Effects of CH_3OH-H_2O and CH_3OH Solvents on Rate of Reaction of Phthalimide with Piperidine

M. NIYAZ KHAN

Department of Chemistry, Faculty of Science, Universiti Malaya, 50603 Kuala Lumpur, Malaysia

Received 12 January 2000; accepted 7 July 2000

ABSTRACT: Pseudo-first-order rate constants (k_{obs}) for the cleavage of phthalimide in the presence of piperidine (Pip) vary linearly with the total concentration of Pip ($[Pip]_T$) at a constant content of methanol in mixed aqueous solvents containing 2% v/v acetonitrile. Such linear variation of k_{obs} against $[Pip]_T$ exists within the methanol content range 10%–~80% v/v. The change in k_{obs} with the change in $[Pip]_T$ at 98% v/v CH_3OH in mixed methanol-acetonitrile solvent shows the relationship: $k_{obs} = k_n^{app}[Pip]_T + k_{gb}^{app}[Pip]_T^2$, where respective k_n^{app} and k_{gb}^{app} represent apparent second-order and third-order rate constants for nucleophilic and general base-catalyzed piperidinolysis of phthalimide. The values of k_{obs}, obtained within $[Pip]_T$ range 0.02–0.40 M at 0.03 M NaOH and 20 as well as 50% v/v CH_3OH reveal the relationship: $k_{obs} = k_0/(1 + \{k_n[Pip]/k_{OX}[^-OX]_T\})$, where k_0 is the pseudo-first-order rate constant for hydrolysis of phthalimide, k_n and k_{OX} represent nucleophilic second-order rate constants for the reaction of Pip with phthalimide and for the XO^--catalyzed cyclization of N-piperidinylphthalamide to phthalimide, respectively, and $[^-OX]_T = [NaOH] + [^-OX_{re}]$, where $[^-OX_{re}] = [^-OH_{re}] + [CH_3O_{re}^-]$. The reversible reactions of Pip with H_2O and CH_3OH produce $^-OH_{re}$ and $CH_3O_{re}^-$ ions. The effects of mixed methanol-water solvents on the rates of piperidinolysis of PTH reveal a nonlinear decrease in k_n^{app} with the increase in the content of methanol. © 2000 John Wiley & Sons, Inc. Int J Chem Kinet 33: 29–40, 2001

INTRODUCTION

Solvent and mixed aqueous-organic solvent play an important yet extremely complex role in the reaction rates and chemical behavior of solution phase reactions. The complexity of the solvent effects on reaction rates is evident from the fact that there is no perfect single theory to deal with such complexity and there are several empirical equations that are claimed to explain only certain specific solvent effect such as polarity, permittivity, hydrogen bonding, and hydrophobicity. The kinetics of aminolysis of organic reactions in aqueous solution have been studied to a great extent with the aims explained elegantly in several reviews [1–6] and books [7–9]. The mechanistic aspects of aminolysis of esters in pure aprotic organic solvents have been studied by a few investigators [10–12]. The systematic kinetic studies on the effects of mixed aqueous-organic solvents on rates of aminolysis of esters and related compounds are relatively rare [13–22]. The most obvious reasons for the limited attempts at such studies are described elsewhere [13,22]. Apart from some importance of such studies to enzyme-catalyzed and micellar mediated reactions (where the reactions are believed to occur in a micro reaction en-

Correspondence to: M. Niyaz Khan (niyaz@kimia.um.edu.my)
Contract grant sponsor: National Science Council for R & D, IRPA
Contract grant number: 09-02-03-0003.

vironment of water concentration much lower than water concentration in pure water solvent [7,23]), these studies are also important for organic synthesis [24].

The effects of mixed aqueous-organic solvents on the rate of intramolecular general base-catalyzed hydrolysis [25], methanolysis [26], and aminolysis [22] of ionized phenyl salicylate have been reported. Recently, the effects of mixed aqueous-acetonitrile and pure acetonitrile solvents on the rate of nucleophilic reaction of piperidine (Pip) with phthalimide [27] have been studied, where the rate of piperidinolysis of phthalimide was uncatalyzed within the acetonitrile content range 2%−80% v/v in mixed aqueous solvents. But the rate of nucleophilic reaction of Pip with phthalimide in pure acetonitrile solvent revealed the absence of uncatalyzed and the presence of intermolecular general base-catalyzed reaction paths, respectively. The permittivity of acetonitrile is not significantly different from that of methanol [28−30]. But acetonitrile and methanol represent aprotic and protic solvent systems, respectively, and mixed aqueous-protic organic solvents and aqueous-aprotic organic solvents show quite different effects on the rate of hydrolysis of esters [31] and imides [24,32]. In the continuation of our search for the effects of mixed aqueous-aprotic and aqueous-protic organic solvents on the rates of aminolysis of esters and imides, the effects of CH_3OH-H_2O and CH_3OH solvents containing 2% v/v CH_3CN on the rate of reaction of Pip with phthalimide have been studied. The results and their probable explanation(s) are described in this article.

EXPERIMENTAL

Materials

All the reagents used were supplied by Fluka, Aldrich, or SIGMA and were of the highest purity commercially available. Stock solutions of phthalimide were prepared in acetonitrile.

Kinetic Measurements

The rates of reactions of piperidine (Pip) with phthalimide were studied by monitoring the disappearance of phthalimide spectrophotometrically at 300 nm. Details of the experimental procedure and data analysis are the same as described elsewhere [33].

All the kinetic runs were carried out under the experimental conditions where the reaction rates obeyed a pseudo-first-order rate law. The reactions were generally followed up to 2−6 half-lives of the reactions. Pseudo-first-order rate constants (k_{obs}) were calculated from Eq. (1),

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

using the nonlinear least-squares technique, where k_{obs}, δ_{app} (apparent molar extinction coefficient), and A_∞ (absorbance at reaction time $t = \infty$) were considered as unknown parameters. In Eq. (1), A_{obs} represents observed absorbance at any reaction time, t, $[X]_0$ is the initial concentration of phthalimide, and $\delta_{app} = \delta_{SH}$-$\delta_P$, where δ_{SH} and δ_P are molar extinction coefficients of phthalimide and products (phthalamic acid and *N*-piperidinylphthalamide), respectively. The fitting of the observed data to Eq. (1) was good, as evident from standard deviations associated with some representative calculated parameters listed in Tables I and III.

Product analysis was carried out spectrophotometrically, as described elsewhere [33,34].

RESULTS AND DISCUSSION

Effect of CH_3OH-H_2O on k_{obs} for Hydrolysis of Phthalimide at 0.01 M NaOH in the Absence of Pip

A few kinetic runs were carried out within the CH_3OH content range 0−80% v/v in mixed aqueous solvents containing 2% v/v CH_3CN and 0.01 M NaOH at 35°C. Pseudo-first-order rate constants (k_{obs}) are shown in Table I. The increase in CH_3OH content from 0 to 80% v/v decreased k_{obs} by 13-fold; a similar increase in CH_3OH and CH_3CN content decreased k_{obs} by 50-fold for *N*-hydroxyphthalimide [35,36] and by 22-fold for phthalimide [37,38], respectively.

The presence of 0.01 M NaOH in mixed H_2O-CH_3OH solvent would cause the production of CH_3O^-, and it may be shown that $[CH_3O^-]/[HO^-] = K[CH_3OH]/[H_2O]$, where $K = K_a^{CH_3OH}/K_a^{H_2O}$. It appears that CH_3O^- reacts with acetyl salicylate ion [39] and phenyl acetate [40] nearly 60 times faster than HO^- in mixed aqueous-methanol solvents. The pK_a of methanol ($pK_a^{CH_3OH} = 15.7$) [41] is not significantly different from pK_a of water ($pK_a^{H_2O} = 15.75$) [41]; hence, the nearly 60 times larger nucleophilic reactivity of CH_3O^- than of HO^- toward carbonyl carbon of esters should make the rate of hydrolysis negligible compared with the rate of methanolysis of phthalimide under the present experimental conditions. It should

Table I Values of k_{obs}, δ_{app} and A_∞ Calculated from Eq. (1) for Hydrolysis of Phthalimide at Different Contents of CH_3OH[a]

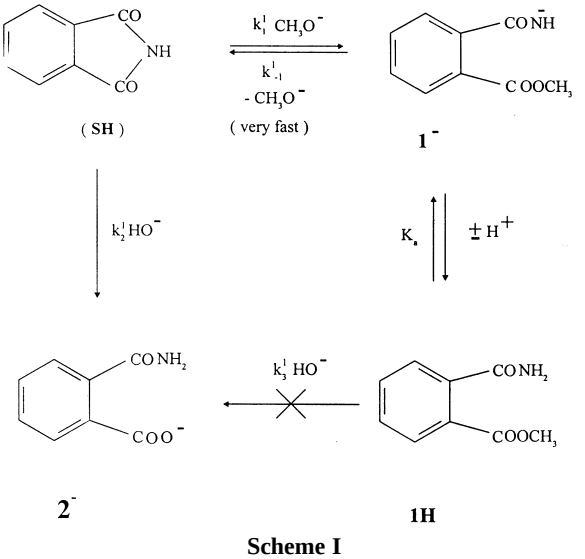
CH_3OH (% v/v)	$10^4\ k_{obs}$ (s^{-1})	δ_{app} ($M^{-1}\ cm^{-1}$)	A_∞
0	22.9 ± 0.5[b]	2100 ± 20[b]	−0.009 ± 0.005[b]
10	18.6 ± 0.2	2077 ± 11	0.000 ± 0.003
20	14.8 ± 0.1	2022 ± 6	0.001 ± 0.001
30	10.8 ± 0.1	2050 ± 12	−0.007 ± 0.003
40	7.64 ± 0.15	2091 ± 20	−0.013 ± 0.004
50	5.69 ± 0.09	2053 ± 18	−0.009 ± 0.004
60	4.20 ± 0.06	1974 ± 19	−0.004 ± 0.004
80	1.73 ± 0.01	1887 ± 5	0.009 ± 0.001

[a] $[\mathbf{SH_0}]_0 = 2 \times 10^{-4}$ M; [NaOH] = 0.01 M; 35°C; λ = 300 nm; mixed aqueous-methanol solvent for each kinetic run contained 2% v/v CH_3CN.

[b] Error limits are standard deviations.

be noted that the rate of hydrolysis of phthalimide at 0.01 M NaOH involves hydroxide ion and nonionized phthalimide (SH) as the reactants [42]. But the rate constants (k_{obs}) listed in Table I represent hydrolysis and not methanolysis of phthalimide. This may be explained as follows.

The rate constants for hydrolysis of phthalimide were found to be almost independent of [HO^-] within its range 0.0025−0.05 M in an aqueous solvent containing 1.6% v/v CH_3CN [43,44]. Under such conditions, the hydrolysis of phthalimide involves HO^- and SH as the reactants [42]. But upon increasing the CH_3OH content in the solution, [HO^-] decreases because CH_3O^- is formed, but [HO^-] + [CH_3O^-] is constant, thus [SH] should be constant. Since [HO^-] decreases, the pseudo-first-order rate constant must decrease.[1] The increase in CH_3OH content from 0 to 80% v/v decreases [HO^-] by nearly 2.5-fold, provided $K_a^{CH_3OH}/K_a^{H_2O}$ remains unchanged with the change in [CH_3OH]. The ionization of both H_2O and CH_3OH constitutes nonisoelectric reactions, and ionization constants of such ionization reactions are significantly affected by the presence of organic cosolvents in mixed aqueous solutions [45]. The pK_W increased from 14.00 to 15.43 [46] and the pK_a of phenol increased from 10.00 to 11.34 [47] with the increase in CH_3OH content from 0 to 70% w/w. In view of these results, the methanolysis of phthalimide may be also assumed to involve SH and CH_3O^- as the reactants at [CH_3O^-] ≤ 0.01 M. Thus, the cleavage of phthalimide in CH_3OH-H_2O solvents containing 0.01 M NaOH may be shown by a simple reaction scheme (Scheme I).



Scheme I

The value of k_2^1 is 26 $M^{-1}\ s^{-1}$ at 30°C in an aqueous solvent containing ≤2% v/v CH_3CN [43]. If $k_1^1/k_2^1 \approx 60$, then $k_1^1 \approx 1560\ M^{-1}\ s^{-1}$ at 30° C. The values of the second-order rate constants (k_{OH}) for HO^--catalyzed cyclization of methyl *o*-carbamoylbenzoate, methyl *o*-(aminomethyl)benzoate, and ethyl *o*-(hydroxymethyl)benzoate are 3.1×10^3 (25.9°C) [48], 7×10^3 (30°C) [49], and $10 \times 10^3\ M^{-1}\ s^{-1}$ (30°C) [50], respectively. These values of k_{OH} predict a value of k_{-1}^1 as $\approx 10^3\ s^{-1}$, provided $K_a/K_w \approx 1\ M^{-1}$ (where K_a is the ionization constant of **1H**), because $k_{OH} = k_{-1}^1 K_a/K_w$. The reported value of pK_a of benzamide is 14−15 [51]. Although *o*-substituent effect on pK_a is not easily predictable [46], the pK_a of **1H** may not be significantly different from that of benzamide. It may be noted that pseudo-first-order rate constants for the cyclization of nonionized phthalamic [24] and *N*-sub-

[1] I thank one of the reviewers for pointing this out.

stituted phthalamic [52] acids to phthalic anhydride remained almost unchanged with the change in the content of CH_3CN from 0 to 80% v/v in mixed aqueous solvent. Thus, the value of k_{OH} or k_{-1}^1 may not be expected to be significantly affected by the increase in the content of methanol in mixed aqueous solvents because, as concluded earlier in the text, such a change in the mixed solvent should not affect significantly the ratio K_a/K_W. The reported values of second-order rate constants (k'_{OH}) for hydroxide ion-catalyzed hydrolysis of methyl benzoate, methyl *o*-methoxybenzoate, and dimethylphthalate are 0.125 (30°C) [53], 0.075 (35°C) [54], 0.031 (35°C) [55], and 0.065 M^{-1} s^{-1} (25°C) [31], respectively. In view of these results, the value of k'_{OH} (= k_3^1 in Scheme I) for the HO^--catalyzed conversion of **1H** to $\mathbf{2}^-$ should be ca. 0.1 M^{-1} s^{-1}. But the value of k_{OH} for HO^--catalyzed cyclization of **1H** to **SH** is 3.1×10^3 M^{-1} s^{-1} (25.9) [48]. Furthermore, at 10% v/v CH_3OH (the lowest methanol content in the present study), the value of $[CH_3O^-] \approx 5 \times 10^{-4}$ M $\{[CH_3O^-] = KX[^-OH]_T/(1 + KX)$, where $K = K_a^{CH_3OH}/K_a^{H_2O}$, $X = [CH_3OH]/[H_2O]$, and $[^-OH]_T$ = 0.01 M$\}$, and hence the value of $k_1^1 \approx 1560$ M^{-1} s^{-1} gives $k_1^1[CH_3O^-] \approx 0.78$ s^{-1}. The value of $k_2^1[HO^-] = 0.26$ s^{-1} at 0.01 M NaOH and 98% v/v H_2O. The values of $k_1^1[CH_3O^-]$ and $k_2^1[HO^-]$ become >0.78 s^{-1} and <0.26 s^{-1}, respectively, at methanol content of >10% v/v. Thus, $k_1^1[CH_3O^-]$ is more than 3-fold larger than $k_2^1[HO^-]$ at 10% v/v CH_3OH. Thus, the nearly 10^4-fold larger value of k_{OH} for the conversion of **1H** to **SH** than that of **1H** to $\mathbf{2}^-$ and >3-fold larger value of $k_1^1[CH_3O^-]$ compared with $k_2^1[HO^-]$ at 10% v/v methanol caused rapid equilibrium formation between **SH** and **1H.** It may be noted that the conclusion remains unchanged even if $k_{-1}^1 \approx 10^4$ s^{-1} because under such conditions, the rate of conversion of **1H** to **SH** becomes $\sim 10^5$-fold larger than that of **1H** to $\mathbf{2}^-$**.**

Based upon Scheme I, $[\mathbf{SH}]/[\mathbf{1H}] = k_{-1}^1K_a/k_1^1[CH_3O^-][H^+] = k_{OH}K_w/k_1^1[CH_3O^-][H^+]$ because $k_{-1}^1 = k_{OH}K_w/K_a$. Since $[\mathbf{SH}] = f_{SH}[\mathbf{SH}]_\mathbf{T}$ where $f_{SH} = [H^+]/([\mathbf{H}^+] + K'_a)$ with $K'_a = [\mathbf{S}^-][H^+])/[\mathbf{SH}]$ and $[\mathbf{SH}]_\mathbf{T} = [\mathbf{SH}] + [\mathbf{S}^-]$. Therefore, the value of $[\mathbf{SH}]_\mathbf{T}/[\mathbf{1H}] = k_{OH}K_w/(f_{SH}\ k_1^1[CH_3O^-][H \approx 8 \times 10^3$ at 10% v/v methanol with $k_{OH} = 3 \times 10^3$ M^{-1} s^{-1} (25.9°C) [48], $K_w = 1.4 \times 10^{-14}$ M^2, $k_1^1 = 1560$ M^{-1} s^{-1} (30°C), $[CH_3O^-] = 5 \times 10^{-4}$ M, $[H^+] = 1.4 \times 10^{-12}$ M, $f_{SH} = 4.7 \times 10^{-3}$ ($K'_a = 3 \times 10^{-10}$ M at 30°C [47]). This analysis shows the presence of an insignificant amount of **1H** compared to that of phthalimide during the course of the cleavage of phthalimide in CH_3OH-H_2O solvent containing 0.01 M NaOH and 10% v/v methanol.

A skeptic may argue that the formation of product $\mathbf{2}^-$ might occur through rapid HO^--catalyzed hydrolysis of **1H** (i.e., the formation of $\mathbf{2}^-$ occurs through the k_3^1 step rather than k_2^1 step in Scheme I). If this is correct, then the overall rate law (rate = $k_{est}[PT]_T$, where $[PT]_T = [\mathbf{SH}]_\mathbf{T} + [\mathbf{1H}] \approx [\mathbf{SH}]_\mathbf{T}$ because $[\mathbf{SH}]_\mathbf{T}/[\mathbf{1H}] \approx 8 \times 10^3$) and Scheme I can lead to the relationship: $k_{est} = k_3^1k_1^1[CH_3O^-]f_{SH}/k_{OH} \approx 1 \times 10^{-7}$ s^{-1} at 10% v/v CH_3OH with $k_3^1 \approx 0.1$ M^{-1} s^{-1}, $k_1^1 = 1560$ M^{-1} s^{-1}, $[CH_3O^-] = 5 \times 10^{-4}$ M, $f_{SH} = 4.7 \times 10^{-3}$, and $k_{OH} = 3 \times 10^3$ M^{-1} s^{-1}. The estimated value of rate constant k_{est} ($\approx 1 \times 10^{-7}$ s^{-1}) is more than 10^4-fold smaller than the experimentally observed value of k_{obs} ($= 18.6 \times 10^{-4}$ s^{-1}) at 10% v/v methanol (Table I). This analysis thus rules out the possibility of the formation of $\mathbf{2}^-$ via intermediate **1H.** This shows that the formation of $\mathbf{2}^-$ must occur via the k_2^1-step (Scheme I). Under such a condition, $k_{est} = k_2^1[HO^-]f_{SH} \approx 12 \times 10^{-4}$ s^{-1} at 30°C, which is not very different from k_{obs} ($= 18.6 \times 10^{-4}$ s^{-1}) at 10% v/v methanol and 35°C (Table I).

The decrease in k_{obs} (Table I) with increasing CH_3OH content in mixed aqueous solvent may be attributed to several factors, such as permittivity, polarity, polarizability, basicity, preferential solvation, hydrogen bonding, and hydrophobicity of the reaction medium. These factors are not equally influential, and some of them oppose each other toward a particular reaction rate. The increase in the content of CH_3OH decreased permittivity (ε) of the reaction medium, which in turn increased the pK_a of conjugate acids of both nucleophile (HO^-) and leaving group (—$CONH^-$). The increase in pK_a of conjugate acids of leaving group and nucleophile should decrease and increase the rate of reaction, respectively. But the nucleophilicity of HO^- is bound to decrease partially due to more stable ion-pair formation between HO^- and its counter ion (Na^+) with decrease in ε. The ion-pair formation between leaving group and Na^+ should be less stable for the reason that full unit negative charge cannot develop on the nitrogen of leaving group in the transition state and such a partial negative charge is also not as localized as full unit negative charge on hydroxide ion in the ground state.

Effects of CH_3OH-H_2O and CH_3OH Solvents on k_{obs} for the Reaction of Phthalimide with Pip in the Absence of Added NaOH

In order to discover the effects of CH_3OH-H_2O on the rate of reaction of phthalimide with Pip, a few kinetic runs were carried out within the attainable total piperidine concentration ($[Pip]_T$) range at a constant content

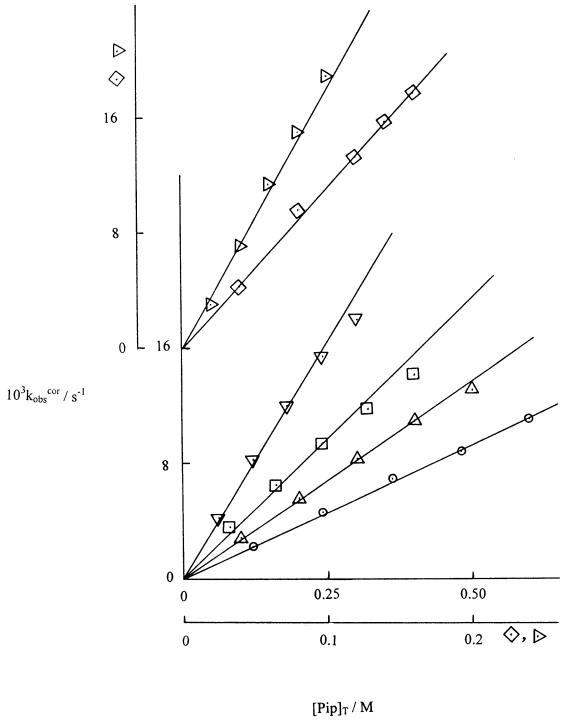


Figure 1 Plots showing the dependence of corrected pseudo-first-order rate constants, k_{obs}^{cor} ($= k_{obs} - k_0$), upon the total concentration of piperidine, $[Pip]_T$, for the reaction of Pip with phthalimide at 10 (▷), 20 (◇), 30 (▽), 40 (□), 50 (△), and 60% v/v CH_3OH (○) in mixed aqueous solvent containing 2% v/v CH_3CN.

of CH_3OH in mixed aqueous solvent at 35°C. Pseudo-first-order rate constants (k_{obs}) at a constant content of CH_3OH but $\leq 60\%$ v/v, as shown graphically in Figure 1, obeyed Eq. (2)

$$k_{obs} - k_0 = k_n^{app}[Pip]_T \quad (2)$$

where k_0 is the pseudo-first-order rate constant for the cleavage of phthalimide obtained within the $[HO^-]$ range where the rate of cleavage of phthalimide is independent of $[HO^-]$ in the absence of Pip (Table I) and k_n^{app} is apparent nucleophilic second-order rate constant for the reaction of Pip with phthalimide. The least-squares calculated values of k_n^{app} at different contents of CH_3OH are summarized in Table II. The fitting of the observed data to Eq. (2) is evident from the plots of Figure 1, where solid lines are drawn through the calculated points.

The calculated values of δ_{app} appeared to be independent of $[Pip]_T$ at a constant content of CH_3OH. The average values of δ_{app} with their standard deviations at different contents of CH_3OH are summarized in Table II. The values of δ_{app} are nearly 25–30% smaller than the corresponding values of δ_{app} obtained in the absence of Pip. Since $\delta_{app} = \delta_{SH} - \delta_P$, where $\delta_P \approx 0$ because **1H, 1⁻,** and **2⁻** do not absorb to a detectable level at 300 nm. Nearly 25–30% lower values of δ_{app} in the presence of Pip indicate that the value of δ_P is no longer zero. Since phthalamic acid (hydrolysis product of phthalimide) and *N*-piperidinylphthalamide (piperidinolysis product of phthalimide) do not absorb at 300 nm, δ_P must be for equilibrium-cyclized product (phthalimide) of *N*-piperidinylphthalamide. In the recent studies, the kinetic evidence for the formation of small but definite amounts of *N*-substituted phthalimides ($\leq 20\%$) has been shown to occur in the cleavage of phthalimide under the buffers of 2-hydroxyethylamine [56], 2-methoxtethylamine [56], and methylamine [57]. Thus, a brief reaction mechanism for

Table II Effects of Methanol Content on k_n^{app} Calculated from Eq. (2) at 35°C[a]

CH_3OH (% v/v)	δ_{app}[b] (M^{-1} cm^{-1})	θ[c]	10^3 k_n^{app} (M^{-1} s^{-1})	10^3 k_n^{app}[d] (M^{-1} s^{-1})	10^3 k_n[e] (M^{-1} s^{-1})	10^3 k_{gb}[f] (M^{-2} s^{-1})
10	1432 ± 90[g]	2.2	180 ± 17[g]	239 ± 6[g]	164	
20	1441 ± 38	2.5	112 ± 5	131 ± 7	93.6	
30	1468 ± 28	2.5	66.1 ± 4.3	73.0 ± 6.9	52.1	
40	1502 ± 15	2.6	39.3 ± 3.3	41.9 ± 4.5	30.3	
50	1538 ± 11	3.0	27.6 ± 0.9	28.8 ± 1.3	21.6	
60	1532 ± 44	3.5	18.7 ± 0.7	19.3 ± 0.6	15.0	
80	1657 ± 27	7.2	10.8 ± 1.0			
			10.2 ± 0.6		9.0	1.86 ± 0.88[g]
98	1458 ± 72		4.92 ± 0.54			8.08 ± 0.81

[a] $[\mathbf{SH_0}]_0 = 2 \times 10^{-4}$ M; $\lambda = 300$ nm; mixed aqueous-methanol solvent for each kinetic run contained 2% v/v CH_3CN.

[b] Average value of δ_{app} obtained at five different $[Pip]_T$ at a constant content of methanol.

[c] $\theta = \delta_{app}/(\delta_0 - \delta_{app})$, where δ_0($= \delta_{app}$ in Table I) is the apparent molar extinction coefficient obtained under similar experimental conditions with $[Pip]_T = 0$.

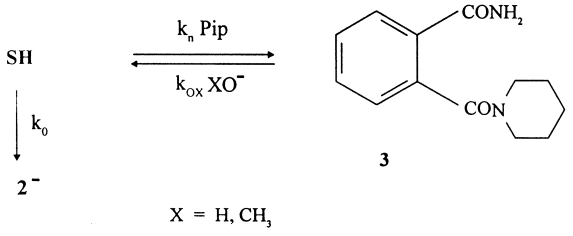
[d] The values of k_n^{app} were calculated from Eq. (2) with $[Pip]_T$ changed to $[Pip]_T - [PipH^+]$.

[e] $k_n = \theta\, k_n^{app}/(1 + \theta)$ (i.e., Eq. (6)).

[f] Calculated from Eq. (7).

[g] Error limits are standard deviations.

the cleavage of phthalimide under the presence of Pip may be shown in Scheme II. It can be shown that $k_n[Pip]_T \gg k_0$ under the experimental conditions of the present study and k_{OH} or $k_{OX} \gg k'_{OH}$ (where k'_{OH} represents the HO^--catalyzed second-order rate constant for hydrolysis of **3.** Thus, the equilibrium between **SH** and **3** is considered to be independent of the k_0 step and hydrolysis of **3** in Scheme II.



Scheme II

The rate of hydrolysis of **3** may be considered to be negligible compared with the rate of hydrolysis of phthalimide under the present experimental conditions ($[HO_{re}^-]$ range 0.008–0.018 M) because pseudo-first-order rate constants for hydrolysis of benzamide and phthalimide at $[HO_{re}^-]$, range 0.008–0.018 M, are 13×10^{-6} to 29×10^{-6} s^{-1} at 100.4°C [58]; 9×10^{-8} to 20×10^{-8} s^{-1} at 25°C [59], 9×10^{-6} to 20×10^{-6} s^{-1} at 100°C [60], and 1.3×10^{-3} s^{-1} at 30°C [61], respectively. The value of k'_{OH} for **3** may not be expected to be significantly different from k'_{OH} for benzamide because the favorable substituent effect is most likely counterbalanced by the unfavorable steric effect of *o*-CON< in **3.** This conclusion is based upon the reported values of k'_{OH} for methyl benzoate (k'_{OH} = 0.125 M^{-1} s^{-1} at 30°C [52], 0.075 M^{-1} s^{-1} at 35°C [53]), methyl *o*-methoxybenzoate (k'_{OH} = 0.031 M^{-1} s^{-1} at 35°C [54]), dimethylphthalate (k'_{OH} = 0.065 M^{-1} s^{-1} at 30°C [31]), benzamide (k'_{OH} = 0.0011 M^{-1} s^{-1} at 100°C [59]), and *o*-methoxybenzamide (k'_{OH} = 0.0011 M^{-1} s^{-1} at 100°C [59]). The values of second-order rate constants (k_{OH}) for HO^--catalyzed cyclization of phthalamide and *N,N′*-dimethylphthalamide are 4.9 M^{-1} s^{-1} and 7.6 M^{-1} s^{-1} at 25.9°C [48], respectively. The value of k_{OH} or k_{OX} (Scheme II) may not be very different from the corresponding k_{OH} for phthalamide or *N,N′*-dimethylphthalamide. Hence the value of k_{OH} or $k_{OX} \approx 5$ M^{-1} s^{-1}, which is many-fold larger than k'_{OH} ($\approx$ 0.0011 M^{-1} s^{-1} at 100°C [59] for HO^--catalyzed hydrolysis of benzamide) for **3.**

Piperidine is a base strong enough to produce a significant amount of HO^- when dissolved in aqueous solvents through the reaction $H_2O + Pip \rightleftharpoons HO_{re}^- + PipH^+$, where Pip and $PipH^+$ represent nonprotonated and protonated piperidine, respectively. The values of $[HO_{re}^-]$ at different $[Pip]_T$ may be calculated from Eq. (3):

$$[HO_{re}^-] = [-Y + (Y^2 + 4Y[Pip]_T)^{1/2}]/2 \qquad (3)$$

where $Y = K_w/K_a^{Pip}$ and $K_a^{Pip} = [Pip][H^+]/[PipH^+]$.

The calculation of k_n^{app} from Eq. (2) is based upon the assumption that $[Pip] \approx [Pip]_T$. But the values of $[HO_{re}^-]$ (= $[PipH^+]$), calculated from Eq. (3) at different $[Pip]_T$, indicate that the assumption $[Pip] \approx [Pip]_T$ is not entirely true. Thus, relatively more accurate values of k_n^{app} were obtained from Eq. (2) with $[Pip]_T$ changed to $[Pip]_T - [PipH^+]$, where $[PipH^+] = [HO_{re}^-]$. These calculated values of k_n^{app} are also summarized in Table II. The values of $[HO_{re}^-]$ at different $[Pip]_T$ were calculated from Eq. (3). The reported values of pK_w at different contents of ethanol [46] were used in the present study assuming the effects of methanol-water and ethanol-water on pK_w are nearly the same. The values of pK_a^{Pip} at different contents of methanol were assumed to be the pK_a^{Pip} at the corresponding contents of acetonitrile [62] in mixed aqueous solvents.

The immediate stable product of piperidinolysis of PTH is **3.** Pthalamide [48] and *N,N′*-disubstituted phthalamide [48] are known to cyclize to produce **SH** and *N*-substituted **SH,** respectively, through intramolecular nucleophilic participation of *o*-carboxyamido group in alkaline aqueous solvents. The presence of HO^- in mixed H_2O-CH_3OH solvent would produce CH_3O^-. But the assumption that HO^- and CH_3O^- are equally effective catalysts for the cyclization of **3** to phthalimide can be made to reduce the kinetic complexity involved in the present reacting system. This assumption is conceivable because these catalysts catalyze cyclization reaction merely by abstracting the acidic hydrogen of the amide group of **3,** and the values of pK_a of conjugate acids of HO^- and CH_3O^- are nearly the same. Anionic phthalimide (**S⁻**) absorbs strongly ($\delta_{S^-} = 2000-2100$ M^{-1} cm^{-1}), while **2⁻** and **3** do not absorb ($\delta_{2^-} \approx \delta_3 \approx 0$) at 300 nm. Thus, the extent of reversibility of the reversible reaction in Scheme II can be easily established by comparing the values of δ_{app} and δ_0, where δ_0 and δ_{app} were obtained under similar conditions with the absence and presence of Pip, respectively. Since the equilibrium between **SH** and **3** is independent of the k_0 step and rate of hydrolysis of **3,** Scheme II leads to Eq. (4):

$$\frac{k_n[Pip]}{k_{OX}[XO_{re}^-]} = \frac{[\mathbf{3}]_e}{[\mathbf{SH}]_e} = \frac{A_0 - A_e}{A_e} = \frac{\delta_{app}}{\delta_0 - \delta_{app}} = \theta \qquad (4)$$

where $[XO_{re}^-] = [HO_{re}^-] + [CH_3O_{re}^-]$, subscripts 0 and e represent initial state (i.e., at reaction time t = 0) and equilibrium state, respectively, and A represents absorbance at 300 nm. The values of δ_{app} were found to be independent of $[Pip]_T$ at a constant content of CH_3OH (Table II). This shows that θ is independent of $[Pip]_T$ and hence the values of $k_n[Pip]/k_{OX}[XO_{re}^-]$ remain constant within the $[Pip]_T$ range of present study. Reaction Scheme II shows that the corrected pseudo-first-order rate constants ($k_{obs} - k_0$) are related to k_n and k_{OX} by Eq. (5):

$$k_{obs} - k_0 = k_n[Pip] + k_{OX}[XO_{re}^-] \qquad (5)$$

Eqs. (2), (4), and (5) yield Eq. (6):

$$k_n^{app} = k_n(1 + \theta)/\theta \qquad (6)$$

The values of k_n at different contents of CH_3OH were calculated from Eq. (6) with known values of θ and $k_n^{app.}$ These results are shown in Table II.

The rate constants (k_{obs}) obtained at 80% v/v CH_3OH and within the $[Pip]_T$ range 0.16–0.80 M, as shown graphically by Figure 2, were found to fit to Eq. (7) slightly better than to Eq. (2):

$$k_{obs} - k_0 = k_n^{app}[Pip]_T + k_{gb}^{app}[Pip]_T^2 \qquad (7)$$

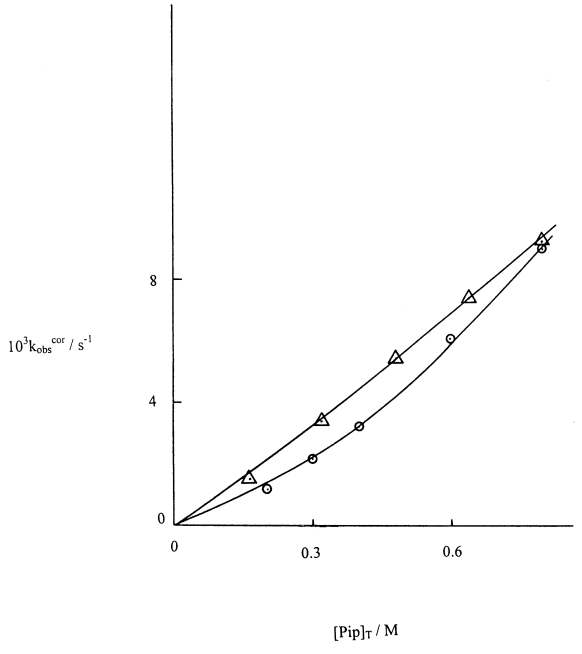


Figure 2 Effect of total concentration of piperidine, $[Pip]_T$, on pseudo-first-order rate constants, k_{obs}, for the reaction of Pip with phthalimide at 80 (△) and 98% v/v CH_3OH (○) in mixed aqueous solvent containing 2% v/v CH_3CN.

In Eq. (7), k_{gb}^{app} represents apparent third-order rate constant for general base-catalyzed piperidinolysis of **SH.** The least-squares calculated values of k_n^{app} and k_{gb}^{app} are shown in Table II. The value of k_n^{app} obtained from Eq. (7) is only 6% lower compared to k_n^{app} obtained from Eq. (2) and the maximum contribution of $k_{gb}^{app}[Pip]_T^2$ term to $k_{obs} - k_0$ is 13% (obtained at $[Pip]_T$ = 0.8 M).

The values of k_{obs} at 98% v/v CH_3OH obeyed Eq. (7), with $k_0 = 0$. The least-squares calculated values of k_n^{app} and k_{gb}^{app} are summarized in Table II. The minimum and maximum contributions of $k_{gb}^{app}[Pip]_T^2$ term in Eq. (7) are 30% (at the lowest $[Pip]_T$ = 0.2 M) and 64% (at the maximum $[Pip]_T$ = 0.8 M), respectively. The fitting of the observed data to Eq. (7) is evident from the plots of Figure 2, where solid lines are drawn through the calculated data points.

Effects of $[Pip]_T$ on the Cleavage of Phthalimide in Aqueous Solvent Containing 20 and 50% v/v CH_3OH and 0.03 M NaOH at 35°C

The equilibrium between phthalimide and **3** (Scheme II) may be expected to be reached much faster if the rate of backward reaction (i.e., k_{OX} step) is increased by external addition of NaOH into the reaction mixture. In order to test this speculation, a few kinetic runs were carried out for the cleavage of phthalimide within the $[Pip]_T$ range 0.02–0.40 M at 0.03 M NaOH at 20 and 50% v/v CH_3OH. The absorbance of the reaction mixture showed a sharp drop in the initial phase followed by a slow monotonic drop in the final phase of the reaction, as evident from some representative plots in Figure 3. The final phase of the reaction followed a pseudo-first-order rate law. Pseudo-first-order rate constants (k_{obs}) and apparent pseudo-molar extinction coefficients, δ'_{app} {$= \delta_{\mathbf{SHe}} - \delta_P$, where $\delta_{\mathbf{SHe}}$ and δ_P represent molar extinction coefficients for reactants ($\mathbf{SH_e}$ and $\mathbf{3_e}$) at equilibrium and product ($\mathbf{2}^-$), respectively, at 300 nm}, were calculated from Eq. (1) with $[X]_0 = [\mathbf{SH}]_0$ (i.e., initial concentration of phthalimide). These results are summarized in Table III. Since $\delta_P \approx 0$ because $\mathbf{2}^-$ does not absorb to a detectable level at 300 nm, $\delta'_{app} \approx \delta_{\mathbf{SHe}}$. The increase in $[Pip]_T$ should increase the concentration of $\mathbf{3_e}$ and consequently decrease $[\mathbf{SH_e}]$ (Scheme II), provided the rate of backward reaction (i.e., the conversion of **3** to **SH**) is not increased proportionately due to a simultaneous increase in ($[HO^-] + [CH_3O^-]$). Such an effect of the increase in $[Pip]_T$ on $[\mathbf{SH_e}]$ should decrease δ'_{app} {obtained from Eq. (1) using data of the final phase of the reaction where the initial concentration of phthalimide ($[\mathbf{SH}]_0 = 2 \times 10^{-4}$ M) was considered as $[\mathbf{SH_e}]_0$}. Thus, δ'_{app} would be concentration-independent only if

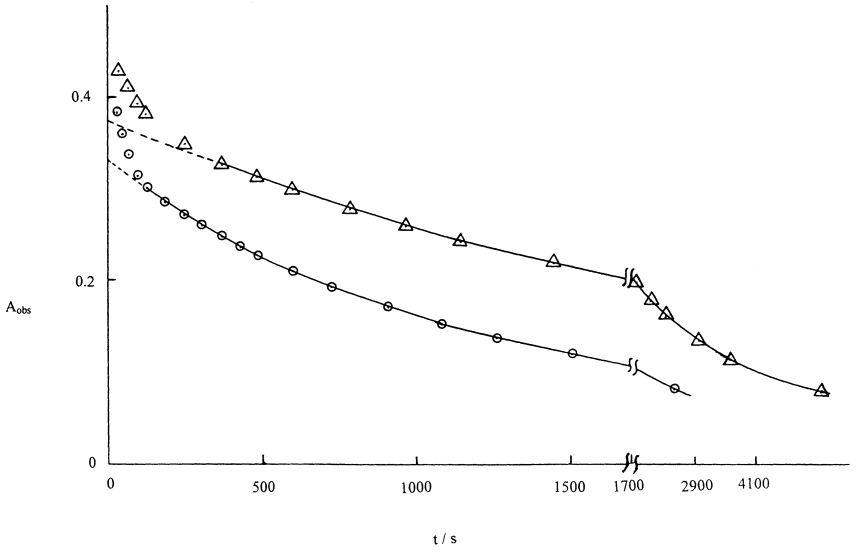


Figure 3 Variation of observed absorbance, A_{obs}, vs. reaction time, t, for the typical kinetic runs where reaction mixture contained $[\mathbf{SH_0}]_0 = 2 \times 10^{-4}$ M, [NaOH] = 0.03 M, $[Pip]_T = 0.1$ M, 35°C and mixed aqueous solvent containing 2% v/v CH_3CN and 20 (○) as well as 50% v/v CH_3OH (△).

$[\mathbf{SH_e}]_0 = [\mathbf{SH}]_0$. The observed decrease in δ'_{app} with increase in $[Pip]_T$ (Table III) indicates that $[\mathbf{SH_e}]_0 \neq [\mathbf{SH}]_0$.

Scheme II shows that the initial fast drop in A_{obs} (Figure 3) represents the attainment of equilibrium between piperidinolysis of **SH** and cyclization of **3,** while the slow drop in A_{obs} in the final phase of the reaction represents the hydrolysis of phthalimide after the attainment of equilibrium between **SH** and **3.** These conclusions are supported by the decrease in δ'_{app} with increase in $[Pip]_T$ at a constant [NaOH] (Table III).

The observed rate law (rate = $k_{obs}[\mathbf{SH}]_\mathbf{T}$, where $[\mathbf{SH}]_\mathbf{T}$ is the total concentration of phthalimide) and Scheme II can lead to Eq. (8):

$$k_{obs} = k_0/\{1 + (k_n[Pip]/k_{OX}[XO^-]_T)\} \qquad (8)$$

where $[Pip] = [Pip]_T - [PipH^+]$, $k_0 = k_{XOH} = k_{OX}K_w/K'_a$ with $K'_a = [S^-][H^+]/[SH]$ as well as k_{XOH} and k_{OX}

Table III Effects of $[Pip]_T$ on Pseudo-First-Order Rate Constants (k_{obs}) and Apparent Pseudo-Molar Extinction Coefficients (δ'_{app}) for the Cleavage of Phthalimide at 0.03 M NaOH and 35°C[a]

	CH_3OH/v/v = 20				CH_3OH/v/v = 50			
$[Pip]_T$ (M)	$10^4\ k_{obs}$ (s^{-1})	δ'_{app} ($M^{-1}\ cm^{-1}$)	t[b] (s)	n[c]	$10^4\ k_{obs}$ (s^{-1})	δ'_{app} ($M^{-1}\ cm^{-1}$)	t[b] (s)	n[c]
0.02	13.1 ± 0.1[d]	1907 ± 3[d]	120–1736	14	5.71 ± 0.07[d]	1948 ± 9[d]	240–2721	12
0.06	11.5 ± 0.1	1554 ± 5	120–1980	14	5.11 ± 0.07	1761 ± 9	360–2955	11
0.10	9.92 ± 0.11	1352 ± 5	120–2540	14	4.75 ± 0.04	1603 ± 4	360–5400	13
0.20	7.26 ± 0.12	1123 ± 8	120–2030	14	4.01 ± 0.11	1328 ± 18	360–2655	11
0.30	6.42 ± 0.14	938 ± 1	120–1896	14	3.66 ± 0.04	1221 ± 7	360–3084	11
0.40	5.76 ± 0.11	789 ± 7	120–3026	14	2.85 ± 0.02	1193 ± 3	360–10,800	10

[a] $[\mathbf{SH_0}]_0 = 2 \times 10^{-4}$ M; $\lambda = 300$ nm; mixed aqueous-methanol solvent for each kinetic run contained 2% v/v CH_3CN; k_{obs} and δ'_{app} were calculated from the relationship: $A_{obs} = [\mathbf{SH_0}]_0\delta'_{app}\exp(-k_{obs}t) + A_\infty$, where A_{obs} and A_∞ represent absorbance at 300 nm and at any reaction time t and at $t = \infty$, respectively. It may be noted that the actual kinetic equation for the calculation of k_{obs} and the apparent molar extinction coefficient (δ_{app}) for the second phase of the reaction should be expressed as $A_{obs} = [\mathbf{SH_e}]_0\delta_{app}\exp(-k_{obs}t) + A_\infty$, where $[\mathbf{SH_e}]_0$ is the concentration of phthalimide when equilibrium between **SH** and **3** is reached. Thus, it is apparent that $\delta'_{app} = ([\mathbf{SH_e}]_0/[\mathbf{SH_0}]_0)\delta_{app}$.

[b] Reaction time range of observed absorbance (A_{obs}) used to calculate k_{obs} and δ'_{app}.

[c] Total number of data points used in the calculation of k_{obs} and δ'_{app}.

[d] Error limits are standard deviations.

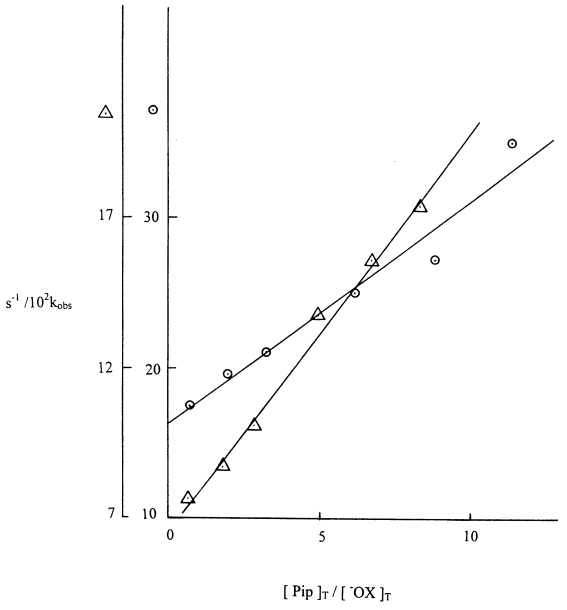


Figure 4 Plots showing the dependence of $1/k_{obs}$ upon $[Pip]_T/[XO^-]_T$ (where X = H, CH_3) for the cleavage of phthalimide within the $[Pip]_T$ range 0.02–0.40 M at 0.03 M NaOH and 20 (△) and 50% v/v CH_3OH (○).

represent rate constants for the reactions of XOH with S^- and XO^- with SH, respectively, and $[XO^-]_T$ = [NaOH] + $[XO_{re}^-]$ with [NaOH] = 0.03 M. In order to treat the observed data (k_{obs} vs. $[Pip]_T$) to Eq. (8), the values of $[XO_{re}^-]$ at different values of $[Pip]_T$ were calculated from Eq. (9):

$$[XO_{re}^-] = [-Z + (Z^2 + 4Y[Pip]_T)^{1/2}]/2 \quad (9)$$

where Z = [NaOH] + Y and $Y = K_w/K_a^{Pip}$. The calculated values of $[XO_{re}^-]$ at different $[Pip]_T$ in the presence of 0.03 M NaOH revealed that the values of $[PipH^+]$ (= $[XO_{re}^-]$) range from 1.36×10^{-3} to 18.2×10^{-3} M at 20% v/v CH_3OH and 0.3×10^{-3} to 5.0×10^{-3} M at 50% v/v CH_3OH within the $[Pip]_T$ range 0.02–0.40 M. These results show that $[PipH^+] < 7\%$ at 20% v/v CH_3OH and <2% at 50% v/v CH_3OH and hence, under such experimental conditions, $[Pip] \approx [Pip]_T$.

Eq. (8) predicts that the plot of $1/k_{obs}$ vs. $[Pip]_T/[XO^-]_T$ should be linear. Such plots, as shown in Figure 4, are essentially linear. The fitting of the observed data to Eq. (8) is evident from the plots of Figure 4, where solid lines are drawn through the calculated data points. The reaction step involving the reaction between S^- and HO^- is not included in Scheme II for the reason that the rate of hydrolysis of phthalimide is independent of $[HO^-]$ within its range 0.0025–0.050 M and the value of the second-order rate constant (k_{OH}) for the reaction of HO^- with S^- is 3.48×10^{-3} M^{-1} s^{-1} at 30°C in aqueous solvent containing <2% v/v CH_3CN [43,44]. Furthermore, reasonably good fitting of observed data to Eq. (8) rules out the significance of $k_{OH}[HO^-][S^-]$ compared with $k_{OH}[HO^-][SH]$ or kinetically indistinguishable $k_{H_2O}[H_2O][S^-]$. The least-squares calculated values of $1/k_0$ and $k_n/k_{OX}k_0$ at different methanol content are summarized in Table IV. The values of k_{obs} obtained at 20 and 50% v/v CH_3OH in the absence of Pip at 0.01 M NaOH (Table I) are comparable with the corresponding values of k_0 (Table IV). The value of k_{OX} at 20 and 50% v/v CH_3OH (Table IV) are within the expected range based upon the reported values of k_{OH} for cyclization of phthalamide (k_{OH} = 2.5 M^{-1} s^{-1}, statistically corrected value at 25.9°C) [48], *o*-aminomethylbenzamide (k_{OH} = 0.16 M^{-1} s^{-1} at 30°C) [59], and *o*-hydroxymethylbenzamide (k_{OH} = 0.04 M^{-1} s^{-1} at 25°C [63] and 0.154 M^{-1} s^{-1} at 30°C [64]).

Mechanistic Speculations

The increase in the content of methanol in mixed aqueous solvent from 10 to 98% v/v changed k_n from a sharp decrease in the water-rich region followed by a slow decrease in the methanol-rich region of k_n vs. the % v/v CH_3OH profile (Table II). Such a solvent effect on the rate of piperidinolysis of phthalimide may be attributed to several factors, as described elsewhere [22]. But it seems more appropriate to discuss the sol-

Table IV Values of $1/k_0$ and k_n/k_0k_{OX} Calculated from Eq. (8)[a]

CH_3OH (% v/v)	$1/k_0$ (s)	k_n/k_0k_{OX} (s)	10^4 k_0 (s^{-1})	k_{OX}[b] (M^{-1} s^{-1})
20	665 ± 30[c]	132 ± 6[c]	15.0	0.47
50	1623 ± 101	150 ± 15	6.16	0.23

[a] Conditions are described in Table III.

[b] The values of k_{OX} were calculated from the calculated values of $1/k_0$ and k_n/k_0k_{OX}, with $k_n = 93.6 \times 10^{-3}$ and 21.6×10^{-3} M^{-1} s^{-1} at 20 and 50% v/v methanol, respectively (Table II).

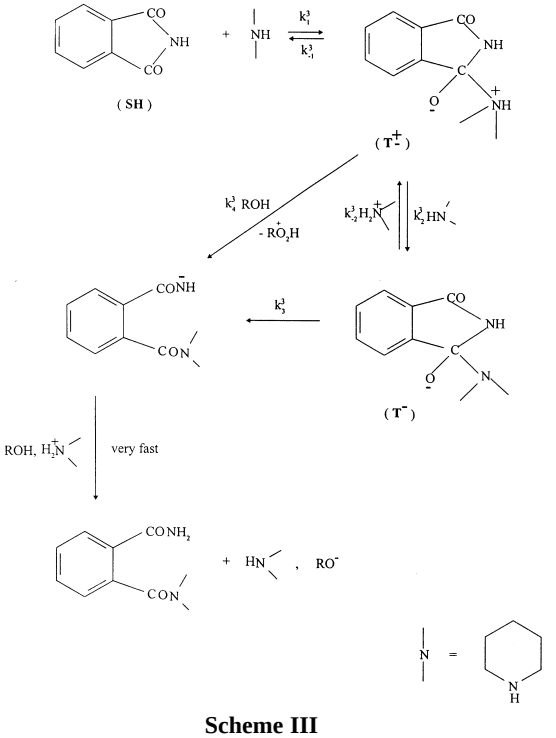
[c] Error limits are standard deviations.

vent effect on the rate of an addition-elimination reaction in terms of the solvent effect on nucleophilicity of nucleophile (i.e., the pK_a of conjugate acid of nucleophile) and on the leaving ability of the leaving group (i.e., the pK_a of conjugate acid of leaving group).

The mixed aqueous-organic solvents (both protic and aprotic organic cosolvents) should have little effect on the ionization constants (K_a) of isoelectric ionization reactions (i.e., reactions of the type: $BH^+ \rightleftharpoons B + H^+$). This may be true only if the reactant and product molecules are not highly hydrophobic and product molecules are neutral. The effects of mixed aqueous-organic solvents on pK_a of conjugate acids of several amines have been reported where the increase in the contents of organic cosolvents increases the K_a to the certain range (~50–80% v/v) of the contents of organic cosolvents [14,22,65,66]. The pK_a values of conjugate acids are larger by several pK units in pure CH_3CN solvent compared to those in pure water solvent [67]. Similarly, pK_a values of several amidines in mixed aqueous-ethanol showed that pK_a at 95.6% w/w > pK_a at 80% w/w < pK_a at 50% w/w < pK_a at 30% w/w ethanol [68]. The pK_a of $PipH^+$ decreased from 11.37 to 10.98 with the increase in the content of acetonitrile from 2 to 50% v/v, while it increased from 10.98 to 11.36 with the increase in acetonitrile content from 50 to 70% v/v [62]. The pK_a of $PipH^+$ became 18.92 at 100% CH_3CN [13–22]. Methanol, being a protic polar solvent, is a better ion-solvating solvent than aprotic acetonitrile solvent. Thus, the effect of mixed methanol-water solvent on the pK_a of $PipH^+$ may be expected to be milder than that of mixed acetonitrile-water solvent. This conclusion is supported by the reported values of pK_a of phenol as 14.36 [47] and 27.2 [13] in pure methanol and pure acetonitrile solvent, respectively.

Unlike the ionization constant (K_a) of an isoelectric ionization reaction, the ionization constant (K_a) of a nonisoelectric ionization reaction ($AH \rightleftharpoons A^- + H^+$) decreased continuously with the increase in the content of organic cosolvent (both protic and aprotic) in mixed aqueous solvent [45,47,69]. The pK_a of phenol increased from 10.17 to 13.38 with the increase in the content of acetonitrile from 2 to 70% v/v [45], and from 10.0 to 11.34 with the increase in methanol content from 0 to 70% w/w [47]. Similarly, the pK_a of benzoic acid showed continuous nonlinear increase from 4.2 to 6.4 with the increase in the content of ethanol from 0 to 70% w/w [46].

The cleavage of phthalimide in the presence of piperidine in mixed aqueous-acetonitrile and pure acetonitrile solvents involves addition-elimination reaction mechanisms, as discussed elsewhere [27]. The same mechanisms are assumed to occur in mixed aqueous-methanol and methanol solvents. The piperidinolysis of phthalimide was found to be uncatalyzed in both mixed aqueous-acetonitrile and aqueous-methanol solvents until the content of organic cosolvent became 80% v/v. But in pure acetonitrile solvent, the uncatalyzed kinetic term ($k_n[Pip]_T[\mathbf{SH}]$) became insignificant compared with the catalyzed kinetic term $\{\Psi[Pip]_T^2[\mathbf{SH}]/(1 + \Phi[Pip]_T)\}$ in the rate law, where the presence of $\Phi[Pip]_T$ in the denominator was attributed as the kinetic evidence for the occurrence of a stepwise mechanism in pure acetonitrile solvent. Figure 2 indicates that both uncatalyzed and catalyzed kinetic terms are significant in methanol solvent containing 2% v/v acetonitrile. The absence of a $k_n[Pip]_T[\mathbf{SH}]$ term in pure acetonitrile solvent and the difference in the kinetic behavior of catalyzed reaction steps $\{\Psi[Pip]_T^2[\mathbf{SH}]/(1 + \Phi[Pip]_T)$ in acetonitrile and $\Psi[Pip]_T^2[\mathbf{SH}]$ in methanol solvents$\}$ in pure acetonitrile and methanol solvents may be explained qualitatively through reaction Scheme III.



Scheme III

The mechanism for piperidinolysis of phthalimide in pure acetonitrile solvent revealed the change in the rate-determining step from the k_2^3 step to the k_3^3 step with the increase in $[Pip]_T$, while the k_4^3 step was the rate-determining step in mixed aqueous-acetonitrile

solvents [27]. The absence of change in the slope of the plot of k_n^{app} vs. $[Pip]_T$ at 98% v/v CH_3OH indicates that the k_3^3 step cannot be the rate-determining step in the $[Pip]_T$ range 0.2–0.8 M. Thus, it appears that the k_4^3 step is the rate-determining step in the mixed aqueous-methanol solvents, while both the k_2^3 and k_4^3 steps are rate-determining steps in the methanol solvent containing 2% v/v CH_3CN.

Although the dielectric constants of acetonitrile and methanol are not significantly different from each other, the protic methanol solvent should stabilize highly unstable zwitterionic intermediate (**T**$^{\pm}$**)** more strongly than aprotic acetonitrile solvent. The value of k_4^3 should be larger in methanol than in acetonitrile solvent for the reason that the pK_a of conjugate acid of leaving group (—$CONH_2$) should be larger in acetonitrile than in methanol solvent. The values of k_2^3 and k_{-2}^3 are not expected to be influenced significantly with the change in the solvent from methanol to acetonitrile because the reactions involved in these steps are isoelectric reactions. Thus, it is apparent that $k_4^3 \ll k_2^3$ [HN<] in acetonitrile solvent, while k_4^3 is no longer insignificant compared with k_2^3 [HN<] in methanol solvent. Just like the value of k_4^3, the value of k_3^3 should be significantly larger in methanol than in acetonitrile solvent. It is therefore obvious that $k_3^3 \gg k_{-2}^3$ [H_2N^+<] in methanol solvent, while k_{-2}^3 [H_2N^+<] $\gg k_3^3$ in acetonitrile solvent at high $[Pip]_T$ (>0.6 M).

It is evident from the results in ref. [27] and in Table II that, at constant content of organic cosolvent in mixed aqueous solvent, the value of k_n^{app} is larger in aqueous methanol than in aqueous-acetonitrile. This is due to larger values of k_1^3/k_{-1}^3 and k_4^3 in aqueous-methanol than in aqueous-acetonitrile because the equilibrium formation of (**T**$^{\pm}$) from SH or S^- and Pip (i.e., equilibrium constant k_1^3/k_{-1}^3) constitutes a non-isoelectric process.

In summary, the absence and presence of general base catalysis in mixed H_2O-Z (where Z = CH_3OH and CH_3CN) with Z ≤ 80% v/v and pure Z solvent, respectively. These observations appear to be the consequence of the decrease in the stability of **T**$^{\pm}$ (Scheme III) and in the value of k_4^3/k_2^3 [HN<] with the increase in the content of Z from 0 to 100%.

CONCLUSION

1. Pseudo-first-order rate constants (k_{obs}) for hydrolysis of phthalimide in the presence of 0.01 M NaOH decrease with the increase in the content of methanol in mixed aqueous solvent, and this solvent effect is attributed to several factors, including the effect of solvent on the pK_a of conjugate acids of nucleophile (HO^-) and leaving group (—$CONH^-$). Although CH_3O^- is a many-fold stronger nucleophile than HO^- toward the nucleophilic attack at carbonyl carbon of esters, it is concluded that the observed rate constants, k_{obs}, represent for hydrolysis and not for methanolysis of phthalimide.
2. The absence and presence of general base catalysis in the reaction of Pip with phthalimide within the methanol content range 0–~80% v/v and at 98% v/v CH_3OH, respectively, are concluded to be from the solvent effect on the stability of highly reactive zwitterionic intermediate (**T**$^{\pm}$) involved in a stepwise addition-elimination reaction mechanism. The monotonic decrease in the values of nucleophilic second-order rate constants (k_n) for the reaction of Pip with phthalimide with the increase in methanol content is attributed to the most probable factor, which involves the solvent effect on the pK_a of conjugate acids of nucleophile (Pip) and the leaving group (—$CONH^-$).
3. The rate of reaction of Pip with phthalimide, studied in the absence of added NaOH, indicates a weak presence of equilibrium between reactants (**SH** + Pip) and product (*N*-piperidinyphthalamide, **3**). The presence of such an equilibrium became more apparent when the rate of reaction of phthalimide with Pip was studied in the presence of 0.03 M NaOH.

The work was supported financially by the National Science Council for R & D, IRPA, Grant No. 09-02-03-0003.

BIBLIOGRAPHY

1. Jencks, W. P. Adv Enzymol 1975, 43, 219.
2. Jencks, W. P. Chem Rev 1972, 72, 705.
3. Jencks, W. P. Acc Chem Res 1976, 9, 425.
4. Jencks, W. P. Acc Chem Res 1980, 13, 161.
5. Williams, A. Adv Phys Org Chem 1992, 27, 1.
6. Bernasconi, C. F. Adv Phys Org Chem 1992, 27, 119.
7. Jencks, W. P. Catalysis in Chemistry and Enzymology; McGraw-Hill: New York, 1969.
8. Bruice, T. C.; Benkovic, S. J. Bioorganic Mechanism; Benjamin: New York, 1966.
9. Bender, M. L. Mechanism of Homogeneous Catalysis from Proton to Proteins; Wiley-Interscience: New York, 1971.
10. Menger, F. M.; Smith, J. H. J Am Chem Soc 1972, 94, 3824 and references cited therein.

11. Hogan, J. C.; Gandour, R. D. J Org Chem 1992, 57, 55 and references cited therein.
12. Maude, A. B.; Williams, A. J Chem Soc, Perkin Trans 1997, 2, 179 and references cited therein.
13. Um, I.-H.; Shin, E.-H.; Kwon, D.-S. Bull Korean Chem Soc 1996, 17, 234.
14. Castro, E. A.; Ureta, C. J Chem Res 1987, (S), 358.
15. Castro, E. A.; Ureta, C. J Chem Res 1987, (M), 3008.
16. Castro, E. A.; Valdivia, J. L. J Org Chem 1986, 51, 1668.
17. Castro, E. A.; Santander, C. L. J Org Chem 1985, 50, 3595.
18. Castro, E. A.; Cubillos, M.; Munooz, G.; Santos, J. G. Int J Chem Kinet 1994, 26, 571.
19. Um, I.-H.; Kwon, H.-J.; Kwon, O.-S.; Prak, J.-Y. J Chem Res 1995, (S), 301.
20. Um, I.-H.; Kwon, H.-J.; Kwon, O.-S.; Prak, J.-Y. J Chem Res 1995, (M), 1801.
21. Castro, E. A.; Hormazabal, A.; Santos, J. G. Int J Chem Kinet 1998, 30, 267.
22. Khan, M. N. Int J Chem Kinet 1998, 30, 301.
23. Bunton, C. A. Catal Rev—Sci Eng 1979, 20, 1.
24. Khan, M. N. J Org Chem 1996, 61, 8063.
25. Khan, M. N.; Fatope, I. L.; Isaak, K. I.; Zubair, M. O. J Chem Soc, Perkin Trans 1986, 2, 655.
26. Khan, M. N.; Arifin, Z.; Yahya, Y. H.; Ahmad, F. React Kinet Catal Lett 1995, 55, 283.
27. Khan, M. N. J Phys Org Chem 1999, 12, 187.
28. Franks, F.; Ives, D. J. G. Quart Rev 1966, 20, 1.
29. Engberts, J. B. F. N. Water, A Comprehensive Treatise; Franks, F., Ed.; Plenum: New York, 1979; Vol 6, p 139.
30. Anantakrishnan, S. V. J Sci Indust Res 1971, 30, 319.
31. Khan, M. N. Indian J Chem 1986, 25A, 831.
32. Khan, M. N. J Phys Org Chem 1994, 7, 412.
33. Khan, M. N. J Chem Soc, Perkin Trans 1989, 2. 199
34. Khan, M. N. J Chem Soc, Perkin Trans 1990, 2, 445.
35. Khan, M. N.; Abdullahi, M. T.; Mohammad, Y. J Chem Res 1990, (S), 52.
36. Khan, M. N.; Abdullahi, M. T.; Mohammad, Y. J Chem Res 1990, (M), 52, 473.
37. Khan, M. N.; Sumaila, M. B. U.; Mohammad, A. M. J Chem Res 1991, (S), 233.
38. Khan, M. N.; Sumaila, M. B. U.; Mohammad, A. M. J Chem Res 1991, (M), 2301.
39. Khan, M. N.; Gleen, P. C.; Arifin, Z. Indian J Chem 1996, 35A, 758.
40. Hupe, D. J.; Jencks, W. P. J Am Chem Soc 1977, 99, 451.
41. Jencks, W. P.; Gilchrist, M. J Am Chem Soc 1968, 90, 2622.
42. Khan, M. N. Int J Chem Kinet 1991, 23, 567.
43. Khan, M. N. Int J Chem Kinet 1987, 19, 143.
44. Khan, M. N. J Pharm Biomed Anal 1989, 7, 685.
45. Khan, M. N.; Arifin, Z.; George, A.; Wahab, I. A. Int J Chem Kinet 2000, 32, 146.
46. Lukkan, O.; Hakoila, E.; Markkola, L. Finn Chem Lett 1978, 2–3, 93.
47. Parson, G. S.; Rochester, C. H. J Chem Soc, Faraday I 1975, 71, 1058.
48. Shafer, J. A.; Morawetz, H. J Org Chem 1963, 28, 1899.
49. Fife, T. H.; DeMark, B. R. J Am Chem Soc 1976, 98, 6978.
50. Fife, T. H.; Benjamin, B. M. J Am Chem Soc 1973, 95, 2059.
51. Barlin, G. B.; Perrin, D. D. Quart Rev Chem Soc 1966, 20, 75.
52. Khan, M. N. J Phys Org Chem 1998, 11, 216.
53. Hegarty, A. F.; Bruice, T. C. J Am Chem Soc 1970 92, 6575.
54. Khan, M. N. Colloids Surf, A 1998, 139, 63.
55. Khan, M. N.; Olagbemiro, T. O. J Org Chem 1982, 47, 3695.
56. Khan, M. N. Int J Chem Kinet 1996, 28, 421
57. Khan, M. N.; Ohayagha, J. E. React Kinet Catal Lett 1996, 58, 97.
58. Bunton, C. A.; Nayak, B.; O'Connor, C. J Org Chem 1968, 33, 572.
59. Fife, T. H.; DeMark, B. R. J Am Chem Soc 1977, 99, 3075 and reference cited therein.
60. Bruice, T. C.; Tanner, D. W. J Org Chem 1965, 30, 1668.
61. Khan, M. N.; Ohayagha, J. E. J Phys Org Chem 1991, 4, 547.
62. Khan, M. N.; Arifin, Z.; Hanifiah, M. A. M.; Lasedik, M. N.; Alex, G. Indian J Chem 1999, 38B, 953.
63. Chiong, K. N. G.; Lewis, S. D.; Shafer, J. A. J Am Chem Soc 1975, 97, 418.
64. Okuyama, T.; Schmir, G. L. J Am Chem Soc 1972, 94, 8805.
65. Dutta, S. C.; Lahiri, S. C. J Indian Chem Soc 1991, 68, 654 and references cited therein.
66. Khan, M. N.; Surajo, Y. M.; Musa, A. I.; Abubakar, A. A.; Gambo, S. I. Indian J Chem 1994, 33B, 752.
67. Foroughifar, N.; Leffek, K. T.; Lee, Y. G. Can J Chem 1992, 70, 2856 and references cited therein.
68. Oszczapowiez, J.; Manaj, J. J. J Chem Soc, Perkin Trans 1991, 2, 1677.
69. Buncel, E.; Um, I.-H.; Hoz, S. J Am Chem Soc 1989, 111, 971.