Co-operative Catalysis of the Cleavage of an Amide by Neighbouring Carboxy Group in Alkaline Medium

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The k_{obs}–[$\bar{\text{O}}$H] profile obtained at 30 °C reveals an insignificant contribution of water-catalysed cleavage of non-ionized ethyl *N*-(*o*-carboxybenzoyl)carbamate (EBCH) compared with its hydroxide ion-catalysed or kinetically equivalent water-catalysed cleavage of ionized ethyl *N*-(*o*-carboxybenzoyl)carbamate (EBC$^-$). A similar k_{obs}–[$\bar{\text{O}}$H] profile obtained for the cleavage of *N*-(3-bromopropyl) phthalamic acid (NBPPH) reveals both water and hydroxide catalysis. The rate constant (k_w) for water-catalysed cleavage of NBPPH is *ca.* 10^4-fold larger than that for phenyl acetate. The presence of water catalysis in the cleavage of NBPPH is attributed to the probable occurrence of co-operative catalysis while the absence of such catalysis in the cleavage of EBCH is presumably the consequence of the non-occurrence of co-operative catalysis in this case. The pK_a of the imide proton of EBCH is 11.3 at 30 °C while no ionization of the amide proton of NBPPH could be detected spectrally within the pH range 10.23—12.00 and 0.05M-NaOH at 30 °C.

Co-operative (also called 'synergistic') catalysis has been proposed in many enzyme-catalysed reactions.[1] The studies on mechanism of such catalysis involving simpler model reactions may therefore be considered of some importance. The mechanistic details of the aqueous cleavages of esters and amides involving intramolecular participation of the carboxy group have been extensively studied.[2–5] Almost all these studies were carried out at moderately low pH where the carboxy group acted as an intramolecular nucleophile for the reaction. Thanassi and Bruice[6] showed that, in the hydrolyses of *o*-carboxybenzoate esters, the non-ionized carboxy group acted as a nucleophile for esters with a leaving group of pK_a higher than 13.6 while an ionized carboxy group acted as nucleophile for esters with a leaving group of pK_a < 13.6. No study on amide hydrolysis has so far been reported, at least to the knowledge of this author, in which a neighbouring carboxylate ion might have acted as a nucleophile. The reason perhaps lies in the energetics of these reactions. In a few such reactions, a neighbouring carboxylate ion has been shown to act as an intramolecular general base catalyst for water attack at carbonyl carbon.[2,7] The intramolecular nucleophilic catalysis is much larger (in magnitude) compared with analogous intramolecular general acid–base catalysis and that is why the latter catalysis could not be detected in comparison with the former one in most studies. The significance of intramolecular general base catalysis may be expected at moderately high pH. But again, if the rate constant for hydroxide ion-catalysed cleavage of substrate is very large, then intramolecular general base catalysis may be masked by efficient hydroxide ion catalysis. We have recently studied the hydrolysis of *N*-(2-bromoethyl)phthalamic acid[8] in a highly alkaline medium where we could not detect intramolecular general base catalysis within the experimental conditions of the study. The significance of the specific base, $\bar{\text{O}}$H, catalysis may be expected to be decreased with increasing basicity of the leaving group. The basicity of the leaving group is presumably higher in the alkaline hydrolysis of *N*-(3-bromopropyl)phthalamic acid (NBPPH) than that of *N*-(2-bromoethyl)phthalamic acid. Similarly, the hydrolysis of ionized ethyl *N*-(*o*-carboxybenzoyl)carbamate (EBCH) undoubtedly involves a leaving group of considerably high pK_a. We decided therefore to study the alkaline hydrolysis of NBPPH and EBCH in order to detect intramolecular general base or nucleophilic catalysis in these reactions. The results and probable mechanism are described in this paper.

Experimental

Material.—Reagent-grade chemicals such as *N*-ethoxycarbonylphthalimide (NCP) and *N*-(3-bromopropyl)phthalimide (NBPP) were obtained from Aldrich. All other chemicals were from B.D.H. D_2O of 99.7% isotopic purity was from B.D.H. The stock solutions of NCP and NBPP were prepared in CH_3CN and hence each kinetic run contained 1% CH_3CN.

Kinetics.—The reactions were initiated by adding the appropriate amounts of NBPP and NCP to preincubated (at 30 °C) mixtures containing the desired ingredients. Rates for the cleavage of NBPPH and EBCH were studied spectrophotometrically by monitoring the appearance of product and the disappearance of reactant at 246 and 260 nm, respectively. A Beckman model 35 u.v.–visible spectrophotometer was used throughout. The pseudo-first-order rate constants for the conversion of *N*-substituted phthalimides into the corresponding phthalamic acids were always larger than those for the conversion of phthalamic acids into phthalic acid by a factor of $\geqslant 400$ in the experimental conditions. Details of the experimental procedure and kinetic analysis are described elsewhere.[9]

Determination of Ionization Constant.—The ionization constant of imide proton of EBCH was determined spectrophotometrically at 260 nm. The pH range 7.74—12.01 was covered using buffer solutions of carbonate (0.2M total buffer concentration), triethylamine (0.02M total buffer concentration), and 0.01M-KOH. The ionic strength was kept constant at 1.0M using a stock solution of KCl. Details of the procedure and calculation of ionization constant K_a are described elsewhere.[9] The least-squares-calculated value of K_a is $(4.75 \pm 0.91) \times 10^{-12}$ mol l^{-1} at 30 °C.

Product Characterization.—The u.v. spectra of the mixture (containing 0.05M-KOH and 2×10^{-4}M-NCP) obtained at 19, 29, and 38 h were identical with that of phthalic acid obtained under identical experimental conditions. Based on these

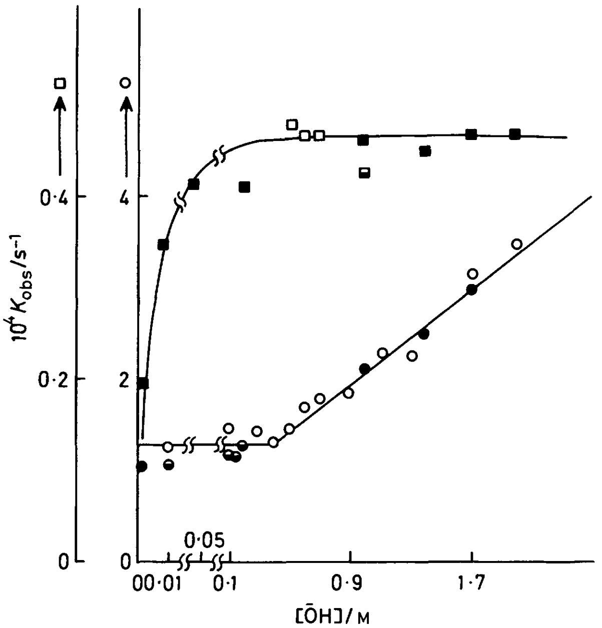


Figure. Dependence of k_{obs} on $[\bar{O}H]$ for hydroxide ion-catalysed cleavage of ethyl *N*-(*o*-carboxybenzoyl)carbamate, EBCH (□, ■, ◧,) and *N*-(3-bromopropyl)phthalamic acid, NBPPH (○, ●, ◒). Points for □ and ■ or ○ and ● were obtained by the use of NaOH and KOH, respectively, and for ◧ or ◒ by the use of KOD in D_2O

observations we conclude that the probable occurrence of an *E*1cB mechanism[10] (*i.e.* the expulsion of $\bar{O}C_2H_5$ from carbamate anion, ionized EBCH) which could lead to the formation of the most probable ultimate product, phthalamic acid, is unlikely compared with an AE ($B_{AC}2$) mechanism which could produce phthalic acid. The conversion of phthalamic acid into phthalic acid at 30 °C and 0.05M-KOH is expected to be < 10% within the period of *ca.* 50 h.[11] Furthermore, it is evident from the reported studies on alkaline hydrolyses of aryl 4-hydroxybenzoates[12] and carbamates[13] (where the occurrence of both $B_{AC}2$ and *E*1cB mechanisms is possible) that the $B_{AC}2$ mechanism operates for esters with poorer leaving groups (p$K_{l.g.} \geq 7$ and 13 for benzoates and carbamates, respectively) while the *E*1cB mechanism occurs for esters with better leaving groups (p$K_{l.g.} < 7$ and 13 for benzoates and carbamates, respectively). Since the pK_a of the conjugate acid of the leaving group in EBCH ($\bar{O}C_2H_5$) is *ca.* 15.5, we presume the non-occurrence of *E*1cB mechanism in the alkaline hydrolysis of EBCH.

Results and Discussion

A series of kinetic runs were carried out at 30 °C within $[\bar{O}H]$ 0.002—2.0M for the cleavage of NBPPH. The observed rate constants are shown graphically in the Figure. These results indicate that the rate is almost independent of $[\bar{O}H]$ within the range *ca.* 0.002—0.4M and then rate constants follow equation (1) up to $[\bar{O}H]$ 2.0M. The least-squares-calculated value of k_{OH} is

$$k_{obs} = k_{OH}[\bar{O}H] \qquad (1)$$

$(1.32 \pm 0.04) \times 10^{-4}$ l mol^{-1} s^{-1}. The values of $k_{obs}^{D_2O}$ were also determined in 98% D_2O within $[\bar{O}D]$ 0.01—0.2M. These results as shown in the Figure reveal $k_{obs}^{H_2O}/k_{obs}^{D_2O}$ *ca.* 1.12 where $k_{obs}^{H_2O}$ represents k_{obs} in 99% H_2O.

The hydroxide ion-catalysed cleavage of EBCH was studied at 30 °C for $[\bar{O}H]$ 0.002—2.0M. The observed data as shown in the Figure fitted well to equation (2).

$$k_{obs} = \frac{\theta\psi[\bar{O}H]}{1 + \psi[\bar{O}H]} \qquad (2)$$

The unknown parameters, θ and ψ, were calculated using least-squares technique and the respective values thus obtained are $(4.63 \pm 0.08) \times 10^{-5}$ s^{-1} and 315 ± 60 l mol^{-1}. The fitting of the observed data to equation (2) is evident from the plot in the Figure where the solid line is drawn through the least-squares-calculated points. The value of $k_{obs}^{D_2O}$ obtained at 1.0M-KOD in 98% D_2O is not significantly different from $k_{obs}^{H_2O}$ obtained at 1.0M-KOH in 99% H_2O ($k_{obs}^{H_2O}/k_{obs}^{D_2O}$ 1.09).

The k_{obs}-$[\bar{O}H]$ profile (Figure) for the cleavage of NBPPH may be explained by the reaction mechanism shown in Scheme 1. The observed rate law and Scheme 1 easily lead to equation (3).

$$k_{obs} = \frac{k_1k_3[H_2O]}{k_{-1} + k_3} + \frac{k_4k_2[\bar{O}H]}{k_{-2} + k_4} \qquad (3)$$

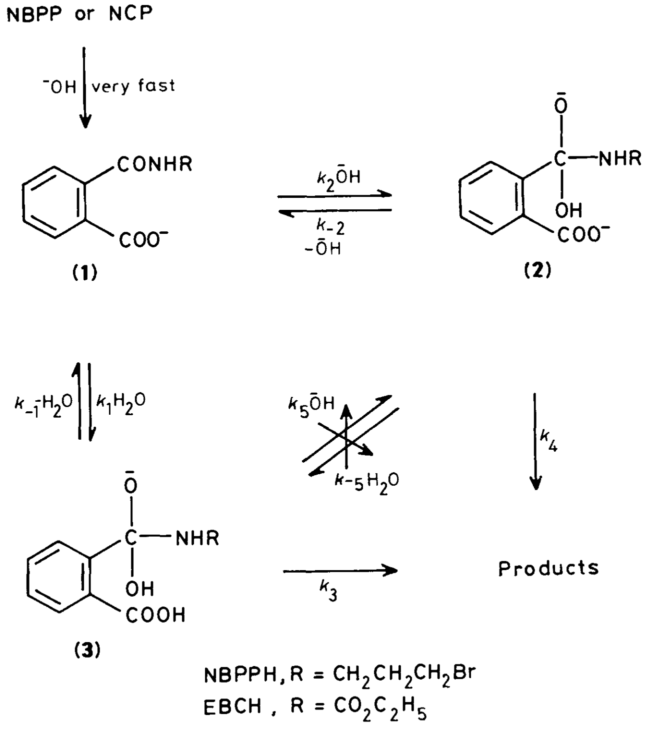
The pK_a values of conjugate acids of nucleophiles (H_2O and $\bar{O}H$), and leaving group are such that the nucleophilic attack may be unlikely to be the rate-determining step. Thus, presumably, $k_{-1} > k_3$ and $k_{-2} > k_4$ and application of these assumptions reduces equation (3) to (4).

$$k_{obs} = \frac{k_1k_3[H_2O]}{k_{-1}} + \frac{k_2k_4[\bar{O}H]}{k_{-2}} \qquad (4)$$

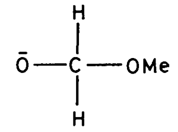
Equation (4) is consistent with the observed k_{obs}-$[\bar{O}H]$ profile with $k_{OH} = k_2k_4/k_{-2} = 1.32 \times 10^{-4}$ l mol^{-1} s^{-1} and $k_1k_3[H_2O]/k_{-1} = (1.27 \pm 0.16) \times 10^{-4}$ s^{-1} (the average value of k_{obs} obtained for $[\bar{O}H]$ 0.002—0.4M, Figure). It is interesting to mention here that the mathematical nature of equation (4) predicts that at $[\bar{O}H]$ 0, the resulting intercept would be equal to $k_1k_3[H_2O]/k_{-1}$. But the observed plot (Figure) indicates that the rate constants, k_{obs}, are independent of $[\bar{O}H]$ within the range *ca.* 0.002—0.4M. The chemical (non-mathematical) reason for this observed fact may be ascribed as follows. In an aqueous medium, the concept of zero concentration of either hydroxide ion or hydronium ion has no precise meaning. The observed results merely indicate that the values of $k_2k_4[\bar{O}H]/k_{-2}$ are negligible compared with that of $k_1k_3[H_2O]/k_{-1}$ within the $[\bar{O}H]$ *ca.* 0.002—0.4M. In the least-squares calculation of k_2k_4/k_{-2} [$= k_{OH}$, equation (1)], the origin of the plot was shifted from 0.0 to the observed point at 0.4M-NaOH.

The probable formation of (**2**) from (**3**) through step k_5 may be ruled out due to the following reason. The value of $k_{-5}[H_2O]$ of *ca.* 1 s^{-1} may be calculated from the relationship $k_{-5}[H_2O] = k_5K_w/K_a$ where K_w (ionic product of water) is *ca.* 10^{-14} mol^2 l^{-2} and K_a [ionization constant of *o*-carboxy group of (**3**)] is presumably of the order of 10^{-4}M (K_a values of benzoic acid[14] and *N*-substituted phthalamic acid[5] are of the order of 10^{-4} mol l^{-1}). The k_5 step involves the proton transfer in a thermodynamically favourable direction and hence the value of k_5 may be considered to be *ca.* 10^{10} l mol^{-1} s^{-1}.[15] The values of the rate constant[16] for the expulsion of methoxide ion from (**4**) is 3×10^2 s^{-1}. The electronic push provided by the electron pair on nitrogen in (**2**) is expected to be larger than that by the hydrogen in (**4**) and hence the magnitude of the rate constant k_{-2} may be larger than 3×10^2 s^{-1}. These arguments thus reveal that $k_{-2} > k_{-5}[H_2O]$. According to the principle of microscopic reversibility, if the k_{-2} step represents the lowest energy path for the breakdown of (**2**) then the k_2 step must be the lowest energy path for its formation.

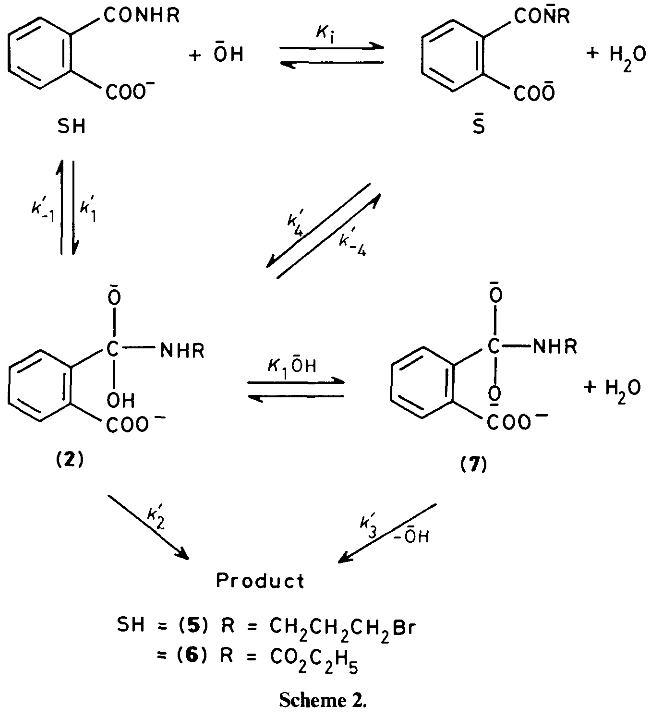
A kinetically indistinguishable mechanism shown in Scheme



Scheme 1.



(4)



Scheme 2.

2 may also apparently fit the observed data. Scheme 2 can lead to equation (5), providing k'_2 and k'_3 are rate-determining steps.

$$k_{obs} = \frac{(k'_1 + k'_4K_i)(k'_2 + k'_3K_1[\bar{O}H])[\bar{O}H]}{(1 + K'_i[\bar{O}H])(k'_{-1} + k'_{-4})} \qquad (5)$$

In equation (5), $K'_i = K_i/[H_2O] = K_a/K_w$ and $K_a = [S^-]a_H/[SH]$. The observed k_{obs}–$[\bar{O}H]$ profile (Figure) could fit equation (5) only if $K'_i[\bar{O}H] \gg 1$ within $[\bar{O}H]$ 0.002—2.0M. This condition requires that $K_a > 10^3K_w$, *i.e.* $K_a > 10^{-11}$ mol l^{-1}. Unlike EBCH, the u.v. spectra of NBPPH obtained at pH 10.23, 11.05, and 0.01M-KOH did not show any detectable change with change of pH which could be attributed to the possible ionization of NBPPH. Also the reported value of pK_a of benzamide is 14—15[17] and presumably the replacement of *o*-H by *o*-CO_2^- and N-H by N-$CH_2CH_2CH_2Br$ would not decrease the pK_a from 14—15. The acid-strengthening effect of $CH_2CH_2CH_2Br$ is significantly smaller than that of CO_2Et ($\sigma^*_{CO_2R} > \sigma^*_{CH_2CH_2CH_2Br}$)[18] and hence the p$K_a$ of NBPPH should be larger than that of EBCH (pK_a of EBCH is 11.3 at 30 °C). A value of K_a of $> 10^{-11}$ mol l^{-1} for NBPPH is therefore certainly inconceivable and hence the mechanism shown in Scheme 2 is not compatible with the observed data.

The k_{obs}–$[\bar{O}H]$ profile for the cleavage of EBCH (Figure) indicates that the rate constants increase sharply with increase in $[\bar{O}H]$ at low $[\bar{O}H]$ range and then become independent of $[\bar{O}H]$ at considerably higher $[\bar{O}H]$. This is consistent with the mechanism shown in Scheme 2. Since an increase in k_{obs} with increase in $[\bar{O}H]$ could not be detected after the rate became independent of $[\bar{O}H]$, it is apparent that the k'_3 step is insignificant compared with the k'_2 step (Scheme 2). Applying this consideration, equation (5) is reduced to (6).

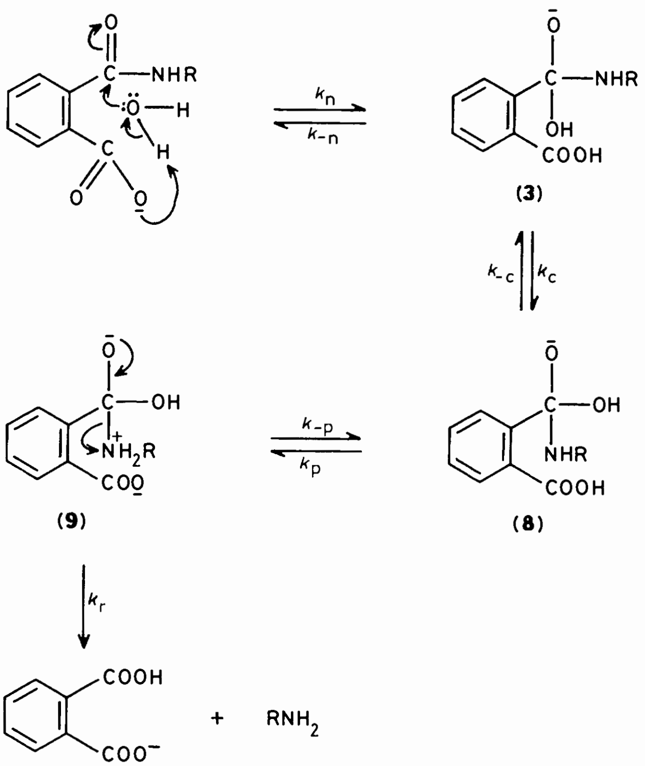
$$k_{obs} = \frac{k'_2(k'_1 + k'_4K_i)[\bar{O}H]}{(1 + K'_i[\bar{O}H])(k'_{-1} + k_{-4})} \qquad (6)$$

The k'_1 and k'_4 steps are kinetically indistinguishable. But for the following qualitative reasons, we rule out any significance for the k'_1 step compared with k'_{-4}. Nucleophilic attack by H_2O in the k'_4 step presumably involves intramolecular general base catalysis and hence k'_4 involves intramolecular general acid catalysis. No such catalysis is anticipated in k'_{-1}. It is therefore feasible to assume that $k'_{-4} > k'_{-1}$. The intramolecular proton transfer as suggested in k'_4 and k'_{-4} steps has been proposed by earlier workers in related studies.[19,20] The lowest energy path for breakdown of (2) is thus the k'_{-4} step and hence, according to the principle of microscopic reversibility, the k'_4 step should be the lowest energy path for its formation. Also if we assume that $k'_1 > k'_4K_i$ then the calculated value of $k'_1k'_2/k'_{-1}$ of *ca.* 13×10^{-3} mol^{-1} s^{-1} is only 3—4 times larger than the corresponding value of 3.7×10^{-3} mol^{-1} s^{-1} obtained for the cleavage of monomethyl phthalate under comparable conditions. This seems to be unlikely because of the fact that although the pK_a of the conjugate acid of MeO^- (leaving group in the hydrolysis of monomethyl phthalate) is comparable to that of $\bar{N}HCO_2Et$ [leaving group in (**6**)], the high carbon basicity of oxygen compared with that of nitrogen for a given basicity toward proton[16] should yield $k'_1k'_2/k'_{-1}$ much larger for (**6**) than that for monomethyl phthalate.

Application of the conclusion that $k'_1 < k'_4K_i$ and k'_{-1} reduces equation (6) to (7). Equation (7) is similar to (2) with

$$k_{obs} = \frac{k'_2k'_4K_i[\bar{O}H]}{k'_{-4}(1 + K'_i[\bar{O}H])} \qquad (7)$$

$\psi = K'_i$ and $\theta = k'_2k'_4[H_2O]/k'_{-4}$. The calculated value of ψ of 315 l mol^{-1} was used to calculate $K_a(= \psi K_w)$ of 4.53×10^{-12} mol l^{-1} which may be compared with the experimentally



Scheme 3.

observed value of K_a (= 4.75 × 10^{-12} mol l^{-1}). The formation of (**2**) from S^- involving an ionized carboxy group acting as intramolecular general base catalyst cannot be completely ruled out.

The observed D_2O solvent isotope effect of nearly unity is consistent with the proposed reaction mechanism (Scheme 2). Since k'_2 does not involve any proton transfer while k'_4 and k'_{-4} involve proton transfer and therefore $k'_2k'_4/k'_{-4}$ is expected to be unchanged by the presence of D_2O. However, the alternative reaction path SH $\longrightarrow$ (**2**) $\longrightarrow$ product may also be shown to be consistent with the observed D_2O solvent isotope effect.

The observed value of $k_1k_3[H_2O]/k_{-1}$ of 1.27 × 10^{-4} s^{-1} is more than 10^3- and 10^4-fold greater than the first-order rate constants k_w observed for the water-catalysed cleavages of phenyl acetate (k_w 1.65 × 10^{-8} s^{-1} at 25 °C)[21] and benzamide (k_{obs} 3 × 10^{-9} s^{-1} at 47 °C and 0.001M-HCl).[22] It is, however, comparable with the analogous rate constants obtained for the cleavages of salicyl phenanthroline-2-carboxylate[2] (k_w 3 × 10^{-5} s^{-1} at 50 °C) and methyl *o*-(2-imidazolyl)benzoate[23] (k_w 8.5 × 10^{-6} s^{-1} at 50 °C). In these reactions, the involvement of intramolecular general base catalysis has been unequivocally ascertained. Capon *et al.*[24] obtained pH-independent first-order rate constants at pH higher than *ca.* 4.3 and 48 °C for hydrolysis of phthalamic acid. The average value of these rate constants (obtained from Figure 5 of ref. 24) is *ca.* 1 × 10^{-4} s^{-1}. More than 10^5-fold rate enhancement caused by the presence of *o*-CO_2^- group in NBPPH may be attributed to carboxylate ion acting as an intramolecular general base catalyst for the nucleophilic attack by water at carbonyl carbon and then the resulting neutral *o*-carboxy group acts as an intramolecular general acid catalyst to help expel the leaving group (RNH_2) in the final step of the reaction. The mechanistic details of this intramolecular bifunctional or co-operative catalysis may be shown in Scheme 3. The suggested mechanism is similar to one suggested and supported by Breslow *et al.*[25] in the cleavages of *N*-substituted maleamic acids.

Water-catalysed cleavage of EBCH could not be detected within the experimental conditions of the present study. This is surprising in view of the fact that NBPPH with a much poorer leaving group compared with that for EBCH showed significant intramolecular general base-catalysed hydrolysis. The only possibility of the difference in the reactivity of NBPPH and EBCH toward H_2O we could suggest at the moment is a change in the rate-determining step with the change in pK_a as well as the structural feature of the leaving group. When R (Scheme 3) is an alkyl group (for NBPPH), the proton transfer in k_p is thermodynamically favourable and hence (**8**) is converted into (**9**) in a fast equilibrium followed by breakdown of (**9**) to product in the rate-determining step (k_r, Scheme 3). But when R is CO_2Et (for EBCH) then the proton transfer in k_p is no longer thermodynamically favourable and the breakdown of (**8**) to product through concerted intramolecular general acid catalysis is presumably the rate-determining step.

The observed D_2O solvent isotope effect ($k_{obs}^{H_2O}/k_{obs}^{D_2O}$ *ca.* 1.12) is consistent with the proposed mechanism (Scheme 3) where k_r is considered to be the rate-determining step. In this mechanism, the proton transfer takes place in the k_n, k_{-n}, k_p, and k_{-p} steps. It is apparent that any D_2O solvent isotope effect in k_n and k_p would be counter-balanced by that in k_{-n} and k_{-p} respectively.

Based on the observed value of $k_{obs}^{H_2O}/k_{obs}^{D_2O}$ of 1.12 in the plateau region of the k_{obs}–[$\bar{O}$H] profile for NBPPH (Figure), one may argue the probable occurrence of an alternative mechanism in which *o*-carboxylate ion is acting as a nucleophile rather than an intramolecular general base catalyst as shown in Scheme 3. Although this mechanism seems to be compatible with the observed data, we are reluctant to favour it for the following reason. This nucleophilic mechanism could explain the observed D_2O solvent isotope effect only if intramolecular nucleophilic attack by carboxylate ion is rate determining. However, the structural feature of the substrate is such that instead of nucleophilic attack, expulsion of the leaving group (catalysed by water acting as an intermolecular general acid catalyst) is presumably the rate-determining step and, consequently, a significant D_2O solvent isotope effect should result. Aldersley *et al.*[26] have, however, preferred the nucleophilic mechanism in the hydrolysis of the methyl di-isopropylmaleate anion (and other related compounds) based on the observed solvent deuterium isotope effect, k_H/k_D, of 1.64 and other evidence. But if we assume that intramolecular nucleophilic attack is rate determining, or a nucleophilic mechanism is operating, then it is difficult to explain why such catalysis could not be detected in the hydrolysis of EBCH where electrophilic carbonyl carbon seems to be relatively more activated because $(\sigma_I + \sigma_R)NHCO_2Et > (\sigma_I + \sigma_R)NH[CH_2]_3Br$.

The second-order rate constant k_{OH} (= 1.32 × 10^{-4} l mol^{-1} s^{-1}) for hydroxide ion-catalysed cleavage of NBPPH is *ca.* 38-fold smaller than that of *N*-(2-bromoethyl)phthalamic acid (k_{OH} 5.03 × 10^{-3} l mol^{-1} s^{-1} at 25 °C[8]). This shows that k_{OH} values are significantly dependent on the acidity of the leaving group, which favours the proposed expulsion of leaving group (k_4, Scheme 1) being the rate-determining step. The value of k_{OH} of 1.32 × 10^{-4} l mol^{-1} s^{-1} for NBPPH may be compared with those of 1.6 × 10^{-3} for benzamide, 0.72 × 10^{-3} for *N*-methylbenzamide, and 1.5 × 10^{-3} l mol^{-1} s^{-1} for *NN*-dimethylbenzamide obtained at 100.4 °C.[27]

We could not detect the pH-independent first-order rate constants in the alkaline hydrolysis of *N*-(2-bromoethyl)-phthalamic acid within the [$\bar{O}$H] range of 0.05 to 2.0M, while in case of NBPPH the rate constants were found to be independent of [$\bar{O}$H] up to *ca.* 0.4M-NaOH. The reason for this may be ascribed to a *ca.* 38-fold larger value of k_{OH} for *N*-(2-bromoethyl)phthalamic acid than that for NBPPH. The rate constants, k_w, for the water-catalysed cleavage of *N*-substituted phthalamic acids are not very sensitive to the structural feature of the leaving groups and therefore a significantly larger value of k_{OH} compared with k_w for *N*-(2-bromoethyl)phthalamic acid masked the significance of k_w even at the lowest $[\bar{O}H]$ of 0.05M of the study. Similar observations were obtained by Fife *et al.*[23] in the aqueous cleavages of aliphatic esters of *o*-(2-imidazolyl)benzoic acid. These authors obtained the pH–rate profile for the methyl ester which is linear with a slope of 1.0 at pH values above 8.0 and at lower pH (<8.0) there is a plateau. Such a plateau could not be detected for the trifluoroethyl ester within the pH range *ca.* 4—11. The rate constant, k_{OH}, for hydroxide ion-catalysed cleavage of the trifluoroethyl ester is *ca.* 10^4-fold larger than that of the methyl ester. Thus, a significantly higher value of k_{OH} for the trifluoroethyl ester would not produce a detectable plateau in the pH–rate profile.

Kinetically, we obtained the existence of an oxydianionic tetrahedral addition intermediate in the alkaline hydrolysis of *N*-(2-bromoethyl)phthalamic acid. But such an intermediate could not be detected in the alkaline hydrolyses of NBPPH and EBCH. The existence of this intermediate in the cleavage of *N*-(2-bromoethyl)phthalamic acid is presumably the consequence of the larger electron-withdrawing ability of $HNCH_2CH_2Br$ than of $HNCH_2CH_2CH_2Br$ and $\bar{N}COOC_2H_5$. These observations are in favour of the conclusion that the existence of an oxydianionic tetrahedral intermediate in the alkaline hydrolyses of esters, amides, and imides depends upon both the structural features of the substrate and the alkalinity of the reaction medium.

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