

Unexpected rate enhancement in the intramolecular carboxylic Acid-catalyzed cleavage of *o*-carboxybenzohydroxamic acid

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ABSTRACT: Phthalic anhydride was detected spectrophotometrically in the hydrolysis of *o*-carboxybenzohydroxamic acid (OCBA) in CH₃CN–H₂O solvent containing 0.03 mol dm^{−3} HCl. Pseudo-first-order rate constants (*k*₁) for hydrolysis of OCBA are almost independent of the change in CH₃CN content from 10 to 80% (v/v) in mixed aqueous solvents. The rate constants *k*₁ are more than 10-fold larger than the corresponding rate constants for hydrolysis of phthalamic acid. These observations are explained in terms of a mechanism slightly different from the mechanism for hydrolysis of phthalamic acid. The activation parameters, Δ*H*[‡] and Δ*S*[‡], are not affected appreciably by an increase in CH₃CN content from 10 to 80% in mixed aqueous solvents. © 1998 John Wiley & Sons, Ltd.

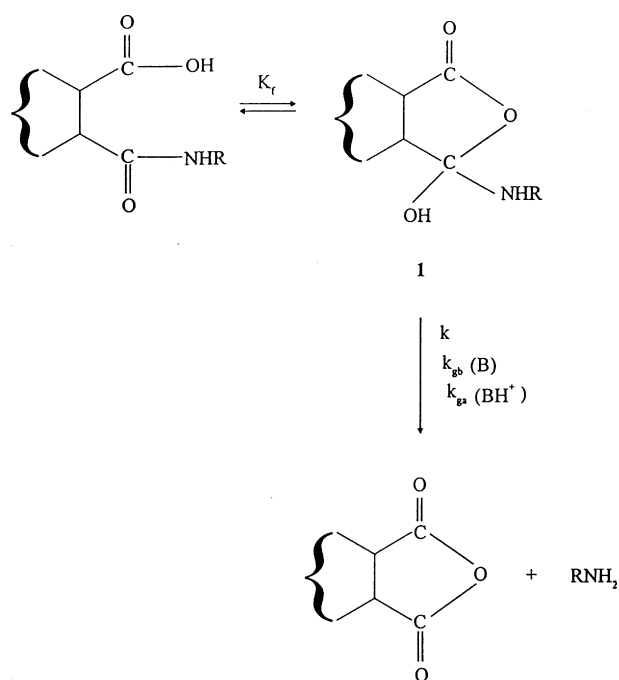
KEYWORDS: *o*-carboxybenzohydroxamic acid; phthalic anhydride; phthalic acid; hydrolysis; intramolecular acid catalysis; kinetics; activation parameters

INTRODUCTION

The mechanistic details of intramolecular carboxylic acid participation in amide hydrolysis have been explored by several workers.^{1–11} Most of these intramolecular reactions involve uncatalyzed, external general acid (GA)- and external general base (GB)-catalyzed hydrolysis. The general mechanism suggested and supported in these reactions is shown in Scheme 1, where B and BH⁺ represent GB catalyst and GA catalyst, respectively. In almost all of these studies,^{6–9} the rate constants (*k*) for uncatalyzed hydrolysis showed negative reaction constants (*ρ* or *ρ*^{*}). It is interesting that the leaving groups (—NHR) in all these mechanistically well studied reactions contain only one basic site (i.e. the nitrogen atom) where internal proton transfer can occur.

o-Carboxybenzohydroxamic acid contains two basic sites (N and O) in the leaving group (—NHOH), although these two basic sites are not of equal basicity, where internal proton transfer can occur. Hydrolysis of *o*-carboxybenzohydroxamic acid has been shown to involve nucleophilic catalysis by the neighboring carboxylate group (*o*-CO₂[−]) and intermediate formation of

phthalic anhydride.¹² The present study was initiated with the aim of exploring the effect of the OH group (in the leaving group) on the rate of uncatalyzed hydrolysis of *o*-carboxybenzohydroxamic acid.



Scheme 1

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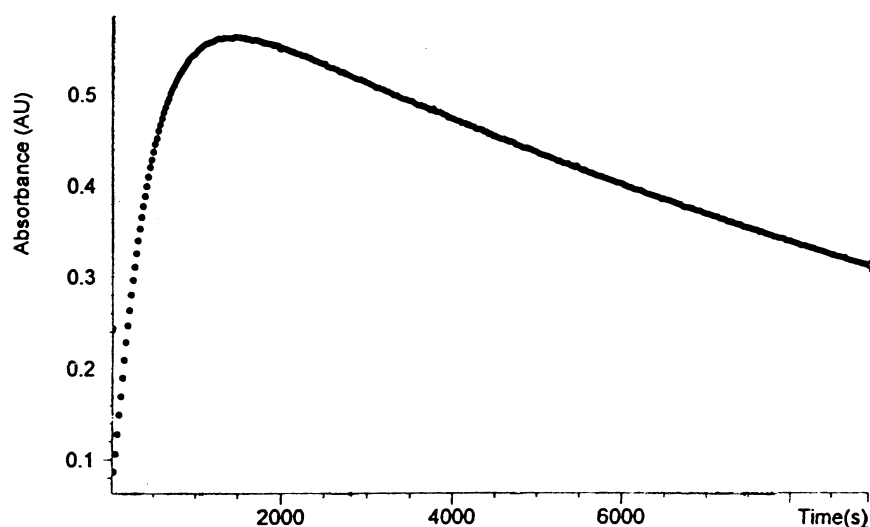


Figure 1. Plot of absorbance at 310 nm against time for a mixed aqueous solution of *o*-carboxybenzohydroxamic acid (2×10^{-3} mol dm $^{-3}$) in 80% CH $_3$ CN and 0.037 mol dm $^{-3}$ HCl at 35°C

EXPERIMENTAL

Materials. All chemicals were of reagent grade and were obtained from Fluka, Aldrich and Merck. Distilled water was used throughout and stock solutions of *N*-hydroxyphthalimide were prepared frequently in acetonitrile.

Kinetic measurements. The formation of phthalic anhydride (PAn) as an intermediate in the hydrolysis of phthalamic acid and its *N*-substituted derivatives has been unequivocally ascertained.^{1,8,11} Phthalic anhydride absorbs significantly whereas phthalamic and *N*-substituted phthalamic acids do not absorb to a detectable extent at 310 nm. If the rate of hydrolysis of PAn is slower than that of phthalamic acid or *N*-substituted phthalamic acid, then the rate of hydrolysis of phthalamic acid or *N*-substituted phthalamic acid can easily be studied spectrophotometrically at 310 nm. Blackburn *et al.*⁸ studied the rate of hydrolysis of phthalamic acid and a few *N*-arylphthalamic acids by monitoring the change in [PAn] spectrophotometrically at 310 nm in the presence of high concentrations of sodium perchlorate, where the rate of hydrolysis of PAn was greatly retarded.¹³ The rate of hydrolysis of *N,N*-dimethylphthalamic acid in acidic medium was found to be almost independent of increasing acetonitrile content [from 10 to 80% (v/v) (all percentage concentrations are by volume in this paper)] in mixed aqueous solvents.¹¹ However, the rate of hydrolysis of PAn in acidic medium decreased nearly 200-fold with increase in acetonitrile content from 2 to 80% in mixed aqueous solvents.¹⁴ These results show that the presence of PAn in the hydrolysis of phthalamic acid or its *N*-substituted derivatives can be easily detected spectrophotometrically by using water–acetonitrile or water–aprotic organic solvents. Hence, the

rates of formation and decay of PAn in the hydrolysis of *o*-carboxybenzohydroxamic acid in an acidic medium were studied spectrophotometrically at 310 nm in water–acetonitrile solvents.

In a typical kinetic run with a total volume of 4.8 cm 3 of the reaction mixture containing 0.5 cm 3 of 0.02 mol dm $^{-3}$ *N*-hydroxyphthalimide (in acetonitrile solvent), 0.2 cm 3 of 0.25 mol dm $^{-3}$ NaOH, 3.5 cm 3 of CH $_3$ CN and 0.6 cm 3 of H $_2$ O, the reaction was allowed to complete a period of more than 30 half-lives (i.e. nearly 900 s) at 35°C. The hydrolysis of the hydrolytic product of *N*-hydroxyphthalimide (NHPI), i.e. hydrolysis of *o*-carboxybenzohydroxamic acid (OCBA), was then initiated by adding 0.2 cm 3 of 1.18 mol dm $^{-3}$ HCl to the reaction mixture. The resulting reaction mixture, having a total volume of 5.0 cm 3 , contained 2×10^{-4} mol dm $^{-3}$ OCBA, 0.037 mol dm $^{-3}$ HCl and 80% CH $_3$ CN. The change in absorbance (AU) at 310 nm was monitored as a function of time (*t*) using a diode-array spectrophotometer. The observed data (for a typical kinetic run) are shown in Fig. 1.

In an earlier report,¹⁵ product analysis of the alkaline hydrolysis of *N*-hydroxyphthalimide in an aqueous solvent containing 2% CH $_3$ CN revealed a 100% conversion of reactant (*N*-hydroxyphthalimide) into the expected product, OCBA. An extremely slow rate of hydrolysis of the product (OCBA) was observed at pH 11.4 (only *ca* <20% hydrolysis occurred within a period of 7 days at ambient temperature¹⁵).

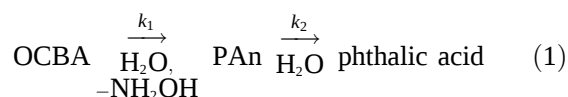
Kinetic data analysis. A monotonic increase in AU in the initial phase of the reaction (hydrolysis of OCBA) followed by a monotonic decrease in AU in the final phase of the reaction (Fig. 1) indicates the involvement of a stable intermediate in the hydrolysis of OCBA. The

Table 1. Values of k_1 , k_2 , ε_{app} and AU_0 calculated from equations (2) and (3) for hydrolysis of *o*-carboxybenzohydroxamic acid and phthalic anhydride in an acidic medium^a

[MeCN] (%, v/v)	Temperature (°C)	$10^3 k_1$ (s ⁻¹)	$10^3 k_{1\text{caled}}^b$ (s ⁻¹)	$10^4 k_2$ (s ⁻¹)	$10^4 k_{2\text{caled}}^b$ (s ⁻¹)	$\varepsilon_{\text{app}}^c$	AU_0	AU_{max}^d	t^e (s)	$10^4 k_{\text{obs}}^f$ (s ⁻¹)
10	35	1.47 ± 0.16^g	1.88	103 ± 10^g	118	720 ± 101^g (688) ^h	0.055	0.208	1800	103
	40	2.92 ± 0.16	2.86	157 ± 1	145	754 ± 62	0.090	0.286	1260	
	45	4.75 ± 0.34	4.28	187 ± 15	177	729 ± 72	0.050	0.290	900	
	50	6.12 ± 0.60	6.34	206 ± 24	214	787 ± 106	0.035	0.331	600	
20	35	2.26 ± 0.10	2.39	70.2 ± 3.1	64.7	631 ± 35 (606)	0.065	0.307	2403	63.7
	40	3.50 ± 0.22	3.85	94.9 ± 6.8	88.7	741 ± 62	0.060	0.372	1563	
	45	6.71 ± 0.73	6.11	102 ± 12	120	621 ± 78	0.065	0.436	1038	
	50	9.37 ± 0.54	9.58	170 ± 11	162	779 ± 56	0.090	0.500	738	
30	35	2.31 ± 0.18	2.70	44.5 ± 3.5	39.1	688 ± 63 (514)	0.050	0.409	2223	32.8
	40	3.70 ± 0.54	4.10	55.4 ± 8.4	56.0	697 ± 115	0.060	0.489	2363	
	45 ⁱ	7.21 ± 0.09	6.31	72.1 ± 0.9	79.4	613 ± 12	0.046 ± 0.006	0.509	1142	
	50	8.63 ± 1.83	9.06	115 ± 25	111	812 ± 188	0.052	0.582	690	
40	35	2.68 ± 0.59	2.85	20.1 ± 4.4	22.1	489 ± 100 (379)	0.018	0.445	3200	16.2
	40	4.00 ± 1.07	4.33	31.9 ± 8.6	28.9	577 ± 146	0.040	0.526	2200	
	45	7.18 ± 0.54	6.50	36.4 ± 2.6	37.4	595 ± 36	0.045	0.648	1338	
	50	9.38 ± 0.83	9.64	48.0 ± 4.0	48.1	650 ± 46	0.050	0.716	903	
50	35	2.41 ± 0.11	2.28	11.8 ± 0.5	13.1	506 ± 19 (308)	0.035	0.554	3147	9.05
	40	3.32 ± 0.25	3.71	18.5 ± 1.4	17.5	535 ± 35	0.040	0.569	4383	
	45	6.28 ± 0.43	5.94	24.0 ± 1.6	23.2	507 ± 26	0.030	0.605	1980	
	50	9.29 ± 0.69	9.38	29.8 ± 2.4	30.4	518 ± 28	0.050	0.672	1460	
60	35	2.45 ± 0.41	2.65	5.96 ± 0.09	6.33	398 ± 4 (254)	0.030	0.540	3663	3.88
	40	4.12 ± 0.12	3.85	8.59 ± 0.29	8.25	378 ± 8	0.040	0.542	5400	
	45	5.45 ± 0.20	5.53	10.8 ± 0.4	10.7	465 ± 11	0.020	0.666	2223	
	50	7.86 ± 0.30	7.86	13.5 ± 0.5	13.6	476 ± 11	0.050	0.735	2058	
67.3 ^j	35	2.84 ± 0.02		3.59 ± 0.03		329 ± 1	0.020	0.486	3600	
	35	2.29 ± 0.09	2.60	2.86 ± 0.17	2.67	320 ± 8 (217)	0.000	0.475	3200	1.63
	40	3.85 ± 0.07	3.83	3.30 ± 0.05	3.60	357 ± 3	0.020	0.592	6463	
	45	6.00 ± 0.05	5.57	4.93 ± 0.04	4.80	363 ± 2	0.070	0.654	5373	
80 ^k	50	7.81 ± 0.16	8.01	6.35 ± 0.20	6.36	383 ± 5	0.070	0.691	1218	
	35	2.27 ± 0.02		0.954 ± 0.010		296 ± 1 (171)	0.050	0.563	8943	0.61
	40	4.40 ± 0.03		1.22 ± 0.01		261 ± 1	0.040	0.507	7200	

^a [OCBA]₀ = 2×10^{-3} mol dm⁻³, [HCl] = 0.027 mol dm⁻³, mixed H₂O–MeCN solvent, λ = 310 nm.^b Calculated from the Eyring equation [equation (4)] using the activation parameters listed in Table 2.^c Units are dm³ mol⁻¹ cm⁻¹.^d Observed maximum absorbance at 310 nm.^e Maximum reaction time attained in the kinetic run.^f Pseudo-first-order rate constants, k_{obs} , for hydrolysis of phthalic anhydride at 0.005 mol dm⁻³ HCl, and 30 °C¹⁴ (it should be noted that pseudo first-order rate constants, k_{obs} , were found to be almost unchanged with change in [HCl] from 0.005 to 1.0 mol dm⁻³ in aqueous solvents containing 2% CH₃CN¹⁴).^g Error limits are standard deviations.^h Values in parentheses were obtained from the hydrolysis of phthalic anhydride at 0.005 mol dm⁻³ HCl and 30 °C.¹⁴ⁱ $k_1 = k_2$.^j [OCBA]₀ = 1.92×10^{-3} mol dm⁻³, [HCl] = 0.072 mol dm⁻³.^k [OCBA]₀ = 2×10^{-3} mol dm⁻³, [HCl] = 0.037 mol dm⁻³.

reaction scheme for hydrolysis of OCBA may be expressed as



where k_1 and k_2 represent pseudo first-order rate constants for hydrolysis of OCBA and PAn, respectively.

The change in AU due to the change in [PAn] during the course of reaction is given by

$$AU = \frac{[X]_0 \varepsilon_{\text{app}} k_1}{k_2 - k_1} [\exp(-k_1 t) - \exp(-k_2 t)] + AU_0 \quad (2)$$

where $[X]_0$ is the concentration of OCBA at reaction time $t = 0$. The value of $[X]_0$ is taken as the initial concentration of *N*-hydroxyphthalimide ($[\text{NHPH}]_0$). It may be noted that any error in $[X]_0$ introduced by assuming that $[X]_0 = [\text{NHPH}]_0$ will affect only the magnitude of ε_{app} (apparent molar absorptivity) and it will not affect the magnitudes of k_1 and k_2 . In equation (2), $\varepsilon_{\text{app}} = \varepsilon_{\text{PAn}} - \varepsilon$, and $AU_0 = \varepsilon[X]_0$ with $\varepsilon = \varepsilon_{\text{OCBA}} \approx \varepsilon_{\text{PA}}$, where $\varepsilon_{\text{OCBA}}$, ε_{PAn} , and ε_{PA} are the molar absorptivities of OCBA, PAn and phthalic acid, respectively. The assumption that $\varepsilon_{\text{OCBA}} \approx \varepsilon_{\text{PA}}$ at 310 nm is supported by the spectra of phthalamic acid and phthalic acid.⁸

The values of k_1 , k_2 , ε_{app} and AU_0 were determined as follows. The values of k_1 , k_2 , ε_{app} and least squares (Σd_i^2 , where $d_i = AU_i - AU_{\text{calcd}i}$ with AU_i and $AU_{\text{calcd}i}$ representing the i th observed and calculated absorbance in a single kinetic run) were calculated from equation (2) at a presumed value of AU_0 using the non-linear least-squares technique. Similar calculations were carried out at several presumed values of AU_0 . The best value of AU_0 was considered to be that for which Σd_i^2 turned out to be minimum. The calculated values of k_1 , k_2 and ε_{app} at the statistically best values of AU_0 under different experimental conditions are summarized in Table 1.

It was found that under certain experimental conditions, $k_1 = k_2$. Equation (2) is valid only when $k_1 \neq k_2$. The

change in AU with reaction time (t), under the reaction conditions when $k_1 = k_2 = k$, is given by

$$AU = kt[X]_0 \varepsilon_{\text{app}} \exp(-kt) + AU_0 \quad (3)$$

The non-linear least-squares technique was used to calculate k , ε_{app} and AU_0 , which are given in Table 1.

RESULTS AND DISCUSSION

Several kinetic runs were carried out within the temperature range 35–50 °C at 0.027 mol dm⁻³ HCl and 10% CH₃CN in mixed aqueous solvents. Similar observations were made with 20, 30, 40, 50, 60 and 70% CH₃CN. These kinetic data were used to calculate k_1 , k_2 , ε_{app} and AU_0 from equations (2) and (3), as summarized in Table 1. The values of k_1 , k_2 , ε_{app} and AU_0 were also obtained at 35 and 40 °C in mixed H₂O–CH₃CN solvents containing 80% CH₃CN (Table 1).

The rate constants k_1 , and k_2 , obtained within the temperature range 35–50 °C at a constant content of CH₃CN in mixed aqueous solvent, obeyed the Eyring equation:

$$k = (K_B T/h) \exp(\Delta S^*/R) \exp(-\Delta H^*/RT) \quad (4)$$

where $k = k_1$ or k_2 and all other symbols have their usual meanings. The activation parameters, ΔH^* and ΔS^* , were calculated from equation (4) using the non-linear least-squares method. The calculated values of ΔH^* and ΔS^* at different contents of CH₃CN are summarized in Table 2. The fitting of the observed data to equation (4) is evident from the calculated values of the rate constants, as shown in Table 1 and from the standard deviations associated with ΔH^* and ΔS^* (Table 2).

The detailed kinetic studies on phthalamic, *N*-substituted phthalamic^{7,8} and related compounds^{6,9} support the mechanism shown as route A in Scheme 2. A similar mechanism (route A) was also proposed by Bender *et al.*^{1b} in their classical paper on the hydrolysis of phthalamic acid. An alternative mechanism, shown as

Table 2. Values of ΔH^* and ΔS^* for hydrolysis of *o*-carboxybenzohydroxamic acid (OCBA) and phthalic anhydride (PAn) in acidic medium at different contents of MeCN in mixed aqueous solvents^a

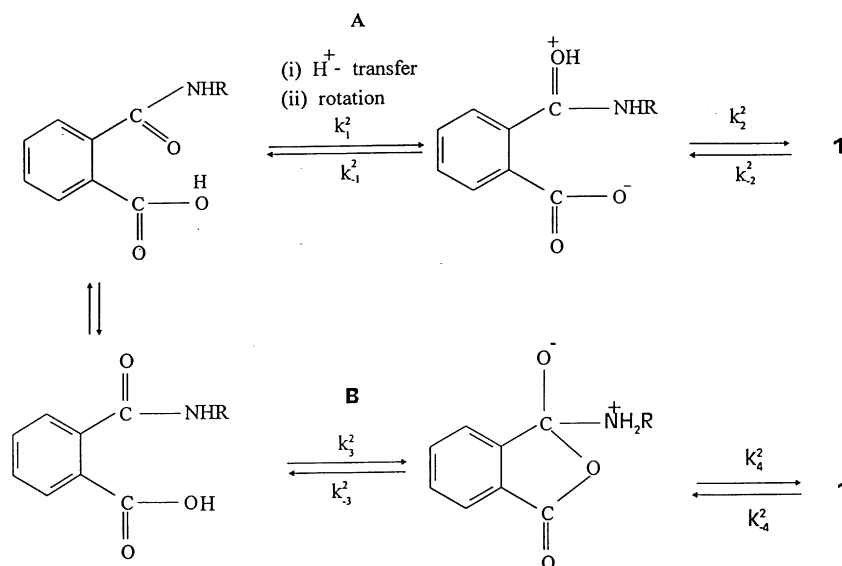
[MeCN] (% v/v)	OCBA ^b		PAn ^c	
	ΔH^* (kcal mol ⁻¹)	$-\Delta S^*$ (cal K ⁻¹ mol ⁻¹)	ΔH^* (kcal mol ⁻¹)	$-\Delta S^*$ (cal K ⁻¹ mol ⁻¹)
10	15.40 ± 2.56 ^d	21.0 ± 8.0 ^d	7.27 ± 1.88 ^d	43.8 ± 5.9 ^d
20	17.68 ± 2.06	13.1 ± 6.4	11.45 ± 2.77	31.4 ± 8.7
30	15.30 ± 3.47	20.6 ± 10.8	13.16 ± 1.96	26.9 ± 6.1
40	15.43 ± 2.07	20.1 ± 6.5	9.60 ± 1.49	39.5 ± 4.7
50	18.01 ± 1.57	12.2 ± 4.9	10.44 ± 1.26	37.8 ± 3.9
60	13.71 ± 1.00	25.9 ± 3.1	9.49 ± 0.76	42.4 ± 2.4
70	14.19 ± 1.64	24.3 ± 5.1	10.80 ± 1.18	39.9 ± 3.7

^a Conditions as given in Table 1.

^b The activation parameters refer to k_1 .

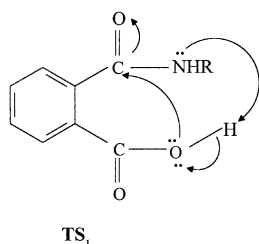
^c The activation parameters refer to k_2 .

^d Error limits are standard deviations.



Scheme 2

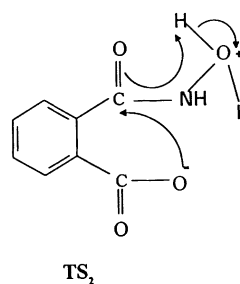
route B in Scheme 2, cannot be completely ruled out. In Scheme 2, the k_3^2 step presumably involves transition state TS_1 . The introduction of substituents in R (Scheme



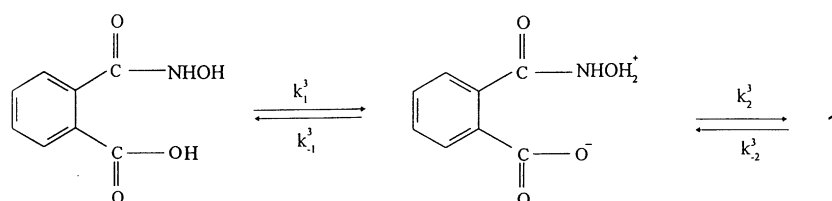
2) resulted in a negative reaction constant (ρ or ρ^*).⁶⁻⁹ These results predict that electron-withdrawing substituents (*i.e.* substituents with positive substituent constants, σ or σ^*) must decrease whereas electron-donating substituents (*i.e.* substituents with negative substituent constants, σ or σ^*) must increase the rate of hydrolysis. A nearly 2.5-fold lower rate of hydrolysis of *N*-(*o*-carboxybenzoyl)glycine ($10^5 k_1 = 7.0 \text{ s}^{-1}$ at 35°C) compared with that of phthalamic acid ($10^5 k_1 = 20 \text{ s}^{-1}$ at 35°C) in $\text{CH}_3\text{CN-H}_2\text{O}$ solvents containing 70% CH_3CN ¹⁶ revealed a negative ρ^* for the reaction because $\sigma^*_{\text{COOH}} > \sigma^*_{\text{H}}$.¹⁷

The rate constants, k_1 , for the hydrolysis of OCBA at different contents of CH_3CN and temperatures (Table 1) are more than 10-fold larger than the corresponding rate constants for the hydrolysis of phthalamic acid (10^5

$k_1 = 18 \text{ s}^{-1}$ at 35°C and 60% CH_3CN ¹⁶ and $10^5 k_1 = 24 \text{ s}^{-1}$ at 47°C and within the pH range 1.3–1.8 in pure water as solvent¹). These observations are considered to be unusual or unexpected because in terms of reported negative ρ and ρ^* values for the related reactions,⁶⁻⁹ the k_1 values for OCBA must be smaller than the corresponding values for phthalamic acid because $\sigma^*_{\text{OH}} > \sigma^*_{\text{H}}$.¹⁷ The strong electron-withdrawing effect of OH compared with H is evident from the ionization constants (K_a) of $+\text{NH}_4$ ($\text{p}K_a = 9.21$)¹⁸ and $+\text{NH}_3\text{OH}$ ($\text{p}K_a = 5.97$).¹⁸ The values of k_1 shown in Table 1 predict a positive ρ^* value for the hydrolysis of OCBA. These observations cannot be explained in terms of the reaction mechanisms shown in Scheme 2. The most probable mechanism for the hydrolysis of OCBA is shown in Scheme 3, where the formation of **1** involves the transition state TS_2 .



One might argue that the transition state TS_2 seems



Scheme 3

unlikely to be at lower energy than that involving prior protonation on the carbonyl oxygen (i.e. Scheme 2, route A). Perhaps the species involving protonation on the carbonyl oxygen is present in greater concentration than otherwise due to stabilization by hydrogen bond formation between the hydrogen on the carbonyl oxygen and the oxygen of the OH group involving a five-membered ring. If this suggested mechanistic explanation for the unusual rate enhancement is considered to be more plausible, then it is difficult to explain the observed nearly 2.5-fold lower rate of acid hydrolysis of *N*-(*o*-carboxybenzoyl)glycine (NCG) compared with that of phthalamic acid under similar experimental conditions.¹⁶ In the acid hydrolysis of NCG, the species involving protonation on the carbonyl oxygen is expected to be stabilized by hydrogen bond formation between the hydrogen on the carbonyl oxygen and the carbonyl oxygen of carboxyl group of the glycine moiety involving a seven-membered ring. Furthermore, the strength of such internal hydrogen bonding is expected to increase with decrease in the dielectric constant of the medium and consequently the rate constants, k_1 , should show an increase with decrease in the dielectric constant of the reaction medium. The rate constants, k_1 , for acid hydrolysis of *N,N*-dimethylphthalamic acid were almost unaffected by an increase in the content of CH₃CN from 10 to 80% in mixed aqueous solvents.¹¹ Similarly, a change in CH₃CN content from 60 to 70% produced essentially no effect on k_1 for acid hydrolysis of phthalamic acid.¹⁶

The rate constants, k_1 , for hydrolysis of OCBA are almost independent of CH₃CN content within the range 10–80% (Table 1). The rate constants, k_1 for hydrolysis of *N,N*-dimethylphthalamic acid showed an increase of nearly twofold with increase in the content of CH₃CN up to ca 60%, after which they showed a decrease of ca twofold with increase in CH₃CN content from 60 to 90%.¹¹ It is interesting that changes in the dielectric constant and in the solvating properties of the reaction medium do not affect greatly the rate of intramolecular reactions involving neutral reacting sites. Hence it seems that the belief that one of the main factors responsible for the unusually high catalytic efficiency of enzymes is the changes in the dielectric constant and in the solvating properties of the micro reaction environment of active sites of enzymes compared with the macro solvent environment needs careful review.

The rate constants, k_2 , shown in Table 1 are comparable to the pseudo first-order rate constants for hydrolysis of authentic PAn obtained under similar experimental conditions¹⁴ (Table 1). Similarly, the values of ϵ_{app} at different contents of CH₃CN in mixed aqueous solvents are not significantly different from the corresponding ϵ_{app} obtained for hydrolysis of authentic PAn under essentially similar experimental conditions (Table 1).¹⁴ Similar comparable results were obtained in the acid hydrolysis of *N*-(*o*-carboxybenzoyl)glycine,¹⁶ phthal-

amic acid¹⁶ and *N,N*-dimethylphthalamic acid.¹¹ These results and the results reported by Blackburn *et al.*⁸ demonstrate that the intermediate which absorbs at 310 nm in these reactions is phthalic anhydride. An increase in CH₃CN content from 10 to 80% decreased k_2 from 103×10^{-4} to $0.95 \times 10^{-4} \text{ s}^{-1}$ at 35 °C (Table 1). The mechanistic explanations of the effects of mixed aqueous–organic solvents on k_2 are described elsewhere.¹⁴

A change in the CH₃CN content from 10 to 70% in mixed aqueous solvents appears to have no appreciable effect on the activation parameters, ΔH^* and ΔS^* , for the hydrolysis of OCBA (Table 2). These activation parameters are comparable to those obtained in various intramolecular nucleophilic reactions.^{1a,19} It seems that an increase in CH₃CN content from 10 to 30% increases both ΔH^* and ΔS^* for the hydrolysis of PAn. A further increase in CH₃CN content beyond 30% does not affect appreciably either ΔH^* or ΔS^* (Table 2). The significantly large negative values of ΔS^* for the hydrolysis of PAn (Table 2) indicate the involvement of several solvent molecules in the transition state. This is in agreement with the proposed mechanism for the hydrolysis of PAn.¹⁴

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