Effects of Mixed Aqueous-Organic Solvents on the Rate of Intramolecular Carboxylic Group-Catalyzed Cleavage of *N*-(4′-Methoxyphenyl)-phthalamic Acid

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ABSTRACT: Kinetic study on the cleavage of *N*-(4′-methoxyphenyl)phthalamic acid (NMPPAH) in mixed H_2O-CH_3CN and H_2O-1,4-dioxan solvents containing 0.05 M HCl reveals the formation of phthalic anhydride (PAn)/phthalic acid (PA) as the sole or major product. Pseudo first-order rate constants (k_1) for the conversion of NMPPAH to PAn decrease nonlinearly from 60.4×10^{-5} to 2.64×10^{-5} s^{-1} with the increase in the contents of 1,4-dioxan from 10 to 80% v/v in mixed aqueous solvents. The rate of cleavage of NMPPAH in mixed H_2O-CH_3CN solvents at $\geq$50% v/v CH_3CN follows an irreversible consecutive reaction path: NMPPAH $\xrightarrow{k_1}$ PAn $\xrightarrow{k_2}$ PA. The values of k_1 are larger in H_2O-CH_3CN than in H_2O-1,4-dioxan solvents. © 2004 Wiley Periodicals, Inc. Int J Chem Kinet 36: 316–325, 2004

INTRODUCTION

Efficient intramolecular carboxyl group catalyzed hydrolysis of amide bond has been found in many related reactions [1]. Hawkins studied the cleavage of many N-aryl substituted phthalamic acids in acidic mixed aqueous-1,4-dioxan solvent and found the absence and presence (20%) of *N*-phenylphthalimide in the cleavage of *N*-phenylphthalamic acid at 20 and 80% v/v 1,4-dioxan, respectively [2]. Hydrolytic cleavage of *N*-(4′-nitrophenyl)phthalamic acid produced detectable and nondetectable amount of *N*-(4′-nitrophenyl)phthalimide in acidic aqueous solvents containing 20% v/v 1,4-dioxan [2] and 4% v/v acetonitrile [3], respectively. Nearly 20% formation of *N*-methylphthalimide has been reported in the cleavage of *N*-methylphthalamic acid in pure aqueous solvent under acidic pH [4]. In the aqueous cleavage of *N*-(*o*-carboxybenzoyl)-L-leucine,

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$\sim<10\%$ imide formation is reported at [HCl] <1.0 M and 50°C [5]. Perry reported the formation of N-(2′-aminophenyl)phthalimide (between ∼80 and ∼100% yields) in the cleavage of N-(2′-aminophenyl)-phthalamic acid under dilute aqueous acids in the pH range 0–6 [6]. Recently, Wu and coworkers studied modeling the reaction mechanisms of the imide formation in an N-(o-carboxybenzoyl)-L-amino acid [7]. These rather limited number of reports on acid hydrolysis of substituted phthalamic acids where both anhydride and imide formation occurred, are not sufficient to draw any convincing conclusion on competitive imide and anhydride formation in these reactions. Studies on the effects of mixed aqueous-organic solvents on the rates of these reactions are rare. Such studies, apart from their intrinsic worth, are partial model to the micro reaction environment for many enzyme-catalyzed reactions. The two organic solvents, acetonitrile and 1,4-dioxan, were selected simply because these are the most common water miscible aprotic organic solvents and some kinetic data on closely related reactions are available in these solvents. We decided to study the effects of mixed H_2O-CH_3CN and H_2O-1,4-dioxan solvents on the hydrolytic cleavage of N-(4′-methoxyphenyl)phthalamic acid where 4′-OCH_3 is a powerful electron-donating group. The observed results and their probable explanations are described in this paper.

EXPERIMENTAL

Materials

Synthesis of N-(4-Methoxyphenyl)phthalimide. Phthalic anhydride (1.84 g, 12.36 mmoles) and p-anisidine (1.01 g, 8.24 mmoles) were added into a 50 ml round bottom flask containing 10.0 ml glacial acetic acid. The reaction mixture was refluxed for 5 h after which TLC indicated the completion of the reaction. The mixture was then allowed to cool slowly to room temperature. The resulting yellow precipitates were filtered through sintered glass and dried to give 1.86 g (89%) yellowish solid. Further purification by recrystallization in 95% ethanol afforded a yellow crystalline solid (1.34 g, 64%). mp: 167–171°C. δ_H (400 MHz, $CDCl_3$): 3.83 (3H, s, -OCH_3), 6.99–7.01 (2H, d J 9, ArH), 7.30–7.33 (2H, d J 9, ArH), 7.75–7.77 (2H, m, ArH), and 7.90–7.94 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$): 55.5 (OCH3), 114.5 (ArCH), 123.7 (ArCH), 124.2 (ArC), 127.9 (ArCH), 131.8 (ArC), 131.8 (ArCH), 134.3 (ArCH), 159.2 (ArC-OMe), and 167.6 (C=O).

All other chemicals used were commercial products of highest available purity. Standard solution (0.01 M) of N-(4′-methoxyphenyl)phthalimide (NMPPT) was prepared in acetonitrile.

Kinetic Measurements

Alkaline Hydrolysis of N-(4′-Methoxyphenyl)-phthalimide (NMPPT). The UV spectra of NMPPT and its alkaline hydrolysis product, N-(4′-methoxyphenyl)phthalamate ion ($NMPPA^-$), in mixed water-acetonitrile and water-1,4-dioxan solvents revealed suitable wavelengths for kinetic measurements as 225 and 300 nm for monitoring the disappearance of NMPPT in the acetonitrile content range 2–30% v/v and appearance of $NMPPA^-$ in the acetonitrile content range 40–80% v/v, respectively, as a function of reaction time. Similarly, UV spectra of NMPPT and $NMPPA^-$ revealed 285 nm as suitable wavelength to monitor the appearance of $NMPPA^-$ as a function of reaction time in mixed aqueous-1,4-dioxan solvents. Details of the kinetic procedure are same as described elsewhere [8].

Pseudo first-order rate constants (k_{obs}) for alkaline hydrolysis of NMPPT were calculated from Eq. (1) (where disappearance of NMPPT was monitored as a function of reaction time, t) or Eq. (2) (where appearance of $NMPPA^-$ was monitored as a function of reaction time, t).

$$A_{obs} = \delta_{app}[X]_0 \exp(-k_{obs}\, t) + A_\infty \tag{1}$$

$$A_{obs} = \delta_{app}[X]_0 \,[1 - \exp(-k_{obs}\, t)] + A_0 \tag{2}$$

In Eqs. (1) and (2), A_{obs} is the observed absorbance, δ_{app} ($= \delta_{NMPPT} - \delta_{NMPPA^-}$ or $\delta_{NMPPA^-} - \delta_{NMPPT}$, with δ representing molar extinction coefficient) is apparent molar extinction coefficient, $[X]_0$ is the initial concentration of NMPPT, $A_\infty = [X]_0\, \delta_{NMPPA^-}$, and $A_0 = [X]_0\, \delta_{NMPPT}$. The reactions were generally carried out for reaction period of more than 6–7 halflives. Details of the data analysis have been described elsewhere [8].

Aqueous Cleavage of N-(4′-Methoxyphenyl)phthalamic Acid (NMPPAH) in Acidic Mixed Aqueous-Organic Solvents. The UV spectra of NMPPAH and its aqueous cleavage products, obtained in mixed water-acetonitrile and water-1,4-dioxan solvents containing different contents of organic cosolvents at 0.05 M HCl revealed suitable wavelengths as 218 and 250 nm to monitor the rate of appearance of products and disappearance of reactant (NMPPAH) in the acetonitrile content range 50–80% v/v and in the 1,4-dioxan range of 10–80% v/v, respectively. Kinetic runs at $<50\%$ v/v CH_3CN could produce insignificant absorbance changes ($\sim\leq 0.050$ absorbance unit) within the reasonable length of reaction period (≥890 s to ≤107340 s) and consequently observed data (A_{obs} versus t) could not fit either Eq. (2) or Eq. (3). Details of the kinetic procedure are same as described elsewhere [8].

The observed data (A_{obs} versus t), obtained at ≥50% v/v CH_3CN, for the cleavage of NMPPAH in mixed H_2O-CH_3CN solvents were found to fit to Eq. (3)

$$A_{\mathrm{obs}} = \frac{k_{1\mathrm{obs}}\delta_{1\mathrm{app}}[\mathrm{X}]_0}{k_{2\mathrm{obs}} - k_{1\mathrm{obs}}}[\exp(-k_{1\mathrm{obs}}\,t) - \exp(-k_{2\mathrm{obs}}\,t)] + \delta_{2\mathrm{app}}[\mathrm{X}]_0[1 - \exp(-k_{1\mathrm{obs}}\,t)] + A_0 \qquad (3)$$

where $k_{1\mathrm{obs}}$, $k_{2\mathrm{obs}}$ are pseudo first-order rate constants for the reaction of the type: $\mathrm{R} \xrightarrow[-P_1]{k_{1\mathrm{obs}}} \mathrm{I}_1 \xrightarrow{k_{2\mathrm{obs}}} P_2$, $A_0 = A_{\mathrm{obs}}$ at $t = 0$ as well as $\delta_{1\mathrm{app}}$ and $\delta_{2\mathrm{app}}$ represent apparent molar extinction coefficients of reaction components.

The rate of cleavage of NMPPAH, studied spectrophotometrically in mixed water-1,4-dioxan solvents (1,4-dioxan content range 10–80% v/v), followed pseudo first-order rate law and pseudo first-order rate constants were calculated from Eq. (1). The absorbance changes between the first and the last observed values of A_{obs} for all kinetic runs are within the range of 0.283–0.388.

Hydrolysis of Phthalic Anhydride (PAn) in Mixed Aqueous-Organic Solvents at 0.05 M HCl and 35°C. The rate of hydrolysis of PAn was studied by monitoring the decrease in the absorbance of reaction mixture at 218 nm (for reaction mixture containing 2×10^{-5} M PAn and CH_3CN) and 250 nm (for reaction mixture containing 4×10^{-5} M PAn and 1,4-dioxan) as a function of reaction time (t). The observed data (A_{obs} versus t) followed Eq. (1). Details of the data analysis have been described elsewhere [8].

RESULTS AND DISCUSSION

Effects of Mixed H_2O-CH_3CN and H_2O-1,4-Dioxan Solvents on the Rate of Alkaline Hydrolysis of NMPPT

In order to know the time period in which the conversion of NMPPT to NMPPA^- was completed to almost 100% under mixed H_2O-OS (OS = CH_3CN and 1,4-dioxan) solvents, a few kinetic runs were carried out within CH_3CN content range of 2–80% v/v in mixed aqueous solvents containing 0.002 M NaOH at 35°C. Similar observations were obtained in mixed H_2O-1,4-dioxan solvents. Pseudo first-order rate constants, obtained under these mixed water-organic solvents, are summarized in Table I. Nearly 10- and 9-fold nonlinear decrease in k_{obs} with increase in CH_3CN and 1,4-dioxan contents from 2 to 70 and 10 to 80% v/v, respectively, are usual but difficult to explain quantitatively with any theoretical model. However, an empirical treatment of such data may be considered of some use, at least, in predicting the value of dependent variable (such as k_{obs}) at any value of independent variable (such as % v/v content of OS). The values of k_{obs}, obtained within CH_3CN content range 2–50% v/v and 1,4-dioxan content range

Table I Values of k_{obs} for Alkaline Hydrolysis of NMPPT in Mixed Water-Acetonitrile and Water-1,4-Dioxan[a]

MS_1[b] (% v/v)	$10^3\,k_{\mathrm{obs}}$ (s^{-1})	$10^3\,k_{\mathrm{cald}}$[c] (s^{-1})	$t_{\max}$[d] (s)	ΔA_{obs}[e]	MS_1[f] (% v/v)	$10^3 k_{\mathrm{obs}}$ (s^{-1})	$10^3 k_{\mathrm{cald}}$[c] (s^{-1})	$t_{\max}$[d] (s)	ΔA_{obs}[e]
2[g]	88.2 ± 0.6[h]	91.3	90	0.174	10	83.3 ± 0.7[h]	78.7	815	0.070
10	70.5 ± 0.2	63.7	500	0.289	20	48.1 ± 0.3	57.1	1154	0.151
20	37.9 ± 0.1	40.6	1160	0.457	30	44.0 ± 0.2	41.5	1158	0.162
30	25.1 ± 0.1	25.8	1112	0.619	40	29.4 ± 0.1	30.1	1196	0.266
40[i]	14.7 ± 0.1	16.5	787	0.141	50	22.9 ± 0.1	21.9	1196	0.333
50	10.7 ± 0.1	10.5	777	0.180	60	17.1 ± 0.1	15.9	1173	0.384
60	9.72 ± 0.04		790	0.206	70	13.2 ± 0.1	11.5	1162	0.463
70	8.53 ± 0.03		782	0.246	80	9.70 ± 0.07	8.39	1150	0.461
80	12.8 ± 0.0		791	0.244					

[a] $[\mathrm{NMPPT}]_0 = 1 \times 10^{-4}$ M, [NaOH] = 0.002 M, 35°C.

[b] $\mathrm{MS}_1 = H_2O$-CH_3CN.

[c] Calculated from Eq. (3) as described in the text.

[d] Maximum reaction time attained in the kinetic run.

[e] $\Delta A_{\mathrm{obs}} = |A_{\mathrm{obs}}{}^{t(\max)} - A_{\mathrm{obs}}{}^{t(\mathrm{first})}|$ where $A_{\mathrm{obs}}{}^{t(\mathrm{first})}$ and $A_{\mathrm{obs}}{}^{t(\max)}$ represent first and last observed value of A_{obs}, respectively.

[f] $\mathrm{MS}_1 = H_2O$-1,4-dioxan and $\lambda = 285$ nm.

[g] $\lambda = 225$ nm.

[h] Error limits are standard deviations.

[i] $\lambda = 300$ nm.

10–80% v/v, showed good fit to empirical Eq. (4)

$$k_{\text{obs}} = k_0 \exp(-\Psi X) \quad (4)$$

where X represents % v/v content of OS, k_0 and Ψ are empirical constants. The magnitude of Ψ is the measure of the rate-inhibition susceptibility of the mixed aqueous organic solvents. The nonlinear least squares calculated respective values of k_0 and Ψ are $(99.9 \pm 4.4) \times 10^{-3}$ s^{-1} and $(4.51 \pm 0.35) \times 10^{-2}$ $(\%\ v/v)^{-1}$ for OS = CH_3CN and $(108 \pm 3) \times 10^{-3}$ s^{-1} and $(3.20 \pm 0.27) \times 10^{-2}$ $(\%\ v/v)^{-1}$ for OS = 1,4-dioxan. It is interesting to note that the values of k_{obs} at different contents of CH_3CN show a minimum at 70% v/v CH_3CN. Such minima have been observed in the related reactions in mixed aqueous-organic solvents and have been attributed to a variety of factors [2]. The values of k_0 (0.099 s^{-1} and 0.108 s^{-1}) give the average value of second-order rate constant (k_{OH}) for hydroxide ion-catalyzed hydrolysis of NMPPT as 52 M^{-1} s^{-1} which is nearly 2-fold larger than k_{OH} (= 26 M^{-1} s^{-1} at 30°C [9]) for phthalimide.

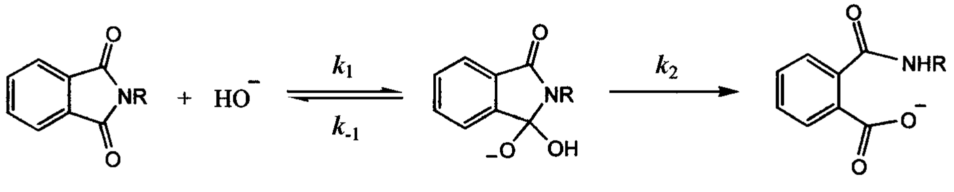
Mixed aqueous-acetonitrile and aqueous-1,4-dioxan solvents are characterized as typically nonaqueous (TNA) and typically aqueous (TA) solution, respectively. These mixed solutions display some different characteristic solution properties [10]. Although it is difficult to assess, even qualitatively, different degree of effects of these solvents on k_{obs} due to different nature of these solvents (TA and TNA), different values of Ψ for water-acetonitrile and water-1,4-dioxan solvents are conceivable. In view of the present and related observations, a probable mechanism for alkaline hydrolysis of N-substituted phthalimides is shown in Scheme 1 where k_1 – step is concluded as the rate-determining step in mixed aqueous solvent containing $\leq$2% v/v acetonitrile [11]. Generally, the change in solvent from pure water to mixed water-organic cosolvent does not change the reaction mechanism of a reaction and present data are not sufficient to determine if there is a mechanistic change with the change in the composition of mixed aqueous-organic solvents.

The nonlinear decrease of k_{obs} values with the increase in the contents of organic cosolvent (acetonitrile or 1,4-dioxan) may be explained qualitatively in terms of the stability of solvated ion-pair (Na^+:HO^-). Nucleophilicity of the reactant hydroxide ion is expected to decrease with the increase in the stability of solvated ion-pair (Na^+:HO^-). The increase of the organic cosolvent (acetonitrile and 1,4-dioxan) decreases the dielectric constant of the reaction medium which in turn increases the stability of solvated ion-pair (Na^+:HO^-) and consequently decreases k_{obs} value. However, at considerably high content of organic cosolvent, because of the insufficient number of water molecules, the organic cosolvent molecules also enter into the salvation shell of the solvated ion-pair (Na^+:HO^-). Since acetonitrile and 1,4-dioxan can preferentially solvate only cations (Na^+), the participation of organic cosolvent molecules into the salvation shell of ion-pair (Na^+:HO^-) is expected to decrease its stability because of the asymmetric structural network of salvation shells of Na^+ and HO^- ions. Thus, under such conditions, the increase in the content of organic cosolvent should increase k_{obs} value.

Nearly 2-fold larger value of k_{OH} for NMPPT than for phthalimide in nearly pure water solvent cannot be explained in terms of polar effect of substituent in leaving group because the value of σ^*_H (= 0.49 [12,13]) is almost similar to $\sigma^*_{4\text{-MeOC6H4}} = 0.52$ [12]. But the values of k_{OH} for a few N-alkyl substituted phthalimides and phthalimide correlate reasonably well with Taft equation (i.e. $\log k_{OH} = \log k_{OH}{}^0 + \rho^*\sigma^*$), with Taft reaction constant $\rho^* = 1.03$ and intercept $\log k_{OH}{}^0 = 1.04$ M^{-1} s^{-1} [14]. It is quite possible that k_{OH} values of N-aryl substituted phthalimides might fit to Hammett equation instead of Taft equation because the resonance interaction between substituent and reaction site in these reactions (especially with 4-substituted aryl groups) cannot be ignored.

Hydrolysis of Phthalic Anhydride (PAn) in Mixed Aqueous-Organic Solvents Containing 0.05 M HCl

It is well established that the acidic hydrolysis of phthalamic and N-substituted phthalamic acids involves PAn as an intermediate [8,15,16]. Thus, in order to



NMPPT, R = 4-MeOC$_6$H$_4$

Scheme 1

Table II Values of k_{obs}, δ_{app}, and A_∞ for Hydrolysis of PAn in Mixed Water-Acetonitrile and Water-1,4-Dioxan[a]

MS_1[b] (% v/v)	$10^5\ k_{obs}$ (s^{-1})	$10^{-4}\ \delta_{app}$ ($M^{-1}\ cm^{-1}$)	A_∞	$10^5\ k_{cald}$[c] (s^{-1})	MS_1[d] (% v/v)	$10^5\ k_{obs}$ (s^{-1})	$10^{-3}\ \delta_{app}$ ($M^{-1}\ cm^{-1}$)	A_∞	$10^5\ k_{cald}$[c] (s^{-1})
2	1717 ± 4[e]	2.39 ± 0.01[e]	0.150 ± 0.000[e]						
10	1280 ± 7	2.51 ± 0.01	0.153 ± 0.001	1300	10	1522 ± 27[e]	1.67 ± 0.01[e]	0.097 ± 0.003[e]	1620
20	776 ± 4	2.50 ± 0.01	0.197 ± 0.001	726	20	1220 ± 36	1.71 ± 0.02	0.106 ± 0.001	1050
30	402 ± 4	2.59 ± 0.01	0.159 ± 0.001	405	30	701 ± 20	1.80 ± 0.02	0.081 ± 0.001	684
40	211 ± 4	2.55 ± 0.02	0.197 ± 0.002	226	40	454 ± 14	1.99 ± 0.02	0.122 ± 0.001	444
50	100 ± 1	2.65 ± 0.01	0.189 ± 0.001	126	50	238 ± 12	2.24 ± 0.04	0.080 ± 0.001	288
60	57.6 ± 0.8	2.57 ± 0.02	0.238 ± 0.001	70.6	60	96.3 ± 2.0	2.31 ± 0.02	0.081 ± 0.001	187
70	25.8 ± 0.2	2.50 ± 0.01	0.253 ± 0.001	39.4	70	37.1 ± 1.0	2.49 ± 0.05	0.097 ± 0.002	121
80	8.60 ± 0.1	2.38 ± 0.01	0.206 ± 0.003	22.0	80	20.7 ± 2.0	1.91 ± 0.07	0.116 ± 0.002	79.0

[a] $[PAn]_0 = 2 \times 10^{-5}$ M, [HCl] = 0.05 M, 35°C.

[b] $MS_1 = H_2O\text{-}CH_3CN$ and $\lambda = 218$ nm.

[c] Calculated from Eq. (4) as described in the text.

[d] $MS_1 = H_2O$-1,4-dioxan and $\lambda = 250$ nm.

[e] Error limits are standard deviations.

ease the complexity of the kinetics of the cleavage of NMPPAH in acidic aqueous-organic solvents, it is desirable to study the rate of hydrolysis of PAn under the reaction conditions in which the rate of cleavage of NMPPAH has been studied. Kinetic runs were carried out within acetonitrile content range of 10–80% v/v in mixed aqueous solvents containing 0.05 M HCl at 35°C. Similar observations were attempted in mixed water-1,4-dioxan solvents. Pseudo first-order rate constants (k_{obs}), calculated from Eq. (1) under these mixed water-organic solvents, are summarized in Table II. These rate constants showed good fit to Eq. (4) and nonlinear least squares calculated values of k_0 and Ψ are $(23.3 \pm 0.8) \times 10^{-3}\ s^{-1}$ and $(5.83 \pm 0.21) \times 10^{-2}$ $(\%\ v/v)^{-1}$ for $H_2O\text{-}CH_3CN$ and $(25.0 \pm 2.3) \times 10^{-3}$ s^{-1} and $(4.32 \pm 0.45) \times 10^{-2}$ $(\%\ v/v)^{-1}$ for H_2O-1,4-dioxan. The values of k_{obs} (Table II) are comparable with the corresponding k_{obs} values obtained by monitoring the absorbance change at 310 nm with $[PAn]_0 =$ 0.002 M [17]. These observations show that the values of k_{obs} for the hydrolysis of PAn in acidic medium are independent of the initial concentrations of PAn and the choice of wavelength for monitoring the rate of reaction. The mechanistic details of the effects of these aqueous-organic mixed solvents on k_{obs} are described elsewhere [17].

Effects of Mixed Acidic H_2O-1,4-Dioxan and $H_2O\text{-}CH_3CN$ Solvents on the Rate of Cleavage of NMPPAH

Acidic aqueous cleavage of a few mono N-substituted phthalamic acids revealed the formation of N-substituted phthalimides (through N-cyclization) as minor products and phthalic anhydride (through O-cyclization) as major product [2,4–6]. In view of these reports, expected reaction paths in the cleavage of NMPPAH at 0.05 M HCl may be shown by Eq. (5)

$$\mathrm{B} \xleftarrow[-\mathrm{H_2O}]{k_1} \mathrm{A} \xrightarrow[\text{-Anis}]{k_1} \mathrm{C} \xrightarrow{k_2} \mathrm{D} \qquad (5)$$

where A, B, C, D, and Anis stand for NMPPAH, NMPPT, phthalic anhydride, phthalic acid, and 4-anisidine, respectively. The values of k_{obs} ($\equiv k_2$) for acidic hydrolysis of C decrease from 128×10^{-4} to $8.6 \times 10^{-5}\ s^{-1}$ and from 152×10^{-4} to $27 \times 10^{-5}\ s^{-1}$ with the increase in the content of CH_3CN and 1,4-dioxan from 10 to 80% v/v (Table II), respectively. But the values of k_1 for a few N-substituted phthalamic acids have been found to be considerably less sensitive to the concentrations of organic cosolvents in mixed acidic aqueous solutions. The values of k_2/k_1 vary from >1 to <1 with increase in the contents of CH_3CN from 2 to 80% v/v in mixed aqueous solvents for a few N-substituted phthalamic acids [8a,18,19]. Thus, it seems unlikely for the rate of cleavage of *A* to obey first-order rate law within the whole range of CH_3CN and 1,4-dioxan content unless $k_2 \gg k_1$ or $\delta_C \approx \delta_D$ where δ represents molar extinction coefficient. If $\delta_C \approx \delta_D = \delta$ then Eq. (5) can lead to Eqs. (1) and (2) with $k_{obs} = k_1 + k_{-1}$, $A_\infty = \{(\delta_D + \delta_{Anis})k_1 + \delta_B k_{-1}\}[X]_0/(k_1 + k_{-1})$, $\delta_{app} = \{(\delta_A - \delta_D - \delta_{Anis})k_1 + (\delta_A - \delta_B)k_{-1}\}/(k_1 + k_{-1})$ or $\delta_{app} = \{(\delta_D + \delta_{Anis} - \delta_A)k_1 + (\delta_B - \delta_A)k_{-1}\}/(k_1 + k_{-1})$ and $A_0 = \delta_A[X]_0$.

The observed data (A_{obs} versus t), obtained at 250 nm in mixed water-1,4-dioxan solvents, obeyed strictly first-order rate law i.e. Eq. (1). The calculated

Table III Values of k_{obs} for Cleavage of NMPPAH in Mixed Water-Acetonitrile and Water-1,4-Dioxan[a]

MS_1[b] (% v/v)	$10^5 k_{1obs}$ (s^{-1})	$10^5 k_{2obs}$ (s^{-1})	MS_1[c] (% v/v)	$10^5 k_{obs}$ (s^{-1})	$10^5 k_{cald}$[d] (s^{-1})	$10^{-3} t_{max}$[e] (s)
10			10	60.4 ± 0.4[f]	60.4	9.80
20			20	36.4 ± 0.1	36.2	10.31
30			30	21.7 ± 0.1	21.7	11.89
40			40	12.7 ± 0.2	13.0	9.65
50	18.8 ± 1.4[f]	136 ± 12[f]	50	7.27 ± 0.07	7.76	154.5
60	15.4 ± 1.1	61.2 ± 4.7	60	4.58 ± 0.05	4.64	154.5
70	8.64 ± 0.20	25.8 ± 0.6	70	3.15 ± 0.04	2.78	154.5
80	8.01 ± 0.08	9.39 ± 0.10	80	2.64 ± 0.06	1.66	154.5

[a] [HCl] = 0.05 M, 35°C.

[b] $MS_1 = H_2O\text{-}CH_3CN$, $[NMPPAH]_0 = 2 \times 10^{-5}$ M and $\lambda = 218$ nm and values of k_{1obs} and k_{2obs} were calculated from Eq. (3).

[c] $MS_1 = H_2O$-1,4-dioxan, $[NMPPAH]_0 = 4 \times 10^{-5}$ M and $\lambda = 250$ nm and values of k_{obs} were calculated from Eq. (1).

[d] Calculated from Eq. (4) with $10^5\ k_0 = 101\ s^{-1}$ and $10^2 \Psi = 5.15\ (\%\ v/v)^{-1}$.

[e] Maximum reaction time attained in the kinetic run.

[f] Error limits are standard deviations.

values of k_{obs} at different contents of 1,4-dioxan are summarized in Table III. These observations predict that either $k_2 \gg k_1$ or $\delta_C \approx \delta_D$ under such conditions. The values of k_2/k_{obs} vary from ~10 to 250 with the decrease in the content of 1,4-dioxan from 80 to 10% v/v in mixed aqueous solvents (Tables II and III). The values of δ_A, δ_B, δ_C, δ_D, and δ_{Anis}, obtained under such conditions as shown in Table IV, show that $\delta_C \approx 2\delta_D$. The values of A_∞, A_0, δ_{app}, δ_A, δ_B, δ_C, δ_D, and δ_{Anis} (Table IV) and relationships: $A_\infty = \{(\delta_D + \delta_{Anis})\ k_1 + \delta_B\ k_{-1}\}[X]_0/(k_1 + k_{-1})$ and $\delta_{app} = \{(\delta_A - \delta_D - \delta_{Anis})k_1 + (\delta_A - \delta_B)k_{-1}\}/(k_1 + k_{-1})$ or $\delta_{app} = \{(\delta_D + \delta_{Anis} - \delta_A)k_1 + (\delta_B - \delta_A)k_{-1}\}/(k_1 + k_{-1})$ showed the absence of NMPPT within 1,4-dioxan range 10–80% v/v. The possibility that imide (NMPPT) formed during the cleavage of NMPPAH might have hydrolyzed back to NMPPAH in a relatively fast step may be ruled out for the following reasons. The value of second-order rate constant (k_{H+}) for acid-catalyzed hydrolysis of phthalimide is $9.83 \times 10^{-5}\ M^{-1}\ s^{-1}$ at 100°C in pure water solvent [20] and this value of k_{H+} may be used to estimate pseudo first-order rate constant (k_{obs})

Table IV Values of A_∞, A_0, δ_{app}, δ_A, δ_B, δ_C, δ_D, and δ_{Anis} for Cleavage of NMPPAH in Mixed Water-Acetonitrile and Water-1,4-Dioxan[a]

MS[b] (% v/v)	A_0 (A_∞)	($10^{-3}\ \delta_{app}$) ($M^{-1}\ cm^{-1}$)	$10^{-3}\ \delta_A$ ($M^{-1}\ cm^{-1}$)	$10^{-4}\ \delta_B$ ($M^{-1}\ cm^{-1}$)	$10^{-3}\ \delta_C$ ($M^{-1}\ cm^{-1}$)	$10^{-3}\ \delta_D$ ($M^{-1}\ cm^{-1}$)	$10^{-3}\ \delta_{Anis}$ ($M^{-1}\ cm^{-1}$)
10	0.265		13.3	4.05	32.7	7.70	8.35
(10)	(0.084)	(8.94)	(11.1)	(1.34)	(4.10)	(2.18)	(0.35)
20	0.300		15.0	4.21	34.8	7.55	10.0
(20)	(0.054)	(9.36)	(10.7)	(1.40)	(4.35)	(2.50)	(0.45)
30	0.292		14.6	4.33	33.9	8.15	8.70
(30)	(0.035)	(9.72)	(10.6)	(1.49)	(3.83)	(2.00)	(0.40)
40	0.377		18.9	4.32	35.3	8.60	9.80
(40)	(0.046)	(10.05)	(11.2)	(1.51)	(5.02)	(2.15)	(0.43)
50	0.296		16.8	4.40	36.0	8.95	10.1
(50)	(0.070)	(9.74)	(11.5)	(1.56)	(4.22)	(2.00)	(0.40)
60	0.292		16.1	4.27	37.6	8.75	9.90
(60)	(0.095)	(9.64)	(12.0)	(1.66)	(4.32)	(2.05)	(0.25)
70	0.279		17.4	4.34	37.6	9.60	10.1
(70)	(0.099)	(8.95)	(11.4)	(1.63)	(4.90)	(2.18)	(0.30)
80	0.297		18.2	4.37	34.1	9.95	11.7
(80)	(0.137)	(9.19)	(12.6)	(1.64)	(4.80)	(2.23)	(0.48)

[a] Parenthesized values stand for H_2O-1,4-dioxan solvent, M [HCl] = 0.05 M, $\lambda = 250$ nm, A = NMPPAH, B = NMPPT, C = phthalic anhydride, D = phthalic acid, Anis = 4-methoxyaniline, and $[A]_0 = [B]_0 = [C]_0 = [D]_0 = [Anis]_0 = 4 \times 10^{-5}$ M.

[b] $MS = H_2O\text{-}CH_3CN$, $\lambda = 218$ nm and $[A]_0 = [B]_0 = [C]_0 = [D]_0 = [Anis]_0 = 2 \times 10^{-5}$ M.

as 1.1×10^{-9} s^{-1} at 0.05 M HCl and 35°C. Thus, it seems that the fraction of NMPPT hydrolyzed within 10–100 h is 4×10^{-5}–4×10^{-4}. The value of $k_{\mathrm{H+}}$ for NMPPT may not be significantly different from that for phthalimide. Thus the observed facts, $k_2/k_{\mathrm{obs}} > 10$, $\delta_{\mathrm{C}} \approx 2\delta_{\mathrm{D}}$, and $k_{-1} \approx 0$, show that $k_{\mathrm{obs}} = k_1$ in view of Eq. (5).

Although the observed data (A_{obs} versus reaction time t) were found to fit to Eq. (1) perfectly despite the fact that $\delta_{\mathrm{C}}/\delta_{\mathrm{D}} \approx 2$ (Table IV), an attempt has been made to fit the observed data at 70 and 80% v/v 1,4-dioxan to Eq. (3) which can be derived from Eq. (5) with $k_{-1} = 0$, $k_{1\mathrm{obs}} = k_1$, $k_{2\mathrm{obs}} = k_2$, $\delta_{1\mathrm{app}} = \delta_{\mathrm{C}} - \delta_{\mathrm{D}}$, $\delta_{2\mathrm{app}} = \delta_{\mathrm{D}} + \delta_{\mathrm{Anis}} - \delta_{\mathrm{A}}$, and $A_0 = \delta_{\mathrm{A}}[\mathrm{X}]_0$. Values of k_1 and A_0 were calculated from Eq. (3) considering $\delta_{1\mathrm{app}}$, $\delta_{2\mathrm{app}}$, and k_2 as known parameters. The values of k_2, $\delta_{1\mathrm{app}}$, and $\delta_{2\mathrm{app}}$ were obtained experimentally from the data summarized in Tables II and IV. The least squares calculated respective values of k_1 and A_0 are $(3.23 \pm 0.01) \times 10^{-5}$ s^{-1} and 0.455 ± 0.001 at 70% v/v and $(2.28 \pm 0.11) \times 10^{-5}$ s^{-1} and 0.502 ± 0.003 at 80% v/v 1,4-dioxan. The calculated values of k_1 and A_0 are almost similar to the corresponding values of k_{obs} and A_0 $(= A_\infty + \delta_{\mathrm{app}}\ [\mathrm{X}]_0)$ calculated from Eq. (1). The residual errors ($= A_{\mathrm{obs\ i}} - A_{\mathrm{cald\ i}}$ where $A_{\mathrm{obs\ i}}$ and $A_{\mathrm{cald\ i}}$ represent respective observed and calculated values of absorbance at the reaction time t_{i}), obtained from the fitting of observed data to Eq. (1) and Eq. (3) are almost same as evident from the values of A_{obs} and A_{calcd} summarized in Table V. These data show that the contribution of $[k_{1\mathrm{obs}}\delta_{1\mathrm{app}}[\mathrm{X}]_0/(k_{2\mathrm{obs}} - k_{1\mathrm{obs}})][\exp(-k_{1\mathrm{obs}}\, t) - \exp(-k_{2\mathrm{obs}} t)]$ is insignificant compared to $\delta_{2\mathrm{app}}[\mathrm{X}]_0 [1 - \exp(-k_{1\mathrm{obs}} t)] + A_0$ in Eq. (3) which is conceivable for the reason that $|\delta_{2\mathrm{app}}|/[k_{1\mathrm{obs}}\delta_{1\mathrm{app}}/(k_{2\mathrm{obs}} - k_{1\mathrm{obs}})] = 35$ and 42 at 70 and 80% v/v 1,4-dioxan, respectively.

Table V Values of k_{obs} for Alkaline Hydrolysis of NMPPT in Mixed Water-1,4-Dioxan[a]

	1,4-Dioxan						
	70% v/v				80% v/v		
Time (s)	A_{obs}	A_{calcd}[b]	A_{calcd}[c]	Time (s)	A_{obs}	A_{calcd}[d]	A_{calcd}[e]
80	0.456	0.455	0.454	60	0.508	0.505	0.502
503	0.451	0.450	0.450	120	0.505	0.505	0.502
1005	0.445	0.445	0.446	180	0.504	0.504	0.501
1541	0.439	0.439	0.441	720	0.496	0.499	0.497
2084	0.434	0.434	0.436	1260	0.490	0.491	0.494
2660	0.427	0.428	0.430	1560	0.488	0.490	0.492
3745	0.417	0.417	0.420	1980	0.485	0.487	0.488
4710	0.408	0.408	0.410	2460	0.479	0.482	0.485
5708	0.398	0.399	0.400	3600	0.471	0.472	0.476
6713	0.389	0.389	0.391	3900	0.468	0.469	0.474
7638	0.381	0.381	0.382	4800	0.461	0.462	0.467
8295	0.375	0.376	0.376	6480	0.448	0.447	0.455
9259	0.367	0.368	0.367	8400	0.433	0.432	0.440
10224	0.361	0.360	0.359	10080	0.419	0.419	0.428
11611	0.351	0.349	0.347	12600	0.400	0.401	0.411
154500	0.100	0.100	0.090	19800	0.363	0.355	0.365
				31080	0.302	0.298	0.306
				38160	0.269	0.271	0.277
				72540	0.185	0.191	0.185
				88140	0.168	0.173	0.161
				99360	0.163	0.164	0.149
				120600	0.153	0.152	0.133
				154500	0.150	0.143	0.119

[a] $[\mathrm{NMPPAH}]_0 = 4 \times 10^{-5}$ M, [HCl] = 0.05 M, 35°C and $\lambda = 250$ nm.

[b] Calculated from Eq. (1) with $10^5\ k_{\mathrm{obs}} = 3.04 \pm 0.02$ s^{-1}, $\delta_{\mathrm{app}} = 8976 \pm 24$ M^{-1} cm^{-1} and $A_\infty = 0.097 \pm 0.001$.

[c] Calculated from Eq. (3) with $\delta_{1\mathrm{app}} = 2720$ M^{-1} cm^{-1}, $\delta_{2\mathrm{app}} = -9190$ M^{-1} cm^{-1}, $10^5\ k_{2\mathrm{obs}} = 37$ s^{-1}, $10^5\ k_{1\mathrm{obs}} = 3.23 \pm 0.01$ s^{-1}, and $A_0 = 0.455 \pm 0.001$.

[d] Calculated from Eq. (1) with $10^5\ k_{\mathrm{obs}} = 2.64 \pm 0.06$ s^{-1}, $\delta_{\mathrm{app}} = 9193 \pm 61$ M^{-1} cm^{-1}, and $A_\infty = 0.137 \pm 0.003$.

[e] Calculated from Eq. (3) with $\delta_{1\mathrm{app}} = 2570$ M^{-1} cm^{-1}, $\delta_{2\mathrm{app}} = -9890$ M^{-1} cm^{-1}, $10^5\ k_{2\mathrm{obs}} = 27$ s^{-1}, $10^5\ k_{1\mathrm{obs}} = 2.28 \pm 0.11$ s^{-1}, and $A_0 = 0.502 \pm 0.003$.

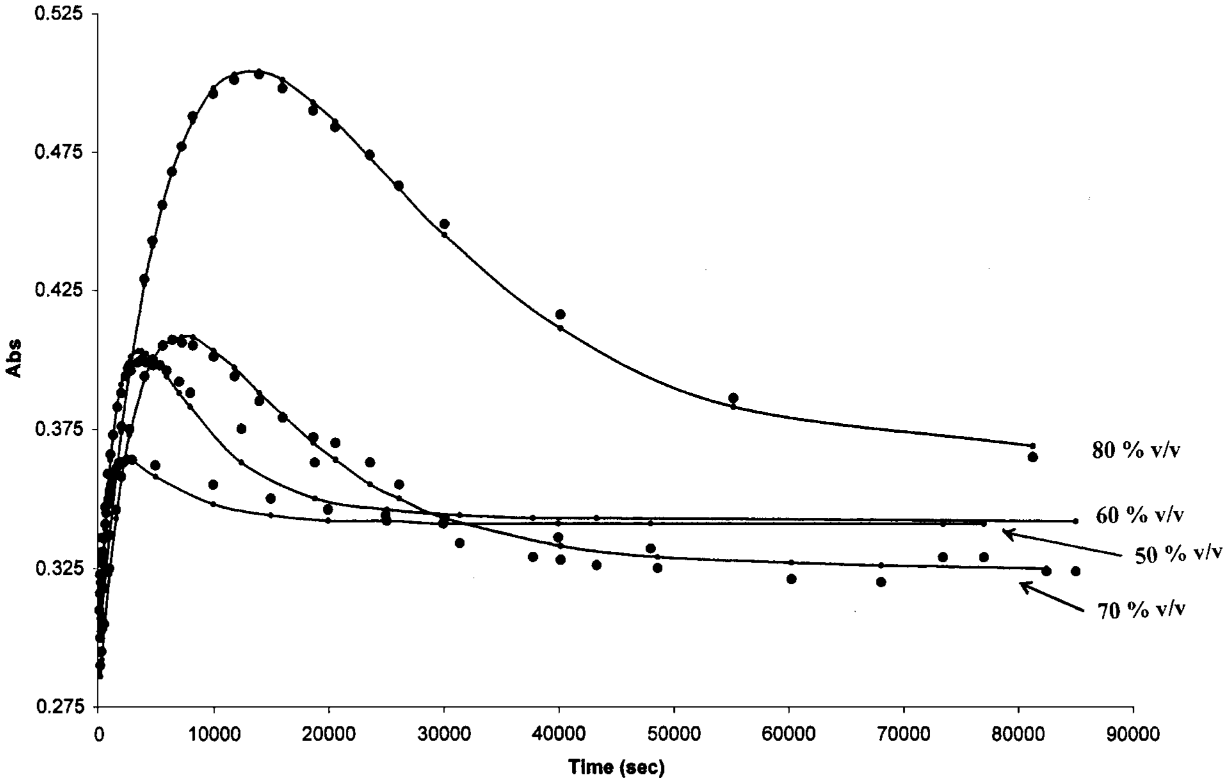
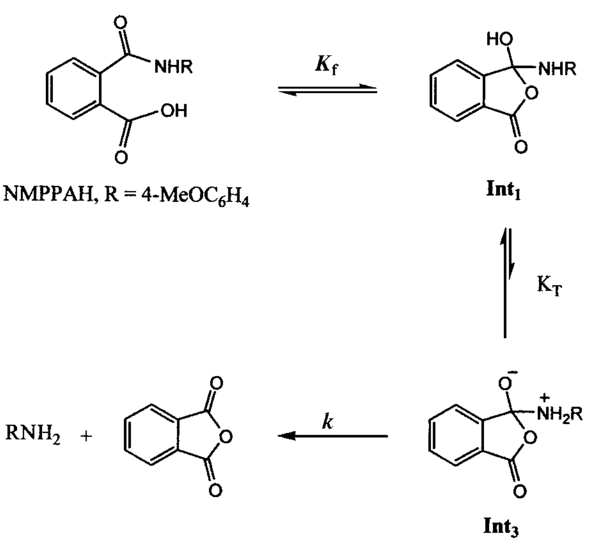


Figure 1 Plots of absorbance (A_{obs}) at 218 nm against reaction time (s) for a mixed aqueous solutions of NMPPAH (2×10^{-5} M) in 50, 60, 70, and 80% v/v CH_3CN, 0.05 M HCl at 35°C. The solid lines are drawn through the calculated data points using Eq. (3) and parameters, $k_{1\text{obs}}$ ($= k_1$), $k_{2\text{obs}}$ ($= k_2$), A_0, $\delta_{1\text{app}}$ ($= \delta_C - \delta_D$) and $\delta_{2\text{app}}$ ($= \delta_D + \delta_{\text{Anis}} - \delta_A$), listed/calculated from data summarized in Tables III and IV.

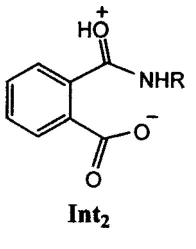
The observed data (A_{obs} versus t), obtained in mixed H_2O-CH_3CN solvent at $\geq 50\%$ v/v CH_3CN and 218 nm, were found to fit to Eq. (3) which can be derived from Eq. (5) with $k_{1\text{obs}} = k_1 + k_{-1}$, $k_{2\text{obs}} = k_2$, $\delta_{1\text{app}} = \delta_C - \delta_D$, $\delta_{2\text{app}} = \{(\delta_D + \delta_{\text{Anis}} - \delta_A)k_1 + (\delta_B - \delta_A)k_{-1}\}/(k_1 + k_{-1})$, and $A_0 = \delta_A[X]_0$. Kinetic runs at 50, 60, 70, and 80% v/v CH_3CN were carried out for reaction periods of ~21–40 h. But the values of A_{obs} remained unchanged within the reaction period of 13–21 h at 50, 12–24 h at 60, 14–23 h at 70, and 23–40 h at 80% v/v CH_3CN (Fig. 1). This shows that these reactions were completed within <23 h. The average values of A_{obs} ($= A_\infty$) within the reaction period of 13–21 h, 12–24 h, 14–23 h, and 23–40 h are 0.330 ± 0.001, 0.326 ± 0.002, 0.323 ± 0.002, and 0.363 ± 0.002 at 50, 60, 70, and 80% v/v CH_3CN, respectively. These values of A_∞ show the presence of D and Anis only under these conditions. The values of δ_B are nearly 2-fold larger than the corresponding values of the sum of δ_{Anis} and δ_D (Table IV). This shows that even the presence of 10% B could have caused significantly larger values of A_∞ compared to observed ones ($A_\infty = 0.323$–0.363) because the fraction of hydrolyzed B within the reaction period of 40 h at 35°C is $\sim 6 \times 10^{-4}$. It is therefore apparent that k_{-1} is negligible compared to k_1 or simply $k_{-1} \approx 0$ under the present experimental conditions and consequently $k_{1\text{obs}} = k_1$, $k_{2\text{obs}} = k_2$, $\delta_{1\text{app}} = \delta_C - \delta_D$, and $\delta_{2\text{app}} = \delta_D + \delta_{\text{Anis}} - \delta_A$. Values of k_1, k_2, and A_0 were calculated from Eq. (3) considering $\delta_{1\text{app}}$ and $\delta_{2\text{app}}$ as known parameters whose values were obtained experimentally (Table IV). The calculated values of k_1 and k_2 are summarized in Table III and those of A_0 are shown in Table IV. The reliability of the fit of the observed data to Eq. (3) is evident from the plots of Fig. 1 where solid lines are drawn through the calculated data points. The values of k_2 may be compared with the corresponding values of k_{obs} obtained in the study on the rate of hydrolysis of PAn (= C) (Table II). However, the calculated values of k_1 and k_2 at 50% v/v CH_3CN may not be considered as very reliable because of considerably low value of ΔA_{obs} (= 0.054, Table III).

The value of k_1 ($= k_{\text{obs}} = 3.64 \times 10^{-4}\ \text{s}^{-1}$, Table III) for O-cyclization of NMPPAH at 20% v/v 1,4-dioxan may be compared with the corresponding value of $3.54 \times 10^{-4}\ \text{s}^{-1}$ estimated from the reported value at 65.8°C [2]. The values of k_1 decrease nonlinearly from 60.4×10^{-5} to 3.15×10^{-5} s^{-1} with the increase in 1,4-dioxan from 10 to 70% v/v. Similar but less pronounced decrease in k_{obs} was obtained in O-cyclization of *N*-phenylphthalamic acid under similar solvent system at 65.8°C [2]. Nearly 20-fold change in k_1 with the change in 1,4-dioxan content from 10 to 70% v/v is very different from ~2- to 3-fold change in k_1 for phthalamic and N-alkyl substituted phthalamic acids [5,17], obtained under almost similar conditions. The values of k_1 at different contents of 1,4-dioxan fit to Eq. (4) and the nonlinear least-squares calculated values of k_0 $(= k_{10})$ and Ψ are $10^5\ k_0 = 101 \pm 1\ s^{-1}$ and $10^2\Psi = 5.13 \pm 0.07\ (\%\ v/v)^{-1}$, respectively.

The effects of mixed aqueous-organic cosolvents on k_1 may be explained qualitatively in terms of conceivable mechanism for O-cyclization of NMPPAH as shown in Scheme 2 where k-step is the rate-determining step. It is well known that such reactions are catalyzed by both specific and general acids in the presence of considerably high concentrations of these acids. But at 0.05 M HCl and in the absence of general acid, these catalyzed reaction paths are ignored in Scheme 2.



Scheme 2



Int$_2$

The value of equilibrium constant, K_f, is expected to decrease with the decrease in the polarity of the solvent, i.e., the increase in the content of organic cosolvent because the formation of neutral reactive intermediate, **Int$_1$**, occurs through a transition state or a more reactive intermediate, **Int$_2$** [2,3], which is more polar than the reactant state. Similarly, the value of K_T should also decrease with the decrease in the content of water in mixed aqueous solvent because **Int$_3$** is more polar than **Int$_1$**. However, the same solvent effect increases the value of k because the transition state in k-step is apparently less polar than the reactant state (**Int$_3$**). Since $k_1 = kK_fK_T$, therefore mixed solvent effect on k_1 depends upon its effect on k, K_f, and K_T.

The values of k_1 at ≥60% v/v CH_3CN are ~3-fold larger than the corresponding k_1 values obtained at ≥60% v/v 1,4-dioxan (Table III). But pseudo first-order rate constants for alkaline hydrolysis of NMPPT, obtained within 30–70% v/v content range of CH_3CN are ~1.5- to 2-fold smaller than the corresponding k_{obs} values for 1,4-dioxan (Table I). Such characteristic effects of mixed H_2O-1,4-dioxan and H_2O-CH_3CN solvents on k_1 for NMPPAH and *N*-alkyl substituted phthalamic acids are interesting but difficult to explain quantitatively. However, a qualitative explanation may be given in terms of different reaction mechanisms (Schemes 1 and 2) as well as typically aqueous (TA) and typically nonaqueous (TNA) nature of mixed water-1,4-dioxan and water-acetonitrile solvent, respectively. The formation of **Int$_2$** from **Int$_1$** (Scheme 2) involves water molecule-mediated 1,3-proton transfer and unlike 1,4-dioxan molecules, acetonitrile molecules breakdown long range three-dimensional structural network of water (a characteristic feature of TNA solutions [10]). Thus, there are more water molecules to mediate 1,3-proton transfer in water-acetonitrile solvent than in water-1,4-dioxan solvent, especially at rather low content of water. Such characteristics of mixed aqueous solvent might cause K_T larger in water-acetonitrile than in water-1,4-dioxan solvent.

The value of k_1 $(\equiv k_{10})$ for NMPPAH $(10^5\ k_{10} = 101\ s^{-1})$ shows rather larger intrinsic reactivity of N-aryl substituted phthalamic acids than that of N-alkyl substituted phthalamic acids because the reported values of k_{10} for *N*-methylphthalamic acid, *N*,*N*-dimethylphthalamic acid, *N*-acetylphthalamic acid, and phthalamic acid are $2.8 \times 10^{-5}\ s^{-1}$ at 37°C [4], $100 \times 10^{-5}\ s^{-1}$ at 35°C [8a], $77 \times 10^{-5}\ s^{-1}$ at 100°C [4], and $9.2 \times 10^{-5}\ s^{-1}$ at 37°C [4], $24 \times 10^{-5}\ s^{-1}$ at 47.2°C [15], $100 \times 10^{-5}\ s^{-1}$ at 48°C [12], respectively, while $\sigma^*_{4\text{-MeOC6H4}} = 0.52$ [12], $\sigma^*_{Me} = 0$ [15], $\sigma^*_{MeCO} = 1.65$ [13], $\sigma^*_H = 0.49$ [12,13] and 0.16 [21]. Similarly, the values of k_1 at 70% v/v CH_3CN $(10^5\ k_1 = 8.64\ s^{-1})$ and 70% 1,4-dioxan $(10^5\ k_1 = 3.15\ s^{-1})$ for NMPPAH are significantly smaller than that for phthalamic acid ($10^5\ k_1 = 20.2\ \mathrm{s}^{-1}$ [8b]). These results may be attributed to the possibility that while the reactivity of N-alkyl substituted phthalamic acids is affected by polar and steric effects, the reactivity of N-aryl substituted phthalamic acids is expected to be influenced by polar and resonance effects.

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