

Correlation of the Rates of Solvolysis of 4-Morpholinecarbonyl Chloride Using the Extended Grunwald-Winstein Equation

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The rates of solvolysis of 4-morpholinecarbonyl chloride (MPC) have measured at 35.0 °C in water, D₂O, CH₃OD, and in aqueous binary mixtures of acetone, ethanol, methanol, and 2,2,2-trifluoroethanol. An extended (two-term) Grunwald-Winstein equation correlation gave sensitivities towards changes in solvent nucleophilicity and solvent ionizing power as expected for a dissociative S_N2 and/or S_N1 (ionization) pathway. For nine solvents specific rates were determined at two additional temperatures and higher enthalpies and smaller negative entropies of activation were observed, consistent with the typical dissociative S_N2 or S_N1 (ionization) pathway. The solvent deuterium isotope effect values for the hydrolysis of MPC of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.27$ and for the methanolysis of MPC of $k_{\text{MeOH}}/k_{\text{MeOD}} = 1.22$ are typical magnitudes of the S_N1 or ionization mechanism.

Key Words: 4-Morpholinecarbonyl chloride (MPC), Grunwald-Winstein equation, Addition-elimination (A-E), Ionization (I), KSIE

Introduction

The Grunwald-Winstein equation (eq. 1) is very useful tool for mechanistic study of the solvolyses of substrates in various binary solvent mixtures.¹ In eq. (1), k and k_0 are the rates of solvolysis of a substrate RX in a given solvent and in the standard solvent (80% ethanol), respectively; m represents the sensitivity to changes in solvent ionizing power Y_{Cl}^2 and c represents a constant (residual) term. However, dispersion into separated lines in the correlation of the specific rates of solvolysis of benzoyl³ and sulfonyl halides in various aqueous solvents mixtures was documented⁴ in early treatments using the Grunwald-Winstein eq. (1).

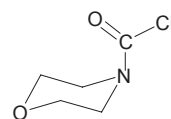
$$\log(k/k_0) = mY_{\text{Cl}} + c \quad (1)$$

In general, dispersion effects in unimolecular solvolysis⁵ make smaller contributions to the overall linear free energy relationship (LFER) than solvent nucleophilicity effects in bimolecular solvolysis.^{4(a),6,7} Therefore, it was suggested that a second term which is governed by sensitivity l to the solvent nucleophilicity N_s^8 should be added in eqn. (1) for bimolecular solvolysis.⁷ The resulting eq. (2) is often referred to as the extended Grunwald-Winstein equation. The eqn. (2) has proven extremely valuable in studies of the mechanism of solvolyses reaction.⁷

$$\log(k/k_0) = lN_T + mY_{\text{Cl}} + c \quad (2)$$

For an ionization reaction without nucleophilic assistance, l will be zero and m closes to unity. For an addition-elimination reaction pathway with extensive nucleophilic assistance, the l value will be greater than 1.5 and the m value will be less than

0.5.⁹ Solvolysis of benzoyl chlorides is known to be solvolyzed through a borderline mechanism.¹⁰ There have been, however, much dispute over the mechanism as to whether it is an ionization ($p\text{-OCH}_3$ and $p\text{-CH}_3$) or a borderline (H and $p\text{-Cl}$) or an addition-elimination pathway ($p\text{-NO}_2$).¹⁰ A particularly important system which contains carbonyl carbon is ArCOCl; alkyl and aromatic acyl chlorides¹⁰⁻¹² are important acyl transfer reagents in organic synthesis and nucleophilic substitution reactions. Solvent effects and LFERs in the solvolyses of alkyl and aromatic acyl halides, especially benzoyl chlorides,¹¹ phenyl chloroformates,¹² and ethyl and phenyl chlorothioformates,¹³ have received much attention, but little work has been done on the solvent effect on mixed solvents, especially for solvolyses of *N*-alkyl carbonyl chloride. In this work, we determined rate constants for solvolyses of 4-morpholinecarbonyl chloride (MPC) with *N*-alkyl group in aqueous binary solvents of acetone, ethanol, methanol, methanol-*d*, 2,2,2-trifluoroethanol (TFE), pure water, and D₂O at various temperatures. Mechanistic variation and/or transition state variation are also discussed in terms of the one-term (simple) equation, two-term (extended) Grunwald-Winstein equation, Z values, kinetic solvent isotope effects (KSIE) and activation parameters.



morpholinecarbonyl chloride (MPC)

Results and Discussion

The specific rates of solvolysis of MPC in the ethanol, methanol, pure water, and aqueous binary solvents of ethanol,

Table 1. Specific rates of solvolysis (k/s^{-1}) of 4-morpholinecarbonyl chloride in binary solvent mixture at 35.0 °C

Solvent ^d	k (s^{-1})	N_T ^a	Y_{Cl} ^b
100% EtOH	1.35×10^{-5}	0.37	-2.52
90% EtOH	7.67×10^{-5}	0.16	-0.94
80% EtOH	2.58×10^{-4}	0.00	0.00
70% EtOH	6.70×10^{-4}	-0.20	0.78
60% EtOH	1.43×10^{-3}	-0.39	1.38
50% EtOH	2.86×10^{-3}	-0.58	2.02
40% EtOH	5.93×10^{-3}	-0.74	2.75
30% EtOH	1.20×10^{-2}	-0.93	3.53
20% EtOH	2.13×10^{-2}	-1.16	4.09
100% H ₂ O	5.50×10^{-2}	-1.38	4.57
100% MeOH	9.79×10^{-5}	0.17	-1.17
90% MeOH	2.58×10^{-4}	-0.01	-0.18
80% MeOH	5.80×10^{-4}	-0.06	0.67
70% MeOH	1.29×10^{-3}	-0.40	1.46
60% MeOH	2.55×10^{-3}	-0.54	2.07
50% MeOH	4.69×10^{-3}	-0.57	2.70
40% MeOH	8.55×10^{-3}	-0.87	3.25
30% MeOH	1.42×10^{-2}	-1.06	3.73
20% MeOH	2.42×10^{-2}	-1.23	4.10
87% Acetone	1.46×10^{-5}	-0.34	-1.81
80% Acetone	5.37×10^{-5}	-0.37	-0.83
75% Acetone	1.31×10^{-4}	-0.39 ^c	-0.28 ^c
63% Acetone	6.14×10^{-4}	-0.54 ^c	0.62 ^c
52% Acetone	1.76×10^{-3}	-0.68 ^c	1.45 ^c
42% Acetone	4.19×10^{-3}	-0.81 ^c	2.21 ^c
97% TFE (w/w)	8.39×10^{-5}	-3.30	2.83
80% TFE (w/w)	4.80×10^{-4}	-2.19	2.90
50% TFE (w/w)	3.38×10^{-3}	-1.73	3.16

^aFrom ref. 8; ^bFrom ref. 2; ^cFrom ref. 18(g); ^dVolume/volume basis at 25.0 °C, except for TFE-H₂O mixtures, which are on a weight/weight basis.

methanol, trifluoroethanol (TFE), and acetone at 35.0 °C are summarized in Table 1. Rate constants for the reaction in deuterated solvent (D₂O and MeOD) were also determined to examine isotope effects. Additional rate constants were measured to obtain thermodynamic parameters of activation such as enthalpies of activation and entropies of activation which are summarized in Table 2.

As shown in Table 1, the first-order rate constants increase in the order TFE-water < acetone-water < ethanol-water < methanol-water. The rate constants also increase as the water content in the mixed solvents increases, indicating that the reaction rate is accelerated by the solvent with higher ionizing power Y , except 97% TFE-H₂O and 80% TFE-H₂O mixtures. The first-order rate constants increase as the ionizing power Y changes from a lower value to a higher one, i.e., k_1 increases from 0.00135×10^{-2} to $5.50 \times 10^{-2} s^{-1}$ as the Y changes from -2.52 (100% EtOH) to 4.57 (H₂O)^{1,5} for the solvolyses of MPC (increases 4000 fold). This means that the rate is remarkably affected by the solvent with higher ionizing power Y , suggesting that bond breaking in the transition state is significantly importance. The observed first-order rate constants for benzyl chlorides, *p*-methoxybenzoyl chloride and thenoyl chloride

Table 2. Specific rate (k/s^{-1}) of solvolysis for 4-morpholinecarbonyl chloride and activation parameters

Solvent ^b	T (°C)	k (s^{-1})	ΔH^\ddagger (kcal/mol) ^a	$-\Delta S^\ddagger$ (cal/mol K) ^a
80% EtOH	25	8.12×10^{-5}	20.5	8.5
	35	2.58×10^{-4}		
	45	8.39×10^{-4}		
50% EtOH	25	9.24×10^{-4}	19.3	7.8
	35	2.86×10^{-3}		
	45	8.15×10^{-3}		
100% MeOH	25	3.11×10^{-5}	19.5	6.8
	35	9.79×10^{-5}		
	45	2.89×10^{-4}		
80% MeOH	25	1.97×10^{-4}	20.7	5.9
	35	5.80×10^{-4}		
	45	2.09×10^{-3}		
50% MeOH	25	1.53×10^{-3}	20.0	4.2
	35	4.69×10^{-3}		
	45	1.50×10^{-2}		
80% Acetone	25	2.09×10^{-5}	20.1	12
	35	5.37×10^{-5}		
	45	2.07×10^{-4}		
42% Acetone	25	1.56×10^{-3}	18.2	10
	35	4.19×10^{-3}		
	45	1.26×10^{-2}		
97% TFE(w/w)	25	2.32×10^{-5}	19.7	14
	35	8.42×10^{-5}		
	45	2.20×10^{-4}		
80% TFE(w/w)	25	1.43×10^{-4}	20.7	6.7
	35	4.80×10^{-4}		
	45	1.51×10^{-3}		

^aObtained from an Eyring plot and using also the specific rate at 25 °C. ^bVolume/volume basis at 25.0, 35.0, and 45.0 °C, except for TFE-H₂O mixtures, which are on a weight/weight basis.

which are known to react *via* an S_N1 (ionization) and/or dissociative S_N2 reaction mechanism varied over several thousand-fold range.^{11(f),15} The rates of solvolysis (Table 1) have been analyzed in terms of the one-term and two-term Grunwald-Winstein equation [eqn. (1) and (2)].

With all 28 solvent systems included, very good correlations are obtained except 97% TFE and 80% TFE aqueous solvent mixture, with an m values of 0.50 ± 0.01 ($r = 0.987$) for the one-term equation (Figure 1). The data points for the 97% TFE aqueous solvent mixtures exhibit deviations from the correlation of one-term Grunwald-Winstein plots for aqueous alcohol and acetone. Greater rate constants in 40% *v/v* ethanol-water than in 97% *w/w* trifluoroethanol-water (solvent of approximately equal ionizing power) show the importance of nucleophilic solvent assistance (S_N2 or addition-elimination character).^{4(c),9,12(d),18} Rate ratio in two solvents which have nearly same Y_{Cl} value, i.e., the same degree of solvent assistance for bond cleavage but large different nucleophilicity provides measures of the minimum extent of nucleophilic solvent assistance (e.g., [k_{40EW} /

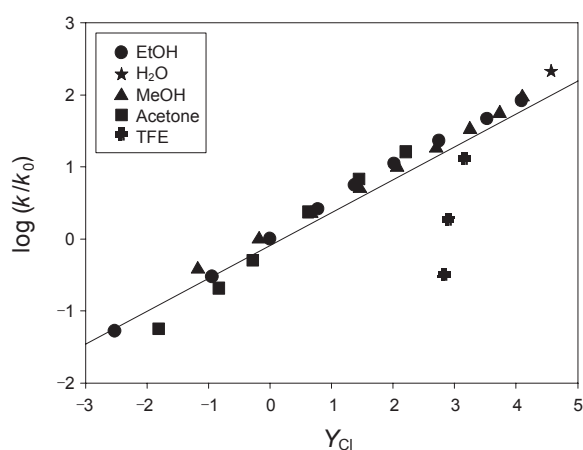


Figure 1. The plot of $\log(k/k_0)$ for solvolyses of 4-morpholinecarbonyl chloride against $0.46 Y_{Cl}$ at 35°C ($r = 0.904$).

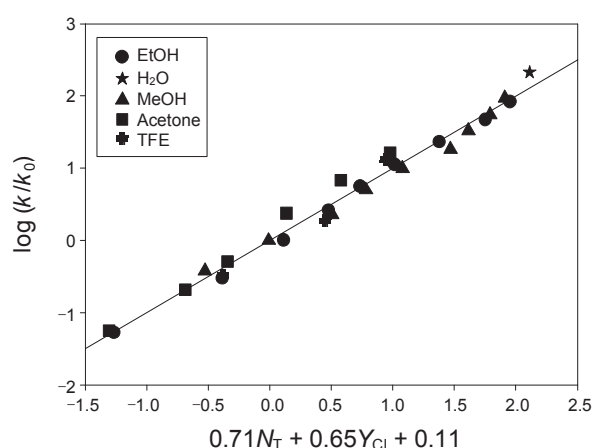


Figure 2. Plots of $\log(k/k_0)$ for solvolyses of 4-morpholinecarbonyl chloride against $0.71N_T + 0.65Y_{Cl} + 0.11$ at 35.0°C ($r = 0.991$).

$k_{97\text{TFE}}] = 71)$.¹⁶ The m value and $k_{40\text{EW}}/k_{97\text{TFE}}$ ratio imply that the solvolyses of MPC in the binary aqueous solvent mixtures proceed through S_N1/S_N2 and/or ionization/(addition-elimination), $[I/(A-E)]$ ¹⁷ pathways rather than through an S_{AN} or addition-elimination channel.^{4(c),9,12(d),18}

An analysis using the two-term (or extended) Grunwald-Winstein equation of the data for the specific rates of solvolyses of MPC in 28 binary solvent mixtures leads to a very good linear correlation with values of 0.71 ± 0.05 for l , 0.65 ± 0.02 for m , 0.11 ± 0.04 for c and 0.991 for the correlation coefficient. Two-term Grunwald-Winstein plots for the specific rates of solvolyses of MPC without the 97% TFE and 80% TFE aqueous solvents data points lead to an excellent linear correlation with values of 0.31 ± 0.11 for l , 0.57 ± 0.03 for m , 0.03 for c and 0.995 for the correlation coefficient. The results of the correlation are presented in Figures 2 and 3 and reported in Table 3, together with the corresponding parameters obtained in the analyses of

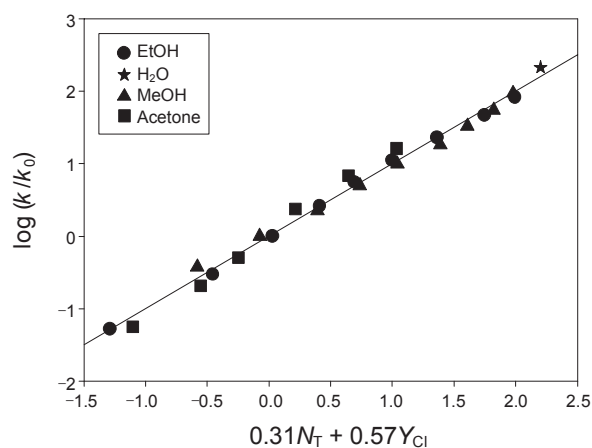
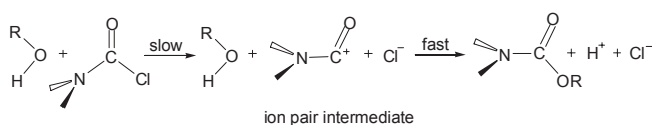


Figure 3. Plots of $\log(k/k_0)$ for solvolyses of 4-morpholinecarbonyl chloride against $0.31N_T + 0.57Y_{Cl}$ at 35.0°C ($r = 0.995$).

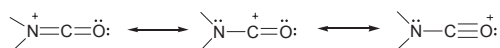
Table 3. Coefficients from the extended Grunwald-Winstein correlations of the specific rates of solvolysis of 4-morpholinecarbonyl chloride at 35.0°C and a comparison with coefficients from the correlations for other acyl chlorides

Substrate	Mech ^a	n^b	l^c	m^c	c^c	R^d
$\text{C}_6\text{H}_5\text{COCl}$	I	32 ^e	0.47 ± 0.03	0.79 ± 0.02	-0.49 ± 0.17	0.990
$p\text{-CH}_3\text{OC}_6\text{H}_4\text{COCl}$	I	37 ^e	0.31 ± 0.05	0.81 ± 0.02	0.08 ± 0.21	0.989
$p\text{-NO}_2\text{C}_6\text{H}_4\text{COCl}$	A-E	34 ^e	1.78 ± 0.08	0.54 ± 0.04	0.11 ± 0.37	0.990
$\text{BzOCOC}l^f$	A-E	15	1.95 ± 0.16	0.57 ± 0.05	0.16 ± 0.15	0.966
$\text{BzOCOC}l^f$	I	11	0.25 ± 0.05	0.66 ± 0.06	-2.05 ± 0.11	0.976
$\text{EtOCOC}l^i$	A-E	28	1.56 ± 0.09	0.55 ± 0.03	0.19 ± 0.24	0.967
$\text{EtOCOC}l^i$	I	7	0.69 ± 0.13	0.82 ± 0.16	-2.40 ± 0.27	0.946
$\text{PhOCOC}l^j$	A-E	21	1.68 ± 0.10	0.57 ± 0.06	0.12 ± 0.41	0.973
$2\text{-AdOCOC}l^k$	I	19	~ 0	0.47 ± 0.03	0.11 ± 0.19	0.970
$\text{EtSCOC}l^l$	I	19	0.66 ± 0.08	0.93 ± 0.07	-0.16 ± 0.31	0.961
$\text{PhSCOC}l$	A-E	16 ^m	1.74 ± 0.17	0.48 ± 0.07	0.19 ± 0.23	0.946
$\text{PhSCOC}l$	I	6 ^m	0.62 ± 0.08	0.92 ± 0.11	-2.29 ± 0.13	0.983

^aThe two reaction channels are designated as addition-elimination (A-E) and ionization (I). ^bNumber of solvent systems included in the correlation. ^cWith associated standard errors, those associated with the c values being the standard errors of the estimate. ^dCorrelation coefficient. ^eData from refs. 3, 10, 11(a), 11(d), 11(e), 11(f), 18(i), and 22(d). ^fValues from ref. 18(k). ^gValues from ref. 13(b). ^hValues from ref. 13(j). ⁱValues from ref. 18(i). ^jValues from ref. 13(b). ^kValues from ref. 7(d).



Scheme 1



Scheme 2

earlier studied substrates. The l/m ratio has been suggested as a useful mechanistic criterion and the values in Table 3 were divided nicely into three classes with values of 1.9 to 3.4 for those entries postulated to represent addition-elimination (A-E), values below 0.84 for those believed to represent ionization (I), and values of 0.84 to 1.9 for those postulated to represent I/(A-E) mechanism.⁹ For MPC, the l/m values of 1.09 (28 all solvents) and 0.54 (excluded 97% TFE and 80% TFE data points) are very similar to those previously observed l/m values for the solvolyses of *p*-methoxybenzoyl chloride,¹⁰ phenyl chloroformate,¹² and phenyl chlorothioformate,^{13(a)} which have been shown to solvolyze with the ionization step of an I and/or I/(A-E) pathway.^{9,17} The mechanism leads to a changeover from a dominant A-E pathway to a I pathway (Scheme 1), because the dominant resonance contribution proposed for benzoyl cation will be operative for the MPC cation, with the positive charge substantially transferred within the carbonyl group from the carbon to the nitrogen atom (Scheme 2). Ion pair intermediate can be stabilization of the developing acylium ion by mesomeric interaction of the lone pair electrons on the nitrogen shown in Scheme 2.¹⁹ The first contributor will be dominant, because nitrogen atom can carry a positive charge in onium-type structure than oxygen,²⁰ and also nitrogen atom can give better π electron donation effect than oxygen atom. In turn, this will lead to an enhanced stability for the resonance hybrid.

The solvent deuterium isotope effect has previously been studied for solvolyses of *p*-methoxybenzoyl chlorides and *p*-methoxybenzyl chloride.^{9,11(f),23} In pure methanol, the $k_{\text{MeOH}}/k_{\text{MeOD}}$ ratio was 1.22 (see Table 4) at 25 °C for a series of substrates believed to react by the $\text{S}_{\text{N}}1$ or ionization mechanism.^{8,11(f),23} In pure water, the $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ ratio was 1.25 and 1.1 for solvolyses of isopropyl chloroformate⁸ and diphenylcarbamoyl chloride,^{19(c),(d)} respectively, which are believed to react by the $\text{S}_{\text{N}}1$ or ionization mechanism. The solvent deuterium isotope effect values (Table 4) for the hydrolysis of MPC of $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}} = 1.27$ and for

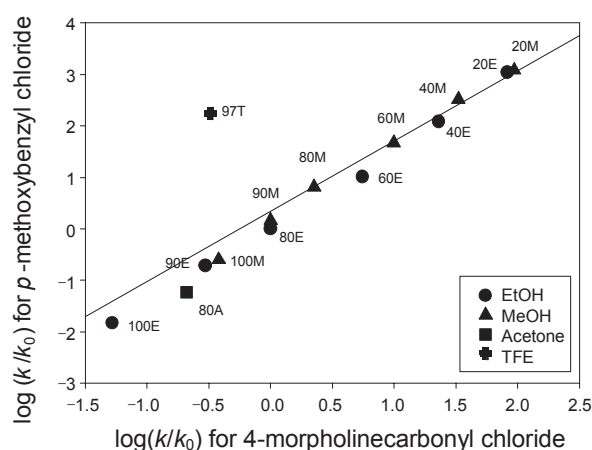


Figure 4. Correlation of logarithms of rate constants for solvolyses of *p*-methoxybenzyl chloride^{11(f)} vs. solvolyses of 4-morpholinecarbonyl chloride at 35.0 °C ($r = 0.879$).

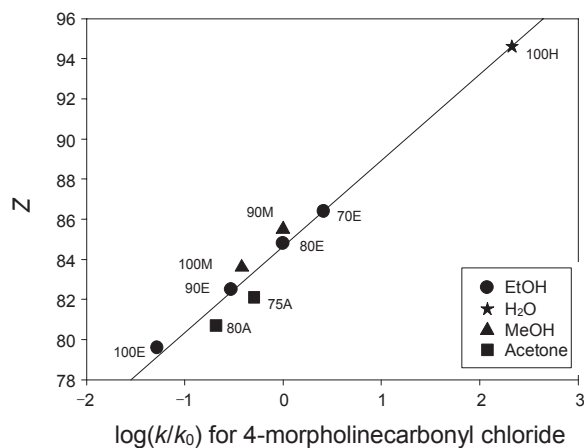


Figure 5. Correlation of Z^{20} values vs. logarithms of rate constants for solvolyses of 4-morpholinecarbonyl chloride^b at 35.0 °C ($r = 0.986$).

the methanolysis of MPC of $k_{\text{MeOH}}/k_{\text{MeOD}} = 1.21$ are typical magnitudes of the $\text{S}_{\text{N}}1$ or ionization mechanism.

Good correlations showing negligible dispersion can also be seen for solvolyses of *p*-methoxybenzoyl chloride vs. solvolyses of MPC (Figure 4), except that there is a significant deviation for 97% TFE/water. The deviation shows that the reaction path of solvolyses of MPC differs from that of *p*-methoxybenzoyl chloride because the TFE has lower nucleophilicity and higher electrophilicity though the solvent ionizing power of 97% TFE

Table 4. Rate constants and kinetic solvent isotope effects (KSIE) in methanol and water

Substrate	$k(\text{s}^{-1})^c$ (MeOH)	$k(\text{s}^{-1})^c$ (MeOD)	KSIE ^d
<i>p</i> -methoxybenzyl chloride ^a	$(2.86 \pm 0.01) \times 10^{-4}$	$(2.35 \pm 0.05) \times 10^{-4}$	1.22 ± 0.04
<i>p</i> -methoxybenzoyl chloride ^a	$(1.13 \pm 0.01) \times 10^{-2}$	$(9.25 \pm 0.07) \times 10^{-3}$	1.22 ± 0.02
4-morpholinecarbonyl chloride ^b	$(9.79 \pm 0.01) \times 10^{-5}$	$(8.11 \pm 0.05) \times 10^{-5}$	1.21 ± 0.02
	(H ₂ O)	(D ₂ O)	
4-morpholinecarbonyl chloride ^b	$(5.50 \pm 0.03) \times 10^{-2}$	$(4.32 \pm 0.02) \times 10^{-2}$	1.27 ± 0.02

^aValues from Ref. 11(f). ^bThis work. ^cStandard deviation. ^dStandard error.

is similar to the that of 40% v/v ethanol-water. The solvatochromic parameter Z ,^{11(0),21} a scale of solvent polarity based on the solvent dependence of intermolecular charge-transfer transition in the prydinium salt,^{11(0),21} shows a good correlation with solvolyses of MPC (Figure 5). These results indicate that the solvolyses of MPC proceed by dissociative S_N2 predominantly or S_N1 (ionization) pathway with a acylium ion pair intermediate or loose S_N2 transition state, supporting that acylium ion pair intermediate is stabilized by solvent polarity.

The activation parameters for solvolyses of MPC in aqueous binary solvent mixtures at 25 °C are summarized in Table 2. The relatively small negative ΔS^\ddagger and large positive ΔH^\ddagger support that the solvolytic reaction proceeds through a typical dissociative S_N2 or S_N1 (ionization) pathway.^{22,23}

Experimental Section

Material. 4-Morpholinecarbonyl chloride (MPC) is a commercial grade (Merck GR-grade > 99%). Merck GR-grade (< 0.1% H₂O) acetone, ethanol, methanol and trifluoroethanol were used without further purification. D₂O and CH₃OD were from Aldrich (99.9% D). Distilled water was redistilled with Buchi Fontavapor 210 and treated using ELGA UHQ PS to obtain specific conductivity of less than 1.0×10^{-6} mhos/cm.

Rate measurements and product identification. Rates were measured conductimetrically at least in duplicate as in the previous work.⁴ Activation parameters were determined using the Arrhenius and Eyring equations. The solvolyses product was identified by ¹H NMR spectrum.

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