DOI 10.5012/bkcs.2011.32.4.1268

Correlation of the Rates of Solvolysis of Phenyl Fluorothionoformate

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Received January 29, 2011, Accepted February 15, 2011

The specific rates of solvolysis of phenyl fluorothionoformate (PhOCSF, **1**) have been determined in 22 pure and binary solvents at 10.0 °C. The extended Grunwald-Winstein equation has been applied to the specific rates of solvolysis of **1** over the full range of solvents. The sensitivities ($l = 1.32 \pm 0.13$ and $m = 0.39 \pm 0.08$) toward the changes in solvent nucleophilicity and solvent ionizing power, and the k_F/k_{Cl} values are similar to those previously observed for solvolyses of acyl haloformate esters, consistent with the addition step of an addition-elimination pathway being rate-determining. The large negative values for the entropies of activation are consistent with the bimolecular nature of the proposed rate-determining step. The results are compared with those reported earlier for phenyl chloroformate and chlorothionoformate esters and mechanistic conclusions are drawn.

Key Words : Phenyl fluorothionoformate, Grunwald-winstein equation, Leaving group effect, Addition-elimination, Solvolysis

Introduction

Alkyl and phenyl halogenoformate esters are important reagents which are widely used in physiological and biological studies.[1-3] In particular, they are very important substrates for the introduction of protecting groups during peptide synthesis.[4] We previously reported that the solvolyses of phenyl chloroformate (PhOCOCl, **2**)[5] in a wide range of solvents and phenyl chlorothionoformate (PhOCSCl, **3**)[6] in solvents of low ionization power and/or high nucleophilicity follow an addition-elimination mechanism (Scheme 1) using either the simple or extended Grunwald-Winstein equation[7] [eqs. (1) and (2), respectively]. Only in solvents of very low nucleophilicity and very high ionizing power (for example, the solvolysis of **3** in aqueous fluoroalcohol solvents) can an ionization pathway be detected (Scheme 2).

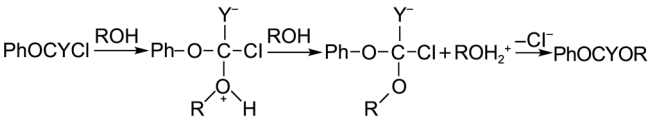
The Grunwald-Winstein equation has been found to be a very powerful tool for the study of a solvolysis reaction:[7]

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

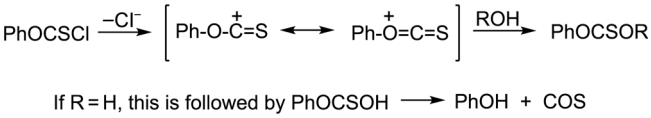
$$\log (k/k_o) = lN_T + mY_{Cl} + c \quad (2)$$

In eqns. (1) and (2), k and k_o represent the specific rates of solvolysis in a given solvent and in the standard solvent (80% ethanol), respectively; m is the sensitivity to changes in solvent ionizing power (Y_{Cl});[8] l is the sensitivity to changes in solvent nucleophilicity (N_T).[9] N_T scales based on the solvolyses of the *S*-methyldibenzothiophenium ion ($MeDBTh^+$) have been developed, in which the leaving group is a neutral molecule, which is little influenced by solvent ionizing power change. The N_T values have been recognized standards for considerations of solvent nucleophilicity. The magnitudes of the l and m values can give important indications regarding the mechanism of solvolysis.

A recently published study of the solvolysis of PhOCSCl (**3**)[6] is extended to PhOCSF (**1**). In spite of intensive experimental examination of the mechanism of alkyl and aryl halogenoformate reactions for many years, the mechanisms of most of these reactions are still not established. Accordingly, a study of the reaction mechanism for alkyl and aryl halogenoformate under solvolytic conditions is a subject of continuing interest. In the present study, we report on the specific rates for solvolyses of **1** in a variety of pure and binary solvents. The results are also discussed in terms of the sensitivity (l) to changes in solvent nucleophilicity (N_T) and the sensitivities (m) to changes in solvent ionizing power (Y_{Cl}). In addition to a detailed extended Grunwald-Winstein equation treatment to the specific rates, the influence of temperature on the specific rate allows enthalpies and entropies of activation to be calculated and a measurement in



Scheme 1. Addition-elimination pathway through a tetrahederal intermediate for phenyl chloroformate (**2**) and phenyl chlorothionoformate (**3**).



Scheme 2. Ionization pathway for phenyl chlorothionoformate (**3**).

methanol-*d* allows a determination of the solvent deuterium isotope effect. These analyses are also combined with a consideration of leaving-group effects to arrive at a reasonable mechanism.

Results and Discussion

The specific rates of solvolysis of **1** at 10.0 °C were determined in ethanol and methanol and in binary mixtures of water with ethanol (EtOH), methanol (MeOH), acetone, 2,2,2-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). Specific rates were also determined in four binary mixtures of 2,2,2-trifluoroethanol and ethanol (T-E). The specific rates of solvolysis are presented in Table 1, together with N_T[9] and Y_{Cl}[8] values. A determination was also made in methanol-*d* (MeOD). For methanol, ethanol, 80% EtOH, 70% TFE, and 90% HFIP, specific rates of solvolysis of **1** were determined at three additional temperatures, and these values, together with calculated enthalpies and entropies of activation, are reported in Table 2.

Table 1. Specific rates of solvolysis of phenyl fluorothionoformate (**1**)[a] in a variety of pure and mixed solvents at 10.0 °C and the N_T, and Y_{Cl} values for the solvents

Solvent[b]	$10^3 k$ (s^{-1}) [c]	N_T [d]	Y_{Cl} [e]
100% MeOH	25.8 ± 0.2[g,h]	0.17	−1.17
90% MeOH	34.5 ± 0.6	−0.01	−0.18
80% MeOH	44.5 ± 1.0	−0.06	0.67
100% EtOH	5.87 ± 0.03[h]	0.37	−2.52
90% EtOH	16.0 ± 0.1	0.16	−0.94
80% EtOH	20.4 ± 0.1[h]	0.00	0.00
70% EtOH	25.2 ± 1.4	−0.20	0.78
90% Acetone	1.89 ± 0.12	−0.35	−2.39
80% Acetone	2.69 ± 0.22	−0.37	−0.80
70% Acetone	4.26 ± 0.07	−0.42	0.17
60% Acetone	7.51 ± 0.08	−0.52	0.95
50% Acetone	8.00 ± 0.08	−0.70	1.73
90% TFE	0.0280 ± 0.0017	−2.55	2.85
70% TFE	0.366 ± 0.022[h]	−1.98	2.96
50% TFE	1.10 ± 0.05	−1.73	3.16
90% HFIP	0.00770 ± 0.00009[h]	−3.84	4.31
70% HFIP	0.370 ± 0.013	−2.94	3.83
50% HFIP	1.10 ± 0.01	−2.49	3.80
80T-20E[f]	0.320 ± 0.007	−1.76	1.89
60T-40E[f]	1.20 ± 0.04	−0.94	0.63
40T-60E[f]	2.49 ± 0.06	−0.34	−0.48
20T-80E[f]	3.89 ± 0.01	0.08	−1.42

[a]Substrate concentration of 5.00-8.00 × 10^{-4}mol dm^{-3}. [b]Volume/volume basis at 25.0 °C, except for TFE-H_2O and HFIP- H_2O mixtures, which are on a weight/weight basis. [c]The average of all integrated specific rates from duplicate runs, with associated standard deviation. [d]From ref. 9. [e]From ref. 8. [f]T-E are 2,2,2-trifluoroethanol-ethanol mixtures. [g]Value in MeOD of 12.2 ± 0.5, and solvent deuterium isotope effect (k_{MeOH}/k_{MeOD}) of 2.11 ± 0.02. [h]Specific rates of **1** at 25.0 °C are calculated from Arrhenius plots using the values at various temperatures reported in Table 2, values in 100% MeOH of 80.4 × 10^{-3} sec^{-1}, $k_{PhOCSF}/k_{PhOCSCl}$ = 493, in 100% EtOH of 17.4 × 10^{-3} sec^{-1}, $k_{PhOCSF}/k_{PhOCSCl}$ = 551, in 80% EeOH of 58.8 × 10^{-3} sec^{-1}, $k_{PhOCSF}/k_{PhOCSCl}$ = 867, in 70% TFE of 1.43 × 10^{-3} sec^{-1}, $k_{PhOCSF}/k_{PhOCSCl}$ = 64, in 90% HFIP of 3.45 × 10^{-5} sec^{-1}, $k_{PhOCSF}/k_{PhOCSCl}$ = 0.21 (ref. 6a).

In Table 1, the specific rates for the solvolysis of **1** increase with increasing the water content in all the mixed solvents, indicating that the specific rate is accelerated by the solvent with higher ionizing power except HFIP-H_2O mixtures, and also increase with increasing the ethanol content in four binary solvents of TFE-EtOH. These phenomena are very similar to those previously studied for phenyl chloroformate (**2**)[5] in all the solvents, suggesting that the addition step of an addition-elimination mechanism is rate-determining.

Although some authors[10] claim that leaving group effects in solvolytic reactions are not very sensitive to mechanistic changes, the consideration of the k_F/k_{Cl} ratios in nucleophilic substitution reactions has long been recognized as a useful tool in studying the reaction mechanism.[11]

Since the carbon-fluoride bond (C-F) is much stronger than the carbon-chloride bond (C-Cl), if the carbon-halogen bond is broken in the rate-determining (ionization pathway), k_F/k_{Cl} ratios would be expected to exhibit a marked leaving group effect, $k_F << k_{Cl}$. These values (k_F/k_{Cl} ratios) reflect an appreciable ground-state stabilization for the fluoride[12] and the need to break a strong carbon-fluorine bond in the rate-determining step.[13] However, a bimolecular pathway through a tetrahedral intermediate formed by rate-determining addition of the solvent at the carbonyl carbon would be characterized by $k_F \geq k_{Cl}$; values of close to unity (and frequently above it), reflecting a large electron deficiency at the carbonyl carbon of a haloformate incorporating fluorine, are frequently observed. For example, for the solvolyses in water with ethanol, acetone, or TFE of *n*-octyl fluoroformate

Table 2. Specific rates of solvolysis of phenyl fluorothionoformate (**1**) at various temperatures and enthalpies ($\Delta H^{\neq}$, kcal mol^{-1}) and entropies ($\Delta S^{\neq}$, cal mol^{-1} K^{-1}) of activation

Solvent[a]	Temp. (°C)	$10^3 k$ (s^{-1})[b]	$\Delta H^{\neq}_{283}$[c]	$\Delta S^{\neq}_{283}$[c]
100% MeOH	5.0	17.9 ± 0.7	11.8 ± 0.7	−24.0 ± 2.6
	7.0	21.8 ± 0.4		
	10.0	25.8 ± 0.2[d]		
	15.0	39.6 ± 0.1		
100% EtOH	5.0	3.62 ± 0.02	12.2 ± 0.4	−25.6 ± 1.4
	7.0	4.39 ± 0.01		
	10.0	5.87 ± 0.03[d]		
	15.0	8.06 ± 0.04		
80% EtOH	5.0	14.6 ± 0.4	11.3 ± 0.3	−26.2 ± 1.2
	7.0	16.6 ± 0.4		
	10.0	20.4 ± 0.1[d]		
	15.0	30.2 ± 1.9		
70% TFE	10.0	0.366 ± 0.002[d]	15.1 ± 0.6	−21.0 ± 2.2
	15.0	0.537 ± 0.004		
	20.0	0.930 ± 0.017		
	30.0	2.22 ± 0.25		
90% HFIP	10.0	0.00770 ± 0.00009[d]	16.4 ± 0.1	−24.1 ± 0.2
	50.0	0.315 ± 0.011		
	55.0	0.469 ± 0.023		
	60.0	0.712 ± 0.054		

[a,b]See footnotes Table 1. [c]With associated standard error. [d]From Table 1.

and *n*-octyl chloroformate, which are believed to solvolyze by an addition-elimination mechanism, k_F/k_{Cl} ratios of 0.6 to 15 were observed.[14] In the comparison of k_F/k_{Cl} ratios for **1** and **3**, one shows that, for four solvents (methanol, ethanol, 80% ethanol, and 70% TFE), the specific rates for the solvolyses of **1** are faster than those for the solvolyses of **3** (footnote Table 1), despite the stronger carbon-fluorine bond. In particular, for the somewhat lower value ($k_F/k_{Cl} = 0.2$) of the solvolysis of **1** in 90% HFIP, the k_F/k_{Cl} ratio can be considered to reflect a comparison of bimolecular reaction of phenyl fluorothionoformate (**1**) with ionization reaction of phenyl chlorothionoformate (**3**).[6] Therefore, the small leaving group effects would be ascribed to the operation of a tetrahedral intermediate formed by rate-determining addition of the solvent at the thiocarbonyl carbon without the rupture of the carbon-halogen bond. In contrast, nucleophilic substitution reactions in which the carbon-halogen bond is believed to be broken in the rate-determining step have considerably lower values (k_F/k_{Cl}) for the leaving group effect.[11]

For solvolyses in ethanol, methanol, 80% ethanol, 70% TFE and 90% HFIP, the values of the enthalpy and the entropy of activation for the solvolysis of **1** (Table 2) are 11.3-16.4 kcal mol^{-1} and −26.2 ~ −21.0 cal mol^{-1} K^{-1}, respectively. For the solvolyses studied kinetically as a function of temperature, the activation parameters for solvolyses of alkyl fluoroformates are consistent with a duality of mechanism, i.e., the addition-elimination pathway (A-E) involving bimolecular attack by solvent for solvolyses of methyl fluoroformate (MeOCOF)[15(a)] and ethyl fluoroformate (EtOCOF)[15(b)] in the range of −41.5 to −27.9 cal mol^{-1} K^{-1}, and the ionization pathway (I) for the solvolysis of *t*-butyl fluoroformate (*t*-BuOCOF)[15(c)] in the range of −6.7 to −2.8 cal mol^{-1}K^{-1}. The entropies of activation for the solvolysis of **1**, in the range of −26.2 to −21.0 cal mol^{-1}K^{-1}, are similar to those of considered to reflect the bimolecular channel within the analyses of the solvolyses of MeOCOF and EtOCOF in five solvents.[15]

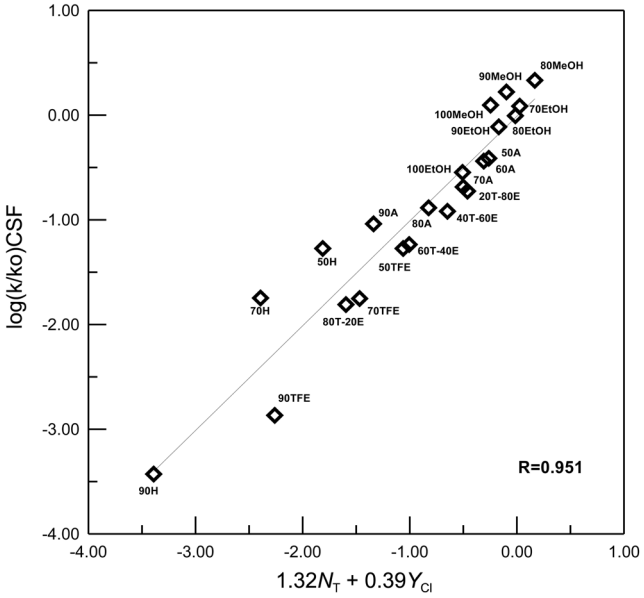


Figure 1. Plot of log (k/k_o) for solvolyses of phenyl fluorothionoformate (**1**) against ($1.32N_T + 0.39Y_{Cl}$) in various binary solvents at 10.0 °C.

The solvent deuterium isotope effect has previously been studied for several solvolyses of haloformate esters. In methanol, the k_{MeOH}/k_{MeOD} ratio was in the range of 1.91 to 3.98 for **2**,[6(b)] MeOCOF,[15(a)] and *i*-PrOCOF[15(d)] believed to react by the bimolecular mechanism. The values for *i*-PrOCOCl,[16] and *t*-BuOCOF[15(c)] in the ionization range, were somewhat lower at 1.25 in pure water and 1.26 in methanol, respectively. The value for methanolysis of **1** of $k_{MeOH}/k_{MeOD} = 2.11$ is of a magnitude usually taken to indicate that nucleophilic attack by a methanol molecule is assisted by general-base catalysis by a second methanol molecule (Scheme 1).[6(b),15(d),17]

Table 3. Correlation of the specific rates of solvolysis of a variety of ROCOCl, ROCOF, ROCSCl, RSCOCl, and ROCSF substrates using the extended Grunwald-Winstein equation

Substrate	Mech.[a]	n^b	l^c	m^c	$c^{c,d}$	R[e]	*l*/*m*
PhOCSF	A-E	22[f]	1.32 ± 0.13	0.39 ± 0.08	−0.02 ± 0.10	0.952	3.38
PhOCOCl	A-E	49[g]	1.66 ± 0.05	0.56 ± 0.03	0.15 ± 0.07	0.980	2.96
PhOCSCl	A-E	9[h]	1.88 ± 0.28	0.56 ± 0.15	0.38 ± 0.15	0.950	3.36
	I	18[h]	0.34 ± 0.05	0.93 ± 0.09	−2.54 ± 0.34	0.955	0.37
PhSCOCl	A-E	16[i]	1.74 ± 0.17	0.48 ± 0.07	0.19 ± 0.23	0.946	3.63
	I	6[i]	0.62 ± 0.08	0.92 ± 0.11	−2.29 ± 0.13	0.983	0.67
PhSCSCl	I	31[j]	0.69 ± 0.05	0.95 ± 0.03	0.18 ± 0.05	0.987	0.73
MeOCOCl	A-E	19[k]	1.59 ± 0.09	0.58 ± 0.05	0.16 ± 0.17	0.977	2.74
MeSCOCl	A-E	12[l]	1.48 ± 0.18	0.44 ± 0.06	0.08 ± 0.08	0.949	3.36
	I	8[l]	0.79 ± 0.06	0.85 ± 0.07	−0.27 ± 0.18	0.987	0.93
i-PrOCOCl	A-E	9[m]	1.35 ± 0.22	0.40 ± 0.05	0.18 ± 0.07	0.960	3.38
	I	16[m]	0.28 ± 0.04	0.59 ± 0.04	−0.32 ± 0.06	0.982	0.47
i-PrSCOCl	I	19[n]	0.38 ± 0.11	0.72 ± 0.09	−0.28 ± 0.10	0.962	0.53

[a]Addition-elimination (A-E) and ionization (I). [b]Number of solvent systems included in the correlation. [c]Using G-W equation with standard errors for *l* and *m* values and with the standard errors of the estimate accompanying the *c* values. [d]Constant (residual) term. [e]Correlation coefficient. [f]This work. [g]Values taken from ref. 5(b). [h]Values taken from ref. 5(b). [i]Values taken from ref. 5(b). [j]Values taken from ref. 5(b). [k]Values taken from ref. 20. [l]Values taken from ref. 18. [m]Values taken from ref. 19. [n]Values taken from ref. 21.

A powerful test in considering detailed mechanisms of solvolysis is to carry out a correlation analysis using the Grunwald-Winstein equation (eqns. 1 and 2). A correlation using the specific rates of the 22 solvents reported in Table 1 within the simple Grunwald-Winstein equation (eqn. 1) leads to an extremely poor correlation with value of 0.642 for the correlation coefficient (R). Again, an analysis in terms of the extended Grunwald-Winstein equation (eqn. 2) of the data for the specific rates of solvolysis of **1** leads to a good linear correlation with values of 1.32 ± 0.13 for l, 0.39 ± 0.08 for m, -0.02 ± 0.10 for c, and 0.952 for the correlation coefficient (Figure 1).

The results of the correlation analysis in terms of equation (2) are shown in Table 3, together with the corresponding parameters obtained in the analyses of earlier studied substrates. The l/m ratio has been suggested as a useful mechanistic criterion and the values of Table 3 divide nicely into two classes with values of 1.7 to 3.38 for those entries postulated to represent addition-elimination pathway (Scheme 1) and 0.37 to 0.93 for those believed to represent ionization pathway (Scheme 2). The l/m ratio of 3.38 obtained for **1** is similar to those previously reported for **2** in all the solvents, and for methyl chlorothioformate (MeSCOCl),[18] *i*-PrOCOCl[19] and **3** in all the solvents except the more ionizing and less nucleophilic solvents, consistent with the bimolecular pathway.

To prove further the similarity between solvent effects upon the specific rates of solvolysis of **1** and **2** or **3**, we have carried out a direct comparison of the log $(k/k_o)_{phOCOCl}$ for **2** against log $(k/k_o)_{phOCSF}$ for **1** for the 12 solvents for which specific rates are available for both substrates. A good linearity (Figure 2, correlation coefficient, R = 0.986) in all the solvents was obtained. Since phenyl chloroformate (**2**) is believed to solvolyze by an addition-elimination pathway in

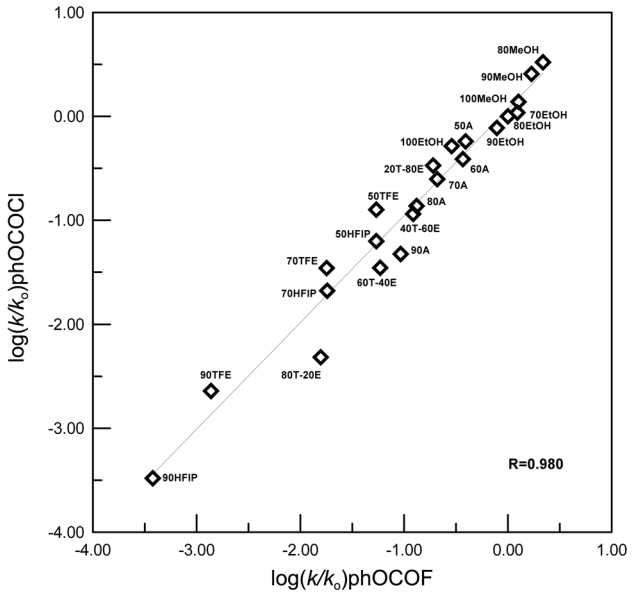


Figure 2. Plot of log (k/k_o) for solvolyses of phenyl fluorothionoformate (**1**) at 10.0 °C against log (k/k_o) for solvolyses of phenyl chloroformate (**2**) at 25.0 °C.

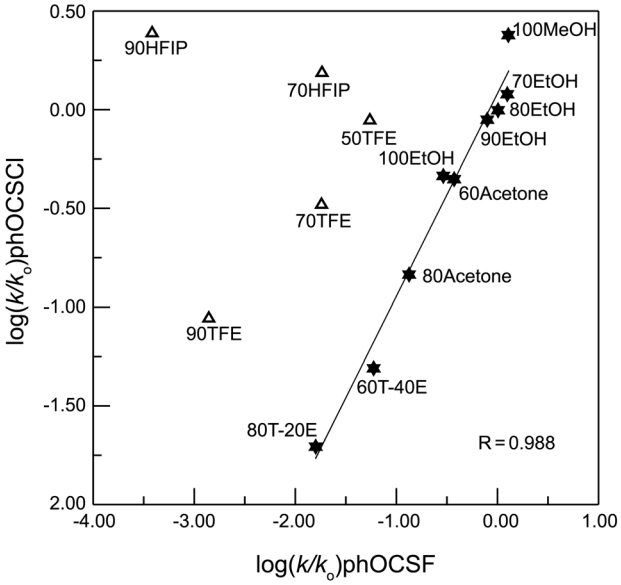


Figure 3. Plot of log (k/k_o) for solvolyses of phenyl fluorothionoformate (**1**) at 10.0 °C against log (k/k_o) for solvolyses of phenyl chlorothionoformate (**3**) at 25.0 °C. The five log (k/k_o) values for the TFE-H_2O and HFIP-H_2O solvents are not included in the correlation. They are shown their considerable deviation from the correlation line.

all the solvents involved in the plot, the similarity in l and m-values for the two solvolyses (**1** and **2**) gives rather strong evidence for an addition-elimination mechanism. Unlike the plot of log (k/k_o) for **1** and **2** solvolyses, where a good linearity is observed, since **3** is believed to react by an addition-elimination mechanism (A-E, Scheme 1) in all the solvent except TFE-H_2O and HFIP-H_2O mixtures, and by an ionization mechanism (I, Scheme 2) in solvents of high ionizing power and relatively low nucleophilicity (TFE-H_2O and HFIP-H_2O mixtures), any contribution from additional mechanisms for the solvolysis of **3** will lead to the (k/k_o) values deviating upward from the plot. The plot of log $(k/k_o)_{phOCSCl}$ for **3** solvolysis against log $(k/k_o)_{phOCSF}$ for **1** solvolysis is shown in Figure 3. In earlier correlations of other haloformate esters,[22] it was found that the data points for TFE-H_2O and HFIP-H_2O solvent systems lie above the correlation line. Indeed, the different responses to changes in solvents of high ionizing power suggest that **1** solvolysis will not be a good similarity model for the unimolecular pathway.

Conclusions

The solvolyses of **1** give a satisfactory extended Grunwald-Winstein equation over wide range of N_T and Y_{Cl} values (R = 0.952). The sensitivities to change in N_T and Y_{Cl} (l = 1.32 and m = 0.39, l/m = 3.38) are very similar to those for **3**, *i*-PrOCOCl and MeSCOCl (Table 3), which are shown to solvolyze with the addition step of an addition-elimination pathway (A-E) being rate determining. The solvent deuterium isotope effect value for methanolysis (k_{MeOH}/k_{MeOD}) of 2.11 is of a magnitude usually taken to indicate that nucleophilic

attack by a methanol molecule is assisted by general-base catalysis by a second methanol molecule. Five measured values for the entropy of activation for **1**, in the range of −26.2 to −21.0 cal $mol^{-1}K^{-1}$, are consistent with the bimolecular nature of the rate-determining step.

In the present study, unlike the solvolyses of phenyl chlorothionoformate (**3**), where the two reaction channals (addition-elimination and ionization pathways) were observed, the solvolyses of **1** have a pathway involving bimolecular attack by solvent at thiocarbonyl carbon, with what is suggested to be the addition step of an addition-elimination pathway being rate determining (Scheme 1).

Experimental

Phenyl fluorothionoformate (**1**, bp 67-69 °C/10 mmHg) was prepared from phenyl chlorothionofor-mate (**3**, Aldrich) by a procedure as described earlier.[23] Solvents were purified and the kinetic runs carried out as previously described.[15(c),24]

The kinetic measurements were made conductometrically using a Metrohm 712 (Swiss), with an immersion measuring cell (Pt 100). All runs were performed in duplicate with at least 150 readings taken at appropriate intervals over three half-lives and infinity readings taken after ten half-lives. The rates of production of hydrofluoric acid were followed for solvolyses in ethanol and methanol and in binary mixtures of water with ethanol (EtOH), methanol (MeOH), acetone, 2,2,2-trifluoroethanol (TFE), and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and also in binary mixtures of 2,2,2-trifluoroethanol and ethanol (T-E). The substrate concentration was about $5.00\text{-}8.00 \times 10^{-4}$ mol·dm^{-3}. The *l* and *m* values were calculated using commercially available computer programs for multiple regression analyses.

Acknowledgments. This work was supported by the research fund of Hanyang University (HY-2009-N).

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