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Effect of $CH_3CN–H_2O$ and CH_3CN solvents on rate of reaction of phthalimide with piperidine

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ABSTRACT: Pseudo-first-order rate constants (k_{obs}) for the reaction of piperidine with phthalimide vary linearly with the total concentration of piperidine ($[Pip]_T$) at a constant content of CH_3CN in $H_2O–CH_3CN$ solvents within the CH_3CN content range 2–80 % (v/v). The change in k_{obs} with the change in $[Pip]_T$ at 100% (v/v) CH_3CN obeys the relationship $k_{obs} = \Psi\ [Pip]_T{}^2/(1 + \Phi\ [Pip]_T)$. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: phthalimide; piperidine; aminolysis; kinetics; acetonitrile–water solvent; acetonitrile solvent; general base catalysis

INTRODUCTION

Aminolyses of esters in aqueous solution have been extensively studied partly because of the importance of such reactions in understanding the complexity of many *in vivo* enzyme-catalyzed reactions.[1] However, the belief that actual enzyme-catalyzed reactions occur in a microscopic medium which does not totally resemble pure water solvent led a few investigators to study the mechanistic aspects of aminolyses of esters in aprotic solvents.[2] Systematic kinetic studies on the effects of mixed aqueous–organic solvents on rates of aminolysis of esters and related compounds are rare.[3] The most obvious reason for the limited attempts at such studies is the requirement for the use of amine buffers. The complex effects of mixed aqueous–organic solvents on the pK_a values of acids complicate the kinetic treatment of rate data obtained in the presence of buffers. If the rate of hydrolysis of a substrate is insensitive to hydroxide ion concentration within the range *ca* 0.001–0.05 M, then the rate of aminolysis of such a substrate can be easily studied without the use of amine buffers. Such reaction characteristics led a few workers to study the effects of ionic micelles on the aminolysis of organic substrates[4–6] and the effects of $H_2O–CH_3CN$ solvents on the aminolysis of ionized phenyl salicylate[7] without the use of amine buffers.

Apart from some significance of such studies to enzyme-catalyzed reactions, these studies are also important for understanding the complexity of micellar- and membrane-mediated organic reactions. This paper describes the effects of $CH_3CN–H_2O$ and CH_3CN solvents on the rates of reaction of piperidine with phthalimide.

EXPERIMENTAL

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

Kinetic measurements. The reaction rates for the piperidinolysis of phthalimide were studied by monitoring the disappearance of phthalimide spectrophotometrically at 300 nm. The details of the procedure are as described elsewhere.[8]

The reactions were generally followed up to 70–99% completion. All the kinetic runs were carried out under experimental conditions where the reaction rates obeyed a pseudo-first-order rate law. Pseudo-first-order rate constants, k_{obs}, were calculated with the equation

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

using a non-linear least-squares technique considering δ_{app} (apparent molar absorptivity) and A_∞ (the absorbance at reaction time $t = \infty$) as unknown parameters. In Eqn. 1, A_{obs} is the absorbance at any reaction time, t, and $[X]_0$ is the initial concentration of phthalimide (PTH), *i.e.* the concentration of PTH at $t = 0$, $\delta_{app} = \delta_{PTH} - \delta_P$ (where δ_{PTH} and δ_P represent the molar absorptivities of PTH and

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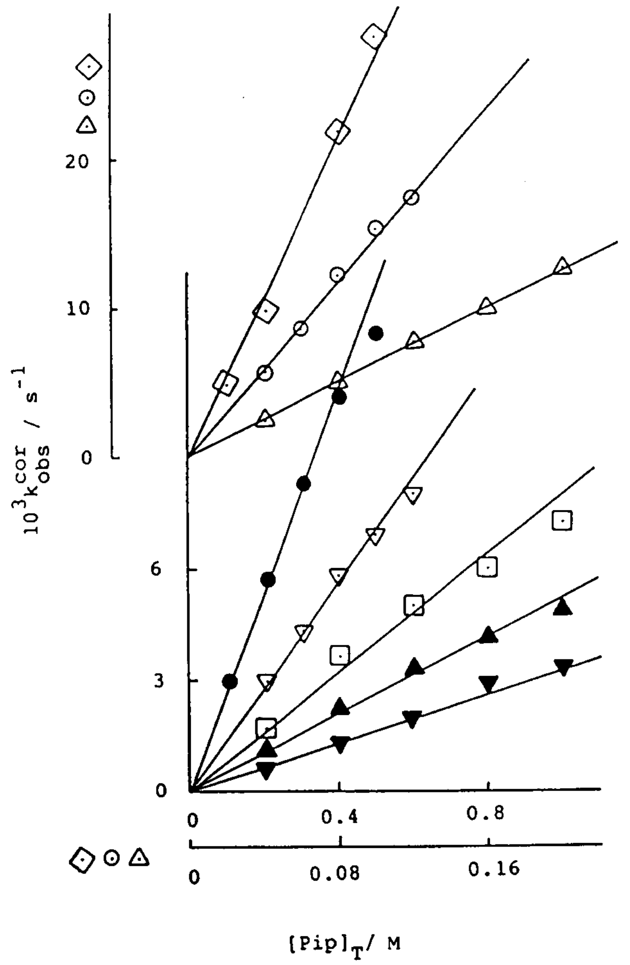


Figure 1. Plots of k_{obs}^{cor} (= $k_{obs} - k_0$) versus $[Pip]_T$ for piperidinolysis of phthalimide at (◊) 2, (○) 10, (△) 20, (●) 30, (▽) 40, (□) 50, (△) 60 and (▽) 80% (v/v) CH_3CN in mixed aqueous solvents. The solid lines were drawn through the calculated points using the equation $k_{obs} - k_0 = k_n[Pip]_T$ and parameters listed in Table 1

products, *N*-piperidinylphthalamide and phthalamic acid, respectively).

Product analysis. The expected products of the cleavage of PTH, in the presence of piperidine in mixed aqueous–acetonitrile and pure acetonitrile solvents, are *N*-piperidinylphthalamide and non-ionized and ionized phthalamic acid. The molar absorptivities of *N*-piperidinylphthalamide and non-ionized and ionized phthalamic acid at 300 nm are nearly zero. Therefore, $\delta_{app} \approx \delta_{PTH}$ at 300 nm. The calculated values of δ_{app} turned out to be almost independent of the total concentration of piperidine ($[Pip]_T$) in mixed aqueous–acetonitrile and pure acetonitrile solvents. These results show that the products of the reaction of piperidine with PTH are chemical species which do not absorb to a detectable level at 300 nm and these products are most likely *N*-piperidinylphthalamide and non-ionized and ionized phthalamic acid.

RESULTS AND DISCUSSION

The rate of reaction of phthalimide with piperidine was studied within the CH_3CN concentration range 2–100% (v/v) in mixed aqueous solvents at 35 °C. Pseudo-first-order rate constants (k_{obs}) at a constant content of CH_3CN but ≤80% (v/v) obeyed the equation

$$k_{obs} = k_0 + k_n[Pip]_T \qquad (2)$$

where k_0 and k_n are the pseudo-first-order rate constant for hydrolysis and the nucleophilic second-order rate constant for the reaction of phthalimide with piperidine, respectively, and $[Pip]_T$ is the total concentration of piperidine. The linear least-squares calculated values of k_0 and k_n [from Eqn. 2] are summarized in Table 1. The calculated values of k_0 are either negative or positive associated with considerably high standard deviations (Table 1). Hence these k_0 values are statistically unreliable. It should be noted that the maximum contributions of k_0 compared with $k_n[Pip]_T$ in Eqn. 2, obtained at the lowest values of $[Pip]_T$, are <40% (Table 1). The significantly low contribution of k_0 compared with $k_n[Pip]_T$ at different contents of CH_3CN in mixed aqueous solvents is a consequence of the unreliable k_0 values calculated from Eqn. 2. The values of k_n were also calculated from Eqn. 2 considering k_0 as a known parameter. The values of k_0 at different contents of CH_3CN were obtained from the literature.[9] These k_n values are not appreciably different from the corresponding k_n values obtained from Eqn. 2 (Table 1). The fitting of the observed data to the equation $k_{obs} - k_0 = k_n[Pip]_T$ is evident from the plots in Fig. 1, where solid lines are drawn through the calculated points.

The increase in $[Pip]_T$ at constant $[H_2O]$ in CH_3CN–H_2O solvent is expected to increase $[^-OH]$ owing to the reaction $H_2O + Pip \rightleftharpoons PipH^+ + {}^-OH$, where Pip and $PipH^+$ represent free and protonated forms of piperidine, respectively. However, such an equilibrium reaction did not increase $[^-OH]$ sufficiently to cause a deviation from linearity in the plot of k_{obs} versus $[Pip]_T$ (Fig. 1). The linearity of the plots in Fig. 1 indicates that the ratio $[Pip]/[Pip]_T$ remains nearly unchanged with change in $[Pip]_T$ at constant $[H_2O]$. It can easily be shown that an increase in $[Pip]_T$ from 0.02 to 0.1 M at 2% (v/v) CH_3CN causes an increase in $[^-OH]$ or $[PipH^+]$ from 0.0058 to 0.0143 M. If we apply such a correction in the calculation of k_n with Eqn. 2, then the corrected value of k_n turns out to be 0.333 ± 0.019 l mol^{-1} s^{-1}, which is comparable with k_n (= 0.290 l mol^{-1} s^{-1}) obtained in the presence of 0.005 M NaOH (unpublished observations).

The rate of hydrolysis, under the present experimental conditions, is independent of $[^-OH]$ and also negligible compared with that of aminolysis. The rate of hydrolysis of phthalimide was found to be almost independent of $[^-OH]$ within the range 0.0025–0.05 M.[10,11] The value of the second-order rate constant (k_{OH}) for the reaction of

Table 1. Effects of content of CH$_3$CN on rate constants, k_0 and k_n, calculated from Eqn. 2[a]

CH$_3$CN (%, v/v)	10^4k_0[b] (s^{-1})	10^3k_n ($l\ mol^{-1}\ s^{-1}$)	[Pip]$_T$ range[c] (M)	Y[d]	W[e]
2	-1.5 ± 14.0[f]	306 ± 21[f]	0.02–0.10	–	12.4
2	(14.4)	268 ± 31	0.02–0.10	21	
10	7.9 ± 7.2	150 ± 9	0.04–0.12	12	2.7
10	(10.5)	146 ± 6	0.04–0.12	15	
20	5.62 ± 0.76	63.4 ± 0.6	0.04–0.20	18	2.7
20	(7.00)	61.7 ± 1.6	0.04–0.20	22	
30	13.5 ± 3.9	23.5 ± 1.2	0.10–0.50	36	16.2
30	(4.46)	27.3 ± 1.9	0.10–0.50	14	
40	8.92 ± 2.22	12.5 ± 0.5	0.20–0.60	26	13.6
40	(3.17)	14.2 ± 0.6	0.20–0.60	10	
50	9.28 ± 3.43	6.66 ± 0.52	0.20–1.00	41	21.3
50	(2.40)	8.08 ± 0.77	0.20–1.00	13	
60	4.05 ± 2.02	4.71 ± 0.30	0.20–1.00	30	10.8
60	(1.43)	5.22 ± 0.30	0.20–1.00	12	
80	-1.8 ± 1.7	3.65 ± 0.25	0.20–1.00	–	15.3
80	(0.642)	3.09 ± 0.46	0.20–1.00	9	

[a] [Phthalimide]$_0$ = 2×10^{-4} M; temperature = 35 °C, λ = 300 nm; co-solvent is water.
[b] Parenthesized k_0 values as determined at 0.01 M NaOH were obtained from Ref. 9.
[c] The range of total concentration of piperidine.
[d] $Y = 100k_0/(k_0 + k_n[\mathrm{Pip}]_T)$, where [Pip]$_T$ is the minimum concentration of piperidine attained in the study.
[e] $W = 100(|k_n - (k_n)|)/k_n$, where k_n is calculated from Eqn. 2 and (k_n) is calculated from the relationship $k_{obs} - k_0 = k_n[\mathrm{Pip}]_T$ with k_0 from Ref. 9.
[f] Error limits are standard deviations.

ionized phthalimide (S^-) with ^-OH turned out to be 3.5×10^{-3} l mol^{-1} s^{-1} at 30 °C.[10,11] The pK_a of PipH$^+$ decreased from 11.37 to 10.99 with increase in the content of CH$_3$CN from 2 to 60% (v/v) and became 11.36 at 70% (v/v) CH$_3$CN in mixed aqueous solvents.[12] pK_w increased from 14.00 to 15.43 with increase in the content of ethanol from 0 to 70% (w/w) at 25 °C in water–ethanol solvent.[13] An increase in the CH$_3$CN content in mixed aqueous solvent is also expected to decrease K_w. It can easily be shown that the effects of CH$_3$CN content on K_a and K_w in mixed aqueous solvents may produce $[^-OH] < 0.05$ M owing to the reaction $\mathrm{Pip} + \mathrm{H_2O} \rightleftharpoons \mathrm{PipH^+} + {}^-\mathrm{OH}$, under the experimental conditions imposed.

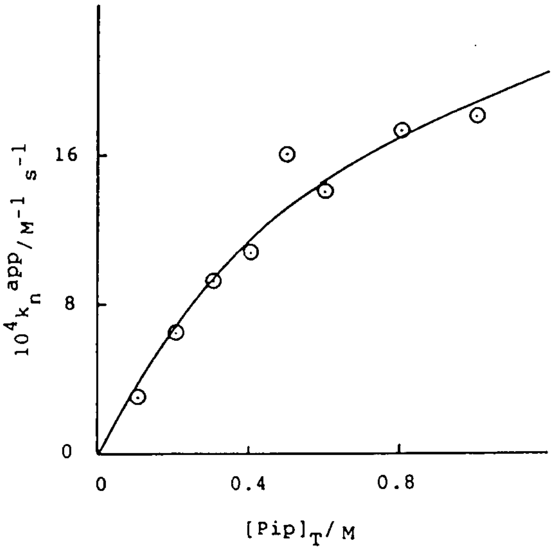


Figure 2. Plot of k_n^{app} (= $k_{obs}/[\mathrm{Pip}]_T$) versus [Pip]$_T$ for piperidinolysis of phthalimide in acetonitrile solvent. The solid line was drawn through the calculated points using Eqn. 3 and parameters mentioned in the text

The experimentally observed value of k_{obs} at 0.01 M NaOH and 80% (v/v) CH$_3$CN is 6.42×10^{-5} s^{-1} (Table 1). If we assume that under such conditions the reactants are only non-ionized phthalimide (SH) and ^-OH, then the value of k_{OH} is 6.42×10^{-3} l mol^{-1} s^{-1}. Now, even if it is assumed that $[^-OH]$ = 0.021 and 0.048 M at 0.2 and 1.0 M Pip and 80% (v/v) CH$_3$CN (which is not correct as it can be shown that under such conditions, $[^-OH] \ll 0.021$ and 0.048 M at 0.2 and 1.0 M Pip, respectively), then the values of k_{obs} turn out to be 1.3×10^{-4} and 3.1×10^{-4} s^{-1} at 0.2 and 1.0 M Pip, respectively. These k_{obs} values are more than 4- and 10-fold smaller than the respective k_{obs} values obtained at 0.2 and 1.0 M Pip and 80% (v/v) CH$_3$CN (Table 1). Similarly, k_{obs} (due to hydrolysis only) may be shown to be 1.44×10^{-3} s^{-1} within the [Pip]$_T$ range 0.02–0.10 M at 2% (v/v) CH$_3$CN, which is more than 4- and 20-fold smaller than k_{obs} values obtained at 0.02 and 0.10 M Pip, respectively (Table 1). This shows that the hydrolysis is negligible compared with aminolysis of phthalimide under the experimental conditions of the present study.

The values of k_{obs} at 100% (v/v) CH$_3$CN obeyed the following empirical equation:

$$k_n^{app} = \frac{\Psi[\mathrm{Pip}]_T}{1 + \Phi[\mathrm{Pip}]_T} \qquad (3)$$

where $k_n^{app} = k_{obs}/[\mathrm{Pip}]_T$ and Ψ and Φ are empirical parameters. The non-linear least-squares calculated values of Ψ and Φ are $(4.39 \pm 0.72) \times 10^{-3}$ l^2 mol^{-2} s^{-1} and 1.32 ± 0.47 l mol^{-1}, respectively. A Reasonably good fit of the experimental data to Eqn. 3 can be seen from the plot in Fig. 2, where a solid line is drawn through the calculated points.

An increase in the content of CH_3CN from 2 to 80% (v/v) decreased k_n 87-fold (Table 1) and k_0 22-fold.[9] Nearly a 26-fold decrease in k_n for the reaction of *p*-nitrophenyl acetate with piperidine was observed with increase in the CH_3CN content from 0 to 80 mol% in mixed aqueous solvents.[3] The pH-independent hydrolysis of phthalimide in aqueous solution containing 1.6% (v/v) CH_3CN involves ^{-}OH and non-ionized phthalimide (SH) as the reactants,[9] whereas with such a solvent and within the pH range 10.8–11.5 the reaction of phthalimide with piperidine involves S^- and free piperidine as the reactants.[14] Based on the Brønsted plot, piperidine (Pip) reacts with SH only *ca* four times faster compared with S^-. The significantly high reactivity of Pip with S^- is attributed to the occurrence of intramolecular general acid–base catalysis.[14] The absence of reaction between Pip and SH in aqueous solution containing 1.6% (v/v) CH_3CN was concluded to be due to the extremely low concentration of SH at pH $\geq$ 10.8. As mentioned earlier, an increase in CH_3CN content in mixed aqueous solvents has little effect on the pK_a of PipH$^+$. However, the pK_a of phenol increased continuously from 9.95 to 18.03 with the increase in DMSO content from 0 to 100 mol% in mixed aqueous solvents.[15] The ionization of both phenol and SH constitutes non-isoelectric ionization reactions. Hence the ionization constant of SH is expected to decrease continuously with increase in CH_3CN content in mixed aqueous solvents. These inferences indicate that an increase in acetonitrile content in mixed aqueous solvents should increase the concentration of SH.

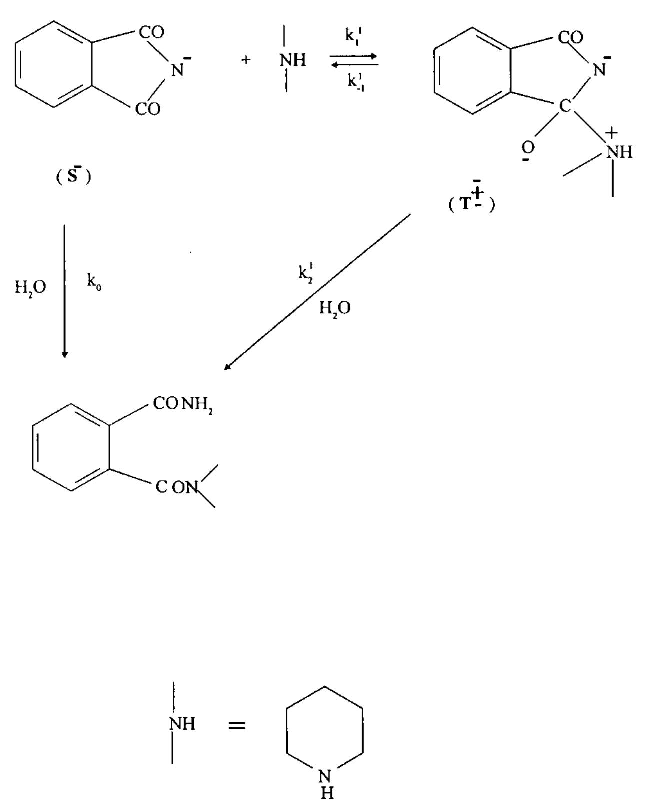
The effects of mixed aqueous–organic solvents on reaction rates may be attributed to several factors, such as permittivity, polarizability, polarity, basicity, preferential solvation, hydrogen bonding and hydrophobicity. These factors are not equally influential and some of them oppose each other towards a particular reaction rate. The transition state involved in the reaction of Pip with either S^- or SH is more polar than the reactant state and hence the decrease in k_n with increase in CH_3CN content may be ascribed to greater destabilization of the transition state than the ground state. However, if this is the only source for the effect of CH_3CN–H_2O solvent on k_n, then it is difficult to explain the extremely slow decrease in k_n with increase in CH_3CN content at >50% (v/v) CH_3CN (Table 1). Similarly, the [CH_3CN]-independent k_n for the reactions of Pip with *p*-nitrophenyl acetate[3] and ionized phenyl salicylate[12] at $\geq$60% (v/v) CH_3CN in mixed aqueous solvents cannot be explained in terms of the relatively larger destabilization of transition state.

Perhaps it is more appropriate to discuss the effect of solvent on the rate of an addition–elimination reaction in terms of solvent effect on the nucleophilicity of a nucleophile (i.e. the pK_a of a protonated nucleophile) and on the leaving ability of the leaving group (i.e. the pK_a of a protonated leaving group). The pK_a of piperidinium ion (PipH$^+$) decreases from 11.37 to 10.98 with increase in CH_3CN content from 2 to 50% (v/v) whereas it increases from 10.98 to 11.36 with the increase in CH_3CN content from 50 to 70% (v/v).[12] Similar observations have been obtained for several protonated amines.[16–18] The pK_a value of PipH$^+$ becomes 18.92 at 100% (v/v) CH_3CN.[3] Unlike the equilibrium constant of an isoelectric reaction ($BH^+ \rightleftharpoons B + H^+$), the equilibrium constant of a non-isoelectric reaction ($AH \rightleftharpoons A^- + H^+$) decreases continuously with increase in the content of organic co-solvent in a mixed aqueous solvent.[12,15,19] The pK_a value of phenol increased from 10.17 to 13.38 with increase in CH_3CN content from 2 to 70% (v/v) (unpublished observations). The pK_a value of phenol is 27.2 at 100% (v/v) CH_3CN.[3] The ionization of the conjugate acid of the leaving group in the aminolysis of phthalimide ($CONH_2$ or $CONH^-$) also constitutes a non-isoelectric reaction. Therefore, an increase in CH_3CN content is expected to increase continuously the pK_a of the leaving group in mixed aqueous solvents.

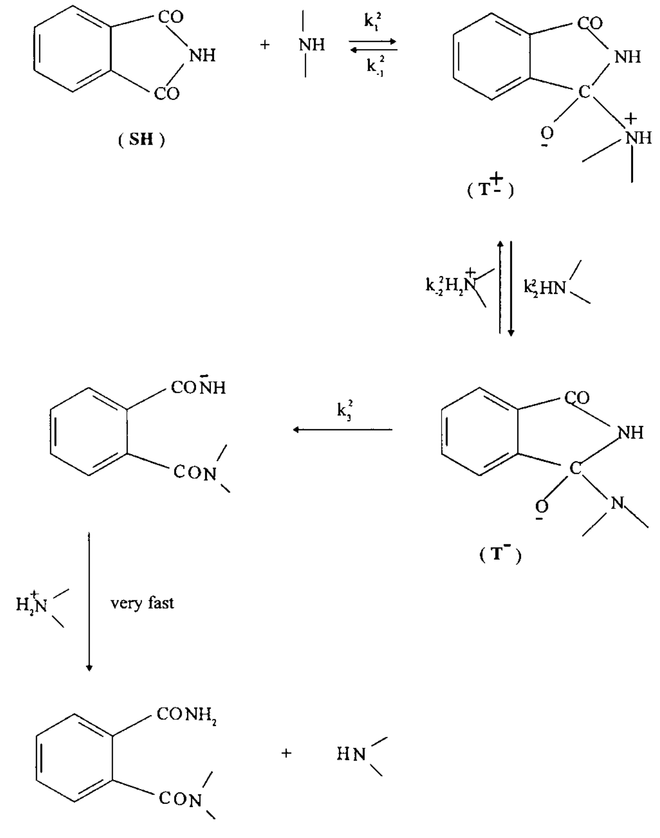
An increase in the pK_a of the conjugate acid of the leaving group should decrease whereas an increase in the pK_a of the conjugate acid of the nucleophile should increase the rate of reaction. Thus, the sharp decrease in k_n with increase in the content of CH_3CN in water-rich mixed acetonitrile–water solvents may be attributed to the increase and decrease in the pK_a of the leaving group and nucleophile, respectively. The moderately slow decrease in k_n with increase in CH_3CN content at >50% (v/v) CH_3CN is due to the increase in the pK_a of the conjugate acid of both the leaving group and the nucleophile.

The significantly large decrease in k_n for the reaction of PTH with piperidine (87-fold) compared with k_0 for hydrolysis of PTH (22-fold) may be explained in terms of the solvent effect on the pK_a of PipH$^+$ and H_2O. The slope of the plot of pK_a versus CH_3CN content should be larger for H_2O (K_a for a non-isoelectric ionization reaction) than for PipH$^+$ (K_a for an isoelectric ionization reaction) and consequently the decreasing effect of the mixed CH_3CN–H_2O solvents should be larger for piperidinolysis than for hydrolysis of phthalimide.

The mechanism of aminolysis of phthalimide in an aqueous solvent containing $\leq$2% (v/v) CH_3CN has been studied in some detail.[14,20] Although the present data obtained in mixed aqueous–acetonitrile solvents are not sufficient to discuss any detailed mechanism, it appears that there is no change in mechanism with change in the composition of CH_3CN–H_2O solvent. The mechanism for the reaction of Pip with PTH in mixed CH_3CN–H_2O solvents may be as shown in Scheme 1, where $\mathbf{T}^{\pm}$ is a highly reactive transient intermediate. It has been concluded elsewhere[14] that $k_{-1}{}^1 \gg k_2{}^1$ and hence the $k_2{}^1$ step, which involves the cleavage of the C—N bond



Scheme 1



Scheme 2

coupled with proton transfer from the cationic amino group to the leaving group through a proton switch mechanism, is the rate-determining step.

The observed rate law (rate = $k_{obs}[\mathrm{PTH}]_T$, where $[\mathrm{PTH}]_T$ is the total concentration of PTH) and Scheme 1 lead to the equation

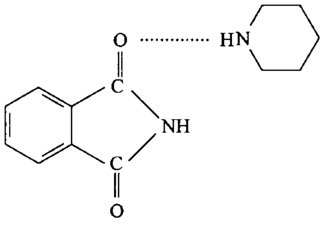
$$k_{obs} = k_0 + k_1{}^1 k_2{}^1 f_a[\mathrm{Pip}]_T/k_{-1}{}^1 \qquad (4)$$

where $K_a^{\mathrm{PTH}} \gg a_H$ with $K_a^{\mathrm{PTH}} = [\mathrm{S}^-]\ a_H/[\mathrm{SH}]$ and $f_a = K_a^{\mathrm{Pip}}/(a_H + K_a^{\mathrm{Pip}})$ with $K_a^{\mathrm{Pip}} = [\mathrm{Pip}]\ a_H/[\mathrm{PipH}^+]$. Equation 4 is similar to Eqn. 2 with $k_n = k_1{}^1\ k_2{}^1\ f_a/k_{-1}{}^1$.

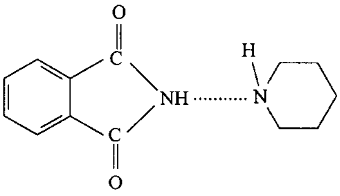
The plots in Figs 1 and 2 show that the mechanisms for the reaction of phthalimide with piperidine in mixed CH_3CN–H_2O and CH_3CN solvents are different. It has been concluded that the negative deviations in the relationship between rate constant and catalyst concentration which are not caused by complexing of reactants or catalyst are caused by the change in the rate-determining step.[1a] The change in the rate-determining step with change in catalyst concentration implies the existence of a transient intermediate on the reaction path. Thus, the plot in Fig. 2 supports the occurrence of a stepwise mechanism for the reaction of phthalimide with piperidine in pure acetonitrile solvent. In terms of proposed and kinetically supported mechanisms for the aminolysis of esters in acetonitrile[2c] and other organic solvents,[2] the mechanism for the reaction of Pip with SH in pure CH_3CN solvent may be as shown in Scheme 2. The existence of a highly reactive zwitterionic tetrahedral intermediate (**T**$^\pm$) and monoanionic tetrahedral intermediate (**T**$^-$) was supported by the break in the Brønsted plot.[2c] The non-linear feature of the plot in Fig. 2 may be explained by the mechanism shown in Scheme 2 where the $k_2{}^2$ step is the rate-determining step at low $[\mathrm{Pip}]_T$ and at high $[\mathrm{Pip}]_T$ the $k_3{}^2$ step becomes the rate-determining step.

The other possibilities for the non-linear nature of the plot in Fig. 2 are (1) self-association of only SH molecules, (2) association of Pip and SH or (3) self-association of Pip molecules. The first possibility may be ruled out because self-association of SH molecules may lead to a rate law which does not agree with the observed rate law (rate = $k_{obs}[\mathrm{PTH}]_T$, where $[\mathrm{PTH}]_T$ is the total concentration of phthalimide).

The second possibility involves the formation of a complex (SH$^\bullet$Pip) between SH and Pip where the electrophilic reactivity towards Pip of SH is negligible compared with that of SH$^\bullet$Pip. Such a complex (**C$_1$**) should involve hydrogen bonding between the amine hydrogen of Pip and the carbonyl oxygen of SH. If the hydrogen of the imide group of SH is hydrogen bonded with the nitrogen of Pip in SH$^\bullet$Pip (**C$_2$**), then such an interaction must cause SH$^\bullet$Pip to be less reactive than SH toward Pip, and this is against the observed results. The second possibility which involves hydrogen-bonded complex (SH$^\bullet$Pip) formation between SH and Pip molecules could lead to the following rate law:



C_1



C_2

$$\text{rate} = \frac{k_2 K_C [\text{Pip}]_T^2 [\text{PTH}]_T}{1 + K_C [\text{Pip}]_T} \qquad (5)$$

where K_C represents the equlibrium constant for the complex formation between SH and Pip and k_2 is the second-order rate constant for the reaction of Pip with SH$^\bullet$Pip. Equation 5 is derived based on the assumption that $[\text{Pip}]_T = [\text{Pip}] + [\text{SH}^\bullet\text{Pip}] \approx [\text{Pip}]$ for $[\text{Pip}] \gg [\text{SH}^\bullet\text{Pip}]$ [the lowest concentration of Pip (0.1 M) is 500-fold larger than the initial concentration of PTH (2×10^{-4} M)]. Equation 5 and the observed rate law may give

$$k_{\text{obs}} = \frac{k_2 K_C [\text{Pip}]_T^2}{1 + K_C [\text{Pip}]_T} \qquad (6)$$

Equation 6 is similar to Eqn. 3 with $\Psi = k_2 K_C$ and $\Phi = K_C$. Although the observed data appear to fit Eqn. 6 reasonably well, such fitting may be regarded as fortuitous because the complex formation between SH and Pip is inconceivable because similar complex formation between phenyl salicylate and *n*-butylamine[2a] and between catechol monoacetate and *n*-butylamine[21] could not be detected in aprotic solvents. Similarly, no such complex formation was detected in other related reactions.[22]

The third possibility that Pip molecules associate themselves may lead to the rate law as expressed by Eqn. 7 provided the associated complex (Pip$^\bullet$Pip) is reactive and the free piperidine molecule is non-reactive.

$$\text{rate} = \frac{k_2 K_A [\text{Pip}]_T^2 [\text{PTH}]_T}{1 + 3K_A [\text{Pip}]_T} \qquad (7)$$

In Eqn. 7, the assumption involved is that $K_A[\text{Pip}] \ll 1$, where K_A represents the association constant for dimerization of Pip. The observed rate law and Eqn. 7 can yield

$$k_{\text{obs}} = \frac{k_2 K_A [\text{Pip}]_T^2}{1 + 3K_A [\text{Pip}]_T} \qquad (8)$$

Equation 8 is similar to Eqn. 3 with $\Psi = k_2 K_A$ and $\Phi = 3K_A$. Hence the observed data in Fig. 2 may be explained in terms of Eqn. 8. However, the fitting of observed data to Eqn. 8 may be considered to be inconceivable because such dimerization of amine molecules (primary and secondary amines) was not detected in several related studies.[2,3,21,22] Furthermore, a tertiary amine was found to act as a general base catalyst in related studies[23] whereas Eqn. 8 indicates that a tertiary amine should not be reactive.

The observed rate law (rate = $k_{\text{obs}}[\text{PTH}]_T$) and Scheme 2 can lead to Eqn. 9 provided that $k_{-1}^2 \gg k_2^2[\text{Pip}]$ and $[\text{SH}] = [\text{PTH}]_T$.

$$k_{\text{obs}} = \frac{k_2^2 K_1^2 f_a^2 [\text{Pip}]_T^2}{1 + f_{aH}(k_{-2}^2/k_3^2)[\text{Pip}]_T} \qquad (9)$$

The feasibility of the inequality $k_{-1}^2 \gg k_2^2[\text{Pip}]$ is discussed in detail elsewhere.[14] In Eqn. 9, $K_1^2 = k_1^2/k_{-1}^2$ and $f_{aH} = 1 - f_a$. Equation 9 is similar to Eqn. 3 with $\Psi = k_2^2 K_1^2 f_a^2$ and $\Phi = (k_{-2}^2/k_3^2) f_{aH}$.

It is interesting that general base (GB) catalysis is negligible compared with the uncatalyzed cleavage of PTH in CH_3CN–H_2O solvents with CH_3CN content $\leq$80% (v/v) whereas the rate of uncatalyzed cleavage of PTH becomes negligible compared with GB-catalyzed cleavage in 100% (v/v) CH_3CN solvent. It should be noted that the reason for the occurrence of a stepwise mechanism in 100% acetonitrile solvent is the conclusion that the change in the slope of k_n versus $[\text{Pip}]_T$ plot is due to the change in the rate-determining step with change in $[\text{Pip}]_T$. The change in the rate-determining step with change in the reaction conditions implies that the reaction involves reactive intermediate(s) on the reaction path.

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