Effects of Mixed H_2O–CH_3CN Solvents on the Brønsted Coefficient for the Intramolecular General Base-Catalyzed Cleavage of Ionized Phenyl Salicylate in the Presence of Primary and Secondary Amines

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ABSTRACT: Nucleophilic second-order rate constants, k_n^{ms}, for the reactions of several primary and secondary amines with ionized phenyl salicylate (PS^-) show a nonlinear decrease with the increase in the content of CH_3CN from 2 to $\leq$50% v/v in mixed aqueous solvent. The values of k_n^{ms} remain almost unchanged with the change in the content of CH_3CN at $>$50% v/v. The nucleophilic reactivity of primary and secondary amines toward PS^- reveal Brønsted plots of different Brønsted coefficients, β_{nuc}, at a constant content of CH_3CN in mixed aqueous solvents. The values of β_{nuc} decrease from 0.4 to nearly 0 for primary amines and from 0.22 to 0.12 for secondary amines with the increase in CH_3CN content from 2 to 70% v/v. The values of k_n^{ms}/k_{MeOH}^{ms} (where k_{MeOH}^{ms} represents the nucleophilic second-order rate constant for the reaction of MeOH with PS^- in H_2O–CH_3CN solvents), obtained within 2–50%v/v CH_3CN, fit to an empirical equation: $\log (k_n^{ms}/k_{MeOH}^{ms}) = \theta + \lambda X$ where X is the % v/v content of CH_3CN, and θ and λ are empirical constants. It has been shown empirically that both θ and λ are the function of Brønsted coefficient β_{lg}. The values of λ are used to calculate β_{lg} and these β_{lg} values for all amines except Tris lie within -0.32 to -0.46. The effects of mixed water–acetonitrile solvents on pK_a of leaving the group, phenol, and conjugate acid of amine nucleophile

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have been concluded to be the major source for the observed solvent effects on k_n^{ms}. The β_{lg} for Tris is unusually very close to zero. © 2000 John Wiley & Sons, Inc. Int J Chem Kinet 32: 153–164, 2000

INTRODUCTION

Almost all the biological reactions and a large fraction of reactions involved in chemical research, including pharmaceutical developments, occur in aqueous or mixed aqueous–organic solvents. Although vigorous efforts have been made for the last several decades to understand theoretically the effects of such solvents on rates of reactions, there seems to be no adequate theory that could explain the complexities of the solvent effects on reaction rates. A huge amount of work on the effects of mixed aqueous–organic solvents on the rates of neutral, and acid- and base-catalyzed solvolysis of organic molecules has been carried out for many decades [1]. However, studies of the effects of mixed aqueous–organic solvents on rates of aminolysis of esters, amides, and imides are rare. A few reports have appeared on mixed aqueous–organic solvent effects on rates of aminolysis of esters [2–9]. The probable cause for the lack of such studies is described elsewhere [3].

Many enzyme-catalyzed and a large fraction of micellar as well as vesicle-mediated reactions are believed to occur in a microreaction medium of considerably low dielectric constant (ε) compared with ε of pure water solvent. Thus, the study on the effects of mixed aqueous–organic solvents of varying ε on the rates of organic reactions may be of considerable importance [10–12]. The effects of H_2O-CH_3CN solvents on rates of hydrolysis [13], alkanolysis [14], and aminolysis [15] of ionized phenyl salicylate (PS^-) have been studied. However, the data on aminolysis of PS^- were not sufficient to draw any mechanistic conclusion. We therefore extended the study on the effects of H_2O-CH_3CN solvents on rates of aminolysis of PS^- by selecting additional primary and secondary amines. The results and their probable mechanistic implications are discussed in this article.

EXPERIMENTAL

Materials

Reagent grade chemicals (obtained from Fluka, BDH, and Aldrich) were used in the entire study. Stock solutions of phenyl salicylate were prepared in acetonitrile. Stock solutions of free amines (i.e., amine bases) were freshly prepared in both acetonitrile and glass-distilled water. However, stock solutions of 0.25 M CH_3NH_3Cl and $(CH_3)_2NH_2Cl$ were freshly prepared in 0.30 M NaOH. Stock solutions of 0.25 M hydrazine sulfate ($NH_2NH_2 \cdot H_2SO_4$) were freshly prepared in 0.56 M NaOH.

Kinetic Measurements

The rates of aminolysis of PS^- were studied by monitoring the disappearance of PS^- spectrophotometrically at 350 nm. In a typical kinetic run, all the reaction ingredients (i.e., desired amount of amine, and 0.01 M NaOH with 4.9 ml of mixed water–acetonitrile solvent containing the required proportion of water and acetonitrile) except phenyl salicylate, were placed in a 25-mL reaction vessel, which was, in turn, placed in a thermostated water bath. The reaction solution (4.9 ml) was allowed to equilibrate for 5–10 min at 35°C. The reaction was then initiated by adding 0.1 ml of 0.01 M phenyl salicylate. An aliquot of ca. 2.5 ml was quickly withdrawn from the reaction mixture and transferred to a 3-ml quartz cuvette kept in the thermostated cell compartment of the spectrophotometer. The decrease in absorbance, A_{obs}, with time, t, at 350 nm was monitored by the use of a Shimadzu UV-visible–near infrared or diode–array spectrophotometer.

Almost all the kinetic runs that involved the stock solutions of nonprotonated amines were studied in the presence of 0.01 M NaOH. However, all kinetic runs involving stock solutions of protonated amines [such as CH_3NH_3Cl, $(CH_3)_2NH_2Cl$, and $H_2NNH_2H_2SO_4$] were carried out in the presence of NaOH ranging from 0.014 to 0.034 M. Details of the data analysis and product characterization study are described elsewhere [16,17].

RESULTS AND DISCUSSION

Effects of $[Am]_T$ on Aminolysis of PS^- in Mixed Aqueous–Acetonitrile Solvents Containing a Constant Concentration of NaOH

A few kinetic runs were carried out at different $[Am]_T$ (= total concentration of amine), at 35°C, and at a constant content of acetonitrile in mixed aqueous solvent. Pseudo-first-order rate constants (k_{obs}) obeyed Eq. (1)

$$k_{obs} - k_0 = k_n^{ms}[Am]_T \qquad (1)$$

where k_0 is the pseudo-first-order rate constant for hydrolysis and k_n^{ms} is the apparent nucleophilic second-order rate constant for the reaction of amine with PS^-. The value of k_0 at a specific experimental condition was obtained from literature [18,19]. The least-squares-calculated values of k_n^{ms} at different contents of CH_3CN are summarized in Table I. The fitting of observed data to Eq. (3) is evident from some representative plots of Figure 1 where solid lines are drawn through the least-squares-calculated points and from the standard deviations associated with the calculated values of k_n^{ms} (see Table I).

The change in $[Am]_T$ at a constant [NaOH] and $[H_2O]$ in mixed acetonitrile solvents is bound to change $[OH^-]_T$ (= total concentration of hydroxide ions) due to reaction: $H_2O + Am \rightleftharpoons AmH^+ + OH_{re}^-$ where Am and AmH^+ represent unprotonated and protonated amine, respectively. However, such a change in $[OH^-]_T$ is not sufficient to cause a nonlinear increase in k_{obs} with the increase in $[Am]_T$ at a constant added [NaOH].

The concentration of protonated amines was considered to be negligible under the experimental conditions of the present study. This assertion is based on the fact that the increase in [NaOH] from 0.01 to 0.04 M did not show an increase in k_n^{ms} (see Table I) for the reaction of PS^- with 1,3-diaminopropane at 70% v/v CH_3CN. Similarly, an increase in [NaOH] from 0.01 to 0.03 M did not reveal a significant effect on k_n^{ms} for dimethylaminolysis of PS^- at 2 and 10% v/v CH_3CN (see Table I). The increase in the content of CH_3CN either decreased slightly or had no effect on pK_a^{ms} of amines of the present study until the CH_3CN content became 50–60% v/v. The pK_a^{ms} values of these amines at 70% v/v CH_3CN became equal to or slightly larger than the corresponding pK_a at 2% v/v CH_3CN (preceding article). The pK_a^{ms} value of H_2O is expected to increase with the increase in the content of CH_3CN in mixed aqueous solvents. Thus, the probability of the presence of AmH^+ decreases with the increase in the content of CH_3CN. A slightly lower value of k_n^{ms} at 0.04 M NaOH than that at 0.01 M NaOH for the reaction of PS^- with 1,3-diaminopropane at 70% v/v CH_3CN may be attributed to negative salt effect [20].

Nonionized phenyl salicylate (PSH) does not absorb to a detectable level while PS^- absorbs strongly (molar extinction coefficient, $\delta \approx 6000\ M^{-1}\ cm^{-1}$) at 350 nm [17]. The values of the initial absorbance (i.e., absorbance at the reaction time, $t = 0$) at 350 nm of the reaction mixtures for the kinetic runs carried out under the present experimental conditions were found to be unchanged with the change in the contents of CH_3CN in mixed aqueous solvents. This shows the presence of a 100% ionized form (PS^-) of phenyl salicylate.

The increase in the content of CH_3CN from 2 to 50% v/v in mixed aqueous solvents decreased k_n^{ms} by ca. 3.6- to 7.0-fold for various primary and secondary amines (see Table I). It is noteworthy that minimum decreases (~3.6-fold) were found for those amines [2-hydroxyethylamine, hydrazine, morpholine, and *N*-(2-hydroxyethyl)piperazine] whose pK_a values were found to be almost independent of % v/v content of CH_3CN within its range of 2–50% v/v (preceding article). The rate constants, k_n^{ms}, were almost independent of acetonitrile content at ≥50% v/v CH_3CN for most of the amines.

The rate constants, k_n^{ms}, for tris-(hydroxymethyl)aminomethane (Tris) revealed an increase, although modest, with the increase in the content of CH_3CN from 2 to 70% v/v (see Table I). These results may be considered to be unusual compared with those for other amines of the present study. Transesterification has been shown to be unimportant compared with aminolysis in the reaction of Tris with PS^- in aqueous solvent containing 0.8% v/v CH_3CN [16].

Effects of Mixed Aqueous–Acetonitrile Solvents on the Rate of Cleavage of PS^- at a Constant [NaOH] in the Presence of Tertiary Amines

The effects of H_2O-CH_3CN solvents on the rate of cleavage of PS^- were studied by carrying out a few kinetic runs at different concentrations of *N*-ethylpiperidine and *N*-(2-hydroxyethyl)morpholine. Pseudo-first-order rate constants (k_{obs}), obtained at different total amine concentrations ($[Am]_T$) and at 2 and 60% v/v CH_3CN, are summarized in Table II. It is evident from the results in Table II that the rate of cleavage of PS^- is independent of [*N*-ethylpiperidine] at both 2 and 60% v/v CH_3CN. Similar results were obtained with several other tertiary amines in aqueous solvents containing <2% v/v CH_3CN [21–23]. The values of k_{obs} at different $[Am]_T$ are comparable with the corresponding values of k_{obs} obtained under similar experimental conditions in the absence of tertiary amines [18,19].

Pseudo-first-order rate constants, k_{obs}, increased slightly with the increase in the total concentration of *N*-(2-hydroxyethyl)morpholine at a constant content of CH_3CN (see Table II). Tertiary amines did not show nucleophilic reactivity toward PS^-, and therefore the amino group of *N*-(2-hydroxyethyl)morpholine cannot be expected to react with PS^-. However, ionized

Table I Nucleophilic Second-Order Rate Constants (k_n^{ms}) Calculated from Eq. (1)[a]

Amine	CH$_3$CN (% v/v)	$10^3 k_n^{ms}$ M^{-1} s^{-1}	[Am]$_T$[b] (M)	No. of Runs
1,4-Diaminobutane	2	149 ± 4[c] (2.59)[d]	0.02−0.10	5
	10	104 ± 3 (2.43)	0.02−0.10	5
	20	65.4 ± 1.6 (2.23)	0.02−0.10	5
	30	42.2 ± 1.1 (2.26)	0.02−0.10	5
	40	31.2 ± 1.0 (2.29)	0.02−0.10	5
	50	23.2 ± 0.3 (2.55)	0.02−0.10	5
	60	22.0 ± 0.5 (2.91)	0.02−0.06	5
	70	20.1 ± 0.7 (3.48)	0.02−0.06	5
1,3-Diaminopropane	2	126 ± 3	0.04−0.20	5
	10	88.2 ± 3.3	0.04−0.20	5
	20	58.0 ± 1.7	0.04−0.20	5
	30	37.7 ± 1.0	0.04−0.20	5
	40	28.9 ± 0.7	0.04−0.20	5
	50	24.6 ± 0.3	0.04−0.20	5
	60	20.8 ± 0.6	0.04−0.12	5
	70	22.1 ± 0.7	0.04−0.12	5
	70[e]	18.1 ± 0.5	0.04−0.12	5
2-Hydroxyethylamine	2	34.8 ± 1.0	0.04−0.20	5
	10	26.6 ± 1.0	0.04−0.20	5
	20	18.7 ± 1.0	0.04−0.20	5
	30	12.6 ± 0.6	0.04−0.20	5
	40	10.9 ± 0.6	0.04−0.20	5
	50	9.63 ± 0.33	0.04−0.20	5
	60	10.0 ± 0.4	0.04−0.12	5
	70	9.84 ± 0.20	0.04−0.12	5
n-Propylamine	2	69.6 ± 1.0	0.04−0.20	5
	10	50.0 ± 1.7	0.04−0.20	5
	20	30.4 ± 1.7	0.04−0.20	5
	30	18.4 ± 1.8	0.04−0.20	5
	40	13.6 ± 1.0	0.04−0.20	5
	50	10.6 ± 0.3	0.04−0.20	5
	60	8.94 ± 0.35	0.04−0.12	5
	70	7.70 ± 0.14	0.04−0.12	5
Methylamine[f]	2	207 ± 3	0.20−0.10	5
	10	161 ± 3	0.02−0.10	5
	20	103 ± 4	0.02−0.10	5
	30	67.7 ± 2.9	0.02−0.10	5
	40	50.7 ± 2.0	0.02−0.10	5
	50	39.4 ± 2.3	0.02−0.10	5
	60	34.0 ± 0.8	0.02−0.06	5
	70	29.5 ± 1.9	0.02−0.06	5
Hydrazine[g]	2	150 ± 4	0.02−0.10	5
	10	114 ± 4	0.02−0.10	5
	20	74.6 ± 1.6	0.02−0.10	5
	30	54.8 ± 2.5	0.02−0.10	5
	40	42.9 ± 8.2	0.02−0.10	5
	50	40.3 ± 3.9	0.02−0.10	5
	60	42.1 ± 3.4	0.02−0.05	5
	70	41.1 ± 7.8	0.02−0.05	5

(Continued)

Table I (Continued)

Amine	CH_3CN (% v/v)	$10^3k_n^{ms}$ M^{-1} s^{-1}	$[Am]_T^b$ (M)	No. of Runs
Benzylamine	2	35.2 ± 1.2	0.03–0.12	5
	10	24.3 ± 2.0	0.03–0.12	5
	20	15.1 ± 0.6	0.03–0.12	5
	30	9.93 ± 0.40	0.03–0.12	5
	40	7.34 ± 0.53	0.03–0.15	5
	50	5.00 ± 0.24	0.03–0.15	5
	60	5.03 ± 0.37	0.03–0.15	5
	70	3.76 ± 0.08	0.03–0.15	5
Tris	2	6.06 ± 0.17	0.2–0.6	5
	10	6.28 ± 0.17	0.2–0.6	5
	20	6.59 ± 0.41	0.2–0.6	5
	30	6.37 ± 0.24	0.2–0.6	5
	40	7.16 ± 0.29	0.2–0.6	5
	50	8.15 ± 0.35	0.2–0.6	5
	60	10.2 ± 1.2	0.2–0.6	5
	70	14.8 ± 1,6	0.1–0.4	4
Morpholine	2	143 ± 3	0.04–0.20	5
	10	107 ± 2	0.04–0.20	5
	20	75.7 ± 1.9	0.04–0.20	5
	30	53.8 ± 1.7	0.04–0.20	5
	40	43.6 ± 1.1	0.04–0.20	5
	50	38.2 ± 1.3	0.04–0.20	5
	60	36.0 ± 0.9	0.04–0.12	5
	70	36.0 ± 0.8	0.04–0.12	5
Dimethylamine[f]	2	613 ± 15	0.02–0.06	5
	2[g]	648 ± 9	0.02–0.06	5
	10	474 ± 5	0.02–0.06	5
	10[g]	478 ± 10	0.02–0.06	5
	20	308 ± 5	0.02–0.06	5
	30[g]	202 ± 4	0.02–0.06	5
	40	145 ± 5	0.02–0.06	5
	50	116 ± 4	0.02–0.06	5
	60	96.6 ± 4.3	0.02–0.06	5
	70	78.6 ± 4.9	0.02–0.06	5
Piperazine	2	419 ± 5	0.02–0.07	5
	10	312 ± 3	0.02–0.07	5
	20	217 ± 2	0.02–0.06	4
	30	155 ± 3	0.02–0.07	5
	40	120 ± 2	0.02–0.07	5
	50	103 ± 2	0.02–0.07	5
	60	100 ± 3	0.02–0.07	5
	70	99.9 ± 3.6	0.02–0.06	5
N-(2-Hydroxyethy)piperazine	2	148 ± 3	0.04–0.20	5
	10	110 ± 6	0.04–0.20	5
	20	75.3 ± 1.6	0.04–0.20	5
	30	55.8 ± 2.3	0.04–0.20	5
	40	44.8 ± 1.4	0.04–0.20	5
	50	40.4 ± 1.3	0.04–0.20	5
	60	39.8 ± 1.1	0.04–0.12	5
	70	42.8 ± 0.7	0.04–0.12	5

[a] $[\text{Phenyl salicylate}]_0 = 2 \times 10^{-4}$ M, 35°C, $\lambda = 350$ nm, and unless otherwise noted [NaOH] = 0.01 M.

[b] Total amine concentration.

[c] Error limits are standard deviations.

[d] Parenthesized values are for k_{MeOH}^{ms} obtained from reference [14].

[e] [NaOH] = 0.04 M.

[f] Stock solution of methylammonium chloride (0.25 M) was prepared in 0.30 M NaOH.

[g] Stock solution of hydrazineammonium sulfate (0.25 M) was prepared in 0.56 M NaOH.

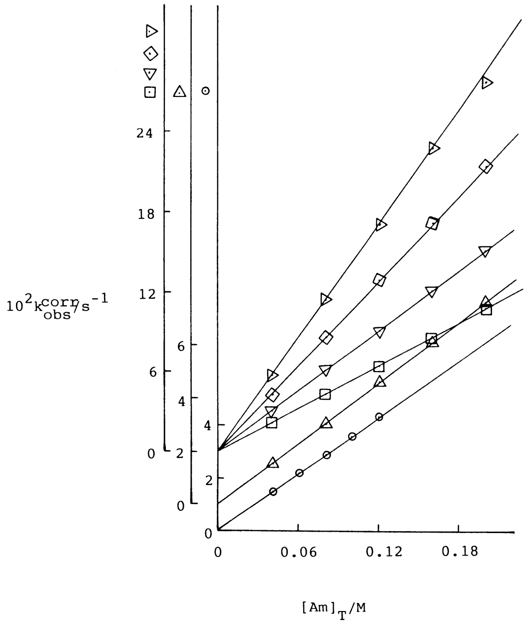


Figure 1 Effect of total concentration of morpholine—$[Am]_T$—on corrected pseudo-first-order rate constants ($k_{obs}^{corr} = k_{obs} - k_0$) for the cleavage of PS^- at 2 (▷), 10 (◇), 20 (▽), 30 (□), 50 (△), and 70% CH_3CN (○). The solid lines are drawn through the least-squares-calculated points using Eq. (1) and parameters listed in Table I.

phenyl salicylate, PS^-, undergoes transesterification in the presence of alcohols [17]. Thus, in the absence of nucleophilic reactivity of the amino group, alcoholic group of *N*-(2-hydroxyethyl)morpholine revealed detectable nucleophilic reactivity toward PS^-. The alcoholic group of triethanolamine showed significant nucleophilic reactivity toward PS^- [16]. The absence of transesterification of PS^- in the presence of primary and secondary amines containing alcoholic groups is due to the fact that amino groups of these amines are much more reactive than their alcoholic groups.

Pseudo-first-order rate constants, k_{obs}, were attempted to fit to equation: $k_{obs} = k_0 + k_{ROH}\,[Am]_T$ and the least-squares-calculated values of k_0 and k_{ROH} are $(7.78 \pm 0.59) \times 10^{-4}\ s^{-1}$ and $(7.04 \pm 2.26) \times 10^{-4}\ M^{-1}\ s^{-1}$ at 2% v/v CH_3CN and $(3.42 \pm 0.16) \times 10^{-4}\ s^{-1}$ and $(6.47 \pm 1.32) \times 10^{-4}\ M^{-1}\ s^{-1}$ at 60% v/v CH_3CN, respectively. The values of k_0 at 2 and 60% v/v CH_3CN may be compared with k_{obs} obtained in the presence of *N*-ethylpiperidine at 2 and 60% v/v CH_3CN (see Table II). The increase in the content of CH_3CN from 2 to 60% v/v decreased k_{ROH} from 7.04×10^{-4} to $6.47 \times 10^{-4}\ M^{-1}\ s^{-1}$. A similar mild effect of CH_3CN was obtained in methanolysis of PS^- [14]. It is interesting to note that the value of k_{ROH} ($= 7.04 \times 10^{-4}\ M^{-1}\ s^{-1}$) at 2% v/v CH_3CN is not significantly different from k_{ROH} obtained for the reactions of PS^- with ethanol ($k_{ROH} = 6.26 \times 10^{-4}\ M^{-1}\ s^{-1}$) [18] and triethanolamine ($k_{ROH} = 5.53 \times 10^{-4}\ M^{-1}\ s^{-1}$, statistically corrected value) [16] at 30°C.

The Dependence of k_n^{ms} on pK_a^{ms} of Conjugate Acids of Primary and Secondary Amines at a Constant Content of CH_3CN

The reactions of PS^- with primary and secondary amine, water, and alcohols involve intramolecular

Table II Pseudo-First-Order Rate Constants (k_{obs}) for the Cleavage of PS^- in the Presence of Tertiary Amines at Different Contents of CH_3CN[a]

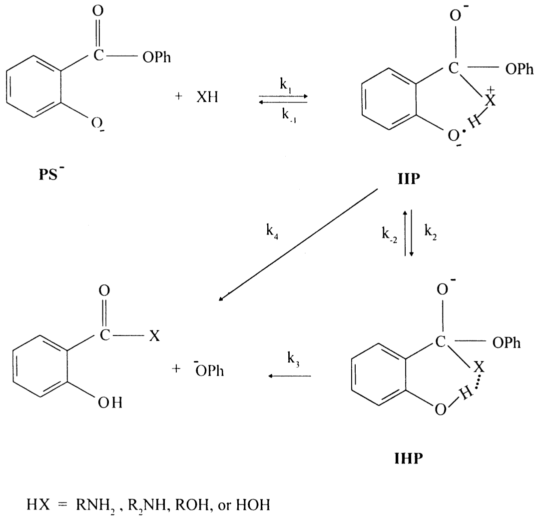
Amine	CH_3CN (% v/v)	$[Am]_T$[b] (M)	$10^4 k_{obs}$ (s^{-1})	$10^4 k_{calcd}$[c] (s^{-1})
N-(2-Hydroxyethyl)morpholine	2	0.04	8.32 ± 0.05[d]	8.06
	2	0.20	8.71 ± 0.11	9.18
	2	0.40	10.8 ± 0.2	10.6
	60	0.04	3.74 ± 0.02	3.68
	60	0.10	3.96 ± 0.02	4.07
	60	0.18	4.63 ± 0.05	4.58
N-Ethylpiperidine	2	0.02	8.07 ± 0.08	
	2	0.10	7.82 ± 0.07	
	2	0.20	8.32 ± 0.07	
	60	0.02	3.04 ± 0.03	
	60	0.05	3.32 ± 0.04	
	60	0.08	3.36 ± 0.02	

[a,b] Notations have same meaning as mentioned in Table I.

[c] Calculated from the equation: $k_{obs} = k_0 + k_{ROH}[Am]_T$ using the calculated values of k_0 and k_{ROH} as described in the text.

[d] Error limits are standard deviations.

general base (IGB) catalysis where the ionized phenolic group ($o-O^-$) of PS^- acts as an IGB catalyst. The simplest mechanism of these reactions is shown in Scheme I, which involves the formation of *intramolecular intimate ion pair* (IIP) and internally hydrogen-bonded complex (IHP). The nature of the rate-determining steps in hydrolysis [28], alkanolysis [23], and aminolysis [16,29] of PS^- has been discussed in the previous reports. In view of these reports, the $k_4$step (see Scheme I) is the rate-determining step for aminolysis of PS^- [16,29].



Scheme I

The dependence of the nucleophilic second-order rate constants (k_n^{ms}) on the pK_a of the conjugate acids of amine nucleophiles at a few CH_3CN contents is shown in Figures 2 and 3. The plots of Figures 2 and 3 at low contents of CH_3CN indicate that the rate constants (k_n^{ms}) for the reactions of PS^- with primary and secondary amines constitute the Brønsted plots of different slopes. The Brønsted slopes (β_{nuc1} and β_{nuc2}) for the nucleophilic reactions of primary and secondary amines with PS^- were calculated from Brønsted Eqs. (2) and (3), respectively.

$$\log k_n^{ms}{}_{,RNH2} = C_1 + \beta_{nuc1} pK_a \quad (2)$$

$$\log k_n^{ms}{}_{,R2NH} = C_2 + \beta_{nuc2} pK_a \quad (3)$$

The least-squares-calculated values of C_1, β_{nuc1}, C_2, and β_{nuc2} at different contents of CH_3CN are summarized in Table III. Statistical corrections to k_n^{ms} and pK_{a2} were made for diamines in the calculation of Brønsted slopes. Although the calculated values of β_{nuc1} and β_{nuc2} may not be considered to be very reliable because of a rather narrow range of pK_a (~3 pK units) of nucleophiles covered in the calculation of these Brønsted slopes, these values do indicate that $\beta_{nuc1} > \beta_{nuc2}$ at different contents of CH_3CN ranging from 2 to 30% v/v. However, the values of β_{nuc1} and β_{nuc2} become almost zero at 70% v/v CH_3CN. In terms of the traditional interpretation of Brønsted slopes (β_{nuc}), the different values of β_{nuc1} and β_{nuc2} indicate the involvement of different locations or structures of transition state on the reaction coordinate [30]. The mechanistic interpretation of the different values of β_{nuc1} and β_{nuc2}, obtained in an aqueous solvent containing 0.8% v/v CH_3CN, is given in some detail elsewhere [16].

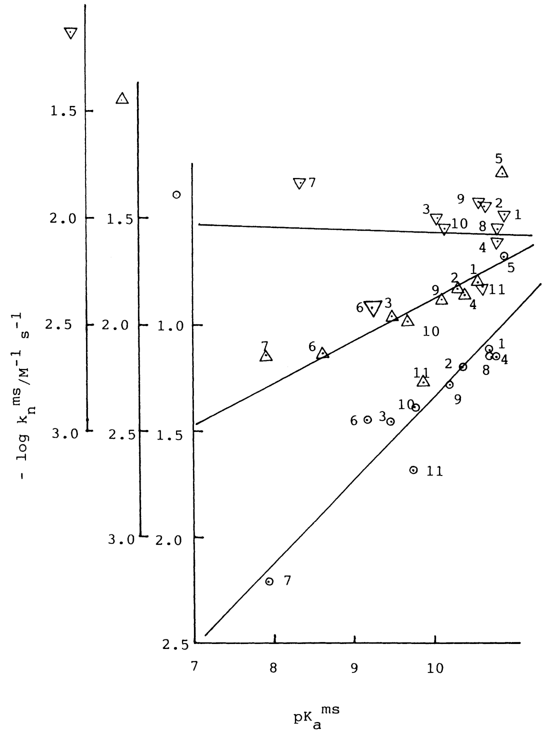


Figure 2 Brønsted plots for the nucleophilic reactivity of primary amines toward ionized phenyl salicylate at 2 (○), 40 (△), and 70% CH_3CN (▽). Statistical corrections were made to both k_n^{ms} and pK_a of diamines. In the plots, 1 represents 1,4-diaminobutane; 2, 1,3-diaminopropane; 3, 2-hydroxyethylamine; 4, *n*-propylamine; 5, methylamine; 6, benzylamine; 7, Tris; 8, *n*-butylamine [9]; 9, 3-hydroxypropylamine [15]; 10, 1,2-diaminoethane [15]; and 11, glycine [15]. The solid lines are drawn through the least-squares-calculated points using Eq. (2) and parameters listed in Table III.

The increase in CH_3CN content from 2 to 70% v/v into the reaction medium decreased both β_{nuc1} and β_{nuc2}. Similar observations have been reported on other acyl-transfer reactions in dimethyl sulfoxide

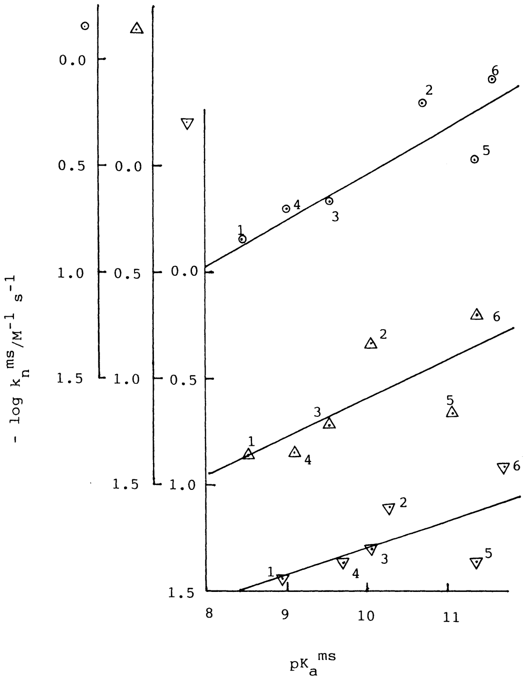


Figure 3 Brønsted plots for the nucleophilic reactivity of secondary amines toward ionized phenyl salicylate at 2 (○), 40 (△), and 70% CH_3CN (▽). Statistical corrections were made to both k_n^{ms} and pK_a of diamines. In the plots, 1 represents morpholine; 2, dimethylamine; 3, piperazine; 4, *N*-(2-hydroxyethyl)piperazine; 5, piperidine [9]; and 6, pyrrolidine [9]. The solid lines are drawn through the least-squares-calculated points using Eq. (3) and parameters listed in Table III.

(DMSO)–H_2O [31] and ethanol–water [2] solvents. If the usual interpretation that the decrease in β_{nuc} values shows the shift of the transition state toward the reactant side is correct, then in terms of the Hammond postulate [32] and the reactivity–selectivity principle [33–36] the reacting system should be more reactive in CH_3CN–H_2O solvent containing 70% v/v CH_3CN than in water solvent. The observed results, however, do not appear to agree with this prediction. For the typical amines of pK_a range 8–11, the values of $k_n^{2\%}/k_n^{70\%}$ ($k_n^{2\%}$ and $k_n^{70\%}$ represent nucleophilic second-order rate constants for the reactions of amine with PS^- in CH_3CN–H_2O solvent containing 2 and 70% v/v CH_3CN, respectively) were 3.5–9.4 for primary amines and 3.0–7.8 for secondary amines. However, $k_n^{2\%}/k_n^{70\%} = 0.4$ for only Tris (see Table I).

The increase in the acetonitrile content from 2 to 70% v/v in mixed aqueous solvent increased pK_a of phenol from 10.17 to 13.38 (see preceding article). Thus, the pK_a^{ms} of PSH (conjugate acid of PS^-) is expected to increase by ~3 pK units with an increase in acetonitrile content from 2 to 70% v/v. However, pK_a^{ms} values of all amines decreased slightly (~0.1–0.4 pK units) with the increase in the content of CH_3CN from 2 to 60% v/v while the pK_a^{ms} values at 70% v/v CH_3CN became equal or slightly larger (by ≤0.7 pK units) than the corresponding pK_a^{ms} at 2% v/v CH_3CN (see preceding article). If the assumption that the pK_a of ammonium ion moiety in IIP is similar to that of the conjugate acid of free amine [37–40], then the increase in the acetonitrile content from 2 to 60% v/v should slightly decrease the pK_a of ammonium ion moiety in IIP. The pK_a of ammonium ion moiety in IIP at 70% v/v should be similar or slightly larger than pK_a at 2% v/v CH_3CN. It should be noted that the amount of the charge density on negatively charged oxygen of phenolate ion and positively charged nitrogen of ammonium ion moieties in IIP (see Scheme I) and hence in the transition state depends on the pK_a of PSH and conjugate acid of amine nucleophile. It is now apparent that the increase in the content of CH_3CN from 2 to 70% v/v should decrease

Table III Values of Parameters, C and β_{nuc}, Calculated from Eqs. (2) and (3) at Different Contents of CH_3CN in Mixed Aqueous Solvents

Class of amine	Primary		Secondary	
CH_3CN/%v/v	$-C_1$	β_{nuc1}	$-C_2$	β_{nuc2}
2	5.32 ± 0.60[a]	0.40 ± 0.06[a]	2.73 ± 0.57[a]	0.22 ± 0.06[a]
10	5.04 ± 0.58	0.36 ± 0.06	2.80 ± 0.68	0.21 ± 0.07
20	4.50 ± 0.62	0.29 ± 0.06	2.92 ± 0.76	0.21 ± 0.08
30	4.24 ± 0.66	0.25 ± 0.07	2.89 ± 0.76	0.19 ± 0.08
40	3.89 ± 0.74	0.20 ± 0.07	2.94 ± 0.78	0.18 ± 0.08
50	3.48 ± 0.72	0.15 ± 0.07	2.84 ± 0.79	0.17 ± 0.08
60	3.02 ± 0.82	0.10 ± 0.08	2.68 ± 0.81	0.15 ± 0.08
70	1.91 ± 0.79	−0.02 ± 0.08	2.56 ± 0.74	0.12 ± 0.07

[a] Error limits are standard deviations.

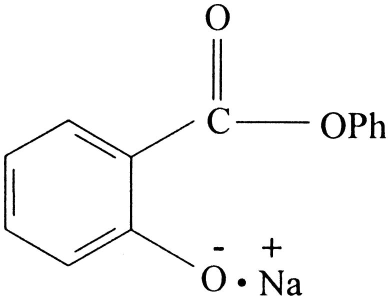
the positive charge density on nitrogen of ammonium ion moiety and negative charge density on the oxygen of phenolate ion moiety in IIP.

It has been elegantly argued by Jencks et al. [41–43] and Williams [44] that the magnitude of β_{nuc} obtained for nucleophilic substitutions may be a measure of the positive charge development on the attacking atom in the critical transition state. Although this proposal is not free from objections [42], if we assume its validity, then the decrease in the values of β_{nuc1} and β_{nuc2} with the increase in the content of CH_3CN is in agreement with the conclusion that the increase in the content of CH_3CN should decrease the positive charge density on cationic nitrogen in IIP and consequently in the transition state of the rate-determining step (i.e., k_4 step of Scheme I).

It is interesting to note that the change in the dielectric constant (ε) from ε for pure water—75.04 at 35°C [45]— to ε for mixed aqueous solvent containing 70% v/v CH_3CN—ε for pure acetonitrile is 37.5 at 20°C [45]—resulted in the values of $k_n^{2\%}/k_n^{70\%}$ in the range of 3.5–9.4 for primary amines and 3.0–7.8 for secondary amines of the present study. This shows that the rates of intramolecular-catalyzed reactions of this kind are not greatly affected by the change in the polarity of the bulk of the reaction medium. An attempt to interpret the enzymatic reactions involving intramolecular general base catalysis as greatly influenced by the change in the polarity of the active site of enzyme compared with that of the bulk solvent requires careful reconsideration.

Effects of Mixed Aqueous–Acetonitrile Solvents on k_n^{ms}

The rate of a chemical reaction is generally influenced by the specific solute–solvent interaction as well as the polarity, permittivity, polarizability, acidity, basicity, and structural features of the solvent. It is almost impossible to dissect these effects from the overall solvent effect on a reaction rate. Generally, all these effects are not equally influential toward the rate of a chemical reaction. Very often some of these effects oppose each other and thus overall solvent effect appears to be small. It is known that aqueous acetonitrile is microheterogeneous on the molecular level [46]*. Such microheterogeneity might produce a microreaction environment of rather low dielectric constant (ε) compared with ε of bulk solvent for a reaction system. However, the presence of such an apparent low ε in the vicinity of the reaction between PS^- and R_1R_2NH is expected to increase k_n^{ms} because the rate of a bimolecular reaction involving a neutral and an ionic reactants should increase with the decrease in ε of the reaction medium [47]. The decrease in k_n^{ms} with partial loss of the efficiency of intramolecular general base (IGB) catalysis due to IP formation at relatively low relative permittivity of the reaction solvent containing a predominantly aprotic cosolvent, CH_3CN, cannot be completely ruled out.



IP

The rate of the reactions of H_2O with PS^-, ionized methyl salicylate (MS^-), and ethyl salicylate (ES^-) resulted in an extremely weak sensitivity to the pK_a of leaving groups ($\beta_{lg} = -0.03 \pm 0.01$) [28]. Similarly, the values of the second-order rate constants for methanolysis of PS^- and ES^- are $25.9 \times 10^{-4}\ M^{-1}\ s^{-1}$ at 35°C [14] and $3.8 \times 10^{-4}\ M^{-1}\ s^{-1}$ at 37°C [24], respectively. However, the secondary amines did not show a detectable nucleophilic reactivity toward MS^- [16,29,48,49]. The values of $(k_n^{PS-}/k_n^{MS-})_{RNH2}$ [where k_n^{PS-} and k_n^{MS-} represent the nucleophilic second-order rate constants for the reactions of primary amines (RNH_2) with PS^- and MS^-, respectively], as summarized in Table IV, show that the respective rates of aminolysis and methanolysis of ionized salicylate esters are highly and weakly sensitive to the basicity of the leaving groups.

The effects of polarity, permittivity, polarizability, specific solute–solvent interaction, structure of the solvent and IP, and formation on reactant state (PS^-, XH, and IIP in Scheme I) are expected to be essentially the same for aminolysis and methanolysis of PS^-. The k_2 step—rate-determining step for hydrolysis [28] and methanolysis [23]—involves internal proton transfer that may be insensitive to the pK_a of the leaving group while the k_4 step—rate-determining step for aminolysis [29]—involves the cleavage of C—O bond coupled with internal proton transfer. Thus, the ratio k_n^{ms}/k_{MeOH}^{ms} (where k_n^{ms} and k_{MeOH}^{ms} represent the

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* We thank one of the reviewers for providing this information.

Table IV Values of the Parameters, θ and λ, Calculated from Eq. (6) for Various Amines

Amine	θ	$-10^2\lambda$ $(\%\ \mathrm{v/v})^{-1}$	$-\beta_{lg}$[a]	(k_n^{PS-}/k_n^{MS-})[b]	$-\beta_{lg}$[c]
1,4-Diaminobutane	1.77 ± 0.03[d]	1.70 ± 0.08[d]	0.45	376	0.47
1,3-Diaminopropane	1.69 ± 0.04	1.52 ± 0.12	0.40	271	0.44
2-Aminoethan-1-ol	1.13 ± 0.04	1.21 ± 0.12	0.32	170	0.41
n-Propylamine	1.45 ± 0.03	1.76 ± 0.11	0.46		
Methylamine	1.93 ± 0.02	1.55 ± 0.08	0.41	223	0.43
Hydrazine	1.76 ± 0.04	1.25 ± 0.13	0.33	22	0.24
Benzylamine	1.15 ± 0.02	1.76 ± 0.07	0.46		
Tris	0.36 ± 0.02	−0.24 ± 0.06	−0.06		
Morpholine	1.74 ± 0.03	1.23 ± 0.10	0.32		
Dimethylamine	2.42 ± 0.02	1.61 ± 0.08	0.42		
Piperazine	2.21 ± 0.03	1.30 ± 0.09	0.34		
N-(2-Hydroxyethyl)piperazine	1.75 ± 0.03	1.21 ± 0.11	0.32		
2-Methoxyethylamine				250	0.44
1,2-Diaminoethane	1.51 ± 0.02	1.38 ± 0.05	0.36	300	0.45
Hydroxylamine				41	0.29
3-Aminopropan-1-ol	1.32 ± 0.02	1.39 ± 0.05	0.36	130	0.38

[a] $\beta_{lg} = \lambda/\Psi$ where $\Psi = 3.81 \times 10^{-2}\ (\%\mathrm{v/v})^{s-1}$.

[b] These values were obtained from references [16,29] and [48,49].

[c] $\beta_{lg} = \log\,(k_n^{P-}/k_n^{MS-})/(\mathrm{p}K_a^{MeOH} - \mathrm{p}K_a^{PhOH})$, where $\mathrm{p}K_a^{MeOH} = 15.2$ and $\mathrm{p}K_a^{PhOH} = 9.67$.

[d] Error limits are standard deviations.

nucleophilic second-order rate constants for the reactions of PS^- with amine and methanol, respectively, in mixed aqueous–acetonitrile solvents) should be the measure of the effect of mixed water–acetonitrile solvents on the pK_a of the leaving group in the k_4 step (i.e., the pK_a of phenol) and the differential effects of the mixed water–acetonitrile solvents on pK_a of conjugate acids of amine bases and methanol (i.e., the pK_a of $CH_3OH_2^+$).

The increase in the content of CH_3CN from 2 to 50% v/v showed a mild effect on pK_a^{ms} or pK_2^{ms} of ammonium ions (preceding article). Although we could not find any report on the effects of mixed water–acetonitrile solvents on pK_a of $CH_3OH_2^+$, the values of pK_a for $CH_3OH_2^+$ should not be significantly affected by the change in the content of acetonitrile in mixed aqueous solvents because the CH_3OH molecule is a highly hydrophilic and ionization of $CH_3OH_2^+$ represents an isoelectric reaction. Thus, it appears that the increase in acetonitrile content from 2 to 50% v/v does not change the nucleophilicity of amine and CH_3OH nucleophiles to a significant extent. Thus, the ratio k_n^{ms}/k_{MeOH}^{ms} may be considered to be essentially dependent on pK_a^{ms} of the leaving group, phenol, within the acetonitrile content range of ~2–50% v/v and hence in terms of Brønsted hypothesis

$$\log\,(k_n^{ms}/k_{MeOH}^{ms}) = \phi + \beta_{lg}\,\mathrm{p}K_a^{ms} \tag{4}$$

where ϕ and β_{lg} (Brønsted coefficient) are empirical constants, and pK_a^{ms} represents the pK_a of phenol.

As discussed in the preceding article, the values of pK_a^{ms} for phenol, obtained within the acetonitrile content range 2–50% v/v, fit an empirical equation

$$\mathrm{p}K_a^{ms} = \eta + \Psi X \tag{5}$$

where X represents % v/v content of CH_3CN in mixed aqueous solvent and η as well as Ψ are empirical parameters. The calculated values of η and Ψ are 10.05 ± 0.04 and (3.81 ± 0.14) × 10^{-2} (% v/v)$^{-1}$, respectively.

Equations (4) and (5) lead to Eq. (6)

$$\log\,(k_n^{ms}/k_{MeOH}^{ms}) = \theta + \lambda X \tag{6}$$

where $\theta = \phi + \eta\beta_{lg}$ and $\lambda = \Psi\beta_{lg}$.

Equation (6) predicts that the plots of log (k_n^{ms}/k_{MeOH}^{ms}) against X should be linear and such plots turned out to be linear as evident from some representative plots of Figure 4 for a few typical amines. The linear least-squares technique was used to calculate θ and λ from Eq. (6) and these results are summarized in Table IV. The calculated values of λ for all amines except Tris were negative (see Table IV). The observed data for Tris yielded considerably small positive values of λ (see Table IV). The observed data

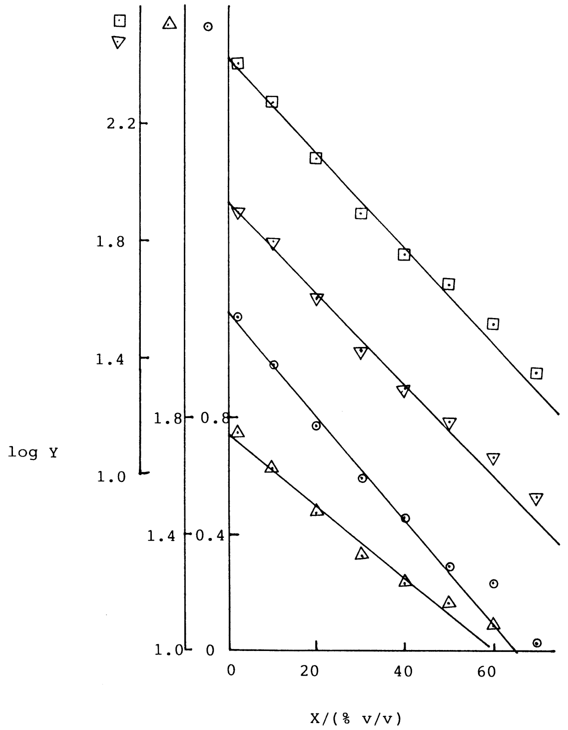

Figure 4 Plots of log Y (where $Y = k_n^{ms}/k_{MeOH}^{ms}$) vs. X—where X = % v/v content of CH_3CN in mixed aqueous solvent—for morpholine (△), benzylamine (○), methylamine (▽), and dimethylamine (□). The solid lines are drawn through the least-squares-calculated points using Eq. (6) and parameters listed in Table IV.

point at >50% v/v CH_3CN deviated positively from linearity of the plot (see Fig. 4). One of the various possible reasons for such deviations is the increase in pK_a of the conjugate acids of amine nucleophiles with the increase in the content of CH_3CN at >50% v/v CH_3CN (preceding article).

The values of β_{lg} for various nucleophiles were calculated from the relationship: $\lambda = \Psi\beta_{lg}$ using known values of λ (Table IV) and Ψ [$= 3.81 \times 10^{-2}$ (% v/v)$^{-1}$] calculated from Eq. (5). These calculated values of β_{lg} are shown in Table IV. The values of β_{lg} for some amines were also calculated from the published values of k_n^{PS-} and k_n^{MS-} (see Table IV) using the relationship: $\beta_{lg} = \log(k_n^{PS-}/k_n^{MS-})/(pK_a^{MeOH} - pK_a^{PhOH})$ where pK_a^{MeOH} (= 15.2) [41] and pK_a^{PhOH} (= 9.67) [50] represent pK_a of methanol and phenol, respectively. These β_{lg} values are also listed in Table IV. Although the β_{lg} values obtained from the relationship: $\beta_{lg} = \log(k_n^{PS-}/k_n^{MS-})/(pK_a^{MeOH} - pK_a^{PhOH})$ are not very reliable because they are derived from only two data points, these β_{lg} values are comparable with the corresponding β_{lg} values obtained from the relationship: $\beta_{lg} = \lambda/\Psi$.

The calculated value of β_{lg} (= 0.06) for Tris, although not very different from zero, seems to be unusual in that all the other primary amines yielded large negative β_{lg}. Similarly, the rate constants k_n^{ms} for Tris did not show any appreciable deviation from Brønsted plots (Fig. 2, Table III, and reference 16). This is surprising in view of the large steric requirements for a nucleophilic attack at carbonyl carbon [51,52]. The nearly zero value of β_{lg} for Tris may be explained if the hydroxyl moiety rather than the amino moiety of Tris is acting as the nucleophilic site. However, the product characterization study had ruled out the occurrence of transesterification [16]. Furthermore, a nearly 10-fold larger value of k_n for Tris (see Table I) than for ethanol ($k_n = 6.3 \times 10^{-4}$ M^{-1} s^{-1} at 30°C) [18,19] is difficult to explain if transesterification is involved in the cleavage of PS^- under the presence of Tris.

CONCLUSION

1. The linear Brønsted plots of log k_n^{ms} vs. pK_a^{ms}, obtained within the CH_3CN content range 2–70%, reveal the absence of a change in the rate-determining step with a change in the content of CH_3CN in mixed aqueous solvents. The increase in the content of CH_3CN is concluded to increase and decrease the pK_a of PSH and protonated amine, respectively. The decrease in the values of β_{nuc1} and β_{nuc2} with the increase in the content of CH_3CN is attributed to the decrease in the positive charge density on the attacking nitrogen atom in the critical transition state (k_4 step of Scheme I).
2. The effects of mixed $H_2O—CH_3CN$ solvents on pK_a of conjugate acids of the leaving group (phenolate ion) and nucleophile (amine) were ascribed to be the major factors for the observed change in k_n^{ms} with the change in the content of CH_3CN in mixed aqueous solvents. The observed data, k_n^{ms} vs. X (where X represents % content of CH_3CN in mixed aqueous solvents), coupled with a few empirical equations, were used to calculate β_{lg} (Brønsted coefficient) for various amine nucleophiles.

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