

Correlation of the Rates of Solvolysis of 1-Piperidincarbonyl Chloride Using the Extended Grunwald-Winstein Equation

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The specific rates of solvolysis of 1-piperidincarbonyl chloride (**1**) have been determined in 26 pure and binary solvents at 25.0 °C. Comparison of the specific rates of solvolyses of **1** with those for *p*-methoxybenzoyl chloride and those for 4-morpholinecarbonyl chloride in terms of linear free energy relationships (LFER) are helpful in mechanistic considerations, as is also treatment in terms of the extended Grunwald-Winstein equation. It is proposed that the solvolyses of **1** in binary aqueous solvent mixtures proceed through an ionization [I] pathway rather than through an S_N1/S_N2 and/or ionization/(ionization-elimination) = [I/(I-E)] pathway.

Key Words : 1-Piperidincarbonyl chloride (PCC), Grunwald-Winstein equation, Addition-elimination (A-E), Ionization (I), KSIE

Introduction

Piperidincarbonyl chlorides are used in large amounts in the pharmaceutical industry.¹⁻⁴ In particular, they are very important reagents for the preparation of P2Y₁₂ antagonists² and the inhibition of platelet aggregation and are play roles as potent hNK1 antagonists³ and anti-HIV agents.⁴ For several years, we have been investigating the mechanisms available for the solvolyses of carbonyl halides;⁵⁻¹⁰ these reactions offer a model for nucleophilic substitution reactions of carbonyl halides in general, including their use within peptide synthesis and many other applications.¹¹

The Grunwald-Winstein equation (eq. 1) is a very powerful tool for mechanistic study of the solvolyses of substrates in various binary mixtures.¹² 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 of the solvolyses to changes in the solvent ionizing power *Y*_{Cl}¹³ and *c* represents a residual term. However, dispersion into separated lines in the correlation of the specific rates of solvolysis of benzoyl¹⁴ and sulfonyl halides¹⁵ in various aqueous solvents mixtures was documented in early treatments using the Grunwald-Winstein equation, given below.

$$\log(k/k_0) = mY + c \quad (1)$$

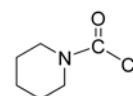
It was realized early^{12(b)} that it would be necessary to incorporate a term governed by sensitivity (*l*) to changes in solvent nucleophilicity *N*,¹⁶ and equation (2) was proposed for bimolecular solvolysis.¹⁷ The resulting equation is often referred to as the extended Grunwald-Winstein equation, and it has proven extremely valuable in studies of the

mechanisms underlying solvolysis reactions.¹⁷

$$\log(k/k_0) = lN_T + mY + c \quad (2)$$

For ionization reactions without nucleophilic assistance, *l* will be zero and *m* close 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 in the region below 0.5.¹⁸

The effects of solvents with the extended Grunwald-Winstein relationships in the solvolysis of alkyl and aromatic acyl halides,^{6(a),6(b),19} chloroformates,²⁰ and thiochloroformates²¹ have received much attention and been discussed extensively, 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 the rate constants for solvolyses of 1-piperidincarbonyl chloride (PCC) with a *N*-alkyl group in aqueous binary solvents of acetone, ethanol, ethanol, methanol-d, trifluoroethanol (TFE), and 50%MeOD-50%D₂O at various temperatures. Mechanistic variation and transition state variation are also discussed by applying the one-term Grunwald-Winstein equation, two-term (extended) Grunwald-Winstein equation, Z values, kinetic solvent isotope effects (KSIE), and activation parameters. We compared the solvolytic mechanism of 1-piperidincarbonyl chloride with that of 4-morpholinecarbonyl chloride.²²



1-piperidincarbonyl chloride (PCC)

Results

The specific rates of the solvolysis of PCC at 25.0 °C are reported in Table 1. The N_T and Y_{Cl} values are also reported in Table 1. Rates were also determined in deuterated aqueous methanol (50%MeOD-50%D₂O), CH₃OD, and D₂O. The specific rates of solvolysis for methanol, 80% methanol, 50% methanol, 80% ethanol, 50% ethanol, 80% acetone, 42% acetone, 97% TFE (w/w), and 80% TFE (w/w) were determined at two additional temperatures, and these values, together with calculated enthalpies and entropies of activation, are reported in Table 2.

Discussion

As shown in Table 1, the first-order rate constants increase in the order TFE-water < acetone-water < ethanol-water < methanol-water. The rate constant increases as the water content increases in the mixed solvents. This shows that the reaction rate is accelerated by solvents with higher ionizing power. 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 0.00907×10^{-2} to $31.9 \times 10^{-2} \text{ s}^{-1}$ as Y changes

Table 1. Specific rates of solvolysis (k/s^{-1}) of 1-piperidinecarbonyl chloride in binary solvent mixtures at 25 °C

Solvent ^d	N_T^a	Y_{Cl}^b	k_{obs}
100% EtOH	0.37	-2.52	9.09×10^{-5}
90% EtOH	0.16	-0.94	5.24×10^{-4}
80% EtOH	0.00	0.00	2.01×10^{-3}
70% EtOH	-0.20	0.78	5.26×10^{-3}
60% EtOH	-0.39	1.38	1.50×10^{-2}
50% EtOH	-0.58	2.02	4.41×10^{-2}
40% EtOH	-0.74	2.75	7.74×10^{-2}
30% EtOH	-0.93	3.53	2.45×10^{-1}
20% EtOH	-1.16	4.09	3.19×10^{-1}
100% MeOH	0.17	-1.17	7.48×10^{-4}
90% MeOH	-0.01	-0.18	2.59×10^{-3}
80% MeOH	-0.06	0.67	6.81×10^{-3}
70% MeOH	-0.40	1.46	1.64×10^{-2}
60% MeOH	-0.54	2.07	3.50×10^{-2}
50% MeOH	-0.57	2.70	7.24×10^{-2}
40% MeOH	-0.87	3.25	1.46×10^{-1}
30% MeOH	-1.06	3.73	2.88×10^{-1}
87% Acetone	-0.34	-1.81	8.23×10^{-5}
80% Acetone	-0.37	-0.83	4.02×10^{-4}
75% Acetone	-0.39	-0.28	9.40×10^{-4}
63% Acetone	-0.54 ^c	0.62 ^c	5.02×10^{-3}
52% Acetone	-0.68 ^c	1.45 ^c	1.94×10^{-2}
42% Acetone	-0.81 ^c	2.21 ^c	5.88×10^{-2}
97% TFE (w/w)	-3.30	2.83	4.40×10^{-3}
80% TFE (w/w)	-2.19	2.90	1.72×10^{-2}
50% TFE (w/w)	-1.73	3.16	6.79×10^{-2}

^aFrom ref. 16. ^bFrom ref. 13. ^cFrom ref. 25 g. ^dVolume/volume basis at 25.0 °C, except for TFE-H₂O mixtures, which are on a weight/weight basis.

Table 2. Additional specific rates and activation parameters of solvolysis (k/s^{-1}) for 1-piperidinecarbonyl chloride

Solvent ^b	t (°C)	k (s^{-1})	ΔH^\ddagger (kcal/mol) ^a	$-\Delta S^\ddagger$ (cal/mol·K) ^a
100% EtOH	15	2.415×10^{-5}	21.4	5.0
	25	9.086×10^{-5}		
	35	2.761×10^{-4}		
80% EtOH	15	5.759×10^{-4}	20.0	3.8
	25	2.013×10^{-3}		
	35	5.567×10^{-3}		
100% MeOH	15	2.420×10^{-4}	19.5	7.3
	25	7.481×10^{-4}		
	35	2.220×10^{-3}		
60% MeOH	15	1.410×10^{-2}	17.7	5.4
	25	3.504×10^{-2}		
	35	1.061×10^{-1}		
63% Acetone	15	1.626×10^{-3}	19.3	4.3
	25	5.019×10^{-3}		
	35	1.450×10^{-2}		
97% TFE	15	1.332×10^{-3}	18.4	7.8
	25	4.409×10^{-3}		
	35	1.069×10^{-2}		
80% TFE	15	4.250×10^{-3}	21.2	4.4
	25	1.719×10^{-2}		
	35	4.707×10^{-2}		

^aObtained from an Eyring plot and using the specific rate constant 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.

from -2.52 (100% EtOH) to 4.09 (20%EtOH-80%H₂O)^{12,13} for solvolyses of the PCC (representing a 3500-fold increase). This indicates that the rate is remarkably affected by the solvent with higher ionizing power, suggesting that bond breaking in the transition state is of importance. The observed first-order rate constants for benzyl chlorides, *p*-methoxybenzoyl chloride, and thenoyl chloride, which are known to react *via* an S_N1 (ionization) and/or dissociative S_N2 reaction mechanism, vary over a several thousand-fold range.²³ The solvolytic rate constants for PCC are very similar to those of the solvolytic reaction of benzyl chlorides,^{18,19(d),24} *p*-methoxybenzoyl chloride, and thenoyl chloride. The specific rates of solvolysis (Table 1) have been analyzed in terms of the one-term and two-term Grunwald-Winstein equations.

With all 26 solvent systems included, very good correlations are obtained except for the 97% TFE and 80% TFE aqueous solvent mixtures, with an m value of 0.54 ± 0.01 ($r = 0.906$) for the one-term equation (Figure 1). The data points for 97%TFE and 80%TFE aqueous solvent mixtures deviate from the linear 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 show the importance of nucleophilic solvent assistance (S_N2 or addition-elimination character), although the ionizing power is approximately equal in both solvents.^{15(c),18,20(d),25} The rate ratio in two solvents that have

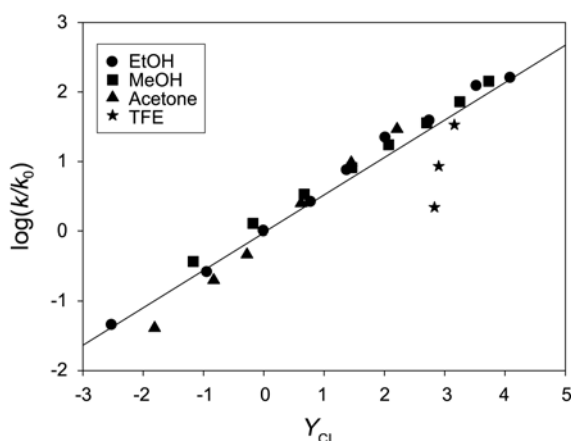


Figure 1. Plot of $\log(k/k_0)$ for solvolyses of 1-piperidinecarbonyl chloride against $0.54Y_{Cl}$ at 25 °C ($r = 0.906$).

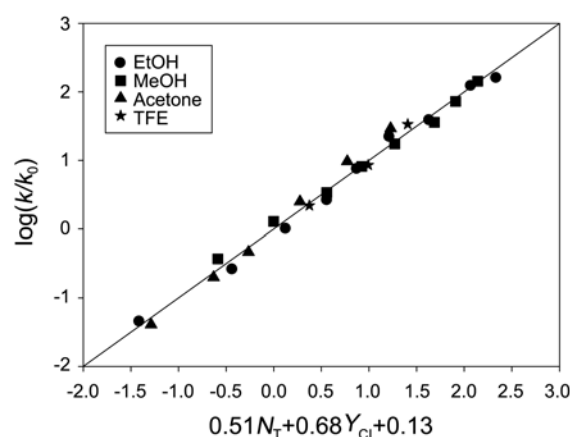


Figure 2. Plot of $\log(k/k_0)$ for solvolyses of 1-piperidinecarbonyl chloride against $0.51N_T + 0.68Y_{Cl} + 0.13$ at 25 °C ($r = 0.988$).

Table 3. Values of solvolyses rate constant ratios of 40%EtOH/H₂O compared to 97%TFE/H₂O binary mixtures at 25.0 °C

	Mechanism ^a	k_{40EW}/k_{97TFE}
(C ₆ H ₅) ₂ CHCl ^b	I	0.180
<i>p</i> -CH ₃ O(C ₆ H ₅)CH ₂ Cl ^b	I	0.700
CH ₃ C≡CC(CH ₃) ₂ Cl ^b	I	1.90
C ₆ H ₅ (CHCl)CH ₃ ^b	I	2.00
CH ₃ (CH ₂) ₂ C(CH ₃) ₂ Cl ^b	I	4.60
CH ₃ CH=CH(CHCl)CH ₃ ^b	I	7.10
(CH ₃) ₃ CCl ^b	I	11.0
2-chloro-2-methylthioacetophenone ^c	S _N 1	27.0
<i>p</i> -nitro- <i>N</i> -methyl- <i>N</i> -phenylcarbamoyl chloride ^d	S _N 1/S _N 2	30.2
2-chloro-2-(methylthio)acetone ^e	S _N 2	109
3,4-dimethoxybenzenesulfonyl chloride ^f	S _N 2	386
Methanesulfonyl chloride ^g	S _N 2/S _A N	535
<i>trans</i> -β-styrenesulfonyl chloride ^h	S _N 2/S _A N	846
Ethyl chloroformate ⁱ	S _N 2/S _A N	982
4-Morpholinecarbonyl chloride ^j	S _N 1/S _N 2	71.0
1-Piperidinecarbonyl chloride ^k	S _N 1/S _N 2	17.0

^aThe two reaction channels are designated as addition-elimination (A-E) and ionization (I). ^bData from Refs. 25(a); 25(b). ^cData from Ref. 25(d). ^dData from Ref. 25(e). ^eData from Ref. 25(f). ^fData from Ref. 15(b). ^gData at -10 °C, from Ref. 25(g). ^hData at 45 °C, from Ref. 25(h). ⁱData at 24.2 °C, from Ref. 21(b). ^jData at 24.2 °C, from Ref. 22. ^kData from this work.

same Y_{Cl} value, *i.e.*, the same degree of solvent assistance for bond cleavage but different nucleophilicity, provides a measure of the minimum extent of nucleophilic solvent assistance (*e.g.*, $[k_{40EW}/k_{97TFE}] = 17.5$, EW = ethanol-water).²⁶ The m value ($= 0.54$) and k_{40EW}/k_{97TFE} ratio ($= 17.5$) imply that the solvolyses of PCC in the binary aqueous solvent mixtures proceed through S_N1 (ionization [I]) and/or dissociative S_N2 pathway channels rather than through normal concerted S_N2 and/or addition-elimination (A-E) pathway channels (See Table 3).^{15(c),18,20(d),25}

An analysis using the two-term (or extended) Grunwald-Winstein equation leads to a very good linear correlation, with values of 0.51 ± 0.01 for l , 0.68 ± 0.01 for m , $0.13 \pm$

0.01 for c , and 0.988 for the correlation coefficient. The results of the correlation are presented in Figure 2 and reported in Table 4, together with the corresponding parameters of other substrates.¹¹⁻¹⁷ The l/m ratio has been suggested as a useful mechanistic criterion and the values of Table 4 divide nicely into three classes, with values of 1.9-3.4 for those entries postulated to represent addition-elimination (A-E), values below 0.84 for those believed to represent ionization (I), and values of 0.84-1.9 for those postulated to represent the I/(A-E) mechanism.^{17,18} For PCC, the ratio of l/m , 0.75 is very similar to that observed for the solvolyses of benzoyl chloride,⁶ *p*-methoxybenzoyl chloride,^{6,27} ethyl chloroformate and, ethyl chlorothioformate,^{5(a)} which have been shown to solvolyze with the ionization step of an I pathway being rate determining.¹⁸

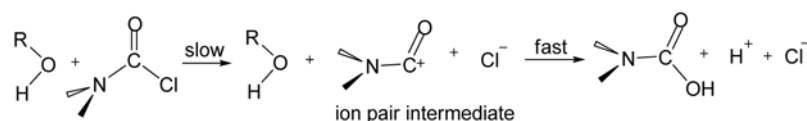
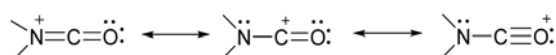
The mechanism changes from a dominant A-E pathway to an I pathway (Scheme 1), because the dominant resonance contribution proposed for benzoyl cation will be operative for the PCC cation, and the positive charge is transferred substantially from the carbonyl carbon to the nitrogen atom (Scheme 2).²² Among the resonance structures, the first structure may be dominant, because positive charge is more likely to develop on the nitrogen atom than on the oxygen atom in an onium-type structure; in addition, the nitrogen atom can donate π electrons better than the oxygen atom. In turn, this will lead to enhanced stability for the resonance hybrid.²²

A simple comparison with specific rates of PCC and MPC is hampered because the rates of the former are observed at 25.0 °C in the present study but the values of the latter are observed at 35.0 °C. Fortunately, for MPC, analyses were also carried out at other temperatures, including 25.0 °C. The following specific rate ratios (k_{PCC}/k_{MPC}) are determined directly at 25.0 °C in the indicated solvent: 80% EtOH ($Y_{Cl} = 0.00$), 24.8; 50% EtOH ($Y_{Cl} = 2.02$), 47.7; MeOH ($Y_{Cl} = -1.17$), 24.1; 50% MeOH ($Y_{Cl} = 2.70$), 47.3; 80% Acetone ($Y_{Cl} = -0.83$), 19.2; 42% acetone ($Y_{Cl} = 2.21$), 37.7; 97% TFE (2.83), 190; 80% TFE ($Y_{Cl} = 2.90$), 120. The rate ratio increases as the ionizing power, Y_{Cl} , increases, indicating that bond breaking at the transition state in PCC is more

Table 4. 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
C ₆ H ₅ COCl	I	32 ^e	0.47 ± 0.03	0.79 ± 0.02	-0.49 ± 0.17	0.990
<i>p</i> -CH ₃ OC ₆ H ₄ COCl	I	37 ^e	0.31 ± 0.05	0.81 ± 0.02	0.08 ± 0.21	0.989
<i>p</i> -NO ₂ C ₆ H ₄ COCl	A-E	34 ^e	1.78 ± 0.08	0.54 ± 0.04	0.11 ± 0.37	0.990
BzOCOC ^f	A-E	15	1.95 ± 0.16	0.57 ± 0.05	0.16 ± 0.15	0.966
BzOCOC ^f	I	11	0.25 ± 0.05	0.66 ± 0.06	-2.05 ± 0.11	0.976
EtOCOC ^f	A-E	28	1.56 ± 0.09	0.55 ± 0.03	0.19 ± 0.24	0.967
EtOCOC ^f	I	7	0.69 ± 0.13	0.82 ± 0.16	-2.40 ± 0.27	0.946
PhOCOC ^f	A-E	21	1.68 ± 0.10	0.57 ± 0.06	0.12 ± 0.41	0.973
2-AdOCOC ^g	I	19	~ 0	0.47 ± 0.03	0.11 ± 0.19	0.970
EtSCOC ^f	I	19	0.66 ± 0.08	0.93 ± 0.07	-0.16 ± 0.31	0.961
PhSCOC ^f	A-E	16 ^m	1.74 ± 0.17	0.48 ± 0.07	0.19 ± 0.23	0.946
PhSCOC ^f	I	6 ^m	0.62 ± 0.08	0.92 ± 0.11	-2.29 ± 0.13	0.983
O(CH ₂ CH ₂) ₂ NCOC ^h	I	28	0.71 ± 0.05	0.65 ± 0.02	0.11 ± 0.04	0.991
PCC ^o	I	26	0.51 ± 0.07	0.65 ± 0.03	0.11 ± 0.05	0.988

^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. 14, 27, 19(a), 19(d), 19(e), 19(f), 25(i), and 24(d). ^fValues from Ref. 25(k). ^gValues from Ref. 21(b). ^hValues from Ref. 25(j). ⁱValues from Ref. 25(i); ^jValues from Ref. 21(b). ^mValues from Ref. 179(d). ⁿValues from Ref. 22. ^oData from this work.

**Scheme 1****Scheme 2**

advanced than in MPC. However, the ratios in the 97% TFE and 80% TFE are much larger than those in other aqueous alcohol and acetone mixtures. This indicates again that the solvolyses of PCC proceed predominantly by S_N1 (ionization) and/or a dissociative S_N2 pathway with an acylium ion pair intermediate or loose S_N2 transition state. This

supports that the acylium ion pair intermediate is stabilized by highly electrophilic solvents such as 97% TFE and 80% TFE.

Good correlations showing negligible dispersion can also be seen for solvolyses of PCC vs solvolyses of *p*-methoxybenzoyl chloride, where the reaction is known to proceed through S_N1 (ionization) and/or a dissociative S_N2 pathway (Figure 3).^{11(d),18,24,28}

The plot of the rate of the solvolyses of PCC with the solvatochromic parameter Z,^{19(d),30} a measure of solvent polarity based on the solvent dependence of the intermole-

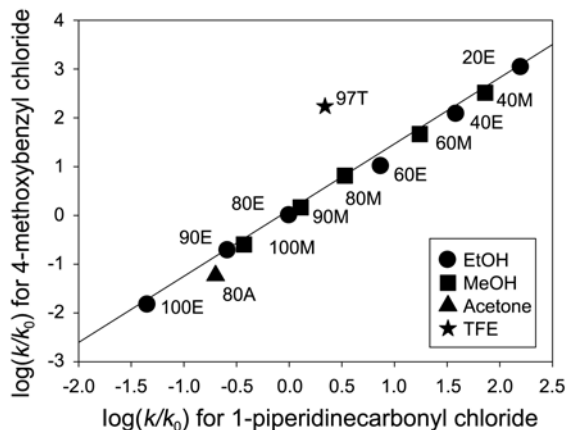
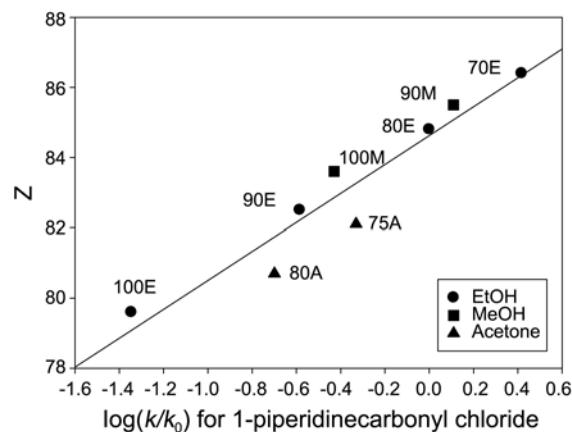
**Figure 3.** Correlation of logarithms of rate constants for solvolyses of *p*-methoxybenzyl chloride vs. solvolyses of 1-piperidinecarbonyl chloride at 25 °C (*r* = 0.891).**Figure 4.** Correlation of Z values vs. logarithms of rate constants for solvolyses of 1-piperidinecarbonyl chloride at 25 °C (*r* = 0.909).

Table 5. Rate constants and kinetic solvent isotope effects (KSIE) in methanol

Substrate	$k(\text{s}^{-1})^d$ (MeOH)	$k(\text{s}^{-1})^d$ (MeOD)	KSIE
<i>p</i> -methoxybenzyl chloride ^a	$(2.86 \pm 0.01) \times 10^{-4}$	$(2.35 \pm 0.05) \times 10^{-4}$	1.22
<i>p</i> -methoxybenzoyl chloride ^a	$(1.13 \pm 0.01) \times 10^{-2}$	$(9.25 \pm 0.07) \times 10^{-3}$	1.22
4-morpholinecarbonyl chloride ^b	$(9.79 \pm 0.01) \times 10^{-5}$	$(8.11 \pm 0.05) \times 10^{-5}$	1.21
1-piperidinecarbonyl chloride ^c	$(7.48 \pm 0.02) \times 10^{-4}$	$(6.35 \pm 0.03) \times 10^{-4}$	1.18
1-piperidinecarbonyl chloride ^c	50% MeOH-50% H ₂ O $(7.24 \pm 0.01) \times 10^{-2}$	50% MeOD-50% D ₂ O $(6.14 \pm 0.01) \times 10^{-2}$	1.18

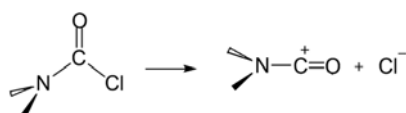
^aValues from Ref. 19(d). ^bValues from Ref. 22. ^cThis work. ^dStandard deviation

cular charge-transfer transition in pyridinium salt, also shows a good correlation, as presented in Figure 4. These results indicate that the solvolyses of PCC proceed predominantly by S_N1 (ionization) and/or a dissociative S_N2 pathway with a acylium ion pair intermediate or loose S_N2 transition state and support that the acylium ion pair intermediate is stabilized by solvent polarity.

The values representing the solvent deuterium isotope effect summarized in Table 5 for hydrolysis of PCC ($k_{50\% \text{MeOH-50\%H}_2\text{O}}/k_{50\% \text{MeOD-50\%D}_2\text{O}} = 1.18$) and for methanolysis of PCC ($k_{\text{MeOH}}/k_{\text{MeOD}} = 1.18$) are of a magnitude usually taken to indicate the S_N1 or ionization mechanism.^{11(d),16,18,24,28,29}

The activation parameters for solvolyses of PCC in aqueous solvents 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 S_N1 (ionization) and/or dissociative S_N2 pathway.^{24,31}

In order to discuss the relative reactivity of PCC and MPC theoretically, we have performed quantum mechanical computations on the heterolytic cleavage of the C-Cl bond to give the corresponding cation and chloride ion, as this is supposed to be the rate determining step of the reactions.



Gibbs energies of the reaction are summarized in Table 6, and the relative Gibbs energies for PCC over MPC are $-6 \sim -7$ kcal/mol and $-3 \sim -4$ kcal/mol in the gas phase and in water, respectively. Therefore, the higher reactivity of PCC over MPC is attributed to the lower reaction energy of the former.

Experimental Section

Material. 1-Piperidinecarbonyl chloride (PCC) is of commercial grade (Merck GR-grade > 99%). Merck GR-grade (< 0.1% H₂O) acetone, ethanol, methanol, and trifluoroethanol were used without further purification. 50%MeOD-50%D₂O and CH₃OD were obtained from Aldrich (99.9% D). Distilled water was redistilled with a 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 previous studies.⁷⁻⁹ Activation parameters were determined using the Arrhenius and Eyring equations. The solvolyses products were identified by 1H NMR spectra.

Computations

Quantum mechanical calculations were performed using the Gaussian 03³² program and the reaction energies were evaluated at the density functional theory of Becke's 3-parameter hybrid method using the correlation functional of Lee, Yang, and Parr (B3LYP)³³ at the 6-31+G(d,p) level and complete basis sets (CBS).³⁴ The polarized continuum model (PCM)³⁵ was also applied to simulate the reaction in water.

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