

Catalytic Activity in the Hydrolysis of Phenyl Esters of α -Furoic Acid

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Hydrolysis of *p*-nitrophenyl- α -furoate (*p*-NPF), *p*-chlorophenyl- α -furoate (*p*-CPF) and phenyl- α -furoate (PF) in 5 % aqueous acetonitrile is catalyzed by hydroxide ion (OH^-), benzimidazole (BI), benzotriazole (BT), hydroxymethylbenzotriazole (HMBT), phenol (PhOH), *p*-cresol (*p*-MP), *p*-chlorophenol (*p*CP), 6-hydroxy-2-picoline (HP), hydrazine (HYD), trihydroxymethylmethyamine (TRIS) and borax (BO). Brønsted β value for varying attacking nucleophiles is obtained as 0.25. Brønsted β value for varying leaving groups is obtained as -0.25. Hammett ρ value of +0.84 is obtained when the substituted phenyl esters are hydrolyzed by hydroxide ion. Kinetic data indicates (1) characteristic strong nucleophilic attack with asymmetric early transition state, (2) catalysis by nucleophile on carbonyl carbon of the acyl group, (3) catalysis by TRIS and BO is following general base mechanism, (4) the relative rate ratios $k_{\text{OH}^-}/k_{\text{cat}}$ support the distinction in catalysis by attacking species, (5) the bond breaking involving leaving group is not significant in the rate determining step, (6) Hammett ρ value obtained is in keeping with the leaving group abilities of substituted phenoxides and (7) inhibition by 2,6-lutidine indicates steric inhibition.

Key Words: Phenyl esters, α -Furoic acid, Catalytic activity, Hammett value.

INTRODUCTION

Histidine has been known to be involved in the catalytic activity of hydrolytic enzymes and much work has been done to prove its role in bioorganic reactions by taking imidazole, a part of histidine as attacking species. Triazole is isoelectronic with imidazole. Benzotriazole and benzimidazole also contain isoelectronic systems similar to imidazole. The N-H bonds in these molecules are prone to rupture due to aromatic nature of the heterocyclic compounds¹. Overberger and Yuen² have shown that the catalytic efficiency of triazoles is due to their anions. Yesodha and Thiagarajan³ have demonstrated that benzotriazoles catalyzed the hydrolysis of 4-nitrophenyl esters in aqueous acetone medium. Acyl transfer reactions are catalyzed by tertiary amines, as they are good nucleophiles. In recent, studies by Kinke *et al.*^{4,5} on α -furoic acid was found to be present

along with phenols in the hydrolyzate resulted on pretreatment of wheat straw with alkaline wet oxidation found to be less inhibiting during the formation of ethanol by fermentation method. Hence the present investigation has been undertaken to unravel the role of similar catalysts in acyl transfer reaction in phenyl esters of α -furoic acid. Here the phenyl esters of α -furoic acid were synthesized and the rates of hydrolysis of the same were studied in presence of various catalysts.

EXPERIMENTAL

Benzotriazole (BT), benzimidazole (BI), 6-hydroxy-2-picoline (HP), α -furoic acid, dicyclohexylcarbodiimide (DCC) were procured from Aldrich chemicals, USA. Substituted phenols, trihydroxymethyl methylamine (TRIS) and borax (BO) were procured from BDH and were used as such.

1-Hydroxymethyl benzotriazole (HMBT) was prepared by mixing 6 g (0.05 mol) of benzotriazole with 4 mL (0.05 mol) of 40 % formalin, 5 mL of acetic acid and 10 mL of water and allowed to stand for over 2 h at room temperature. The precipitated product was filtered, dried and recrystallized from hot water (m.p. 148°C)⁶. 4-Nitrophenyl ester (*p*-NPF) was prepared using the known literature procedure⁷.

Phenyl- α -furoate (PF) and *p*-chloro- α -furoate were prepared according to the procedure described by Vogel⁸ by converting the acid into acid chloride and treating later with corresponding phenols [phenyl- α -furoate (PF) m.p. 42 °C and *p*-chlorophenyl- α -furoate (*p*-CPF) m.p. 82 °C].

All the solvents used were purified according to standard procedures. Deionized water was distilled with alkaline permanganate in an all glass apparatus and then boiled to expel dissolved CO₂ before use. Solutions of the esters and catalysts were prepared afresh in appropriate solvents and stored in a refrigerator. Buffers were made such that 90 % of the catalysts exist in anionic form.

The rates of hydrolysis of the phenyl esters were followed spectrophotometrically using a Carl-Zeiss VSU2-P spectrophotometer. A typical kinetic run for the hydrolysis of phenyl esters was performed as follows: The buffer mixture in the proper solvent (1.9 mL) was equilibrated in a quartz cell at the desired temperature. To this, ester solution (0.1 mL) in acetonitrile was added and the resulting mixture was shaken well. The release of the corresponding phenoxide was followed at the appropriate wavelength λ (phenoxide at 292 nm, 4-nitrophenoxide at 400 nm and 4-chlorophenoxide at 300 nm). The reactions were followed upto four half-lives. Infinity values were obtained after 99 % of the reaction had taken place. At least three concentrations of the catalyst were used in the case of each catalyst and values were obtained in triplicate. Pseudo first order rate

constants (k_{obs}) were calculated from a least square plot of $\log (A_{\infty}-A_t)$ vs. time. Evaluation of catalytic constant k_{cat} for the reactions catalyzed by various catalysts was made by plotting k_{obs} vs. [catalyst]. The slope of the linear plot gave k_{cat} .

RESULTS AND DISCUSSION

The hydrolysis of *p*-nitrophenyl- α -furoate (*p*-NPF) in aqueous acetonitrile (95 % H₂O-5 % CH₃CN v/v) at 303 K found to have first order dependence in [ester] (Fig. 1). The reaction is found to follow the rate law (1)

$$\begin{aligned} \text{rate} = -d[\text{ester}]/dt = d[\text{phenoxide}]/dt &= \{k_{\text{CAT}}[\text{Catalyst}] + k_0'\}[\text{ester}] \\ &= k_{\text{obs}}[\text{ester}] \end{aligned} \quad (1)$$

where k_0' represents the composite rate coefficient for the hydrolysis, hydroxide ion and water; k_{cat} is the catalytic rate coefficient for the added nucleophile.

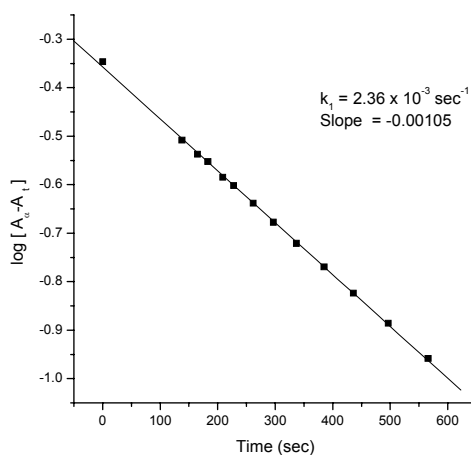


Fig. 1. Order plot for the hydrolysis of *p*NPF catalyzed by BT (pH = 9.0) in aq. acetonitrile (95 % - 5 % v/v) at 303 K

The plots of k_{obs} vs. [catalyst] for the hydrolysis of *p*-NPF by catalysts like OH, BT, BI, HMBT, HYD, PhOH, HP, *p*-MP and *p*-CP exhibit zero intercept on the k_{obs} axis indicating no or negligible role of unionized form acting as catalyst (Figs. 2 and 3). The plots of k_{obs} vs. [catalyst] for the hydrolysis of *p*-NPF by catalysts like BO and TRIS have a finite intercept on k_{obs} axis indicating the catalysis by hydroxide and water in those reactions. The intercept becomes more perceptible as these catalysts are less efficient than those mentioned above. The line depicting catalysis by 2,6-lutidine is having negative slope indicating the inhibitive nature of catalyst (Fig. 4).

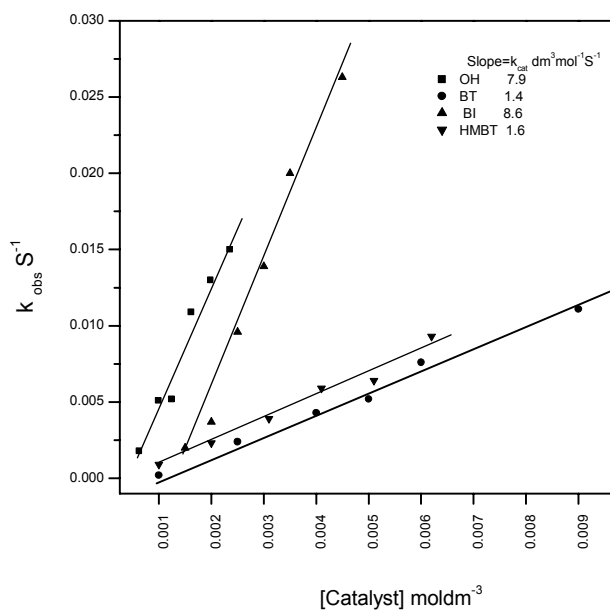


Fig. 2. Concentration dependence of catalyst on the rate of hydrolysis of *p*-NPF in aq. acetonitrile (95-5 % v/v) at 303 K

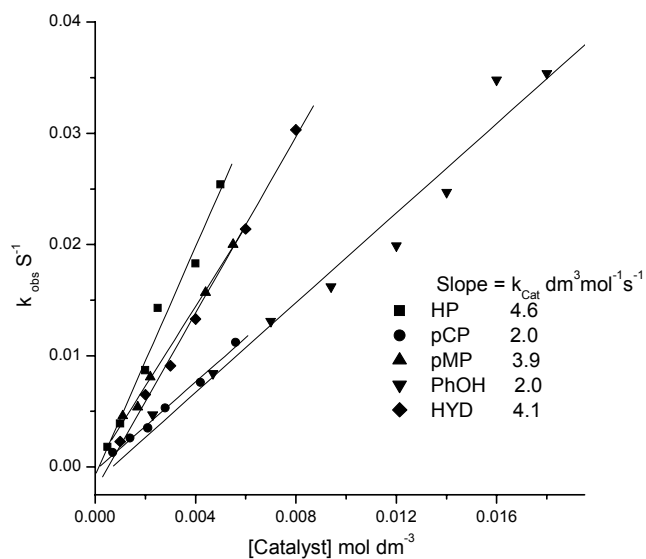


Fig. 3. Concentration dependence of catalyst on the rate of hydrolysis of *p*-NPF in aq. acetonitrile (95-5 % v/v) at 303 K

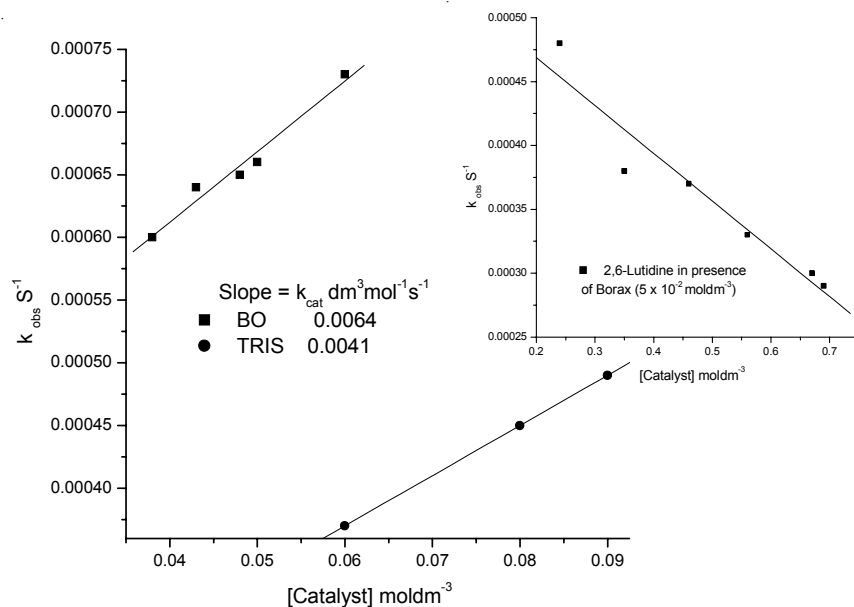


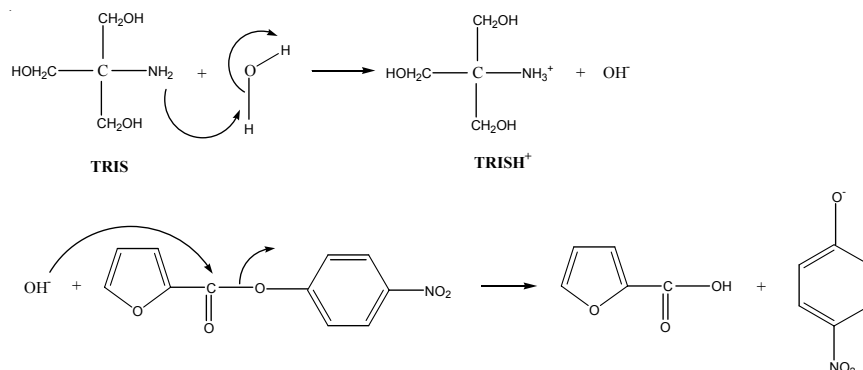
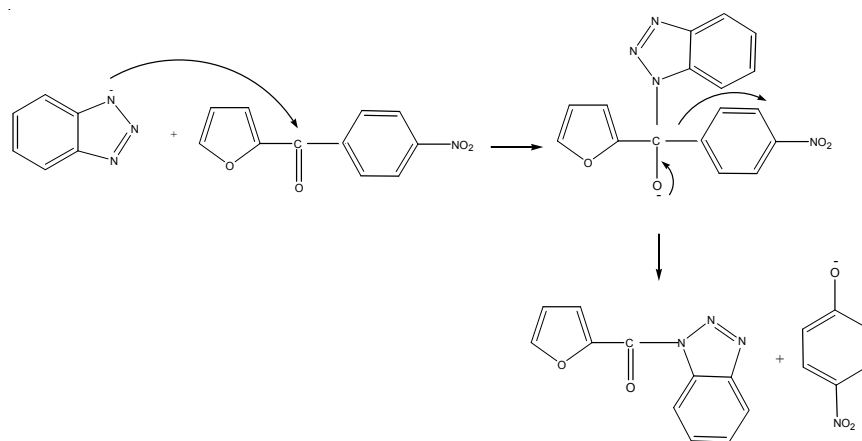
Fig. 4. Concentration dependence of catalyst on the rate of hydrolysis of *p*-NPF in aq. acetonitrile (95-5 % v/v) at 303 K Inset shows retardation effect of 2,6-lutidine

The catalytic rate coefficients for the hydrolysis of *p*-NPF by various catalysts shows catalysts such as OH, BI, BT, HMBT, PhOH, *p*-MP, *p*-CP, HP and HYD are acting as very efficient catalysts and catalysts such as TRIS and BO are showing least catalytic efficiency (Table-1).

TABLE-1
CATALYTIC RATE COEFFICIENTS FOR THE HYDROLYSIS OF
p-NPF BY VARIOUS CATALYSTS

Catalyst	pH	k_{cat} ($dm^3\ mol^{-1}\ s^{-1}$)
Hydroxide (OH)	—	7.800
Benzimidazole (BI)	11.2	8.600
Benzotriazole (BT)	9.0	1.400
Hydroxymethyl benzotriazole (HMBT)	9.5	1.600
Phenol (PhOH)	9.4	2.000
<i>p</i> -Cresol (<i>p</i> -MP)	10.8	3.900
<i>p</i> -Chlorophenol (<i>p</i> -CP)	10.0	2.000
6-Hydroxy-2-picoline (HP)	11.5	4.600
Hydrazine (HYD)	8.7	4.100
Trihydroxymethyl methylamine (TRIS)	9.0	0.004
Borax (BO)	9.2	0.006

A catalyst can function either as a nucleophile, by attacking the carbonyl group of the ester directly and leading to product formation (**Scheme-I**) or as a general base, by attacking the hydrogen of water and releasing hydroxide ion, which in a subsequent step attacks the ester carbonyl and leads to product formation (**Scheme-II**)



The Brønsted β value for the hydrolytic reaction of *p*NPF by various catalysts was obtained from the plot of $\log k_{\text{cat}}$ vs. $\text{p}K_{\text{a}}$ values of the catalyst (Fig. 5). The observed β value for the hydrolysis of *p*NPF is 0.25. According to the classification of Fersht and Jencks⁹, β values ranging from 0 to 0.4 are characteristic of strong nucleophiles with asymmetric early transition state. The nucleophilicity of the anionic form of catalyst used here is less sensitive to basicity than that of imidazole as revealed by the observed β value of 0.8 for imidazole catalysed hydrolysis of *p*-nitrophenylacetate^{10,11}. Yesodha and Thiagarajan³ also observed β values ranging from 0.11 to

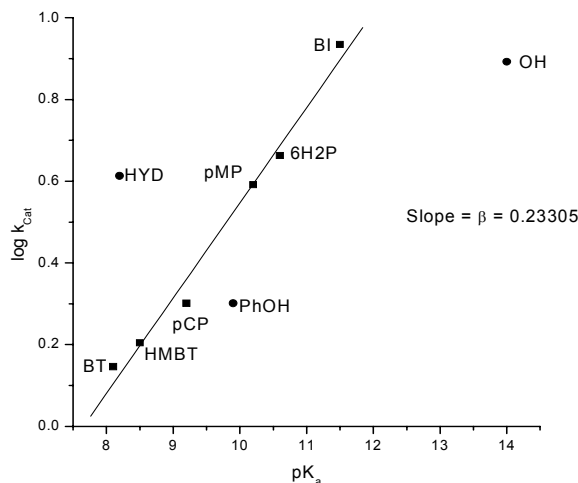


Fig. 5. Brønsted plot - Correlation of $\log k_{cat}$ with pK_a of the catalyst (attacking nucleophiles) in the hydrolysis of *p*-NPF in aq. acetonitrile (95-5 % v/v) at 303 K

0.58 in the case of phenyl ester hydrolysis catalyzed by BT anion and attributed the low β value for the strong nucleophilic character of the BT anion. The value of β for the total transfer of benzoyl group to BT is found to be 1.7^{10,12}. Therefore, the transition state for the BT catalysed hydrolysis involves a bond between the N-atom of BT and the carbonyl carbon which is not formed completely or the degree of advancement of the reaction is by far less than that in the case of imidazole catalysed reactions. The value of β for the transfer of thiophene-2-carboxyl group to N-atom of BT is found to be +0.6¹³. This is reasonable since the thiophene ring is less aromatic than the phenyl ring. The k_{OH^-}/k_{cat} ratio is relatively low for catalysts like BI, BT, HMBT, PhOH, *p*-MP, *p*-CP, HP and HYD while the same is higher by 10³ order of magnitude for BO and TRIS (Table-2). According to the Jencks and Kirsch⁹ diagnostic criteria, the k_{OH^-}/k_{cat} ratio exceeding 10³ points to a general base behaviour, while a low value suggesting nucleophile action by the catalyst. Based on this, it can be concluded that in the present case BO and TRIS exhibit general base behavior (**Scheme-II**), whereas other catalysts employed participate as nucleophiles (**Scheme-I**).

The relative rate ratio k_{BT}/k_{TRIS} is 3.5×10^2 and k_{HYD}/k_{TRIS} is 10³, though the catalysts have same pK_a of 8.1. This indicates that the catalysts BT and HMBT acts as nucleophiles while the catalyst TRIS acts as a general base catalyst¹⁴.

The $\beta_{attacking\ group}$ (+0.25) is equal to $\beta_{leaving\ group}$ (-0.25) (Fig. 6) in magnitude but opposite in sign. This equivalence is inferred to mean that the bond formation between the nucleophile and the acyl carbon and the bond

TABLE-2
 k_{OH^-}/k_{CAT} RATIO FOR VARIOUS CATALYSTS

Catalyst	pK _a	k_{CAT} (dm ³ mol ⁻¹ s ⁻¹)	k_{OH^-}/k_{CAT}
Hydroxide	14.0	7.800	1.0
Benzimidazole	11.5	8.600	0.9
Benzotriazole	8.1	1.400	5.5
Hydroxymethyl benzotriazole	8.5	1.600	5.0
Phenol	9.9	2.000	3.9
<i>p</i> -Cresol	10.2	3.900	2.0
<i>p</i> -Chlorophenol	9.2	2.000	3.9
6-Hydroxy-2-picoline	10.6	4.600	1.7
Hydrazine	8.2	4.100	1.9
Trihydroxymethyl methylamine	8.1	0.004	1902.0
Borax	9.1	0.006	1219.0

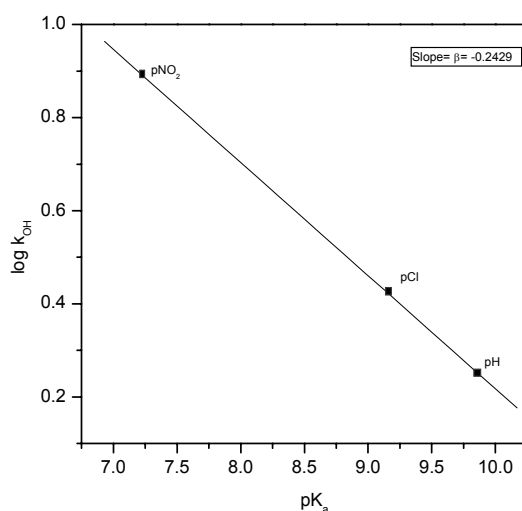


Fig. 6. Brønsted plot-Correlation of $\log k_{OH^-}$ with pK_a of the leaving group in the hydrolysis of substituted phenyl furoates in aq. acetonitrile (95-5 % v/v) at 303 K

cleavage between the acyl carbon and the leaving group have proceeded to the same extent in the transition state¹³. This is a key observation supporting the nucleophilic type of attack by the catalyst¹¹.

Hammett correlation of $\log k_{OH^-}$ vs. σ , the Hammett substituent constant (Fig. 7) for the hydrolysis of α -furoates results in a linear plot with ρ value equal to +0.84. This is in keeping with the leaving group abilities of the substituted phenoxides. It suggests slight development of negative charge during the formation of intermediate.

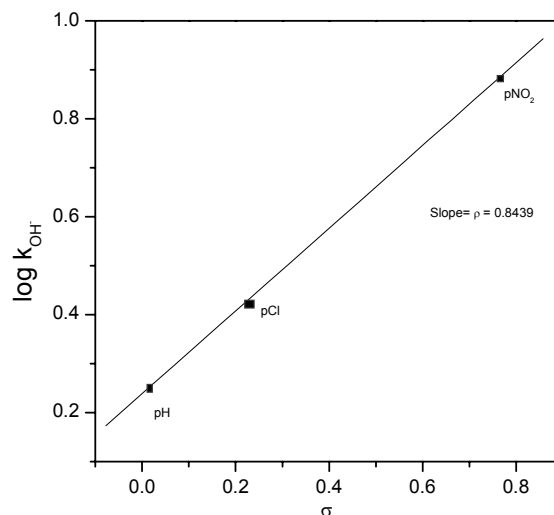


Fig. 7. Hammett plot-Correlation of $\log k_{OH^-}$ with Hammett's substituent constant for the hydrolysis of substituted phenylesters of furoic acid

From the Table-3, it is clear that k_{OH^-}/k_{BI} is less than 10^3 , is indicative of attack by the catalyst is not as a general base but as a nucleophile.

TABLE-3
 k_{OH^-}/k_{BI} RATIO FOR VARIOUS SUBSTRATES

Ester	k_{OH^-}	k_{BI}	k_{OH^-}/k_{BI}
<i>p</i> -NPF	7.80	8.60	0.9
PF	1.68	0.47	3.6
<i>p</i> -CPF	2.72	2.13	1.2

The decrease in the rate of hydrolysis of *p*-NPF with increasing concentration of 2,6-lutidine (Fig. 4) is due to inaccessibility of N atom of 2,6-lutidine for attacking acyl carbon because of steric hinderance due to two methyl groups present in *ortho* positions of the pyridine nucleus with respect to N-atom. This rules out the general base mechanism.

Hence a possible mechanism for the hydrolysis of *p*-NPF by catalysts like BT, BI, HMBT, HP, HYD, PhOH, *p*-MP and *p*-CP is as depicted by **Scheme-I** and by catalysts like BO and TRIS is as depicted in **Scheme-II**.

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