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SYNTHESIS OF SOME BENZIMADAZOLE DERIVATIVES AND KINETICS STUDIES OF THEIR OXIDATION USING CHLORAMINE-T IN ALKALINE MEDIUM

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Abstract

The kinetics of oxidation of 2-phenyl-1Hbenzimidazole (BzlH), 2-(4-methoxyphenyl)-1H-benzimidazole (OMeBzlH), 2-(4-nitrophenyl)-1H-benzimidazole (NO_2BzlH) by chloramine-T; (CAT) in presence of NaOH has been investigated at 297 K. Under similarexperimental conditions, the oxidation reactions follow identical kinetics for all the threebenzimidazoles with first order dependence each on [CAT]0 and [substrate] 0 and inverse fractional order dependence on [OH^-]. Solvent composition shows negative effect indicating the involvement of negative ion-dipolar molecule in the rate determining step. Variation of ionic strength of the medium and addition of halide ions had no effect on the reaction rate. Addition of *p*-toluenesulphonamide (PTS), the reduction product had no effect on the rate of reaction.The reactions were studied at different temperatures and the composite activation parameters have been computed. Relative reactivity of oxidation of these follow the order: OMeBzlH >BzlH> NO2BzlH. This trend may be attributed to inductive effects. Finally a related rate law has been deduced.

Key Words: Benzimadazole, CAT, kinetics, Reaction Mechanism, NaOH

INTRODUCTION

Benzimidazole which is a heterocyclic aromatic organic compound and a very important pharmacophore and plays a vital role in medicinal chemistry. It is bicyclic compound i.e it is a fusion of benzene and imidazole. N-ribosyl- dimethyl benzimidazole is the most prominent benzimidazole compound available in nature and serves as an axial ligand for cobalt in vitamin B12. Oxidation of benzimidazoles to imidazole carboxylic acids brought about by various oxidizing agents under different sets of conditions, have been reported in literature. But only less information is reported in the literature on the oxidation kinetics of benzimidazoles using an oxidant.Nandibewoor *et al*., reported the kinetics of oxidation of pyridylmethylsulphinyl benzimidazole by cerium(IV) in perchloric acid medium.Puttaswamy *et al*., oxidized imidazole, benzimidazole and its derivatives(2-HyBzlH, 2-AmBzlH, and 2-PhBzlH) by sodium-N-chloro-p-toluenesulfonamide (Chloramine-T) using ruthenium chloride as catalyst in acid medium Oxidation product of the reactions is o-phenylenediamine and benzoic acid. Puttaswamy *et al*., also reported, oxidation of imidazole, benzimidazole and its derivatives(2-HyBzlH, 2- AmBzlH, and 2-PhBzlH) by sodium-N-chloro-p-toluenesulfonamide (Chloramine-T) using Os(VIII) as catalyst in alkaline medium at room temperature. Oxidation products of the reactions are orthanilic acid and its derivatives.Sodium N-chloro-p-toluenesulfonamide (Chloramine-T) is the most important member of organic haloamine family and behaves as a mild oxidizing agent in both acidic and basic medium (Armesto, 1998; Cambell, 1978;Gupta, 1998; Manjunatha, 2015; Mahadevappa, 1981;Puttaswamy, 2005; Prashanth, 2014 Ramachandra, 1996). On the basis of these observations, we will explore the oxidation and mechanistic investigation of benzimidazole and derivatives by Sodium N-chloro-p-toluenesulfonamide (Chloramine-T). The main Objectives were 1. Synthesis of benzimidazoles 2. Development of efficient synthetic process for the facile conversation of benzimidazole, derivatives to corresponding oxidation products. 3. deduce an appropriate rate law. 4. Ascertain the various reactivity species. 5. Finally, assess the relative relativities of the substrates.

Synthesis of benzimadazole derivatives

Step 1 Secondary amine (1) (2eq) was added to a mixture of substituted fluoro benzene (2) (1 equiv) and K_2CO_3 (1.5equiv) in dimethyl sulphoxide (7ml/g).

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The reaction mixture was stirred at 90°C and followed by TLC.After completion of the reaction, the mixture was diluted with ethyl acetate (60ml/g), and washed with water (2X50ml/g) followed by brine (50ml/g). The ethyl acetate fraction was dried over Na_2SO_4 and concentrated. The crude products were purified bycolumn chromatography to get pure products.

Step 2 A suspension of an appropriate nitro compound (3) (5mmol) and Raney Ni (0.2-0.3g) in methanol (3ml) was stirred with ammonium formate (0.5g) at room temperature. After completion of the reaction (which was monitored with the help of TLC), the mixture was filtered off. The organic layer was evaporated and the residues dissolve in $CHCl_3$. It was washed with saturated NaCl to remove ammonium formate. The organic layer on evaporation gave the desired amino derivatives (4).

Step 3 To a solution alcohol (5) (0.5-0.6mmol) and IBX (1.1 equiv) were stirred in DMSO at 20°C. Once the oxidation of alcohol to aldehyde was complete, as judged from TLC analysis, O-phenyldiamine (1.1 equiv) was introduced in to the reaction mixture and was allowed to stir at room temperature until the aldehyde disappeared. At the completion of the reaction, DMSO was removed with the help of high vacuum, and the residue was treated with 1.0 M NaHCO3 solution until the PH was 8-9. The organic matter was extracted with ethyl acetate. Regular work-up followed by separation bycolumn chromatography gave pure benzimidazoles (6)

Experimental

2.1 CAT (Sigma Aldrich) was purified by the method of (Morris *et al.*, 1948). An aqueous solution of CAT was prepared, standardized iodometrically and stored in amber colored stoppered bottles until further use to prevent its photochemical deterioration. The concentrations of stock solutions were periodically determined. An aqueous solution of NO_2BzlH, BzlH and OMeBzlH, were freshly prepared whenever required. All other chemicals used were of analytical grade. Triple distilled water was used for preparing solutions.

Kinetic measurement

The kinetic runs were performed under pseudo-first-order conditions by ensuring an excess of CAT over substrate in sodium hydroxide at 297 K using UV-Vis spectrophotometry (Shimadzu-1800). A constant temperature was maintained with an accuracy of ±0.1°C. Reactions were carried out in glass stoppered Pyrex boiling tubes whose outer surface were coated black to eliminate any photochemical effects. The oxidant as well as requisite amounts of substrate, NaOHsolutions and water (to keep the total volume constant for all runs) were taken in separate tubes. The absorbance reading were thermo stated for nearly 30 minutes at 297K. The reaction was initiated by the rapid addition of a measured amount of oxidant to the stirred reaction mixture. 3 ml of aliquot of the solution was pipetted into a cuvette placed in the spectrophotometer. Absorbance measurements were made at λ_{max} = 268nm, 293 nm and 283nm forBzlH, OMeBzlH, NO_2BzlH respectively for more than 75% of completion of the reaction. Plots log (abs) Vs time were made to evaluate the pseudo-first-order rate constants k' (s^{-1}). Regression analysis of the experimental data was carried out on fx-991MS scientific calculator to evaluate the regression coefficient.

Reaction stoichiometry

Reaction mixtures containing different ratios of CAT and substrate in 4×10^{-3}mol dm^{-3}NaOH were allowed to react for 24hrs at 297 k. The determination of unreacted CAT in the reaction mixture showed that one mole of the substrate consumed two moles of CAT.

RESULTSAND DISCUSSION

Effect of varying reactant concentration on the rate

With the oxidant in excess and keeping $[CAT]_o$, [NaOH] and temperature constant, plot of log(abs) Vs time was found to be linear (R^2=0.99) indicating a first order dependence on $[subs]_o$. The valuesof Pseudo-First order rate constants (k' s^{-1}) are listed in Table 1. Also under the same experimental conditions an increase in $[CAT]_o$ increased the value of k' (Table1). Plot of log k' Vs log [CAT] were linear (R^2=0.99) with a slope of 0.91, 0.65 and 0.58forNO_2BzlH, BzlH, OMeBzlH, respectively which indicated a fractional order dependence on [CAT] (Figure 1).

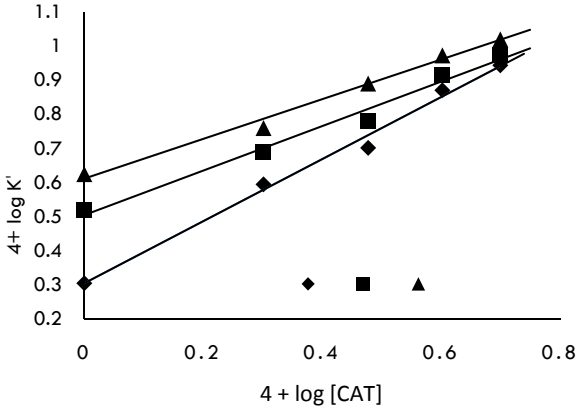


figure 1 log k' VS log [CAT]

Table 1 Effect of varying concentrations of oxidant, substrate and medium on the rate at 297k

10^4×[CAT] mol dm^{-3}	10^5×[Subs] mol dm^{-3}	10^3 ×[NaOH] mol dm^{-3}	10^4 k′ (s^{-1})		
			NO_2BzlH	BzlH	OMeBzlH
1.0	4.0	4.0	2.24	3.31	4.22
2.0	4.0	4.0	3.94	4.88	5.76
3.0	4.0	4.0	5.04	5.98	7.79
4.0	4.0	4.0	7.44	8.23	9.41
5.0	4.0	4.0	8.81	9.44	10.44
2.0	1.0	4.0	3.66	4.60	5.54
2.0	2.0	4.0	3.69	4.66	5.58
2.0	3.0	4.0	3.73	4.81	5.69
2.0	4.0	4.0	3.94	4.88	5.76
2.0	5.0	4.0	3.91	4.95	5.88
2.0	4.0	1.0	8.04	10.11	11.24
2.0	4.0	1.5	7.44	9.24	9.76
2.0	4.0	2.0	6.21	7.88	8.39
2.0	4.0	3.0	4.67	5.34	7.02
2.0	4.0	4.0	3.94	4.88	5.76
2.0	4.0	5.0	3.54	4.30	5.11

Effect of varying NaOH concentration on the rate

The effect of NaOH on the rate of the reaction was studied by varying in the concentration of [NaOH] (table2). Plot of log k′ versus log [NaOH] were linear (R^2= 0.99) with a negative slope of 0.49, 0.57 and 0.55 for NO_2BzlH, BzlH, OMeBzlHrespectively which indicated an inverse fractional order dependence on [NaOH] (Figure 2)

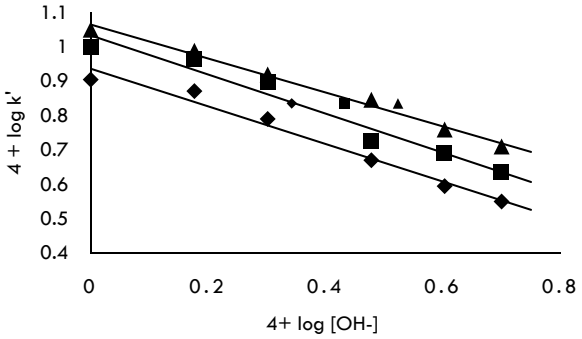


Figure 2 Plot of logk' Vs log [OH-]

Table 2 Effect of dielectric constant on the rate of the reaction with [subs] =4.0x10^{-5} mol dm^{-3} [CAT] = 2.0x10^{-4}mol dm^{-3} [NaOH] =4.0x10^{-3}mol dm^{-3}

% MeOH (v/v)	D	10^4 k′ (mol dm^{-3} s^{-1})		
		NO_2BzlH	BzlH	OMeBzlH
0	76.73	3.94	4.88	5.76
5	74.50	4.82	5.81	6.65
10	72.37	5.97	6.89	7.89
20	67.48	6.42	8.03	9.01

Effect of halide ions, ionic strength and p-toluenesulphonamide on the rate

Addition of halide ions, Cl^- and Br^- ions in the form of their sodium salts (1.0×10^{-3}- 5.0 × 10^{-3} mol dm^{-3}) had negligible effect on the reaction rate. This suggests that no interhalogen or free halogen is formed in the reaction sequence. Ionic strength (μ) of the medium was varied byvarying the concentration of Sodium perchlorate ($NaClO_4$) (0.1-0.4mol dm^{-3}).No significant effect was noticed. It indicates the involvement of non-ionic species in the rate determining step. Hence no attempt was made to keep ionic strength of the medium constant during kinetic runs. The addition of *p*-toluene sulfonamide (reduction product of CAT) had no significant effect on the rate of the reaction which indicates that there is no involvement of the reduction product in a fast pre-equilibrium to the rate limiting step.

Effect dielectric constant (D) on the rate

The effect of solvent on the reaction kinetics has been discussed in detail in the well-known monographs of (Amis.,1966; Benson, 1960; Entelis and Tiger, 1976; Frost *et al*., 1961; Laidler, 1963., Moelwyn-Hughes, 1961). The solvent composition was varied by adding methanol (0%-30%). The rate of the reaction decreased with the increase in the methanol content of the reaction medium (table 2) and plot of logk′ vs 1/D was linear (figure 3, R^2= 0.98) with negative slope. Blank experiments with methanol indicated that the oxidation of methanol was negligible. The values of D for various MeOH-H_2O mixtures reported in the literature [16] were employed.

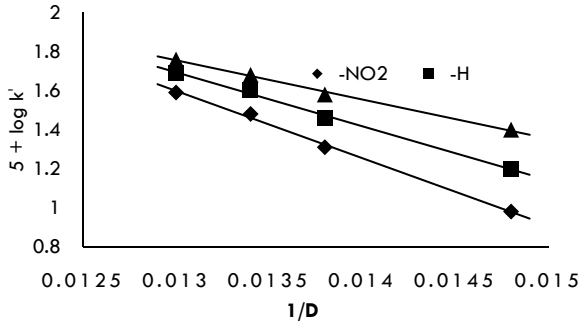


Figure 3 Plot of log k' vs 1/D

Effect of temperature on the rate and calculation of activation parameters

The reaction was studied ad different temperatures in the range 297-317 K keeping other experimental conditions constant. Arrhenius plot of log k′ Vs 1/T were plotted (Figure 4) and with the help of the graph activation parameters were evaluated and average values for each parameter is reported along with errors (table 3)

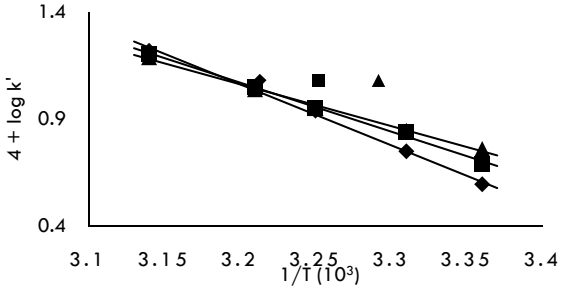
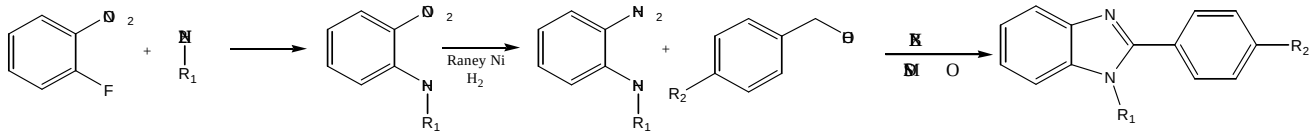


Figure 4 Plot of log k' VS 1/T

Table 3 Effect of temperature on the rate of the reaction and corresponding values of activation parameters for the oxidation of NO_2BzlH, BzlH and OMeBzlH by CAT in acid medium with [sub] =4.0x10^{-5} mol dm^{-3} [CAT] = 2.0x10^{-4} mol dm^{-3} [NaOH] = 4.0x10^{-3}mol dm^{3}

T(K)	$10^4k'$ (mol dm^{-3} s^{-1})			Activation parameters			
	NO_2BzlH	BzlH	OMeBzlH	NO_2BzlH		BzlH	OMeBzlH
297	3.94	4.88	5.76	Ea(KJ mol^{-1})	54.58	43.86	37.54
302	5.61	6.94	7.01	$\triangle H^{\#}$(KJ mol^{-1})	52.09 ± (0.04)	41.30± (0.05)	34.97 ± (0.04)
307	8.67	8.96	8.94	$\triangle G^{\#}$(KJ mol^{-1})	93.88 ± (0.06)	93.18± (0.04)	93.19 ± (0.06)
311	10.99	11.21	11.01	$\triangle S^{\#}$(JK^{-1}mol^{-1})	-147.03± (0.1)	-168.22±(0.2)	-189.60± (0.2)
317	14.45	13.96	12.44	log A	5.56 ± (0.05)	4.413± (0.04)	3.34 ± (0.02)



(1) (2) (3) (4) (5) (6)

Scheme-1

Test for free radicals

Addition of reaction mixture to aqueous acrylamide monomer solutions did not initiate polymerization, indicating the absence of in situ formation of free radical species in the reaction sequence

Reaction mechanism and rate law in alkaline medium

The possible oxidizing species in alkaline CAT solutions are $TsNCl^-$, TsNHCland HOCl. According to Hardy and Johnston the following equilibria also exists in alkaline solution of CAT.

$$TsNCl^- + H_2O \rightleftharpoons TsNHCl + OH^- \quad (2)$$

$$TsNHCl + H_2O \rightleftharpoons TsNH_2 + HOCl \quad (3)$$

If $TsNH_2$ is the reactive species then there would be retardation in the rate due to the addition of PTS, which is contrary to the observed kinetics. Hence one can conclude that TsNHCl which is formed from the hydrolysis of anion, is the probable active species for the oxidation of QY by CAT in NaOH medium. From the above discussion scheme-2 is proposed to explain the reaction mechanism for the oxidation of QY by CAT in NaOH medium.

$$\xrightarrow[\text{fast}]{k_1} + Na^+ \quad (4)$$

$$TsNCl^- + H_2O \xrightarrow[\text{fast}]{k_2} TsNHCl + OH^- \quad (5)$$

$$TsNHCl + S \xrightarrow[\text{r.d.s}]{k_3} X \quad (6)$$

$$X + H_2O \xrightarrow[\text{fast}]{k_4} \text{products} \quad (7)$$

Scheme-2

In the proposed scheme, Chloramine-T dissociates according to equation (4).The anion undergoes hydrolysis to give the free acid monochloramine-T (active species), which interacts with the substrate in the slow step to give complex (x), which undergoes hydrolysis to give the oxidized products.

From equation 4,

$$k_1 = \quad (8)$$

From equation 5,

$$k_2 = \quad (9)$$

Rearranging equation (9), we get

$$= \quad (10)$$

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

$$[CAT]_t = [TsNCl^-] + [TsNHCl] \quad (11)$$

Substituting equation (9) in (10), and solving for [TsNHCl]

$$\frac{k_2 [CAT]_t [H_2O]}{[OH^-] + k_2 [H_2O]} \quad (12)$$

Also from equation (6),

$$\text{Rate} = k_3[TsNHCl][S] \quad (13)$$

Finally Substituting equation (12) in (13),

$$\frac{k_2 k_3 [CAT]_t [S] [H_2O]}{[OH^-] + k_2 [H_2O]} \quad (14)$$

The above rate law (14) agrees well to the observed kinetic data i. e a first order dependence of rate on [S] [CAT] and inverse fractional order on [OH^-].

CONCLUSIONS

All the benzimidazoles exhibit an identical kinetic behavior and the rate of oxidation of benzimidazoleswas found to decrease in the order: OMeBzlH >BzlH> NO_2BzlH. The Kinetics of Oxidation was studied by CAT as an oxidant in acid medium at 297 K. The experimental rate law was fopund to be –d [CAT]/dt =k[NO2BzlH]^1 [CAT]$^{0.91}$[NaOH]$^{-0.49}$and –d [CAT]/dt=k [BzlH]^1[CAT] $^{0.65}$[NaOH]$^{-0.57}$ and –d [CAT]/dt= k[OMeBzlH] ^{1}[CAT]$^{0.58}$ [NaOH]$^{-0.55}$.The oxidation kinetics was also studied by varying the ionic strength, dielectric constant of the medium. Finally the reaction was

studied at different temperatures. Based on the observations made an appropriate rate law was derived.

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