 0.995).

Keeping all experimental conditions constant, concentration of NaOH and $HClO_4$ was varied, the pseudo first order rate constant k calculated and tabulated in Table 2. The figure of log [NaOH] *versus* log k was linear with a positive slope 0.06 (Figure 3b, R^2=0.972) and the figure of log [$HClO_4$] *versus* log k was linear with a negative slope 0.13 (Figure 3b, R^2=0.891). The experimental data shows that the oxidation of PPL with CBT is zero order with respect to both [NaOH] and [$HClO_4$].

Table 2: Effect of reactants [PPL], [CBT] and [NaOH]/ [$HClO_4$] on the reaction rate

$[CBT] \times 10^4$ (Min)	$PPL \times 10^3$ (Min)	$[NaOH] \times 10^4$ (Min)	$[HClO_4] \times 10^4$ (Min)	$k \times 10^4$ (s^{-1})	
				[NaOH]	[$HClO_4$]
4	5	10	5	0.75	0.42
6	5	10	5	1.64	0.89
8	5	10	5	**3.15**	**1.41**
10	5	10	5	4.39	2.29
12	5	10	5	5.82	3.31
8	6	10	5	3.16	1.42
8	7	10	5	3.16	1.44
8	8	10	5	3.17	1.45
8	10	10	5	3.18	1.48
8	5	10	5	3.16	1.4
8	5	20	10	3.27	1.39
8	5	30	15	3.32	1.36
8	5	40	20	3.41	1.24
8	5	50	25	3.51	1.17
8	5	100	30	3.63	1.09
8	5	120	50	3.74	1.01

Temperature=303 K; λ_{max}=314 nm

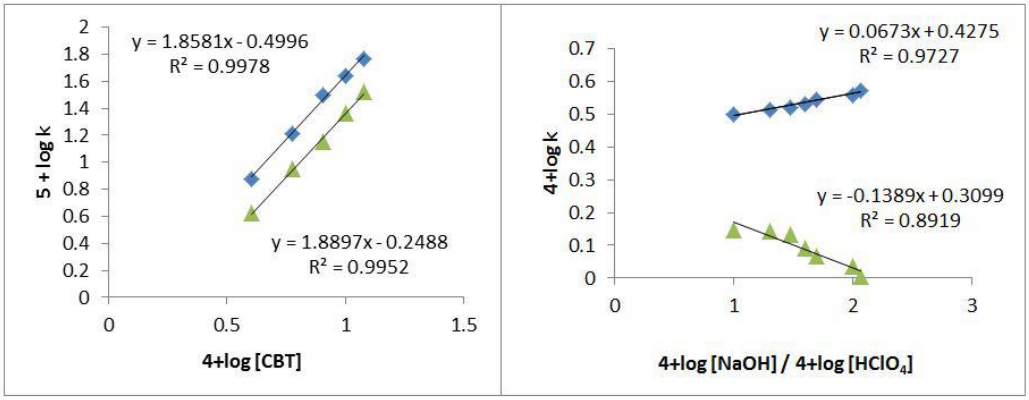


Figure 3: (a) log [CBT] *vs.* log k, (b) log [NaOH]/[$HClO_4$] *vs.* log k

Effect of temperature on the reaction rate

Oxidation reaction was studied over a range of temperature 299-315 K, at constant [PPL] and [CBT] in both [NaOH] and [$HClO_4$] medium. It was found that the rate increases with increase in temperature. From the linear Arrhenius figure of log k *vs.* 1/T (Figure 4), activation parameters were calculated in both basic and acidic solution (Table 3).

Table 3: Effect of temperature in basic and acidic medium

Temperature (K)	$k \times 10^4$ (s^{-1})		Activation parameters	
	[NaOH]	[$HClO_4$]	[NaOH]	[$HClO_4$]
299	2.26	1.04	Ea: 51.67 KJ/mol	Ea: 63.15 KJ/mol
303	3.15	1.41	$\Delta H^{\#}$: 49.15 KJ/mol	$\Delta H^{\#}$: 60.63 KJ/mol
307	3.76	2.09	$\Delta S^{\#}$: -130.58 J/K/mol	$\Delta S^{\#}$: -99.37 J/K/mol
311	4.98	2.93	$\Delta G^{\#}$: 95.85 KJ/mol	$\Delta G^{\#}$: 30.52 KJ/mol
315	7.34	3.68	Log A=6.40	Log A=8.04

[PPL]=5×10^{-3} M, [CBT]=8×10^{-4} M and [NaOH]=10×10^{-4} M/[$HClO_4$]=5×10^{-4} M, Temperature=303 K, λ_{max}=314 nm

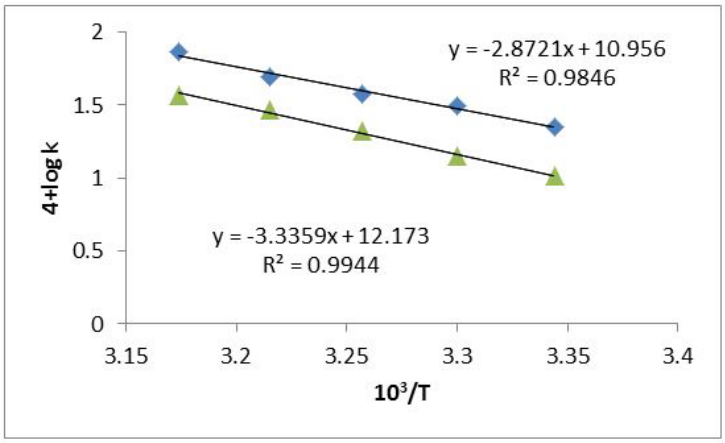


Figure 4: log k *vs.* 10^3/T

Effect of dielectric constant by varying [MeOH] on the reaction rate

In the present study the methanol effect on the reaction rate is in conformity with the Amis concept of dipole-dipole interaction or dipole-ion interactions [31]. The rate of the reaction decreased with increasing methanol content in both basic and acidic solutions (Table 4). Several approaches [32-35] have been made to explain quantitatively the effect of dielectric constant of the medium on the rates of reactions in solutions. The slope of the figure log k *versus* 1/D should be negative for a reaction between a negative ion and a dipole or between two dipoles, while a positive slope obtained for positive ion-dipole interactions [35]. Plots of log k *versus* 1/D in basic and acidic solutions (Figure 5) were linear with negative slopes, thus supporting the involvement of the two dipoles in the rate-determining step (Scheme 1).

Table 4: Effect of methanol in basic and acidic medium

MeOH (%)	Dielectric constant (D)	1/D	$k \times 10^4$ (s^{-1})	
			[NaOH]	[$HClO_4$]
0.0	76.73	0.0130	3.15	1.41
10.0	72.37	0.0138	3.12	1.39
20.0	67.48	0.0148	3.08	1.37
30.0	62.71	0.0159	3.04	1.34

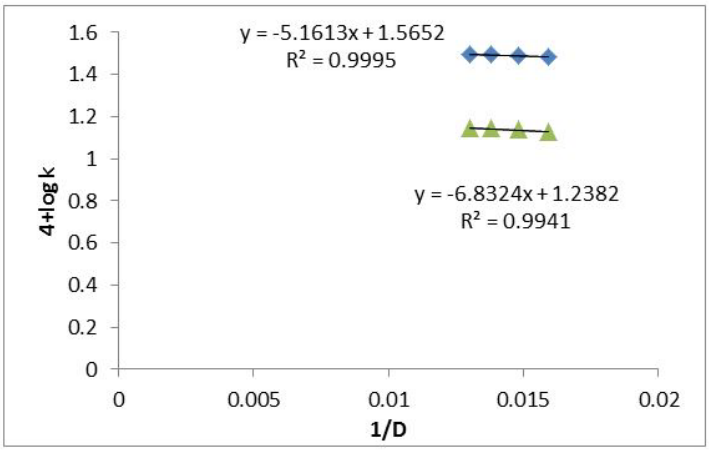


Figure 5: 1/D *vs.* log k

Effect of reduced product [BTA] on the reaction rate

The effect of added reduction product, BTA on the rate keeping other experimental conditions same in both basic and acidic solutions was studied in the range -10 × 10^{-4} M to 40 × 10^{-4} M. Negligible effect was observed by the addition of [BTA] in both cases Table 5.

Table 5: Effect of BTA in basic and acidic medium

[BTA] × 10^4 M	k × 10^4 (s^{-1})	
	[NaOH]	[$HClO_4$]
0.0	3.15	1.41
10.0	3.00	1.42
20.0	3.05	1.39
30.0	3.12	1.45
40.0	3.16	1.38
50.0	3.09	1.34

Effect of varying ionic strength and halide ions on the reaction rate

The reaction mechanism has been proposed based on the observed zero effect of ionic strength on the rate of the reaction in both basic and acidic medium. The primary salt effect on the reaction rate has been described by Bronsted and Bjerrum theory. In the present investigation, neutral molecules are involved in the rate determining step. Hence, variation of the ionic strength of the medium does not alter the rate in confirming of the above theory [31-35].

Addition of halide ion (10 × 10^{-4} to 50 × 10^{-4} mol dm^{-3}) in the form of NaCl to the reaction mixture also had negligible effect on the rate in both the cases Table 6.

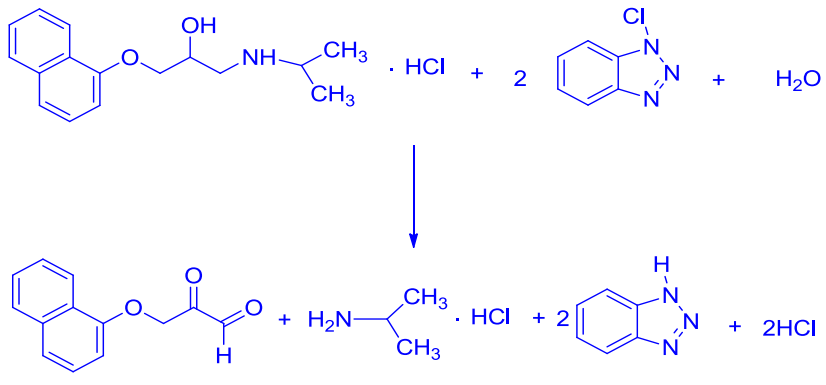
Table 6: Effect [$NaClO_4$] and [NaCl] in basic and acidic medium

[$NaClO_4$] × 10^4 M/[NaCl] × 10^4 M	[$NaClO_4$] k × 10^4 (s^{-1})		[NaCl] k × 10^4 (s^{-1})	
	[NaOH]	[$HClO_4$]	[NaOH]	[$HClO_4$]
0.0	3.15	1.41	3.15	1.41
10.0	3.16	1.42	3.14	1.40
20.0	3.18	1.44	3.13	1.38
30.0	3.20	1.45	3.12	1.35
40.0	3.21	1.48	3.21	1.38
50.0	3.22	1.46	3.11	1.42

Reaction stoichiometry and product analysis

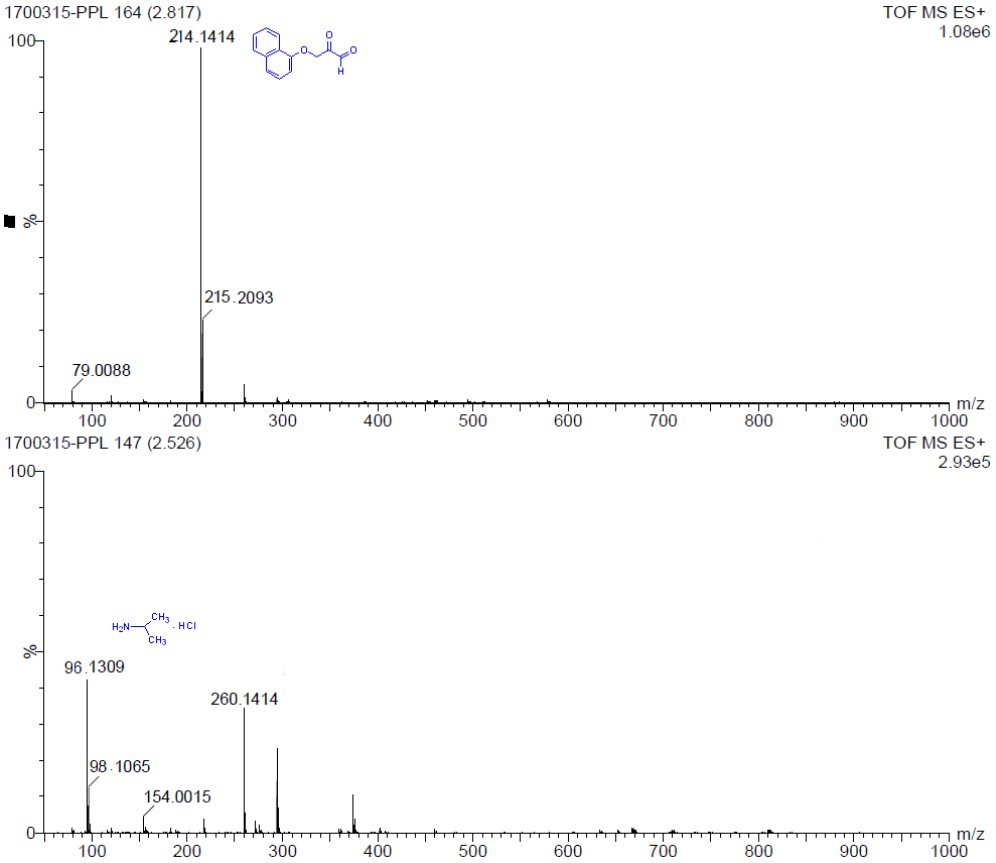
Varying proportions of the oxidant (CBT) to the reactant PPL in acidic and basic solutions were equilibrated at 303 K for 48 hrs. Aliquots of the reaction mixture were idometrically titrated with a standard thiosulphate solution, utilizing starch indicator, to decide the centralizations of unaltered CBT. The mole proportion (Number of moles of CBT expended per mole of PPL) was ascertained. The consequences of PPL response with CBT demonstrated a distinct stoichiometry of 1: 2 (Schemes 1 and 2).

$$C_{16}H_{21}NO_2.HCl + 2C_6H_4N_3Cl + H_2O \longrightarrow C_{13}H_{10}O_3 + C_3H_9N.HCl + 2\,C_6H_5N_3 + 2HCl$$

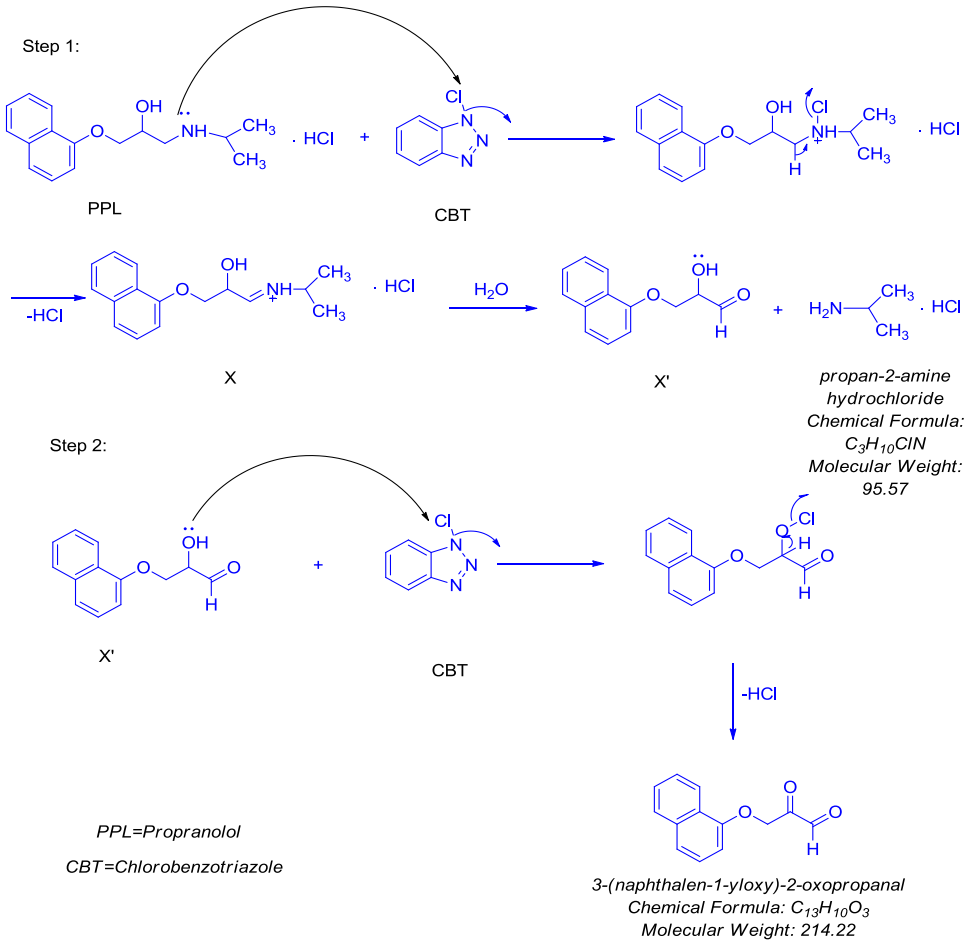


Scheme 1: Mole ratio of PPL: CBT is 1:2

Reduction product of the oxidant, Benzotriazole (BTA) was detected by thin layer chromatography using butanol-acetic acid-water (4:1:1 v/v/v) as solvent and iodine as reducing agent (R_f=0.92). The reported R_f value is consistent with that given in the literature [36]. Further it was confirmed by its melting point 101-102°C (melting point: 100°C). Oxidation products 3-(naphthalene-1-yloxy)-2-oxopropanal and isopropyl amine hydrochloride was detected by spot tests [37] i.e., 2,4-DNP test and sodium nitroprusside test and was confirmed by LC-MS data (Spectra 1).



Spectra 1: LC-MS spectra showing the oxidized products peak at m/z 214 and 96



Scheme 2: Oxidation of PPL with aqueous solution of 1-CBT mechanistic path way

DISCUSSION

Reactive species of CBT

1-CBT being N-haloamine gives few oxidizing species in aqueous solution. The concentration of each species depends on the concentration of 1-CBT, the nature (polar or nonpolar) and pH of the medium.

$$CBT + H_3O^+ \rightleftharpoons CBTH^+ + H_2O$$

Because of the weakening of the N–Cl bond, it might solvalize further to give H_2OCl^+,

$$CBTH^+ + H_2O \rightleftharpoons BTA + H_2OCl^+$$

H_2OCl^+ may generate Cl^+ on cleavage [38]. But, it rarely participates in the oxidation reaction under the experimental conditions. Therefore, the possible oxidizing species in aqueous CBT solution are: CBT, $CBTH^+$, H_2OCl^+ in acidic medium. CBT, HOCl and OCl^- in basic medium. If H_2OCl^+ and HOCl is the active oxidant species, a retardation of rate by added reduced product BTA is expected. However, no such observation was found, hence CBT or $CBTH^+$ is assumed to the reactive species for PPL kinetics. The following reaction mechanism (Scheme 3**)** appears plausible to account for the rate law and showed that CBT is assumed to be reactive species.

$$PPL + CBT \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} X \qquad \text{Fast}$$

$$X + H_2O \xrightarrow{k_2} X' \qquad \text{Fast}$$

$$X' + CBT \xrightarrow{k_3} \text{Products} \qquad \text{Slow RDS}$$

Scheme 3: Kinetic mechanism of PPL with CBT in acidic and basic solutions

$$\text{Rate} = \frac{d[CBT] = k_3[X^1][CBT]}{dt} \quad (1)$$

$$k_1 = \frac{[X]}{[PPL][CBT]} \quad (2)$$

$$k_2 = \frac{[X^1]}{[X][H_2O]} \quad (3)$$

$$[X^1] = k_2[X][H_2O] \quad (4)$$

$$[X^1] = k_1 k_2[PPL][CBT][H_2O] \quad (5)$$

Substitute equation (5) in (1):

$$\text{Rate} = \frac{-d[CBT]}{dt} = k_1 k_2 k_3[PPL][CBT]^2[H_2O] \quad (6)$$

The rate law 6 is in close agreement with the trial comes about that pseudo first order for [PPL] and second order on [CBT]. Solvent isotope studies in D_2O medium show the decrease in the reaction rate that is $k_{D20}/k_{H2O} < 1$. It is well known that D_3O^+ is a stronger acid [39] than H_3O^+ and hence this observation supports the proposed mechanism. The insignificant impact of BTA on the rate of reaction shows that it was not included in pre-balance. Addition of acrylonitrile to the reaction mixture had no impact on the reaction rate, showing the nonappearance of free radical species amid the oxidation reaction. The change in the ionic strength of the medium during the oxidation reaction by using $NaClO_4$ did not alter the rate, indicating that non-ionic species involved in the rate determining step.

A slight negative dielectric constant effect on the rate supports the fact that the dipole-dipole interaction in the rate determining step. The proposed mechanism is supported by the moderate values of energy of activation and other thermodynamic parameters. The fairly positive values of free energy of activation and enthalpy of activation indicate that the transition state is highly solvated, while the high negative entropy of activation suggests the formation of compact activated complex with fewer degrees of freedom. Rate law 6 is in accordance with the experimental findings. The proposed schemes and the derived rate law are also substantiated by the experimental observations discussed earlier.

CONCLUSION

Kinetics of oxidation of Propranolol Hydrochloride by 1-Chlorobenzotriazole (1-CBT or CBT) in NaOH and $HClO_4$ medium has been studied spectrophotometrically. The rate of the oxidation increase slightly in basic medium and decreases in acidic medium. Activation parameters were computed in both basic and acidic medium. Major oxidized products were identified as 3-(naphthalene-1-yloxy)-2-oxopropanal and isopropyl amine. CBT itself is the reactive species in aqueous solution which reacts with the PPL. The oxidation reaction of PPL with CBT is independent of base and acid concentration.

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