

Articles

Unexpected Rate Retardation in the Formation of Phthalic Anhydride from *N*-Methylphthalamic Acid in Acidic H₂O-CH₃CN Medium

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Received April 18, 2005

Kinetic study on the cleavage of *N*-methylphthalamic acid (NMPA) in mixed acidic aqueous-acetonitrile solvent reveals the formation of both phthalic anhydride (PAn) (through O-cyclization) and *N*-methylphthalimide (NMPT) (through N-cyclization). The formation of NMPT varies from ~20% to ~3% with the increase in the content of acetonitrile from 2 to 70% v/v. Pseudo first-order rate constants for the formation of PAn are more than 4-fold larger than those for the formation of NMPT at 2% v/v CH₃CN in mixed aqueous solvents. Pseudo first-order rate constants for alkaline hydrolysis of NMPT reveal a nonlinear decrease with increase in the content of CH₃CN in mixed aqueous solvents.

Key Words : Phthalic anhydride, Kinetics, Hydrolysis, O-Cyclization and N-cyclization of *N*-methylphthalamic acid

Introduction

Mechanistic studies on the intramolecular carboxylic group-catalyzed cleavage of amide bond in phthalamic acid, its derivatives and related compounds have been the subject of immense interest since the awareness of the fact that these reactions are partial models to many enzyme-mediated reactions.¹⁻⁶ Substituents in the leaving groups of phthalamic and *N*-substituted phthalamic acids resulted in negative values of ρ and ρ^* .⁷⁻¹⁰ Recently, unusual large rate enhancement (based upon reported negative ρ^* value) has been observed in the formation of phthalic anhydride (PAn) from *N*-hydroxyphthalamic acid under acidic mixed CH₃CN-H₂O medium.¹¹

Intramolecular reactivity behavior is a ubiquitous feature of many enzyme-mediated reactions and it is widely believed that these reactions occur in the micro reaction environment of considerably low water activity compared to the water activity of pure water solvent. Thus, the kinetic study on the effects of mixed aqueous-organic co-solvents on the rate of the intramolecular carboxylic group-catalyzed cleavage of amide bond is considered to be of some importance. The rate of hydrolysis of NMPA in pure aqueous acidic medium involves both intramolecular nucleophilic carboxylic group (~80%) and amide group (~20%) participations.¹² We therefore decided to carry out the kinetic study on the rate of cleavage of NMPA in mixed CH₃CN-H₂O solvents. Direct experimental detection of the formation and decay of phthalic anhydride in the hydrolysis of phthalamic acid and NMPA could not be achieved because of the typical experimental conditions.¹² The choice of acetonitrile as an organic co-solvent is merely because of the fact that at high content of acetonitrile in

mixed aqueous solvents, the presence of phthalic anhydride could be detected spectrophotometrically.^{10,11,13} The observed results and probable explanation(s) are described in this paper.

Experimental Section

Materials. *N*-Methylphthalimide (NMPT) was obtained from Aldrich and all other chemicals used were analytical reagents. Stock solutions of NMPT, 0.01 M, 0.02 M and 0.2 M, were prepared in acetonitrile.

Kinetic Measurements. (a) *Hydrolysis of NMPT:* The molar extinction coefficient (E) of NMPT at 300 nm shows a slight change from 2200 to 1900 M⁻¹ cm⁻¹ with change in acetonitrile content from 10 to 80% v/v in mixed aqueous solvents containing 0.001 M NaOH at 30 °C. The E values of alkaline hydrolysis product (anionic *N*-methylphthalamic acid, NMPA) at 300 nm are almost zero under such conditions. Thus, the rate of alkaline hydrolysis of NMPT was conveniently studied spectrophotometrically by monitoring the disappearance of NMPT periodically at 300 nm. Pseudo first-order rate constants (k_{1obs}) for alkaline hydrolysis of NMPT were calculated from eqn. (1)

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

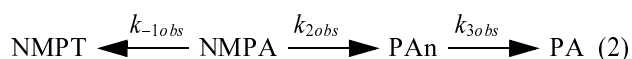
where all the symbols have their usual meanings as described elsewhere.¹⁴ The observed data (A_{obs} versus t) were found to fit to eqn. (1) up to 7-20 half-lives of the reactions.

(b) *Hydrolysis of NMPA:* The E values of NMPT at 300 nm and 310 nm vary from 2200 to 1900 M⁻¹ cm⁻¹ and from 1600 to 860 M⁻¹ cm⁻¹, respectively, with change in acetonitrile content from 10 to 80% v/v in mixed aqueous

solvents containing 0.03 M HCl. Similarly, the E values of PAn at 310 nm vary from 690 to 180 M⁻¹ cm⁻¹ while the E values of phthalic acid at 310 nm are nearly zero under essentially similar conditions.¹⁴ Thus, the rate of aqueous cleavage of NMPTA was conveniently studied spectrophotometrically by monitoring the change in absorbance (A_{obs}) at 310 nm with change in reaction time (t).

In a typical kinetic run with a total volume of 4.8 mL of the reaction mixture containing 1.0 mL of 0.02 M NMPT (in acetonitrile solvent), 0.2 mL of 0.5 M NaOH, 3.0 mL of acetonitrile and 0.6 mL H₂O, the reaction mixture was allowed to complete a reaction period of more than 50 half-lives (*i.e.* nearly 600 s) at 30 °C. The hydrolysis of the hydrolytic product of NMPT, *i.e.* hydrolysis of *N*-methylphthalamic acid (NMPTA), was then initiated by adding 0.2 mL of 1.25 M HCl to the reaction mixture. The resulting reaction mixture, having a total volume of 5.0 mL, contained 4 × 10⁻³ M NMPTA, 0.03 M HCl and 80% v/v CH₃CN. The change in absorbance (A_{obs}) at 310 nm was monitored as a function of reaction time (t) using a diode-array spectrophotometer.

The cleavage of NMPTA in pure aqueous acidic solvent is expected to follow reaction scheme as shown by eqn. (2)



where PAn and PA represent phthalic anhydride and phthalic acid (1,2-benzenedicarboxylic acid), respectively. The reported value of k_{3obs} at 0.005 M HCl and 30 °C is 0.0128 s⁻¹¹⁴ which is more than 500-fold larger than k_{2obs} (= 2.40 × 10⁻⁵ and 2.70 × 10⁻⁵ s⁻¹ at 0.002 and 0.04 M HCl, respectively) obtained at 37 °C.¹² These results show that the concentration of PAn at any time during the course of the reaction is < 0.002[X]₀ (where [X]₀ is the initial concentration of NMPTA and [PAn]_{max}/[X]₀ = $\chi^{\lambda/(1-\lambda)}$ with $\chi = k_{3obs}/k_{2obs}$ and [PAn]_{max} is the maximum concentration of PAn attained in a kinetic run).¹⁰ Thus, under such conditions, [PAn] is negligible compared with [NMPTA], [NMPT] and [PA] during the course of the reaction. Hence, in view of eqn. (2), the absorbance of the reaction mixture (A_{obs}) at 310 nm may be given by eqn. (3)

$$A_{obs} = \frac{k_{-1obs}E_{NMPT}[X]_0}{k_{2obs} + k_{-1obs}} \times [1 - \exp(-(k_{2obs} + k_{-1obs})t)] + A_0 \quad (3)$$

where $E_{NMPT} \gg E_{NMPTA}$, $E_{NMPTA} \approx E_{PA}$ at 310 nm and E stands for molar extinction coefficient. The values of E_{app} [= $k_{-1obs}E_{NMPT}/(k_{2obs} + k_{-1obs})$], k_{obs} (= $k_{2obs} + k_{-1obs}$) and A_0 were calculated from eqn. (3) using the nonlinear least squares technique.

But, at acetonitrile content of ≥ 60% v/v, the observed data (A_{obs} versus t) could not fit to eqn. (3) because under such conditions, [PAn] cannot be ignored compared with [NMPTA], [NMPT] and [PA]. Under such conditions, the observed data were found to fit to eqn. (4)

$$A_{obs} = E_1[X]_0 [1 - \exp(-(k_{2obs} + k_{-1obs})t)] + \frac{k_{2obs}E_2[X]_0}{k_{3obs} - k_{2obs} - k_{-1obs}} \times [\exp(-(k_{2obs} + k_{-1obs})t) - \exp(-k_{3obs}t)] + A_0 \exp(-(k_{2obs} + k_{-1obs})t) \quad (4)$$

where $E_1 = [(E_{NMPT} - E_{PA})k_{-1obs}/(k_{2obs} + k_{-1obs})] + E_{PA}$, $E_2 = E_{PAn} - E_{PA}$, $A_0 = E_{NMPTA}[X]_0$ and k_{-1obs} , k_{2obs} as well as A_0 were considered as unknown parameters and the values of k_{3obs} , E_{NMPT} , E_{PA} (≈ 0) and E_{PAn} were obtained experimentally and from ref 14 under reaction conditions.

Results and Discussion

Effects of Mixed CH₃CN-H₂O Solvent on k_{1obs} for Alkaline Hydrolysis of NMPT. In order to know the time period in which the conversion of NMPT to *N*-methylphthalamate was completed to almost 100% under mixed CH₃CN-H₂O solvents containing 0.001 M NaOH, a few kinetic runs were carried out within the acetonitrile content range of 10-80% v/v at 30 °C in mixed aqueous solvents. The observed data (A_{obs} versus t) were found to fit to eqn. (1) and the least squares calculated kinetic parameters, k_{1obs} , E_{app} and A_{∞} , at different contents of acetonitrile are summarized in Table 1. There seems to be no perfect theory which could be used to analyze quantitatively the effects of pure as well mixed aqueous-organic solvents on rates of organic reactions. However, empirical treatment of such data is often useful, at least, in predicting the values of dependent variable (*i. e.* rate constants) at different contents of organic co-solvents (independent variable). The values of k_{1obs} were found to fit reasonably well to the empirical eqn. (5)

$$k_{1obs} = k_1^0 \exp(-\Psi X) \quad (5)$$

where k_1^0 and Ψ are empirical constants and X represents % v/v content of acetonitrile co-solvent in mixed aqueous solvents. The least squares calculated values of k_1^0 and Ψ are

Table 1. Effect of [CH₃CN] on k_{1obs} , E_{app} and A_{∞} calculated from eqn. (1), for the cleavage of NMPT in an alkaline medium^a

[CH ₃ CN] %, v/v	10 ³ k_{1obs} s ⁻¹	E_{app} M ⁻¹ cm ⁻¹	A_{∞}	t^b s	10 ³ k_{1calc}^c s ⁻¹
10	16.2 ± 0.3 ^d	2102 ± 17 ^d	0.016 ± 0.002 ^d	868	16.8
20	14.8 ± 0.3	2027 ± 16	0.003 ± 0.002	868	13.2
30	9.29 ± 0.17	1978 ± 13	0.008 ± 0.002	854	10.3
40	7.73 ± 0.13	1911 ± 9	-0.004 ± 0.002	528	8.09
50	6.40 ± 0.24	1847 ± 22	0.006 ± 0.004	843	6.35
60	5.05 ± 0.16	1753 ± 20	0.014 ± 0.003	1973	4.98
70	4.13 ± 0.10	1571 ± 24	0.062 ± 0.004	1973	3.90
80	5.08 ± 0.24	1533 ± 26	0.073 ± 0.003	1973	-

^a[NMPT]₀ = 2 × 10⁻⁴ M, [NaOH] = 0.001 M, mixed H₂O-CH₃CN solvent, 30 °C, λ = 300 nm. ^bMaximum reaction time attained in the kinetic run. ^cCalculated from eqn. (5) with $k_1^0 = 21.4 \times 10^{-3}$ s⁻¹ and $\Psi = 2.43 \times 10^{-2}$ (% v/v)⁻¹. ^dError limits are standard deviations.

Table 2. Effect of [CH₃CN] on k_{obs} , k_{-1obs} , k_{2obs} , k_{3obs} and E_{app} , calculated from eqns. (3) and (4), for the cleavage of NMPA in an acidic medium^a

[CH ₃ CN] %, v/v	[HCl] M	$10^6 k_{obs}$ s ⁻¹	E_{app} M ⁻¹ cm ⁻¹	A_0	$10^6 k_{-1obs}$ s ⁻¹	$10^5 k_{2obs}$ s ⁻¹	$10^5 k_{3obs}^b$ s ⁻¹	A_{fin}^c	t^d h	E_{Pan}^e M ⁻¹ cm ⁻¹
2	0.01	10.4 ± 0.6 ^{f,g}	315 ± 14 ^{f,g}	0.058 ± 0.00 ^{f,g}	2.18 ^h	0.822 ⁱ	1280	0.523	12.2	
2	0.03	8.99 ± 0.24	368 ± 8	0.062 ± 0.001	2.16	0.683		0.597	13.9	
2	0.08	8.61 ± 0.16	402 ± 6	0.046 ± 0.000	2.32	0.629		0.547	12.1	
2	0.18	9.91 ± 0.21	393 ± 7	0.017 ± 0.000	2.58	0.733		0.572	12.2	
10	0.03	11.4 ± 0.1	252 ± 2	0.015 ± 0.000	1.82	0.956	1030	0.453	13.9	
20	0.03	13.2 ± 0.4	166 ± 4	0.023 ± 0.001	1.45	1.18	637	0.339	13.5	
30	0.03	18.1 ± 0.7	103 ± 2	0.028 ± 0.001	1.30	1.68	328	0.343	23	
40	0.03	16.6 ± 0.2	69 ± 0.4	0.038 ± 0.001	0.88	1.61	162	0.312	206	
50	0.03	29.7 ± 3.7	46 ± 3	0.033 ± 0.011	1.10	2.86	90.5	0.231	326	
60	0.03			0.007 ± 0.0 ^{f,j}	1.08 ± 0.05 ^{f,j}	3.48 ± 0.03 ^{f,j}	38.8	0.124	12.5	254
60	0.03			0.013 ± 0.003	1.23 ± 0.01	3.47 ± 0.11	38.8	0.145	30.8	254
70	0.03			0.013 ± 0.001	1.08 ± 0.01	3.29 ± 0.04	16.3	0.154	12.6	217
70	0.03			0.006 ± 0.005	1.16 ± 0.02	3.88 ± 0.14	16.3	0.114	30.8	217
80	0.03			0.014 ± 0.001	1.93 ± 0.02	4.06 ± 0.03	6.1	0.246	13.8	171
80	0.03			0.002 ± 0.011	2.21 ± 0.08	4.91 ± 0.24	6.1	0.138	30.8	171

^a[NMPT]₀ = 4 × 10⁻³ M, mixed H₂O-CH₃CN solvent, 30 °C, λ = 310 nm. ^bPseudo-first-order rate constants, k_{obs} , for hydrolysis of phthalic anhydride at 0.005 M HCl, and 30 °C (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 M in aqueous solvents containing 2% CH₃CN).¹⁴ ^cThese values represent A_{obs} at maximum reaction time attained in the kinetic run. ^dMaximum reaction time attained in the kinetic run. ^eMolar extinction coefficient of PAN.¹⁴ ^fError limits are standard deviations. ^gCalculated from eqn. (3) where $k_{-1obs} + k_{2obs} = k_{obs}$ and $k_{-1obs}E_{NMPT}/(k_{-1obs} + k_{2obs}) = E_{app}$. ^h $k_{-1obs} = k_{obs}F_{NMPT}$ with F_{NMPT} values summarized in Table 3. ⁱ $k_{2obs} = k_{obs} - k_{-1obs}$. ^jCalculated from eqn. (4) with $E_{PA} = 0$.¹⁴

(21.4 ± 0.14) × 10⁻³ s⁻¹ and (2.43 ± 0.22) × 10⁻² (% v/v)⁻¹, respectively. The value of k_1^0 (= k_{1obs} at [CH₃CN] = 0) gives second-order rate constant, k_{1OH} (= $k_1^0/[NaOH]$), as 21.4 M⁻¹ s⁻¹ which may be compared with the value of k_{1OH} (= 20.2 M⁻¹ s⁻¹ at 30 °C) derived from the reported data at 37 °C¹² and the calculated value of k_{1OH} (= 11.0 M⁻¹ s⁻¹) by the use of Taft plot of slope ($\rho^* = 1.03$) and intercept log $k_{OH}^{CH_3}$ (= 1.04 M⁻¹ s⁻¹) obtained for phthalimide and *N*-substituted phthalimides.¹⁵

A few kinetic runs were carried out at 30 °C, a constant ionic strength (0.2 M by NaCl) as well as a constant content of CH₃CN and different concentrations of NaOH. Pseudo first-order rate constants, k_{1obs} , were found to fit to the relationship: $k_{1obs} = k_2[HO^-]$ where k_2 represents second-order rate constant for the reaction of HO⁻ with NMPT. The calculated values of k_{1OH} are 23.0 ± 0.7 M⁻¹ s⁻¹ and 7.1 ± 0.8 M⁻¹ s⁻¹ at 10 and 50% v/v CH₃CN, respectively. An attempt was also made to fit the observed data to the relationship: $k_{1obs} = k_0 + k_{1OH}[HO^-]$ and the least squares calculated respective values of k_0 and k_{1OH} turned out to be (-3.8 ± 2.1) × 10⁻³ s⁻¹ and 24.8 ± 0.9 M⁻¹ s⁻¹ at 10% v/v CH₃CN and (-5.4 ± 1.0) × 10⁻³ s⁻¹ and 9.6 ± 0.4 M⁻¹ s⁻¹ at 50% v/v CH₃CN. The negative values of k_0 at both 10 and 50% v/v CH₃CN are physically/chemically meaningless and consequently k_0 values may be considered as negligible compared with $k_{1OH}[HO^-]$ within the experimental conditions of the study. These observations show that the change in the content of CH₃CN in mixed aqueous solvent does not change the order of hydrolytic reaction of NMPT.

Effects of Mixed CH₃CN-H₂O Solvent on k_{-1obs} , k_{2obs} and k_{3obs} for the Cleavage of NMPA in Acidic Medium.

Effects of mixed CH₃CN-H₂O solvents on the rate of cleavage of NMPA at 0.03 M HCl and 30 °C were studied by carrying out a few kinetic runs at varying acetonitrile content ranging from 2 to 80% v/v in mixed aqueous solvents. The observed data (A_{obs} versus t) were used to calculate $k_{-1obs} + k_{2obs}$ (= k_{obs}), $k_{-1obs}E_{NMPT}/[k_{2obs} + k_{-1obs}]$ (= E_{app}) and A_0 from eqn. (3) at ≤ 50% v/v CH₃CN. These results are summarized in Table 2.

A skeptic might argue that the fitting of observed data to eqn. (3) does not show the intermediacy of PAN and hence PA could be formed directly from NMPA. However, this perception may be ruled out for the fact that the values of first-order rate constant (k_{obs}) for the hydrolytic conversion of NMPA to PA must be much more smaller than k_{obs} for hydrolysis of NMPT under similar experimental conditions because of ring strain and better leaving ability of leaving group in the hydrolysis of NMPT. The estimated value of k_{obs} for hydrolysis of NMPT is ~3 × 10⁻¹⁰ s⁻¹ at 0.03 M HCl and 30 °C. The value of k_{obs} obtained for hydrolysis of NMPA, is 6.83 × 10⁻⁶ s⁻¹ at 0.03 M HCl and 30 °C (Table 2 where $k_{obs} = k_{2obs}$). Thus, more than 10⁴-fold larger value of k_{obs} for hydrolysis of NMPA compared to k_{obs} for hydrolysis of say C₆H₅CONHMe or 4-COOHC₆H₄CONHMe rules out the direct hydrolytic conversion of NMPA to PA.

The observed data, obtained at > 50% v/v CH₃CN, were found to fit to eqn. (4) and the nonlinear least squares calculated values of k_{-1obs} , k_{2obs} and A_0 are shown in Table 2. A few kinetic runs were also performed at 2% v/v CH₃CN to find out the effect of [HCl] on k_{-1obs} and k_{2obs} . These results are also shown in Table 2. The reaction for most of the kinetic runs was allowed to progress for 326 h. The reliability

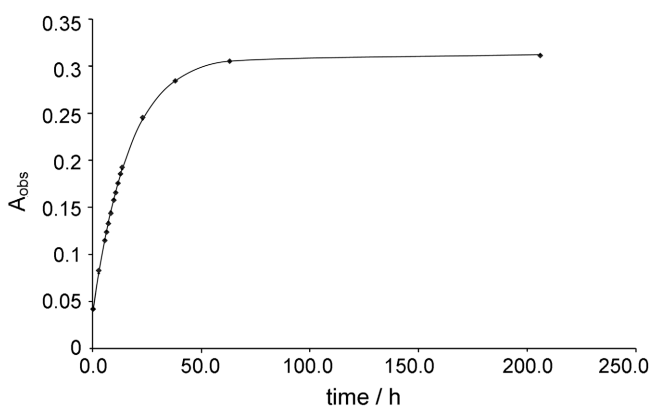


Figure 1. Plot of absorbance (A_{obs}) at 310 nm against reaction time (in h) for a mixed aqueous solution of NMPA (4×10^{-3} M) in 40% v/v CH_3CN , 0.03 M HCl at 30 °C. The solid line is drawn through the calculated data points using eqn. (3) and parameters listed in Table 2.

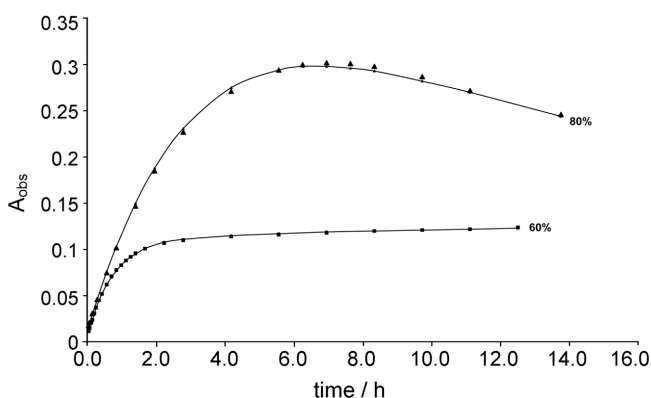


Figure 2. Plots of absorbance (A_{obs}) at 310 nm against reaction time (in h) for mixed aqueous solutions of NMPA (4×10^{-3} M) in 60 and 80% v/v CH_3CN , 0.03 M HCl at 30 °C. The solid lines are drawn through the calculated data points using eqn. (4) and parameters listed in Table 2.

of the fit of observed data to eqns. (3) and (4) is evident from some typical plots of Figure 1 and Figure 2, respectively, where solid lines are drawn through the calculated data points.

The value of second-order rate constant (k_{H^+}) for acid-catalyzed hydrolysis of phthalimide is $9.83 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$ at 100 °C in pure water solvent¹⁶ and this value of k_{H^+} is used to estimate pseudo first-order rate constant, k_{obs} , as $3 \times 10^{-10} \text{ s}^{-1}$ for hydrolysis of phthalimide at 0.03 M HCl and 30 °C. The value of k_{OH} ($= 26 \text{ M}^{-1} \text{ s}^{-1}$)¹⁵ for alkaline hydrolysis of phthalimide is not significantly different from k_{OH} ($= 21 \text{ M}^{-1} \text{ s}^{-1}$) for NMPT obtained under similar kinetic conditions. Linear Taft plot obtained for alkaline hydrolysis of phthalimide and N-alkyl substituted phthalimides shows the occurrence of same mechanism in the alkaline hydrolysis of these imides.¹⁵ It is highly unlikely that acidic hydrolysis of phthalimide and NMPT will involve different reaction mechanisms. Thus, it seems conceivable to assume that the value of k_{obs} for hydrolysis of NMPT at 30 °C and 0.03 M HCl should be nearly 10^{-10} s^{-1} . An attempt was made to

determine pseudo first-order rate constants, k_{obs} , for hydrolysis of NMPT at 0.03 M HCl, 30 °C and varying content of acetonitrile (10-80% v/v) in mixed aqueous solvents. But the observed absorbance, A_{obs} , at 300 and 310 nm remained unchanged for a reaction period of 836 h. Nearly 0.010 absorbance change is expected with 1% progress of the reaction and even 0.010 absorbance change was not observed at acetonitrile content of $\geq 20\%$ v/v. However, absorbance change ($= 0.028$) corresponding to $\sim 2.5\%$ progress of the reaction within the reaction period of 836 h was noticed at 10% v/v acetonitrile. The value of k_{obs} , calculated based upon 2.5% completion of the reaction within the reaction period of 836 h, is $8 \times 10^{-9} \text{ s}^{-1}$ and hence the values of k_{obs} at $\geq 20\%$ v/v acetonitrile are much smaller than $8 \times 10^{-9} \text{ s}^{-1}$. The value of k_{obs} of the order of 10^{-9} s^{-1} at 10% v/v acetonitrile may be comparable with estimated (from k_{obs} obtained at 100 °C in nearly pure aqueous solvent for phthalimide) value of 10^{-10} s^{-1} within the domain of the uncertainties involved in the estimation of rate constant and execution of kinetic runs for such extremely slow reactions.

The values of A_{obs} at 310 nm remained almost unchanged with the change in reaction time (t) from ~ 100 h to 326 h within the acetonitrile content range of 10-50% v/v (Figure 1). These observations show that the formation of NMPT from NMPA was completed at $t \leq 100$ h at different contents of acetonitrile ranging from 10 to 70% v/v in mixed aqueous solvents. The reaction time of 100 h corresponds to ~ 6 - and ~ 34 -half-lives for the disappearance of NMPA (*i.e.* k_{-1} and k_{-2} -steps) and appearance of PA (*i.e.* k_{3} -step), respectively, in eqn. (2). The values of k_{2obs} and k_{3obs} show that $k_{3obs}/k_{2obs} \geq 5$ at $\leq 70\%$ v/v CH_3CN . Thus, the constant values of A_{obs} , obtained at $t > 100$ h is due to the presence of NMPT only. It may be noted that the expected value of k_{obs} ($\approx 10^{-10} \text{ s}^{-1}$) for hydrolysis of NMPT at 0.03 M HCl is nearly 10^4 -fold slower than k_{-1obs} . The fraction of NMPT, F_{NMPT} , ($= [\text{NMPT}]/[X]_0$ with $[X]_0 = 0.004 \text{ M}$), formed at $t = 100$ -326 h, were calculated from the relationship: $F_{NMPT} = A_{obs}$ (at $t = 100$ -326 h)/ $(E_{NMPT}[X]_0)$ and these results are summarized in Table 3. These values of F_{NMPT} are regarded as the spectrophotometrically characterized values of the fraction of product NMPT in the acidic aqueous cleavage of NMPA. It is evident from eqn. (3) that $F_{NMPT} = E_{app}/E_{NMPT} = k_{-1obs}/(k_{2obs} + k_{-1obs})$. The values of F_{NMPT} were also calculated from this relationship for those kinetic runs which followed eqn. (3) and these calculated values of F_{NMPT} are also summarized in Table 3 which are comparable with the corresponding F_{NMPT} values calculated from the relationship: $F_{NMPT} = A_{obs}$ (at $t = 100$ -326 h)/ $(E_{NMPT}[X]_0)$. The values of F_{NMPT} ($= 0.21$ - 0.27) at 2% v/v CH_3CN may be compared with the reported value of F_{NMPT} ($= 0.20$)¹² obtained under essentially similar experimental conditions.

The relationships: $F_{NMPT} = k_{-1obs}/(k_{2obs} + k_{-1obs})$ and $k_{obs} = k_{2obs} + k_{-1obs}$, where k_{obs} was calculated from eqn. (3) were used to calculate k_{-1obs} and k_{2obs} using the calculated values of F_{NMPT} and k_{obs} (Tables 2 and 3) as described earlier. These results are summarized in Table 3. The calculated values of k_{-1obs} ($= 2.2 \times 10^{-6}$ - $2.6 \times 10^{-6} \text{ s}^{-1}$) and k_{2obs} ($= 6.8 \times 10^{-6}$ -

Table 3. Values of E_{NMPT} , A_0 , A_∞ , F_{NMPT} , k_{-1obs} and k_{2obs} at different contents of CH_3CN^a

$[\text{CH}_3\text{CN}]$ %, v/v	$[\text{HCl}]$	E_{NMPT}^b $\text{M}^{-1} \text{cm}^{-1}$	E_{NMPT}^c $\text{M}^{-1} \text{cm}^{-1}$	A_0^d	A_∞^e	F_{NMPT}^f
2	0.01					0.21
2	0.03	1508	1984			0.24
2	0.08					0.27
2	0.18					0.26
10	0.03	1622	2162	0.043	1.045 ± 0.005^g	0.16 (0.16)
20	0.03	1558	2168	0.037	0.671 ± 0.003	0.11 (0.11)
30	0.03	1436	2108	0.032	0.445 ± 0.008	0.072 (0.077)
40	0.03	1308	2082	0.045	0.310 ± 0.009	0.052 (0.059)
50	0.03	1266	2120	0.046	0.219 ± 0.006	0.037 (0.043)
60	0.03	1042	1912	0.045	0.163 ± 0.004	(0.039) 0.041 ^h
70	0.03	986	1912	0.047	0.140 ± 0.003	(0.035) 0.033 ^h
80	0.03	864	1850			0.045 ^h

^a $[\text{NMPT}]_0 = 4 \times 10^{-3} \text{ M}$, $[\text{HCl}] = 0.03 \text{ M}$, mixed $\text{H}_2\text{O}-\text{CH}_3\text{CN}$ solvent, 30°C , $\lambda = 310 \text{ nm}$. ^bMolar extinction coefficient of NMPT at 310 nm. ^cMolar extinction coefficient of NMPT at 300 nm. ^d $A_0 = A_{obs}$ at reaction time $t = 0$. ^e A_∞ = average value of A_{obs} obtained within $t = 99\text{-}326 \text{ h}$. ^f $F_{NMPT} = E_{app}/E_{NMPT}$ where E_{app} values are summarized in Table 2. Parenthesized values were obtained from the relationship: $F_{NMPT} = A_\infty/(E_{NMPT} [\text{NMPT}]_0)$. ^gError limits are standard deviations. ^h $F_{NMPT} = k_{-1obs}/(k_{-1obs} + k_{2obs})$ with k_{-1obs} and k_{2obs} values summarized in Table 2.

$8.2 \times 10^{-6} \text{ s}^{-1}$) at 2% v/v CH_3CN and different $[\text{HCl}]$ are not very different from the corresponding values of rate constants ($10^6 k_{-1obs} = 2.1\text{-}2.5 \text{ s}^{-1}$ and $10^6 k_{2obs} = 11 \text{ s}^{-1}$ at 30°C) estimated from the reported values at 37°C .¹² The values of k_{-1obs} show a modest decrease with increase in the content of acetonitrile from 2-70% v/v. But the values of k_{2obs} show a nonlinear increase with increase in the content of acetonitrile from 2-70% v/v. Similar observations were obtained in the related O-cyclization reaction.¹⁰

The mean values of k_{-1obs} and k_{2obs} , calculated from eqn. (4), vary from $1.15 \times 10^{-6}\text{-}2.07 \times 10^{-6} \text{ s}^{-1}$ and $3.48 \times 10^{-5}\text{-}4.49 \times 10^{-5} \text{ s}^{-1}$, respectively, with the change in the content of acetonitrile from 60 to 80% v/v (Table 2). The kinetic runs at 60, 70 and 80% v/v CH_3CN were also repeated with larger reaction time range but the repeat kinetic runs gave almost same values of k_{-1obs} and k_{2obs} as shown in Table 2.

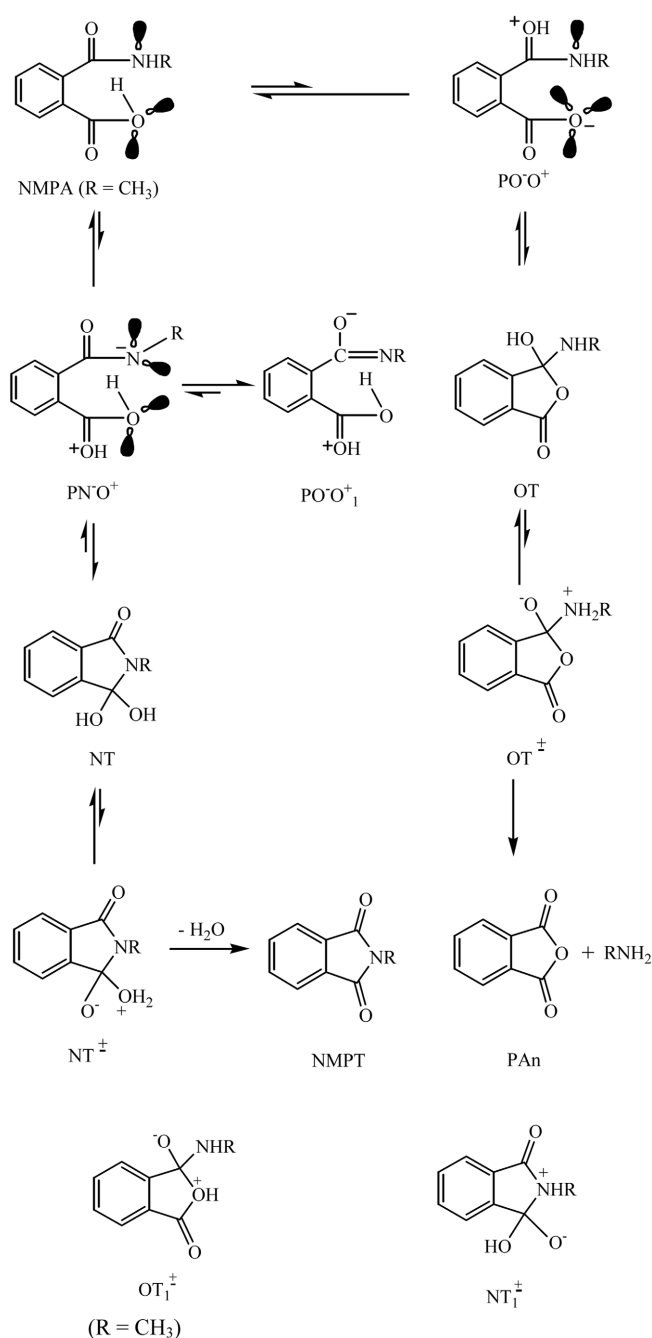
It is interesting to note that the plot of Figure 2 at 60% v/v CH_3CN shows an apparent perfect monotonic change in A_{obs} with reaction time t . Such plots are generally the characteristic features of reactions involving only one rate-determining step. Thus, the observed data (A_{obs} versus t) at 60% v/v CH_3CN were also tried to fit to eqn. (3) and the calculated values of k_{obs} , E_{app} and A_0 are $(31.3 \pm 1.6) \times 10^{-5}$ [$(21.4 \pm 1.5) \times 10^{-5}$] s^{-1} , 27.1 ± 0.6 [26.5 ± 1.1] $\text{M}^{-1} \text{cm}^{-1}$ and 0.010 ± 0.002 [0.030 ± 0.005], respectively, where bracketed values stand for the repeat run. The fitting of observed data to eqn. (3) may be considered to be satisfactory in terms of residual errors, RE ($= (A_{obsi} - A_{cali})/A_{obsi}$, where A_{cali} represents calculated absorbance at i th reaction time t). But the values of k_{obs} and E_{app} produced k_{-1obs} and k_{2obs} as 8.1×10^{-6} [5.4×10^{-6}] s^{-1} and 30.5×10^{-5} [20.9×10^{-5}] s^{-1} , respectively, where the values of both k_{-1obs} k_{2obs} are abnormally high compared to the corresponding values at 50% v/v CH_3CN . Thus, the fitting of observed data at 60% v/v CH_3CN to eqn. (4) is considered to be more satisfactory.

The increase in the content of CH_3CN from 2 to 80% v/v caused nearly 2- and 4-fold changes in k_{-1obs} and k_{2obs} ,

respectively, while under such conditions, k_{3obs} changed nearly 200-fold. Mild changes in k_{-1obs} and k_{2obs} with change in CH_3CN content from 2 to 80% v/v may be attributed to the general feature of the intramolecular nucleophilic addition-elimination reactions involving neutral nucleophilic sites. Similar observations were obtained in the cleavages of *N,N*-dimethylphthalamic acid,¹⁰ *N*-hydroxyphthalamic acid¹¹ and *N*-methoxyphthalamic acid.¹⁷

The probable reasons for the observed values of $k_{2obs}/k_{-1obs} \geq 4$ may be described qualitatively in terms of the suggested mechanisms for present and related O-cyclization reaction¹⁻¹² and N-cyclization reaction¹² in pure aqueous solvent as shown in Scheme 1. It is known that the rate of O-cyclization reactions in the present¹² and related reactions^{4,5,7-9} is catalyzed by hydronium ion, but such catalysis is not included in Scheme 1 simply because, under the present experimental conditions (*i.e.* at 0.03 M HCl), the rate of hydronium ion-catalyzed reaction is negligible compared with non-catalyzed reaction.⁸ The increase in $[\text{HCl}]$ from 0.01 to 0.18 M caused insignificant change in k_{-1obs} and k_{2obs} at 2% v/v CH_3CN (Table 3). The formation of OT and NT through respective reactive intermediates OT^\ddagger and NT^\ddagger may be ruled out for the reason that both OT^\ddagger and NT^\ddagger might exist for less than 10^{-13} s and hence they may not be considered as intermediates on the reaction paths.^{18,19}

Based upon the expected acidity-basicity of the basic-acidic groups, the relative stability of the suggested highly reactive intermediates in Scheme 1 varies in the order $\text{PO}^-\text{O}^+ > \text{PN}^-\text{O}^+$; $\text{PO}^-\text{O}^\ddagger > \text{PN}^-\text{O}^\ddagger$; $\text{NT} > \text{OT}$ and $\text{OT}^\ddagger > \text{NT}^\ddagger$. This pattern of relative stability of these reactive intermediates and the fact that $\text{PO}^-\text{O}^\ddagger$ cannot lead to N-cyclization product predict larger rate of O-cyclization than that of N-cyclization. The other reason may be related to the fact that the intramolecular nucleophilic attack to form OT from PO^-O^+ and NT from PN^-O^+ require the molecular orbital containing lone pair of electrons be aligned in the plane perpendicular to the plane containing C-O σ -bond of



carbonyl group where carbon atom acts as the electrophilic site. Oxygen nucleophile (*i.e.* O-cyclization) contains two orbitals with lone pair of electrons while nitrogen nucleophile (*i.e.* N-cyclization) contains only one orbital with lone pair of electrons. Thus, the probability of proper orbital alignment in the transition state for the formation of OT is higher than that of NT (Scheme 1) and consequently the rate of formation of PAn is higher than that of NMPT.

The values of k_{2obs} at different contents of CH₃CN in mixed aqueous solvents are more than 5-fold and 100-fold smaller than the corresponding values of k_{2obs} for phthalamic acid^{10b} and *N,N*-dimethylphthalamic acid,^{10a} respectively. However, the value of k_{2obs} for NMPA is almost similar to

k_{2obs} for *N*-(*o*-carboxybenzoyl)glycine^{10b} and nearly 25-fold smaller than k_{2obs} for *N*-phenylphthalamic acid,^{8,20} obtained under almost similar experimental conditions. These observations are difficult to explain in terms of only polar effects because $\sigma_{Me}^* = 0$, $\sigma_H^* = 0.49$, $\sigma_{Ph}^* = 0.6$ and $\sigma_{CH_2COOMe}^* = 0.7$.²¹ A decrease in the rate upon *N*-methylation is often observed in related cyclization and is attributed to an increase of steric strain in the tetrahedral intermediates.²² But this argument cannot explain easily more than 100-fold larger reactivity of *N,N*-dimethylphthalamic acid compared to that of NMPA.

The occurrence of N-cyclization compared to O-cyclization in the cleavage of phthalamic acid, *N*-substituted phthalamic acids and related compounds under acidic mixed aqueous-organic solvents is generally insignificant or undetectable.^{5-9,23} Literature search reveals that the cleavage of *N*-phenylphthalamic acid produced 20% and 0% *N*-phenylphthalimide in mixed aqueous solvent containing 80% v/v 1,4-dioxan⁷ and 4% v/v CH₃CN²⁰ as well as 20% v/v 1,4-dioxan,⁷ respectively. Similarly, 4'-nitrophenylphthalamic acid produced detectable and undetectable amount of 4'-nitrophenylphthalimide in mixed aqueous solvents containing 20% v/v 1,4-dioxan⁷ and 4% v/v CH₃CN,²⁰ respectively. These results led Granados and de Rossi²⁰ to conclude that pH and co-solvent concentration are important factors which determine the competition between imide and anhydride formation. However, present study shows that the fraction of imide formation decreases non-linearly from 0.24 to ~0.04 with the increase in the content of CH₃CN from 2 to 80% v/v in mixed aqueous solvents (Table 3). In the aqueous cleavage of *N*-(*o*-carboxybenzoyl)-L-leucine, ~ < 10% imide formation is reported at [HCl] < 1.0 M and 50 °C.²⁴ Perry reported the formation of *N*-(2'-aminophenyl)phthalimide (between ~80 to ~100% yields) in the cleavage of *N*-(2'-aminophenyl)phthalamic acid under dilute aqueous acids in the pH range 0-6.²⁵ Recently, Wu and co-workers studied modeling the reaction mechanisms of the imide formation in an *N*-(*o*-carboxybenzoyl)-L-amino acid.²⁶ It might be worth to mention that the imide formation could be detected only in those reactions where rates of anhydride formation became unexpectedly (based upon Hammett or Taft plot) slow for correct reason(s) unknown yet, at least, to us.

Acknowledgements. We wish to thank MOSTI for financial support under IRPA (Grant No. 09-02-03-0147).

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