Kinetics of General & Specific Catalysis During Hydrolysis of 1-Benzoylbenzotriazoles†

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The hydrolysis of 1-benzoylbenzotriazole is independent of *p*H in the range 2.0 - 7.0 and catalysed by OH⁻ at *p*H > 7 at 25°C in acetonitrile - water medium (10%, v/v) at ionic strength = 0.5 mol dm⁻³. Based on the solvent deuterium isotope effect and structure-reactivity considerations, a mechanism involving at least two water molecules in the transition state is proposed for the *p*H independent hydrolysis. The results of the effect of substituents on the phenyl ring of the benzoyl group on the rate constant lead to Hammett's rho value of + 1.7 and Bronsted β value of − 1.7. Aquopentaamminocobaltic perchlorate catalyses the hydrolysis and the ratio of rate constants for metal complex catalysed reaction and the corresponding hydroxide ion catalysed reaction has been found to be 1.2×10^3 - 5.7×10^3 suggesting a nucleophilic attack of hydroxy group of the complex on the carbonyl of the amide.

Benzotriazole catalysed hydrolysis of 4-nitrophenyl acetate involving a tetrahedral intermediate has already been reported[1]. As a part of our investigation on the benzotriazole catalysed hydrolysis of phenyl acetates and benzoates[2], we report herein the hydrolysis of unsubstituted and substituted benzoylbenzotriazoles (BzBTs) in acetonitrile - water mixture (10%, v/v).

Materials and Methods

Benzotriazole (BTH) and 5-nitrobenzotriazole (5NO₂-BTH) were Aldrich samples. 4'-Nitrobenzoyl-(*p*NO₂-BzBT), 4'-chlorobenzoyl-(*p*Cl-BzBT), 3'-nitrobenzoyl- (*m*NO₂-BzBT), 3'-chlorobenzoyl-(*m*ClBzBT), 4'-methoxybenzoyl- (*p*MeO-BzBT), 1-benzoyl-5-nitro-(5NO₂-BzBT), and 1-benzoyl-benzotriazoles and the substituted benzoyl chlorides were prepared by well-known methods, recrystallised from ethyl acetate and their purities checked. Aquopentaamminocobalt(III) perchlorate was prepared by the literature method and recrystallised from aqueous perchloric acid. Acetonitrile was purified according to the standard procedure and inorganic chemicals used were of AR grade. Doubly distilled conductivity water was used throughout. Solutions of the amides were prepared in acetonitrile and kept in the refrigerator. Deuterium oxide (D₂O) obtained from BARC, Bombay was of 99.7% purity.

In a typical kinetic run benzoyl derivative in acetonitrile (20 μl) was injected in the buffer (1.98 ml)

containing the required amount of acetonitrile and potassium chloride or sodium perchlorate. The mixture was shaken well and the absorbances at 316, 245 (unsubstituted); 306, 270, 260 (*p*MeO-BzBT); 306, 265 (*p*NO₂-BzBT); 300, 255 (*m*NO₂-BzBT); 300, 248 (*p*Cl-BzBT); and 300, 250 nm (*m*Cl-BzBT) were then recorded on a Carl Zeiss VSU2-P at regular time intervals. The disappearance of the amide was followed upto 75% completion of the reaction and for each concentration of the buffer, triplicates were run.

Pseudo-first order rate constants (k_{obs}) were calculated from a least square plot of log (A_t-A_∞) versus time.

The rate constant (k_o) in the absence of buffer was evaluated by extrapolating the linear plot of k_{obs} versus [buffer] to zero buffer concentration. The slope of the linear plot gave catalytic rate coefficient (k_{cat}).

Results and Discussion

Hydrolysis of BzBTs in various buffer media is first order each in [amide] and [buffer]. The rate constant (k_o) for the hydrolysis of the amide in the absence of any external buffer is given by Eq. (1)

$$k_o = k_w + k_{OH^-}[OH^-] \qquad \ldots (1)$$

where k_{OH^-} and k_w are the rate constants for hydroxide ion and water catalysed reactions respectively. From a study of the *p*H-rate profile (Fig. 1) for 1-BzBT, it is found that for a substantial *p*H region water is a dominant catalyst, although the rate constant for water catalysis is smaller than that obtained for 1-acetyl 1,2,4-triazole[3]. Further the hydroxide ion catalysis is preponderant at *p*H 7 and above.

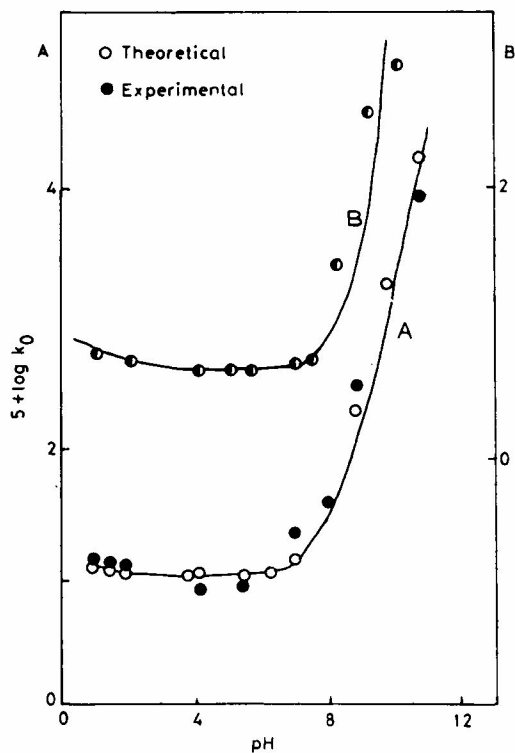Figure 2 shows the Bronsted plot with $\beta = 0.18$ for the hydrolysis of 1-BzBT where the nucleophiles used

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Fig. 1—pH-rate profiles for the hydrolysis of 1-BzBT(A) and p MeO-BzBT(B); $\mu = 0.5$ mol dm^{-3} in aqueous acetonitrile (10%, v/v) (A at 25°C, B at 30 C)

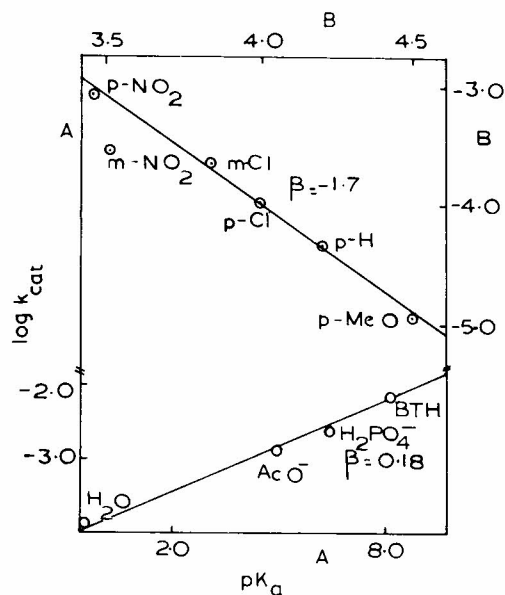Fig. 2—(a) Bronsted plot for the reaction of 1-BzBT with nucleophiles-acetate (AcO$^-$), phosphate (H$_2$PO$_4^-$), H$_2$O and BTH at 25°C in aqueous acetonitrile (10%, v/v); $\mu = 0.5$ mol dm^{-3} (B) Bronsted plot-log k_o versus pK_a for the substituted benzoic acids, the product of hydrolysis of 1-BzBTs, at pH 6.47 in aqueous acetonitrile (30%, v/v) at 30°C; $\mu = 0.5$ mol dm^{-3}

Table 1—Rate Coefficients and Isotopic Effects for the Hydrolysis of Acyl Benzotriazoles

{ $\mu = 0.5$ mol dm^{-3}(KCl); solvent: acetonitrile-water (10%, v/v); temp.: 30°C }

| Substrate	$k_{obs} \times 10^4$ s^{-1}		k_{H_2O}
	H$_2$O	D$_2$O	k_{D_2O}
1-BzBT	1.16	0.32	3.6
	3.50	1.09	3.2†
5NO$_2$-1BzBT	3.18	0.911	3.5
	9.60	2.87	3.3†
1-AcBT			3.0‡

†in acetate buffer 0.1 mol dm^{-3}; pH 6.85
‡Ref.(15)

are water, phosphate, acetate, BTH and hydroxide. It is significant to observe that water falls on the Bronsted line, indicating that water functions as a general base in the hydrolytic reaction[1]. The observed solvent isotopic effect for the pH independent hydrolysis of 1-BzBT suggests that the hydrolysis of 1-BzBT is similar to that reported for 1-methylimidazole catalyzed hydrolysis of 1-benzoylimidazoles (Table 1)[4]. Numerous solvent isotopic effects for the general base catalysed acyl derivatives fall within the range 2 to 3 (refs. 5-8). On account of the correlation of kinetic isotopic effect in these hydrolytic reactions, a satisfactory mechanism as shown in Scheme 1 can be suggested for the hydrolysis of 1-BzBT[9,10].

Scheme 1
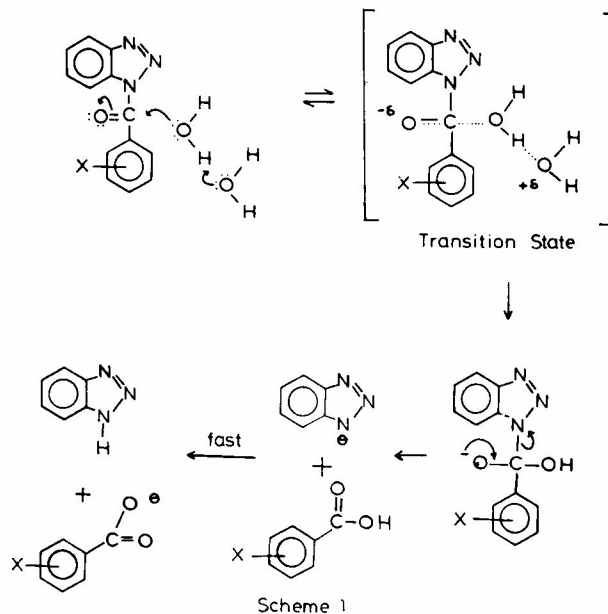
The Hammett's plot (log k_0 versus σ) for the hydrolysis of p- and m-substituted 1-BzBT at pH 6.47, in acetonitrile - water mixture (30%, v/v) at 30°C and

ionic strength 0.5 ml dm^{-3}, was found to be linear and the rho value has been found to be $+1.7$ which is close to the value reported for the hydrolysis of benzoylimidazoles. It is reasonable to assume that the proposed mechanism implicates a transition state closely resembling a tetrahedral intermediate with a finite life time, which would have nearly the same β value whether the formation or breakdown of the tetrahedral intermediate is the rate determining step. The β values may be equal for a broad range of reactions, if $\beta_{entering\ group}$ is equal to $\beta_{leaving\ group}$. According to Hammonds postulate if the transition state geometries closely resemble the tetrahedral intermediate than the above conclusion is justified[11]. A true tetrahedral intermediate as shown in Scheme 1 is likely because structures based on good Lewis representation generally exist in the form as stable equilibrium nuclear geometries with finite life time. The transition state for the reaction involving one water molecule as a general base aiding the removal of proton from the nucleophilic water may be depicted as in (I), (II) or (III).

I

II

III
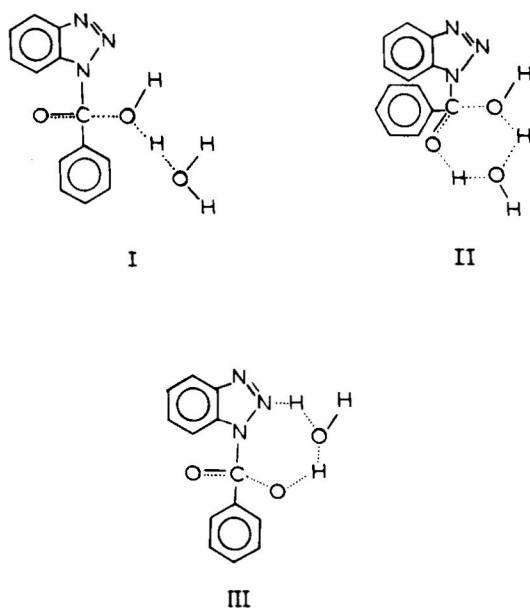
Since water falls on the Bronsted line and not above the line as is expected for a cyclic mechanism, the structures (II) and (III) may be unlikely to represent the true transition state. Recent proton inventory studies also provide evidence for transition state structure similar to (I) (ref. 12).

At $pH > > 7$ the hydroxide ion catalysed hydrolysis becomes predominant and the mechanism can be depicted as shown in Scheme 2.

The pH-rate profile for the hydrolysis of pMeO-BzBT (Fig. 1) is similar to the parent compound with a
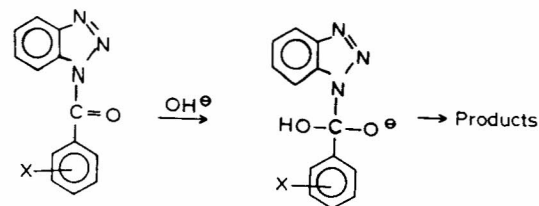
Scheme 2

well-marked pH independent region whereas the pH independent regions are not discernible from the pH-rate profiles for the hydrolysis of pNO_2-BzBT and pCl-BzBT because the latter reactions are akin to the hydrolysis of 4-nitrobenzoylimidazole which are catalysed by both hydroxide ion and hydronium ion (Fig. 3). In contrast to this behaviour, the *meta*-isomers are catalysed essentially by hydroxide ion (Fig. 3).

It is surmised that in general base catalysis with addition of water to the carbonyl groups, the leaving groups play a significant role[8,13,14]. Weak nucleophiles having a removable proton on the basic atom will react in a general base catalysed reaction as in acetylimidazole involving the addition of nucleophile to the carbonyl, the general base assisting the removal of proton from the nucleophilic atom. It is therefore concluded that the tetrahedral intermediate thus found in general base catalysed hydrolysis will eject the leaving group. It is probable that the 4'-nitro substituent makes the water attack on the carbonyl
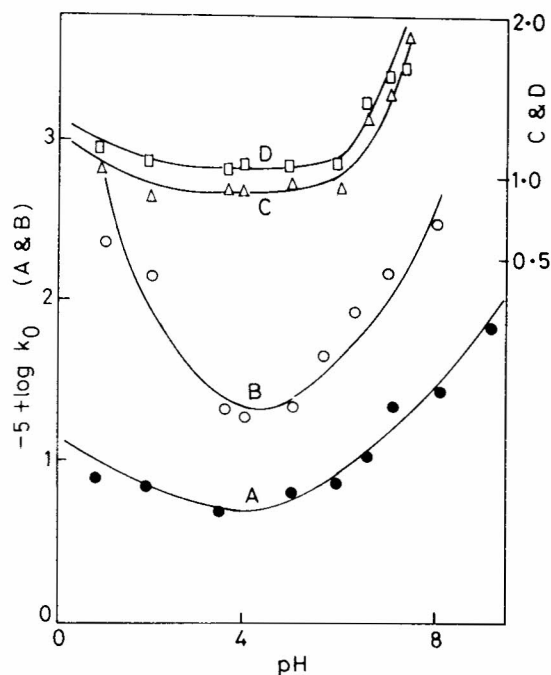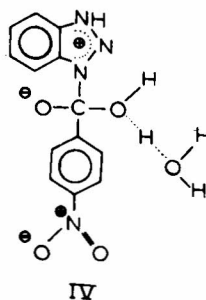
Fig. 3—pH-rate profiles for the hydrolysis of pCl-BzBT(A), pNO_2-BzBT(B), mCl-BzBT(C) and mNO_2BzBT(D) at 30°C in aqueous acetonitrile (30%, v/v); $\mu = 0.5$ mol dm^{-3}

more difficult and hence the protonated form of the benzotriazole leaves from the tetrahedral intermediate (IV) more easily resulting in net increase in the rate.

IV

For acid catalysis, protonation may occur either on the nitrogen or on the oxygen atom of the carbonyl group. However, a general acid and general base catalysis may be the preferred mechanistic path for these reactions.

Benzotriazole is a better leaving group than 1,2,4-triazole (pK_a of triazole is 10.1 and pK_a of BTH is 8.32)[1]. In fact the tetrahedral intermediate once formed by the reaction of 1-BzBT is more stable than the reactant and hence the benzotriazole moiety does not leave in spite of the fact that pK_a of BTH is smaller than 1,2,4-triazole. In the case of 1,2,4-triazole the tetrahedral intermediate or transition state is not stabilised or there is no quasi-aromatic structure in the ground state as in the case of benzoylbenzotriazoles.

The hydrolysis of N-benzoylbenzotriazoles catalysed by the aquopentaamminocobaltic perchlorate has also been studied with a view to understanding the mechanism of the metal ion activity in biological acyl transfer processes. The value of rate coefficient (k_o) in the absence of buffer for cobalt (III) catalysed hydrolysis is constant suggesting that the region chosen for the study is independent of pH. The values of k_{cat}, k_{OH^-} and k_{OH^-}/k_{cat} for the Co(III) catalysed hydrolysis of N-benzoylbenzotriazoles are given in Table 2. It has been observed that the k_{cat} increases with the increase in pH in the pH range 6.13-6.91 indicating that the metal hydroxide complex catalyses to a greater extent than the metal aquo complex.
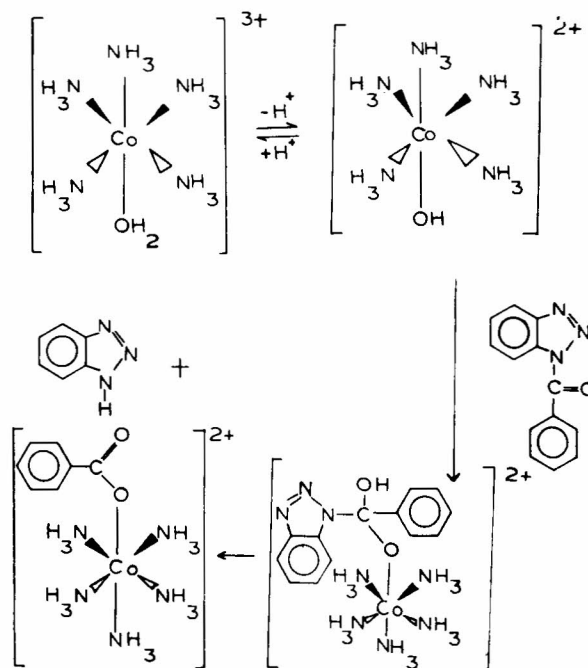
A plot of log k_{cat} versus pK_a of the substituted benzoic acids, is linear with a slope of -1.8. Thus the transition state for Co(III) catalysed reaction seems to simulate the hydrolysis of benzoylbenzotriazole catalysed by general base. The Hammett's reaction constant ($\rho = +1.69$) confirms the development of a partial negative charge in the transition state. The values of relative rate coefficients, k_{OH^-}/k_{cat} ranges from 1.2×10^3 to 5.7×10^3. For a reaction proceeding by nucleophilic catalysis, this ratio generally lies between 10 and 10^3 and for a hydrolysis proceeding by general base mechanism, it is greater than 10^5.

Table 2—Relative Rates of Hydrolysis of Benzoylbenzotriazoles

{[BzBTs] $= 1 \times 10^{-4}$ mol dm^{-3}; solvent: acetonitrile-water (10%, v/v); $pH = 6.5$; $\mu = 0.2$ mol dm^{-3} (NaClO$_4$); temp.: 30°C }

Substrate	$k_{cat} \times 10^2$ (dm^{3}mol^{-1}s^{-1})	$k_{OH^-} \times 10^{-2}$ (dm^{3}mol^{-1}s^{-1})	$\dfrac{k_{OH^-}}{k_{cat}} \times 10^{-3}$
1-BzBT	4.14	1.60	3.86
pMeO-BzBT	1.15	0.66	5.74
mCl-BzBT	14.10	5.22	3.70
mNO$_2$-BzBT	6.00	3.33	5.56
pNO$_2$-BzBT	85.46	10.55	1.23
pCl-BzBT	7.51	2.78	3.70

Benzoatopentaaminocobaltic complex has characteristic absorption at 505 nm similar to acetatopentaaminocobaltic complex (501 nm). In a buffer catalysed hydrolysis of N-benzoylbenzotriazole in the presence of aquopentaamminocobalt (III) the UV absorption spectrum at 505 nm shows an increase in the absorbance as a function of time proving thereby that the complex is formed as the product. Therefore, it is presumed that Co(III) perchlorate complex catalysed hydrolysis proceeds by a mechanism involving nucleophilic attack of hydroxypentaamminocobaltic perchlorate complex on carbonyl oxygen leading to a tetrahedral intermediate which breaks up in a slow step to give the products (Scheme 3).

Scheme 3

Acknowledgement

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