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The Effect of Solvent on Reactions of *p*-Nitrophenyl Acetate with Alicyclic Secondary Amines and with Anionic Nucleophiles in MeCN-H₂O Mixtures of Varying Compositions

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Second-order rate constants have been measured spectrophotometrically for the reaction of *p*-nitrophenyl acetate (PNPA) with morpholine, piperazine and piperidine in MeCN-H₂O mixtures of varying compositions. The rate of the present aminolysis decreases upon additions of MeCN into H₂O up to near 30-40 mole % MeCN and remains nearly constant upon further additions of MeCN. The reaction of PNPA with anionic nucleophiles, such as HO⁻, *p*-chlorophenoxide and butane-2,3-dione monoximate, has also exhibited two distinguishable reactivity zones. However, the reactivity trend for the anionic nucleophiles is quite different from the one obtained for the amine system, *e.g.* an initial rate decrease in the H₂O-rich region followed by an increasing rate trend upon further additions of MeCN in the MeCN-rich region. The rate behaviors shown by the amine system in the MeCN-rich and by the anionic system in the H₂O-rich region are unexpected based on the Hughes-Ingold rules. The present unusual rate trends have been attributed to changes in the solvent structure and pK_a of the nucleophiles upon the addition of MeCN into H₂O. The effect of solvent appears to be more significant for the TS than the GS, and the TS structure is considered to become tighter in the higher MeCN concentration.

Introduction

The effect of solvent on organic reactions have been extensively studied.[1~5] Current research is mostly focused on the investigation of solvent effect on reaction rates and mechanisms in binary mixtures of H₂O with dipolar aprotic solvents, such as dimethyl sulfoxide (DMSO)[4] and acetonitrile (MeCN).[5] Significant rate accelerations have often been reported upon additions of aprotic dipolar solvents into H₂O for the reactions involving anionic nucleophiles.[6] However, on the contrary, rate retardations have also been observed for reactions of neutral species developing a charge in the transition state (TS) upon solvent changes from H₂O to aqueous diolar aprotic solvent mixtures.[7] Such solvent effects on reaction rates could be nicely explained by the Hughes-Ingold rules in a qualitative manner,[8] since gradual increase of the mole % of such organic solvents is considered to change H-bonding structure of H₂O and the microenvironment of the reactant and TS.

We have performed a systematic study for the reaction of *p*-nitrophenyl acetate (PNPA) with alicyclic amines and with anionic nucleophiles, as shown in Scheme 1 for the aminolyses. Aminolyses of esters have been extensively studied due to importance of acyl transfer reactions in biological processes, such as the acylation of chymotrypsin and other serine proteases by amides or the analogous acylation of
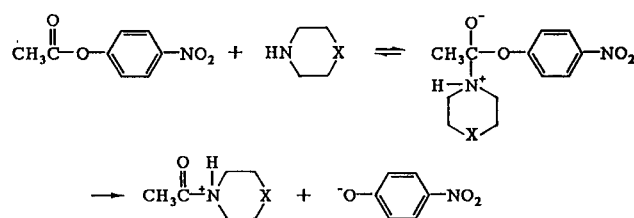
X = CH₂ ; piperidine
X = NH ; piperazine
X = O ; morpholine

Scheme 1.

papain and other cystein proteases.[9] However, systematic studies of solvent effect on aminolyses have been lacking. Since dissection of solvent effect into the ground state (GS) and TS contributions would be expected to give us useful information about solvent effect, we have measured enthalpies of solution (ΔH_{sol}) of the nucleophilic amines as well as activation parameters (ΔH^* and $T\Delta S^*$) for the aminolyses. In the present paper, we wish to report unexpected rate trends based on the Hughes-Ingold rules and plausible explanations for the unusual rate trends upon the present solvent change.

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Table 1. Summary of Second-Order Rate Constants ($M^{-1}s^{-1}$) for the Reactions of PNPA with Piperidine, Piperazine and Morpholine in Various MeCN-H_2O Mixtures at 15.0, 25.0, 35.0 ℃

mole % MeCN	piperidine			piperazine			morpholine		
	15.0 ℃	25.0 ℃	35.0 ℃	15.0 ℃	25.0 ℃	35.0 ℃	15.0 ℃	25.0 ℃	35.0 ℃
0	24.6	41.2	61.7	3.23	5.72	10.6	0.251	0.485	0.886
10	–	14.5	–	–	2.83	–	–	0.281	–
20	–	6.68	–	–	1.35	–	–	0.146	–
30	2.49	3.79	6.09	0.568	0.942	1.58	0.0577	0.104	0.176
40	–	2.73	–	–	0.777	–	–	0.0858	–
50	–	2.14	–	–	0.703	–	–	0.0787	–
60	1.23	1.95	2.69	0.419	0.662	1.08	0.0426	0.0734	0.121
70	–	1.56	–	–	0.677	–	–	0.0718	–
80	–	1.61	–	–	0.730	–	–	0.0715	–
90	1.1	1.69	2.33	0.591	0.851	1.37	0.0463	0.0702	0.103

Experimental

Materials. *p*-Nitrophenyl acetate was easily prepared by the reaction of acetyl chloride and *p*-nitrophenol in methylene chloride. Piperidine, piperazine, morpholine and other chemicals were of the highest quality available (Aldrich) and generally recrystalized or distilled before use. MeCN was distilled over P_2O_5 under a nitrogen atmosphere. Doubly glass distilled water was further boiled and cooled under a nitrogen atmosphere just before use.

Kinetics. The kinetic studies were performed with a Hitachi U-2000 Model UV-vis spectrophotometer (for slow reactions, $t_{1/2} \geq 10$ sec) or with an Applied Photophysics SX-17MV Model Stopped-flow Apparatus (for fast reactions, $t_{1/2} <$ 10 sec) equipped with a Neslab RTE-110 Model constant temperature circulating bath to keep the temperature in the reaction cell at 25.0± 0.1 ℃. The reactions were followed by monitoring the appearance of the leaving p-nitrophenoxide at 400 nm. All the reactions were carried out under pseudo-first-order conditions in which the concentrations of nucleophiles were generally 20 times, but at least 10 times greater than that of the substrate. All the solutions were transfered by Hamilton gas-tight syringes under a nitrogen atmosphere.

Enthalpies of solution. Enthalpies of solutions for the nucleophilic amines (piperidine and morpholine) were measured using an LKB-2277 Thermal Activity Monitor Calorimeter at 25.0± 2×10^{-4} ℃. The accuracy of the calorimeter was checked by determining the enthalpy of solution of KCl in water. The mean of four measurements (17.606± 0.076 kJmol^{-1}) was found to be in a good agreement with the literature value (17.510 kJmol^{-1}) for KCl. The concentration range of sample was 5×10^{-3}-2×10^{-2} molL^{-1}. Other detailed methods for the experiment were described in previous papers.[10]

Results

All the reactions in this study obeyed pseudo-first-order kinetics up to over 90% of the total reaction. Pseudo-first-order rate constants (k_{obs}) were obtained from the equation, $\ln(A_\infty - A_t) = -k_{obs}t + C$. Correlation coefficients of the linear

Table 2. Summary of Second-Order Rate Constants ($M^{-1}s^{-1}$) for the Reactions of PNPA with HO^-, 2,3-Butanedione Monoximate (Ox^-) and p-ClPhO$^-$ in Various MeCN-H_2O Mixtures at 25.0 ℃

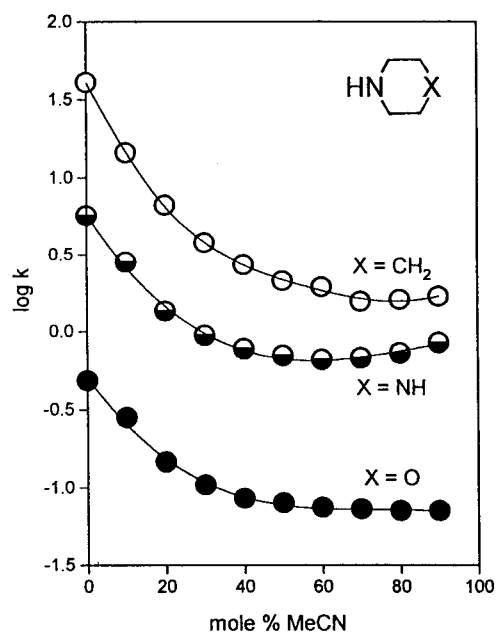| mole % MeCN	$k_2/M^{-1}s^{-1}$		
	HO^-	$Ox^{-(a)}$	*p*-ClPhO$^{-(a)}$
0	11.6	65.8	0.685
10	7.29	37.2	0.385
20	4.84	29.5	0.255
30	4.68	29.2	0.197
40	4.66	35.6	0.198
50	5.56	45.6	0.217
60	8.43	67.6	0.266
70	15.7	122	0.391
80	36.3	263	0.712
90	–	943	2.12

(a) The data from ref. 14 (b).

regressions were always higher than 0.9995. Generally, more than 5 different concentrations of a nucleophile solution were used to determine apparent second-order rate constants (k_2) from the slope of the plot of k_{obs} vs. amine concentration. Second-order-rate constants obtained in this way are summarized in Tables 1 and 2. As shown in Figure 1, the linear plots of k_{obs} vs. amine concentrations indicate that the amines used in the present system do not act as a general base catalyst. In Figures 2 and 3 are graphically demonstrated the effect of solvent on the reactivity of the neutral and anionic nucleophiles in various MeCN-H_2O mixtures, respectively. The pK_a's of the amines, phenol and benzoic acid are listed in Table 3. In the Tables 4 and 5 are summarized enthalpies of solution (ΔH_{sol}, for piperidine and morpholine) and activation parameters (ΔH^* and $T\Delta S^*$) for the reaction of PNPA with the amines, respectively.

Discussion
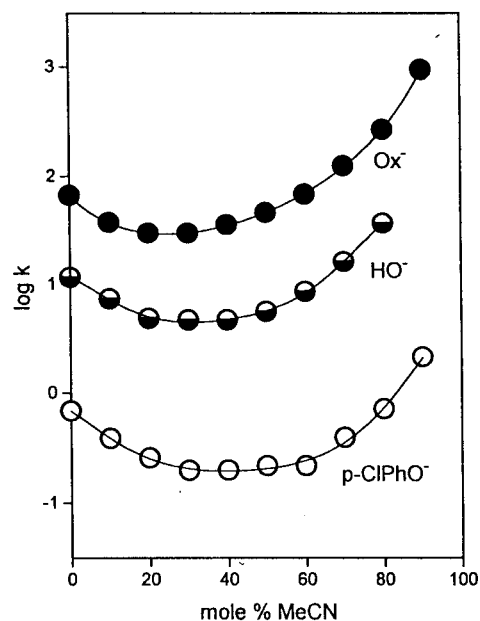
Solvent Effect on Reaction rates. As shown in Table

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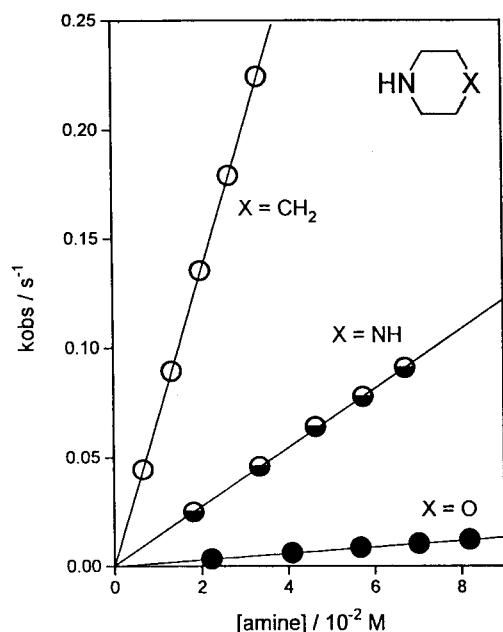
Figure 1. Plots of pseudo-first-order rate constants *vs* amine concentrations for the reactions of PNPA with secondary cyclic amines in 20 mole % MeCN at 25.0 °C.

Figure 3. Plots of logarithmic second order rate constants for reactions of PNPA with anionic nucleophiles in MeCN-H₂O mixtures of varying compositions at 25.0 °C.

Figure 2. Plots of logarithmic second order rate constants for the reactions of PNPA with secondary cyclic amines in MeCN-H₂O mixtures of varying compositions at 25.0 °C.

Table 3. pK_a's of Some Brönsted Acids in H_2O and in MeCN

	pK_a in H_2O	pK_a in MeCN	ΔpK_a
Acids			
benzoic acid	4.2	20.7[a]	16.5
phenol	10.0	27.2[a]	17.2
p-nitrophenol	7.2	20.7[a]	13.5
Ammonium ions			
ammonia	9.21	16.46[b]	7.25
aniline	4.58	10.56[b]	5.98
pyridine	5.17	12.33[b]	7.16
piperidine	11.22	18.92[b]	7.70
piperazine	9.82	–	–
morpholine	8.36	16.61[b]	8.25

[a] The data from ref. 21 (a). [b] The data from ref. 21 (b).

Table 4. Heats of Solution (ΔH_{sol}) and Heats of Solvent Transfer ($\Delta\Delta H_{sol}$)[a] for Piperidine and Morpholine in MeCN-H₂O Mixtures at 25.0 °C

mole % MeCN	piperidine		morpholine	
	ΔH_{sol}/kJ mol^{-1}	$\Delta\Delta H_{sol}$/kJ mol^{-1}	ΔH_{sol}/kJ mol^{-1}	$\Delta\Delta H_{sol}$/kJ mol^{-1}
0	−25.0± 1.4	0	−24.2± 0.1	0
30	−12.5± 1.4	12.5	−16.6± 0.9	7.6
60	−10.2± 0.2	14.8	−12.9± 0.5	11.3
90	−5.04± 0.00	20.0	−6.10± 0.10	18.1

[a] $\Delta\Delta H_{sol} = \Delta H_{sol}$ in mixed solvent-ΔH_{sol} in water.

1 and Figure 2, the reactivity of secondary cyclic amines toward PNPA decreases significantly upon additions of MeCN into H₂O up to near 30-40 mole % MeCN and remains nearly constant upon further additions of MeCN into the reaction medium. The aminolysis of aryl acetates as in the present system has generally been suggested to proceed *via* addition-elimination pathways in which the rate determining step depends on the basicity of the nucleophilic amines and

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Table 5. Activation Parameters for the Reaction of PNPA with Piperidine, Piperazine and Morpholine in MeCN-H$_2$O Mixtures at 25.0 °C

| mole % MeCN	ΔH^*/kJmol^{-1}	$T\Delta S^*$/kJmol^{-1}	ΔG^*/kJmol^{-1}
piperidine			
0	39	−25	64
30	30	−39	70
90	25	−46	72
piperazine			
0	41	−27	69
30	35	−38	73
90	28	−45	73
morpholine			
0	44	−31	75
30	39	−40	79
90	27	−53	80

the leaving aryloxides.[11~13] Generally, the leaving group departure has been suggested to be the rate determining step, unless the nucleophilic amines is more basic than the leaving aryloxide by 5 pK_a units.[12,13] In the present aminolyses, the reactants are uncharged but the TS is a charged species. Since MeCN can not solvate such ionic species as strong as H$_2$O, one would expect rate retardations upon additions of MeCN into the reaction medium. Therefore, one can consider that the decreasing rate trend in the H$_2$O-rich region is consistent with the Hughes-Ingold rules. However, the rate trend showing levelling off beyond 40 mole % MeCN is quite unexpected based on the Hughes-Ingold rules.

We have also observed quite unusual reactivity trends for the nucleophilic substitution reaction of PNPA with various anionic nucleophiles in MeCN-H$_2$O mixtures. As shown in Table 2 and Figure 3, the logarithmic rate constant for the reaction of PNPA with p-chlorophenoxide (p-ClPhO$^-$) decreases remarkably upon initial additions of MeCN into H$_2$O up to 30-40 mole % MeCN, followed by a gradual increase upon further additions of MeCN. Similar rate trends have been also observed for the corresponding reaction with butane-2,3-dione monoximate (Ox$^-$) and hydroxide (HO$^-$) ions, e.g. two distinguishable reactivity zones, one in the H$_2$O-rich and one in the MeCN-rich region. The decreasing rate trend in the H$_2$O-rich region is quite an unexpected result on the basis of Hughes-Ingold rules, since these anionic nucleophiles are expected to be significantly desolvated upon the addition of MeCN into H$_2$O due to decreasing in H-bonding and increasing repulsion between the anion and the negative end of the dipole in MeCN.

In our previous reports,[14,15] the TS for the reaction of PNPA with anionic nucleophiles has been suggested to resemble the addition intermediate (I), in which the negative charge is highly localized on the carbonyl oxygen, i.e. the charge developed on the carbonyl oxygen atom has been
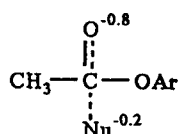
suggested to be about −0.8 based on the magnitude of Brönsted β_{nuc} value. On the other hand, the negative charge on p-ClPhO$^-$ and Ox$^-$ would be fully delocalized by direct resonance as shown below. Therefore, one might expect that the TS would be more desolvated than the GS (p-ClPhO$^-$ and Ox$^-$) in MeCN since the charge density of the former would be higher in the TS than in the GS. This would account for the initial rate retardation upon the addition of
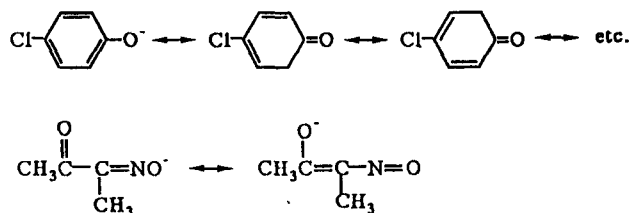
MeCN into H$_2$O. On the other hand, HO$^-$ cannot have any resonance structure and the negative charge would be fully localized on the oxygen atom. Accordingly, HO$^-$ would be more desolvated than the TS in MeCN and a large rate acceleration would be expected as the concentration of MeCN increases in the reaction medium. However, HO$^-$ also exibits significant rate decelerations up to 30-40 mole % MeCN, implying that HO$^-$ is also less desolvated than the TS upon the solvent change. Therefore, the present rate behaviors cannot be explained simply by the Hughes-Ingold rules.[8]

Solvent Properties of MeCN-H$_2$O mixtures. In order to understand the rate trend obtained in the present system, knowledge of solvent properties of MeCN-H$_2$O mixtures are essential. MeCN and H$_2$O have been known to interact strongly through H-bonding at the nitrogen site. It has been proposed that the initially added MeCN molecules occupy the cavities inside the aqueous frame-work of the H$_2$O lattice and to increase the structure of H$_2$O up to near 30 mole % MeCN.[15,16] On the basis of numerous physicochemical properties of aqueous MeCN, the structure of the mixed solvent has been determined to become most compact near 33 mole % MeCN.[17] Studies of physicochemical properties of aqueous MeCN have revealed extrema at this composition, such as excess entropy of mixing,[18] energy-volume coefficient, isothermal compressibility[19] and enthalpies of transfer for various anions.[16] The extrema observed near 33 mole % MeCN appears to stem from the strong tendency of MeCN to form complexes with two H$_2$O molecules, since 33.3 mole % MeCN is the stoichiometric ratio of 1 : 2 for MeCN : H$_2$O. In fact, spectroscopic evidence for 1 : 2 MeCN-H$_2$O complex has been reported.[17]

It has been suggested that the structure of H$_2$O containing MeCN is broken progressively beyond 33 mole % MeCN upon further additions of MeCN,[16] which would become the main solvent to govern solvent properties. It is well known that MeCN is a poor solvent for anions, since the negative dipolar end of MeCN is exposed, whereas the positive one is buried in the middle of the molecule. There is no doubt that the repulsion between the negative dipole and anionic species would be stronger for the smaller anion. Consequently, the anionic nucleophiles would be significantly more desolvated than the large TS upon the addition of MeCN beyond 33 mole % MeCN. Therefore, one can attribute the rate

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enhancement observed for the reaction of PNPA with the anionic nucleophiles to a differential desolvation between the anionic nucleophile and the TS. On the other hand, the secondary cyclic amines in the present system would also suffer from desolvation in the MeCN-rich medium but the degree would be much lesser for the amines than for the anionic species. This might account for rate trend showing levelling off in the MeCN-rich region for the reaction of PNPA with the amines.

As mentioned in the preceding section, the reactivity of both the amine and anionic nucleophiles toward PNPA decreases with increasing the concentration of MeCN up to near 30-40 mole % MeCN. The rate retardation shown by the amine system is predictable on the basis of the Hughes-Ingold rules. However, the rate deceleration observed for the reaction with the anionic nucleophiles is unusual and cannot be explained by the Hughes-Ingold rules. As shown in Figure 3, the rate retardation occurs mainly in the region where the solvent structure is considered to become stronger. In this region, the larger solute would require higher cavity formation energy than the smaller one. Therefore, the small nucleophlies appear to be less desolvated than the large TS in the H_2O-rich region, and one can attribute the rate deceleration in this region to the solvent structure change, at least in part.

Dissection of Solvent Effect into GS and TS contributions. As pointed out in the preceding section, the reactivity of the present amines decreases upon the additions of MeCN into the reaction medium. A careful examination of Figure 2 reveals that such a rate retardation is most significant for the piperidine system (*e.g.* the rate retardation is in the order $X=CH_2>X=NH>X=O$). The replacement of CH_2 by an electronegative atom (NH or O) would reduce the basicity of amine. In order to explain the difference in rate retardation in terms of amine basicity, pK_a's of the amines, phenol and benzoic acid are summarized in Table 3. As shown in the Table, the pK_a in MeCN is much larger than the one in H_2O for all the acids. Although there is no correlation between the pK_a in H_2O and the one in MeCN, the difference in pK_a upon the solvent change from H_2O to MeCN ($\Delta pK_a = pK_a$ in MeCN-pK_a in H_2O) for phenol (or benzoic acid) is much larger than the one for the amines. Since the basicity is a measure of nucleophilicity, the magnitude of ΔpK_a is considered to be responsible for the difference in the rate trends obtained for the present system, at least in part. In fact, ΔpK_a for piperidine is smaller (7.70) than that of morpholine (8.25), and the former exhibits more rate retardation upon the solvent change. This argument can be further supported from a comparison of the rate trends shown by the amines and oxyanionic nucleophiles in the MeCN-rich region, *i.e.* the oxyanionic nucleophiles show larger ΔpK_a value (16-17) and larger rate enhancement while the amines demonstrate smaller ΔpK_a (7-8) and negligible rate enhancement upon the solvent change from H_2O to MeCN.

In order to dissect the effect of solvent into GS and TS contributions, enthalpies of solutions (ΔH_{sol}) and activation parameters (ΔH^*, ΔS^*) are determined in H_2O and aqueous MeCN. The ΔH_{sol} value are summarized in Table 4. H-bonding is considered to be the strongest interaction between solvent and solute in the present system. Therefore, one

might expect that morpholine would be more destabilized than piperidine upon the additions of MeCN into H_2O, since the former has two H-bonding sites. Besides, this expectation is consistent with the rate data, *i.e.* the rate retardation for the former is smaller than the one for the latter upon the addition of MeCN. However, as shown in Table 4, ΔH_{sol} for piperidine is larger than the one for morpholine (-25.0 *vs* -24.2 kJmol^{-1} in water) and $\Delta\Delta H_{sol}$ for the former is also larger than the one for the latter in all the mixed solvents. Clearly, the present result is opposite to what would have been expected based on the rate data and the structure of the amines. Therefore, the fact that piperidine is more destabilized than morpholine upon the addition of MeCN suggests that the number of H-bonding site is less important than the basicity of these amines.

In Table 5 are summarized activation parameters for the reaction of PNPA with the amines in H_2O, 30 and 90 mole % MeCN. As shown in the Table, ΔH^* values decrease upon the addition of MeCN, indicating that the reaction rate for all the amine system is enthalpically favorable. On the contrary, $T\Delta S^*$ values increase negatively upon the addition of MeCN, indicating that the reaction rate would be entropically unfavorable.

It is well known that magnitudes of ΔH^* and ΔS^* reflect TS structure. ΔH^* represents the sum of the energy released by forming new bonds and the one required for breaking bonds, while ΔS^* is a measure of the degree of order produced in the formation of TS. The TS structure for the present system has been suggested to be addition intermediate-like, in which the leaving group departure is partially advanced.[11~13] Consequently, the present ΔH^* would represent mostly the energy required for the leaving group departure. Therefore, the decreasing ΔH^* trend suggests that leaving group departure becomes less advanced, *i.e.* the TS becomes tighter as the concentration of MeCN increases. $T\Delta S^*$ value are also consistent with this proposal. In the present system, the magnitude of $T\Delta S^*$ is very large with a negative sign. Such a large negative $T\Delta S^*$ value is typical for bimolecular nucleophilic substitution reactions. Besides, $T\Delta S^*$ value becomes more negative upon the addition of MeCN into the reaction medium, which can support that the TS becomes tighter by reducing the degree of the leaving group departure upon the additions of MeCN into the reaction medium. Therefore, it is proposed that the leaving group departure would become less advanced upon the addition of MeCN into H_2O. This proposal is consistent with recent reports that solvent variations could result in a change in the TS structure for the present type reactions.[7,20]

Conclusions

The present study has allowed us to conclude the following. (1) The change in the structure of the mixed solvents and the difference in ΔpK_a are considered to be responsible for the unusual rate trends and the reactivity differences observed for the present reaction system, at least in part. (2) Solvent effect appears to be more important for the TS than the GS. (3) The TS structure for the present aminolysis is considered to become tighter (*e.g.* less leaving group departure) based on the magnitude of ΔH^* and $T\Delta S^*$ values as MeCN becomes more concentrated in the medium.

Interaction of Mastoparan B with Phospholipid Matrices

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The Interaction of Mastoparan B from Venom of a Hornet *Vespa Basalis* with Phospholipid Matrices

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Mastoparan B (MP-B) that is a novel MP isolated from the hornet *Vespa basalis*, was studied as compared with MP, in terms of interaction with phospholipid bilayer and antimicrobial activity. MP-B has more hydrophilic amino acid residues in hydrophilic face of amphiphilic α-helical structure than MP. The both peptides exhibited considerably different effect on interaction with lipid bilayers, e.g. their conformation in the presence of acidic and neutral liposomes, dye-release ability from encapsulated liposomes, but on the whole the interaction mode was similar. On antimicrobial activity, MP had a strong activity against Gram-positive bacteria but no against Gram negative ones. Contrary to this, MP-B had a strong activity against Gram-positive and potent against Gram-negative ones. Since both peptides have almost same residues on the hydrophobic side, such more hydrophilic surface on the molecule seems to lead to the subtle change in its interaction with membranes, resulting in the alternation in its biological activity.

Introduction

Mastoparan (MP), a major component of the wasp venom, is a basic amphiphilic α-helical peptide composed of fourteen amino acid residues and a few of related peptides have been isolated from the natural source[1] (Figure 1). It possesses