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Solvolysis of (1S)-(+)-Menthyl Chloroformate in Various Mixed Solvents

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The solvolysis of (1s)-(+)-menthyl chloroformate (**1**) were studied kinetically in 28 pure and various mixed solvents. The analysis using the extended Grunwald-Winstein equation in the solvolysis of **1** obtained the *l* value of 2.46 ± 0.18, the *m* value of 0.91 ± 0.07, and the correlation coefficient of 0.950. The solvolysis of **1** might proceed *via* an associative S_N2 mechanism enhancing bond making than bond breaking in the transition state (TS). The value of *l/m* is 2.7 within the ranges of value found in associative S_N2 reaction. This interpretation is further supported by a relatively large solvent kinetic isotope effect (SKIE, 2.16).

Key words: (1s)-(+)-Menthyl chloroformate, Extended Grunwald-Winstein equation, Associative S_N2 mechanism, Solvent kinetic isotope effect

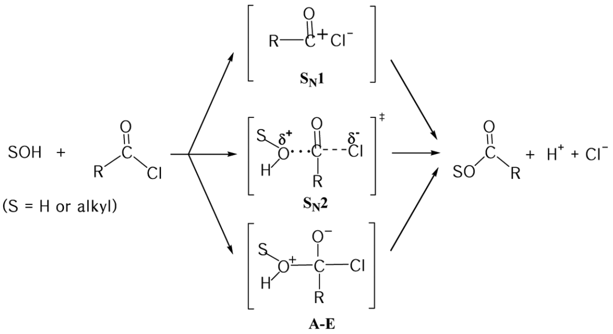
INTRODUCTION

The first study of solvolysis was done by Berthelot and St. Gille.[1] Hughes and Ingold[2] studied the solvolysis to establish the theoretical concept of the nucleophilic single-molecule substitution reaction and the nucleophilic bimolecular substitution reaction.

Kevill and co-works[3] applied the extended Grunwald-Winstein equation (eq. 1) to study the reaction pathways of the solvolysis by calculating the *l* and *m* values. In equation 1, *k* and k_o represent the rate constants of solvolyses of a substrate RX in a given solvent and in the standard solvent (80% ethanol), respectively; *l* is the sensitivity of the solvolysis to changes in solvent nucleophilicity (N_T); *m* is the sensitivities of the solvolysis to changes in solvent ionizing power (Y_{Cl}), for leaving group X); *c* is a constant term. This study uses the solvent nucleophilicity (N_T) scale based on the solvolyses of S-methyldibenzothiophenium ion and the solvent ionizing power (Y_{Cl}) scale based on the solvolyses of 1-adamantyl chloride.

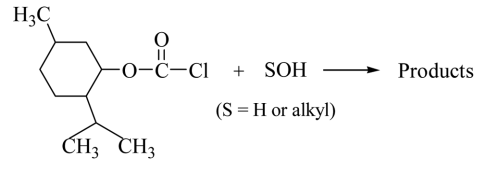
$$\log (k/k_o) = lN_T + mY_{Cl} + c \qquad (1)$$

In previous papers in this series, we have reported that solvent effects on the TS variation in the reaction of carbonyl derivatives (RCOCl or ROCOCl) in various mixed solvents.[4] These solvolysis can be shown as *Scheme* 1. It is known that the solvolysis of carbonyl compounds proceeds as an S_N1 (ion pair intermediate) reaction, an S_N2 reaction, or an addition-elimination (A-E) reaction depending on the reaction conditions.



***Scheme* 1.** Reaction pathways for the solvolysis of carbonyl derivatives.

In the present study we measure rate constants of solvolysis **1** as eq. 2. The reaction mechanism was investigated by applying the rate constants of the solvolysis of **1** to the extended Grunwald-Winstein equation (eq. 1).[3] In addition, the solvent kinetic isotope effect and activation parameters were discussed in order to obtain more information for the reaction mechanism.



(2)

RESULTS AND DISCUSSION

The rate constants of solvolysis **1** were determined in 28 solvents at 55.0 °C. The solvents consisted of ethanol and methanol, binary mixtures of water with ethanol, methanol, 2,2,2-trifluoroethanol (TFE), acetone, and four binary mixtures of TFE and ethanol. The rate constants of solvolysis are

***Table* 1.** Rate constants (*k*) for solvolysis of **1** at 55.0 °C

Solvent-mixture[a]	k (s^{-1})
100%EtOH	4.47×10^{-5}
90%EtOH-H_2O	2.63×10^{-4}
80%EtOH-H_2O	3.69×10^{-4}
70%EtOH-H_2O	5.16×10^{-4}
60%EtOH-H_2O	6.20×10^{-4}
50%EtOH-H_2O	9.29×10^{-4}
40%EtOH-H_2O	17.7×10^{-4}
100%MeOH[b]	3.80×10^{-4}
90%MeOH-H_2O	1.91×10^{-3}
80%MeOH-H_2O	4.96×10^{-3}
70%MeOH-H_2O	7.94×10^{-3}
60%MeOH-H_2O	1.27×10^{-2}
50%MeOH-H_2O	2.29×10^{-2}
40%MeOH-H_2O	3.43×10^{-2}
90%Me_2CO-H_2O	3.24×10^{-6}
80%Me_2CO-H_2O	3.98×10^{-5}
70%Me_2CO-H_2O	9.31×10^{-5}
60%Me_2CO-H_2O	2.51×10^{-4}
50%Me_2CO-H_2O	3.77×10^{-4}
40%Me_2CO-H_2O	7.92×10^{-4}
80%TFE-H_2O[c]	3.46×10^{-6}
70%TFE-H_2O	1.11×10^{-5}
60%TFE-H_2O	3.11×10^{-5}
50%TFE-H_2O	5.31×10^{-5}
80%TFE-EtOH	6.61×10^{-6}
60%TFE-EtOH	1.04×10^{-5}
40%TFE-EtOH	1.91×10^{-5}
20%TFE-EtOH	2.66×10^{-5}

[a] Prepared on a volume/volume basis with other component water.

[b] Value of k (= 1.76×10^{-4} s^{-1}) in methanol-d (MeOD), corresponding to a k_{MeOH}/k_{MeOD} value of 2.16.

[c] Prepared on a weight/weight basis with other component water.

reported in *Table* 1.

The rates of reactions were relatively fast in strongly nucleophilic solvent (e.g., H_2O) and were relatively slow in strongly electrophilic solvent in *Table* 1. The reaction rate constants (k) are 3.24×10^{-6} s^{-1} at 90% acetone-H_2O (Y=–2.39), 2.63×10^{-4} s^{-1} at 90% EtOH-H_2O (Y=–0.94), and 1.91×10^{-3} s^{-1} at 90% MeOH-H_2O (Y=–0.18). The rate constants were more dependent on the solvent nucleophilicity than on the solvent ionization power.[4a]

Bimolecular reactions have been reported to have larger rate constants in nucleophilic solvent (H_2O) systems and smaller rate constants in electrophilic solvent systems, it can be suggested that the solvolysis of **1** is a bimolecular reaction mechanism.[3]

An analysis in terms of the simple Grunwald-Winstein equation ($\log (k/k_o) = mY_{Cl} + c$)[5] leads to an extermely poor correlation (*Fig.* 1). This means that the solvolysis of **1** should consider not only the interaction between the leaving group on the substrate and the solvent (electrophilic assistance) but also the interaction between the solvent and the reaction center on the substrate (nucleophilic assistance).

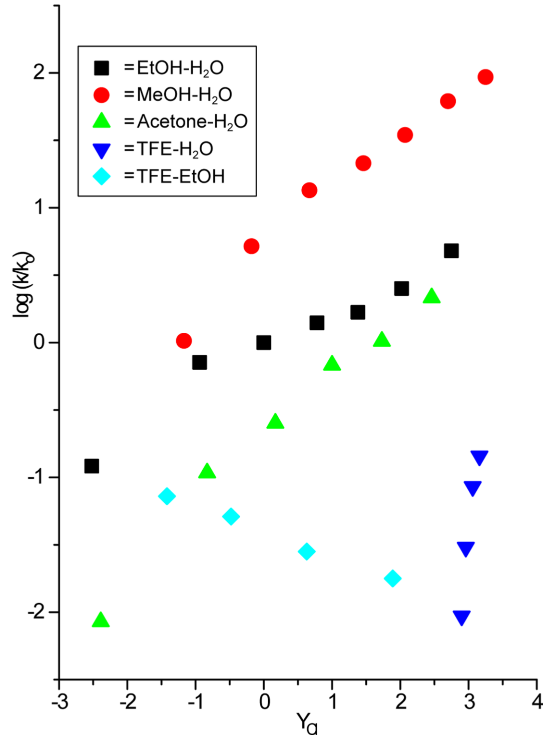


***Figure* 1.** Plot of log (k/k$_o$) for (1s)-(+)-Menthyl Chloroformate solvolysis at 55.0 °C against Y_{Cl}.

The correlation is greatly improved by the use of the extended Grunwald-Winstein equation,[3] with an l value of 2.46±0.18, m value of 0.91±0.07, c value of 0.37±0.20, and a correlation coefficient (R) of 0.950 (*Fig.* 2). The very large l value to changes in solvent nucleophilicity suggests a very pronounced involvement of the solvent as a nucleophile in the rate-determining step.[4a]

When the nucleophilic substitution reaction proceeds *via* the S_N1 reaction, the l value is ≈ 0 and the m value is ≈ 1, whereas the l value is ≈ 1.0 and the m value is ≈ 0.50 in the S_N2 reaction, and the l value is ≈ 1.9 and the m value is ≈ 0.60 in the associative S_N2 (or addition-elimination) reaction.[6]

The results showed that the solvolysis of **1** proceeds *via* the associative S_N2 reaction. The value of l (=2.46) is greater than the value of m (=0.91), it can be expected that the bond formation is more advanced than the bond breaking in the TS.

The l value of 2.46 is similar to those previously reported

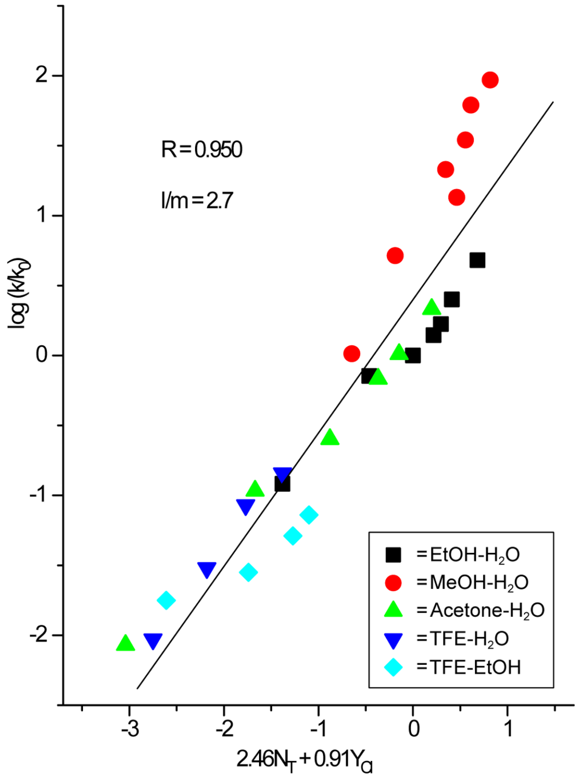


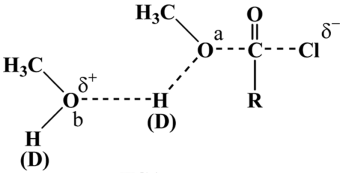
***Figure* 2.** Plot of log (k/k_o) for (1s)-(+)-Menthyl Chloroformate solvolysis at 55.0 °C against ($2.46N_T + 0.91Y_{Cl}$).

for associative S_N2 reactions. Solvolysis of the benzyl chloroformate[7] ($C_6H_5CH_2OCOCl$, $l = 1.95$), phenyl chloroformate[4a,8] (C_6H_5OCOCl, $l = 1.68$), and methyl chloroformate[9] (CH_3OCOCl, $l = 1.59$) in which a chloride ion is displaced from carbonyl carbon.

According to previous reports,[9,10] when the value of *l/m* in the extended Grunwald-Wintein equation is 1, it is known as a typical bimolecular reaction (synchronus S_N2) in which bond formation and bond breakage occur simultaneously. If the value of *l/m* is greater than about 2, it is known as an associative S_N2 reaction (addition-elimination reaction). On the other hand, if the value of *l/m* is less than 1, it is known that the reaction proceeds as a single-molecule reaction. The value of *l/m* is 2.7 within the ranges of value found in associative S_N2 reaction in the solvolysis of **1**.

In previous studies, the rate constant ratio ($k_{80\%EtOH}/k_{100\%EtOH} = 320$) of the solvolysis of 1-adamantyl chloride,[11] which represents a single-molecular reaction, is very sensitive to the ionizing power of the solvent. However, the rate constant ratios ($k_{80\%EtOH}/k_{100\%EtOH}$) of benzyl chloroformate[7] and *p*-methylbenzoyl chloride,[12] known as bimolecular reactions, were 3.4 and 5.3, respectively, indicating that they were not sensitive to the ionizing power of the solvent. Therefore, it can be seen that the solvolysis of **1** is not sensitive to the ionizing power of the solvent and is similar to the bimolecular reaction.

The solvolysis of carbonyl derivative compounds proceeding with bimolecular reaction may undergo the transition state (TS1) as the general base catalysis reaction. The contribution of the second methanol solvent may be closely related to the reaction rate in TS1 because the first molecule of methanol (a) affects the ability attacks the carbonyl carbon of the substrate in TS1. In the case of bimolecular (S_N2) reactions, the force constant of the H-O (a) vibration modes will decrease and this will lead to a primary solvent kinetic isotope effect in TS1.[13] The SKIE (k_{MeOH}/k_{MeOD}) is 2.16 in the solvolysis of **1**, which showed a relatively large primary solvent kinetic isotope effect. From these results, it can be expected that the solvolysis of **1** proceeds an S_N2 reaction pathway.[13]



TS1

Rate constants (*k*) and the activation parameters for (1s)-(+)-menthyl chloroformate in pure and aqueous solvents at various temperatures in *Table* 2. The activation parameters ($\Delta H^{\neq}$ and $\Delta S^{\neq}$) were calculated by Eyring equation.[14]

Relatively low $\Delta H^{\neq}$ (12.6~14.4 kcal/mol) and large negative $\Delta S^{\neq}$ values (−31.0~−37.0 cal/mol·K) in *Table* 2 are characteristic of a reaction involving partial development of change with a low degree of bond cleavage in the TS. It can be expected to proceed an associative S_N2 mechanism.[8,10]

CONCLUSIONS

The analysis using the extended Grunwald-Winstein equation in the solvolysis of **1** obtained the *l* value of 2.46 ± 0.18, the *m* value of 0.91 ± 0.07, and the correlation coefficient of 0.950. The solvolysis of **1** might proceed *via* an associative S_N2 mechanism enhancing bond making than bond breaking in the TS. This interpretation is further supported by a relatively large solvent kinetic isotope effect (2.16) and activation parameters.

EXPERIMENTAL

The (1s)-(+)-menthyl chloroformate (**1**) was purchased. Two-component mixed solvents such as an aqueous meth-

***Table* 2.** Rate constants and activation parameters for the solvolyses of (1s)-(+)-menthyl chloroformate

Solvent	Temp. (°C)	$10^4 k^a$ (s^{-1})	$\Delta H^{\neq b}$ (kcal/mol)	$-\Delta S^{\neq b}$ (cal/mol·K)
80%EtOH-H_2O	25.0	0.412	13.1±0.5	35.4±1.6
	35.0	0.853		
	45.0	1.79		
	55.0	3.69		
100%MeOH	25.0	0.495	12.6±0.4	37.0±0.13
	35.0	0.989		
	45.0	1.93		
	55.0	3.80		
50%Acetone-H_2O	25.0	0.371	14.4±0.5	31.0±1.5
	35.0	0.811		
	45.0	1.71		
	55.0	3.77		

[a]Averages of three or more runs, with standard deviation. [b]The activation parameters are accompanied by the standard error. [c]On a volume-volume content at 25.0 °C. The other component is water.

anol solution, an aqueous ethanol solution, an aqueous acetone solution, and an ethanol-TFE solution were prepared in a volume ratio, and an aqueous TFE solution was prepared in a weight ratio. The kinetic experiments were carried out by allowing a conductivity cell containing 12.5 mL of solvent to equilibrate, with stirring, in a constant-temperature water bath. A 12 μL portion of a 1.0 mol dm^{-3} stock solution of **1** in acetonitrile was then added. The monitoring of increases in conductivity with time and the calculation of the rate constants were conducted by the Guggenheim method.[15] The multiple regression analyses were performed using commercially available packages. The rate constants in *Table* 1, 2 are the averages of more than three runs and the uncertainty value is within ±3%.

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