

Evaluation of Methylthio and Phenylthio Group Effects in the Solvolyses of 2-Chloro-2-(methylthio)acetone and 2-Chloro-2-(phenylthio)acetophenone Using Extended Grunwald-Winstein Equations

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The specific solvolysis rates of 2-chloro-2-(methylthio)acetone (**3**) at 25.0 °C, and 2-chloro-2-(4-methoxyphenylthio)-acetophenone (**4**) at 50.0 °C have been measured in more than 34 aqueous solvent mixtures including aqueous 2,2,2-trifluoroethanol (TFE), for **4**, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), and in TFE-ethanol. The kinetic solvent isotope effect in methanol and solvolysis rate ratios, at identical ionizing power in 40 (v/v)% ethanol/water compared with 97 (w/w)% TFE/water have been determined. Additional data were also obtained for solvolyses of other substrates related to this work. The investigation of structural effects, caused by the existence of neighboring sulfur-containing and carbonyl (C=O) groups, on the solvolytic reactivity and/or mechanism and the possibility for the stabilization of the solvolytic TS by the developing mesomeric cation, due to the role of the PhS-group, have been attempted using various Grunwald-Winstein (GW) parameter treatments. Regardless of -COPh or -COCH₃ neighboring groups as neighboring group, the solvolytic reactions for both **3** and **4** were evaluated as reactions primarily influenced by the sulfur atom of the -SR group as the activator to make the positive polar TS. In particular, the solvolytic reactions of **4**, having an electron donating *p*-OCH₃ substituent, were indicative of the possibility of an ionization pathway with development of a mesomeric cation, stabilised by the sulfur atom and its attached group.

Key Words : Grunwald-Winstein (GW) parameter treatment, Solvolysis, Kinetics, Kinetic solvent isotope effect

Introduction

Studies of solvolytic reactions for various substrates having the reaction center at sp³ and sp²-hybridized carbon have been a theme of interest for a long time.¹

Recently, for groups adjacent to a reaction center (C=O) with sp²-hybridized carbon, we reported that solvolytic reactivity was influenced by the adjacent groups (with or without an aromatic ring) through the studies of various aliphatic substituted acyl (C=O) derivatives.^{2,3}

More recently, our results⁴ for the study of solvolyses of chloroacetyl chloride, the “parent” phenylacetyl chloride and α -methoxy- α -trifluorophenylacetyl chloride,⁵ with on the α -carbon powerfully electron withdrawing [methoxy (-OCH₃) and trifluoromethyl (-OCF₃)] groups, in aqueous organic solvents including fluorinated solvent systems also showed different reaction channels, determined by the neighboring groups. Much faster ($\sim 10^6$ times) specific rates of solvolysis of chloroglyoxalate esters (ROCOCOCl), with the insertion of a carbonyl (C=O) group, were observed relative to those of corresponding ROCOCl solvolyses. The acceleration, caused by enhanced reactivity (addition-elimination channel with addition step being rate determining) was due to the inductive effect of the alkoxy carbonyl (RCO₂-) group (super electron withdrawing group), as was demonstrated by Kevill *et al.*⁶

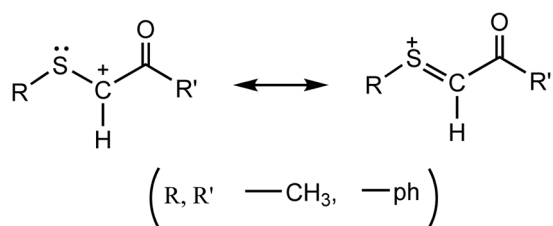
In certain solvent systems, these reactions were more recently shown to give a quite different reaction pathway (with an O-atom replacing a S-atom: addition-elimination

channel \rightarrow ionization channel with carbocation stabilization in part through nucleophilic solvation) by Kevill *et al.*⁷⁻¹⁰ Presumably, these phenomena may be relevant to the differences in the capacity of the O-atom and the S-atom to undergo the positive polarization.

On the other hand, introduction of a carbonyl (C=O) group as substituent adjacent to the reaction center with sp³-hybridized carbon in benzyl derivatives showed a significant influence on the reactivity of solvolysis according to the position substituted [*eg.* C=O group as internal nucleophile in solvolysis of benzyl^{11,12} and 1-(2,6-dicarbomethoxyphenyl)ethyl bromide¹³ with *ortho*-carbomethoxy (COOCH₃) groups]. In the case of acetolysis of *o*-thiolcarbophenoxybenzyl bromide¹⁴ having *ortho*-substituent (COSC₆H₅- group) including the S-atom, the S-atom enhanced the capacity of the *o*-substituent to act as internal nucleophile.

Both OCH₃ and SCH₃ groups strongly stabilize the methyl cation (by *ca.* 70 kcal/mol). Although there is a slight (*ca.* 2 kcal/mol) thermodynamic preference for stabilization by SCH₃,^{15a} kinetic factors may favour stabilization by MeO.^{15b} Also, for solvolyses of cumyl chlorides (the basis of σ_p^+ constants), a *para*-OCH₃ is more activating than *para*-SCH₃.^{15c} In contrast, neighboring sulfur (S) participation as an intramolecular nucleophile in solvolytic reactions being more effective in facilitating solvolysis rates was also reported.^{16,17}

Reactivity and/or mechanistic changes in reaction of compounds previously mentioned have been explained as results caused by structural effects of groups adjacent to the reac-



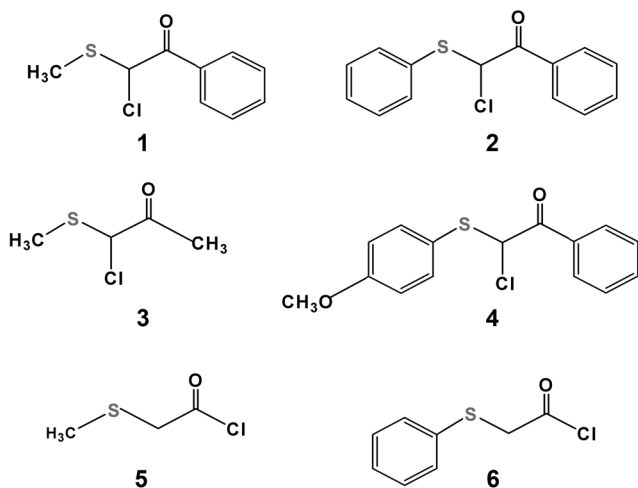
Scheme 1

tion center or by the interaction of a neighboring S-atom.

Especially, studies of structural effects on the solvolytic reactivity of organic compounds, proceeding through bimolecular reaction-type transition states, are currently a matter of great interest.

A probe for the structural effect and mechanistic change, which may be caused by both the existence of the neighboring group involving a sulfur (S)-atom as well as by the carbonyl (C=O) group, in solvolysis of organic compounds with sp^3 -hybridized carbon as the reaction center is a topic worthy of study.

The 2-chloro-2-(methylthio)acetone (**3**) and the 2-chloro-2-(4-methoxyphenylthio) acetophenone (**4**), which both have the possibility of developing a mesomeric cation due to the-SR group under the solvolytic conditions (Scheme 1) in addition to the influence of the inductive or the steric hindrance effect of the $R'C=O$ group, were chosen as suitable substances for study.



Kinetic studies of solvolysis reactions of these compounds were performed using at least 34 aqueous organic solvents including fluorinated alcohols, and these results were analyzed by the one-term Grunwald-Winstein (GW) treatment (1),^{18,19} expressed as the relationship between the specific solvolysis rates and solvent ionizing power (Y), the two-term GW treatment (2),^{20,21} inserting a solvent nucleophilicity (N) term to equation (1), and the three-term GW treatment (3) including the aromatic ring parameter (I).

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

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

$$\log(k/k_0) = mY_{Cl} + lN_T + hI + c \quad (3)$$

In equations (1), (2) and (3), k and k_0 are the specific solvolysis rates in a given solvent and in 80 (v/v)% ethanol-water, respectively; m is the sensitivity to changes in ionizing power (Y_{Cl} : based on the solvolyses of 1-adamantyl chloride¹⁹ as a unimolecular process term); l is the sensitivity to changes in solvent nucleophilicity (N_T : based on the solvolyses of the S-methyldibenzothiophenium ion²² as the bimolecular process term); h is the sensitivity to the aromatic ring parameter (I)²³ and c is a constant (residual) term.

Our results obtained from GW type correlation analyses [equations (1-3)], the rate-ratios between groups adjacent to reaction center and rate-rate profiles are helpful for obtaining further insight into how changes in the structure affect the reactivity of **3** and **4**. Also, the results are compared with our recent data for solvolyses of 2-chloro-2-(methylthio)acetophenone(**1**), 2-chloro-2-(phenylthio)acetophenone(**2**),²⁴ methylthioacetyl chloride (**5**) and phenylthioacetyl chloride (**6**);²⁵ the benzoyl (-COPh) group of **1** is replaced by acetyl (COCH₃) group in **3**, and the benzoyl group in **2** includes a *p*-OCH₃ in **4**. Also, the kinetic solvent isotope effect in methanol, and the value of solvolysis rate ratios, $[k_{40E}/k_{97T}]_Y$, in 40 (v/v)% ethanol/water compared with 97 (w/w) % TFE/water, as additional data, are presented for solvolyses of various substrates related to this work.

Results and Discussion

The specific solvolysis rates for solvolyses of **3** at 25.0 °C and **4** at 50.0 °C in 39 pure and binary solvent mixtures including aqueous 2,2,2-trifluoroethanol (TFE), aqueous 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, for **4**) and TFE-ethanol solvent systems are shown in Tables 1 and 2.

TFE-EtOH solvent systems are nearly isodielectric mixtures ($\epsilon = 26.14$ for TFE and $\epsilon = 24.32$ for EtOH), and provide a contrast with the trend of relationships²⁶ between Y and N values for commonly used aqueous solvent systems. Inclusion of fluorinated alcohol solvents helps to avoid the problem of multicollinearity^{27,28} in linear correlations. Our results obtained from GW type correlation analyses [equations (1-3)] along with a linear correlation coefficient (r) and the F-test value are shown in Figures 1-4 and listed in Table 3.

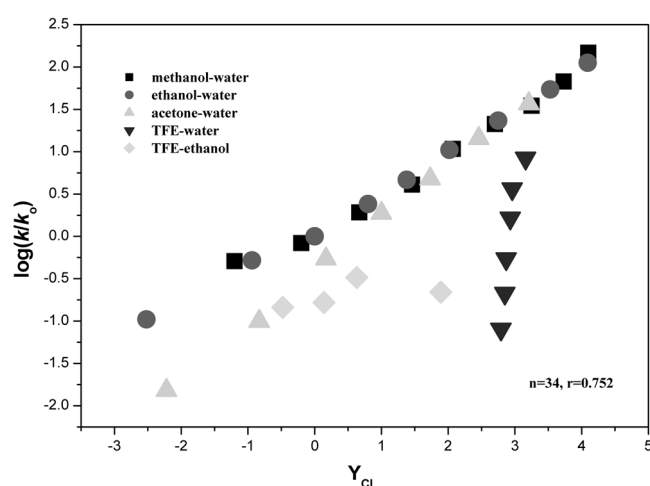
Dispersion ($r = 0.752$ - 0.901) in the one-term parameter GW (equation 1) plots are observed for all substrates (**1**, **2**, **3**, and **4**) relevant to this work. Such phenomena are frequently observed, mainly due to nucleophilic solvent effects or to other specific solvation effects or occasionally to mechanistic changes.

Regression analysis using the two parameter (Y_{Cl} and N_T) GW treatment (2) in solvolysis rates of **3** over a full range of 35 solvents gives a good linear correlation with $\log(k/k_0) = (0.71 \pm 0.02)Y_{Cl} + (0.86 \pm 0.04)N_T + (0.04 \pm 0.05)$ and $r = 0.983$ (F-test value = 451), see Figure 2 and Table 3. Probably because of the difference in the neighboring groups (-COPh for **1** hinders attack at the reaction site more than

Table 1. Specific rate constants (k/s^{-1}) for solvolyses of 2-chloro-2-(methylthio)acetone (**3**) in binary solvent mixtures at 25.0 °C^a

Solvent Composition ^b	$k/10^{-3}s^{-1}$		
	methanol-water	ethanol-water	acetone-water
100	1.51 ± 0.01	0.31 ± 0.01	—
90	2.49 ± 0.04	1.54 ± 0.02	0.045 ± 0.006
80	5.68 ± 0.01	2.96 ± 0.06	0.30 ± 0.01
70	12.1 ± 0.02	7.13 ± 0.03	1.61 ± 0.08
60	31.9 ± 0.3	13.8 ± 0.4	5.57 ± 0.18
50	62.8 ± 1.8	31.1 ± 0.35	14.2 ± 0.4
40	103 ± 5	68.9 ± 0.9 ^c	42.6 ± 0.2 ^c
30	199 ± 12 ^c	161 ± 3 ^c	109 ± 9 ^c
20	437 ± 20 ^c	332 ± 10 ^c	—
0	2140 ± 110	—	—
	TFE-ethanol ^f	TFE-water ^f	
100	0.24 ± 0.02	—	—
97	—	0.63 ± 0.01	—
90	—	1.61 ± 0.01	—
80	0.650 ± 0.006	4.86 ± 0.02	—
70	0.595 ± 0.047	10.8 ± 0.1	—
60	0.97 ± 0.01	16.1 ± 0.9	—
50	0.49 ± 0.01	24.8 ± 0.21	—
40	0.43 ± 0.01	76.7 ± 0.5	—

^aDetermined conductimetrically at least in quadruplicate typically by injection of 4 μ L of 10% (w/w) substrate in dry acetonitrile into the conductivity cell, with a turbo-stirrer and containing 2 mL of each solvent mixtures; errors shown are average deviations. ^bSolvent composition v/v % of alcohol or acetone. ^cInjected 4 μ L of 5% (w/w) solution of the substrate in dry acetonitrile. ^dSolvent composition v/v % of trifluoroethanol. ^eSolvent composition w/w % of trifluoroethanol (water contents were confirmed as having errors $\leq 0.3\%$ by using Karl Fisher Titration).

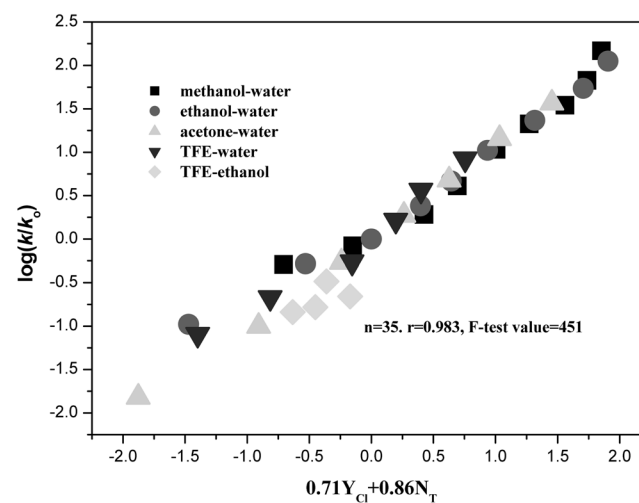
**Figure 1.** One-term GW plot of solvolytic reaction in a wide range of solvents for **3** at 25 °C.

-COCH₃ for **3**), the sensitivity of **3** to N_T is greater than that previously obtained from a similar range of solvolyses of **1**²⁴ [$\log(k/k_0) = (0.70 \pm 0.02)Y_{Cl} + (0.60 \pm 0.04)N_T + (0.01 \pm 0.05)$, $r = 0.979$, F-test value = 364; the reaction mechanism for both **1** and **3** is probably a dissociative S_N2 , with a loose TS ($l/m = 0.86$ -1.2: useful mechanism indicator), mainly determined by the CH₃S-group.

Table 2. Specific rate constants (k/s^{-1}) for solvolyses of 2-chloro-2-(4-methoxy phenylthio)acetophenone (**4**) in binary solvent mixtures at 50 °C^a

Solvent Composition ^b	$k/10^{-3}s^{-1}$		
	Methanol-water	Ethanol-water	Acetone-water
100	3.51 ± 0.06	0.73 ± 0.03	—
90	8.83 ± 0.10	2.05 ± 0.03	0.020 ± 0.001
80	21.6 ± 0.50	4.11 ± 0.03	0.253 ± 0.01
70	42.9 ± 0.1	5.86 ± 0.07	1.19 ± 0.06
60	69.5 ± 0.1	15.5 ± 0.10	3.58 ± 0.04
50	140 ± 3	28.8 ± 0.10	10.4 ± 0.1
40	372 ± 5	79.8 ± 0.50	58.7 ± 0.5
30	835 ± 18	288 ± 9	133 ± 2
	TFE-ethanol ^c	TFE-water ^d	HFIP-water ^e
100	19.0 ± 0.8	19.0 ± 0.80	—
97	—	33.6 ± 0.5	90.9 ± 1.4
90	—	56.7 ± 0.6	—
80	12.5 ± 0.1	93.6 ± 0.4	—
70	8.36 ± 0.19	147 ± 2	—
60	7.37 ± 0.04	182 ± 8	—
50	3.48 ± 0.04	279 ± 19	583 ± 19
40	3.09 ± 0.01	—	—
20	1.58 ± 0.06	—	—
0	0.73 ± 0.03	—	—

^{a,b}See footnote *a* and *b* of Table 1. ^cSolvent composition v/v % of trifluoroethanol. ^dSolvent composition w/w % of 2,2,2-trifluoroethanol (water contents were confirmed as having errors $\leq 0.3\%$ by using Karl Fisher Titration). ^eSolvent composition w/w % of 1,1,1,3,3,3-hexafluoro-2-propanol (water contents were confirmed as having errors $\leq 0.3\%$ by using Karl Fisher Titration).

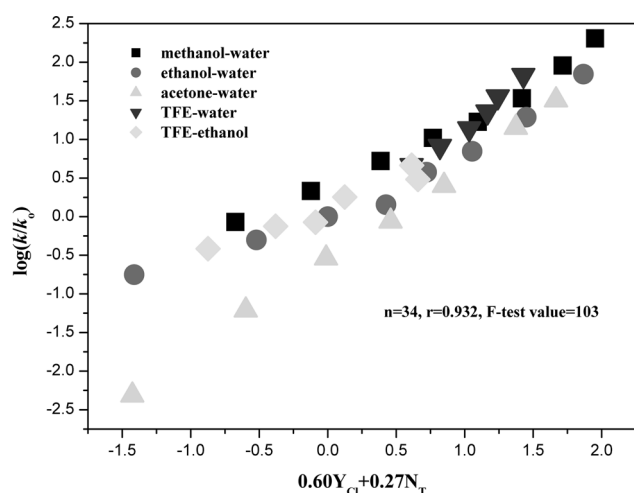
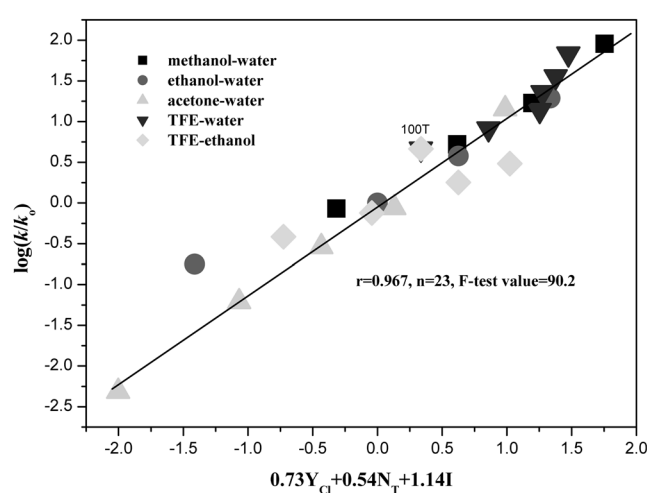
**Figure 2.** Plot of $\log(k/k_0)$ for solvolyses of **3** in a wide range of solvents at 25 °C against $(0.71Y_{Cl} + 0.86N_T)$.

In particular, in spite of having the neighboring group -COCH₃ for **3** and -COPh for **1**, the essentially identical m -values of 0.71 (0.70) can be regarded as a reflection of the magnitude of the contribution for the role for the CH₃S-group as the activator to make the positive polar TS. Convincing evidence for such a role for a CH₃S-group comes from the comparison of results obtained from GW correlation

Table 3. Grunwald-Winstein regression analysis results for solvolyses of various compounds mostly with an S-Atom adjacent to reaction center^a

Compound	Parameter	n ^b	m ^c	l ^c	h ^c	c ^d	r ^e	F ^f
1 ^g (25 °C)	Y _{Cl}	43	0.46 ± 0.05			-0.22 ± 0.13	0.838	
	Y _{Cl} , N _T	43	0.70 ± 0.02	0.60 ± 0.04		0.01 ± 0.05	0.979	364
2 ^g (50 °C)	Y _{Cl}	42	0.44 ± 0.04			0.07 ± 0.11	0.881	
	Y _{Cl} , N _T	41	0.58 ± 0.04	0.33 ± 0.06		0.16 ± 0.08	0.932	137
	Y _{Cl} , N _T , I	27	0.63 ± 0.06	0.47 ± 0.11	0.66 ± 0.30 (0.026) ^h	0.130 ± 0.09	0.936	57
3 (25 °C)	Y _{Cl}	35	0.43 ± 0.07			-0.31 ± 0.15	0.752	
	Y _{Cl} , N _T	35	0.71 ± 0.02	0.86 ± 0.04		-0.04 ± 0.05	0.983	451
4 (50 °C)	Y _{Cl}	34	0.50 ± 0.05			-0.09 ± 0.09	0.901	
	Y _{Cl} , N _T	34	0.60 ± 0.05	0.27 ± 0.08		0.03 ± 0.09	0.932	103
	Y _{Cl} , N _T , I	23	0.73 ± 0.05	0.54 ± 0.09	1.14 ± 0.24 (0.00013) ^h	0.04 ± 0.08	0.965	90
5 ⁱ (10 °C)	Y _{Cl} , N _T	33	0.46 ± 0.03	1.02 ± 0.10		-0.02 ± 0.07	0.942	117
6 ⁱ (10 °C)	Y _{Cl} , N _T	35	0.39 ± 0.02	1.02 ± 0.05		0.03 ± 0.05	0.963	215

^aThe multiple regression analysis were performed by the Origin 6.0 program. ^bNumber of solvents. ^cSensitivity to each solvent parameter chosen. ^dConstant value obtained from the correlation. ^eCorrelation coefficient. ^fF-test value. ^gResult from ref. 24. ^hProbability that hI term is statistically significant. ⁱResult from ref. 25.

**Figure 3.** Plot of $\log(k/k_0)$ for solvolyses of **4** in a wide range of solvents at 50 °C against $(0.60Y_{Cl} + 0.27N_T)$.**Figure 4.** Plot of $\log(k/k_0)$ for solvolyses of **4** in a wide range of solvents at 50 °C against $(0.73Y_{Cl} + 0.54N_T + 1.14I)$.

analyses between the solvolyses of **1** and those of 2-phenyl-2-ketoethyl bromide, corresponding to **1** (**2**) without the CH₃S- (PhS-) group, with $\log(k/k_0) = (0.46 \pm 0.04)Y_{Cl} + (1.15 \pm 0.08)N_T + (0.08 \pm 0.05)$,²⁹ suggesting a conventional S_N2 mechanism ($l/m = 2.5$, the leaving effect is very small).

Identical l -values of 1.02, as seen in Table 3, were observed for solvolyses of the carboxylic acid chlorides, methylthioacetyl chloride (**5**) and the phenylthioacetyl chloride (**6**),²⁵ having the C=O group as the reaction site (sp^2 hybridized carbon), activating it as regards nucleophilic solvent participation in the TS. The relatively small effect of the RS-group is probably due to the intervening -CH₂- group of **5** and **6**, increasing the distance between the SR groups and the reaction site.

Structural effects on reactivity for various SMe and SPh compounds (Table 4) can also be explained. When the SR groups are more remote from the reaction site, as with

Table 4. Comparison of four rate ratios in listed solvent at given temperatures

solvent	$k_{SCH_3(1)}/k_{SPh(2)}$	$k_{SCH_3(3)}/k_{SCH_3(1)}$	$k_{SPh(2)}/k_{SPh(4)}$	$k_{SCH_3(5)}/k_{SPh(6)}^e$
ethanol ^a	34 ^b (50 °C)	1.8 (25 °C)	0.17 (50 °C)	1.0 (10 °C)
water	69 ^{c,d} (25 °C)	1.8 (25 °C)	—	2.7 (10 °C)
TFE ^a	—	0.2 (25 °C)	0.088 (50 °C)	2.1 (10 °C)

^aEthanol, $N_T = 0.37$; TFE, $N_T = -3.93$. ^bKinetic data from ref. 24 and determined rate constant for **1** at 50 °C as $k_{SCH_3} = 4.25(\pm 0.03) \times 10^{-3} s^{-1}$. ^cDetermined rate constant for **2** at 25 °C as $k_{SPh} = 1.76(\pm 0.08) \times 10^{-2} s^{-1}$. ^dObtained the activation entropy (ΔS^\ddagger) = 9.19 cal mol⁻¹ K⁻¹ and the activation enthalpy (ΔH^\ddagger) = 22.6 kcal mol⁻¹ for **2** from kinetic data for hydrolyses of $k_{25^\circ C} = 1.76(\pm 0.08) \times 10^{-2} s^{-1}$, $k_{30^\circ C} = 3.39 \times 10^{-2} s^{-1}$, $k_{40^\circ C} = 1.07 \times 10^{-1} s^{-1}$ and $k_{50^\circ C} = 3.74 \times 10^{-1} s^{-1}$, respectively, using a Eyring plot. ^eResult from ref. 25.

SCH₃(**5**) and S-Ph(**6**) compounds, the rate ratios $k(5)/k(6)$ are close to unity. For ethanolysis and hydrolysis of **1** and **2**, both having COPh groups but with different SR groups

(SCH₃ and SPh respectively), the greater $k_{\text{SCH}_3(\mathbf{1})}/k_{\text{SPh}(\mathbf{2})}$ ratio values of 34 (50 °C) for ethanol and 69 (25 °C) for water respectively, show that the less hindered compound is more reactive in nucleophilic solvents.

Recently, specific solvolysis rates at 0 °C were studied by Kevill *et al.*³⁰ for chloromethylmethyl sulfide (CH₃SCH₂Cl, **7**) and chloromethylphenyl sulfide (PhSCH₂Cl, **8**), lacking the benzoyl (-COPh) group present in **1** and **2**. The $k_{\text{SCH}_3(\mathbf{7})}/k_{\text{SPh}(\mathbf{8})}$ ratio values are 315 ($1.30 \times 10^{-4} \text{ s}^{-1}/4.13 \times 10^{-7} \text{ s}^{-1}$) for ethanol and 45 ($1.33 \times 10^{-2} \text{ s}^{-1}/2.95 \times 10^{-4} \text{ s}^{-1}$) for 97% TFE. The similarity of the trend in our results and in the results of Kevill and colleagues offer another indication that the -COPh group of **1** and **2** relative to the group with the S-atom do not significantly influence the determination of reaction mechanism. Also, it suggests that the CH₃S- group allows a better nucleophilic solvation at the TS than the PhS-group, and these are delineated as the $l = 0.60$ for **1** and the $l = 0.33$ for **2** using equation 2. The relatively highly value (*ca.* 9 fold) of the ratio $\{[k_{\text{SCH}_3(\mathbf{7})}/k_{\text{SPh}(\mathbf{8})}]/[k_{\text{SCH}_3(\mathbf{1})}/k_{\text{SPh}(\mathbf{2})}]\}$ for ethanolysis may be attributed the electronic and steric influence of neighboring group (-COPh) on the reactivities of these solvolytic reactions³¹ (although the comparison between these is at a different temperature).

Now considering the effect of substituents in the SPh ring, the effect of electron withdrawal can be seen from ratios of the specific solvolysis rates,³⁰ $k_{\text{SPh}(\mathbf{8})}/k_{\text{S-Ph-Cl}(\mathbf{9})}$, at 0 °C for chloromethylphenyl sulfide (PhSCH₂Cl; **8**) and chloromethyl-4-chlorophenyl sulfide (4-ClPhSCH₂Cl; **9**) the latter with a chloro (-Cl)-substituent as an electron withdrawing group. The values are 7.0 ($2.95 \times 10^{-4} \text{ s}^{-1}/4.21 \times 10^{-5} \text{ s}^{-1}$) for 97% TFE and 0.15 ($4.13 \times 10^{-7} \text{ s}^{-1}/2.78 \times 10^{-6} \text{ s}^{-1}$) for ethanol, respectively. The values not very far from unity for the $k_{\text{SPh}(\mathbf{8})}/k_{\text{S-Ph-Cl}(\mathbf{9})}$ ratio indicate only a modest influence on the effect of the phenylthio (PhS-) group upon introduction of the chloro substituent as regards the stabilization of TS. But the results are probably indicative of the increased possibility for the formation of a mesomeric cation in the TS for solvolysis of **4**, due to the strongly electron-donating *p*-OCH₃ group.

In a developing mesomeric cation (Scheme 1), the partial positive charge on sulfur can be further delocalized into the aromatic ring. Consequently, aromatic ring solvation effects could cause dispersion ($r = 0.901$) in the one-term GW plot (equation 1) for solvolysis of **4**, and we will now discuss the results from a three-term GW correlation, including the *h*_l term (equation 3).

The result of the regression analysis in solvolyses of **4** in 35 solvents at 50 °C using equation 2 was estimated as a marginally acceptable linear correlation with $\log(k/k_0) = (0.60 \pm 0.05)Y_{\text{Cl}} + (0.27 \pm 0.04)N_{\text{T}} + (0.03 \pm 0.09)$ and $r = 0.932$ as shown in Figure 3 and Table 3. When equation 3 was employed, the *r*-value increased to 0.965 corresponding to a considerably improved correlation, and the *F*-test value drops only slightly from 103 to 90. The high *h*-value of 1.14 ± 0.24 , within this correlation is accompanied by a probability that the *h*_l term was not statistically significant of only 0.00013 (confidence level for the relevance of the *h*_l term of: 99.97%).

Whereas, for **2** at 50 °C having the PhS-group without *p*-OCH₃ substituent, the earlier result²⁴ analyzed by equations 2 and 3 included a relatively high probability for the *h*_l not being statistically significant of 0.026 (associated with the smaller *h*-value of 0.66 ± 0.30) and the only small improvement in the *r*-value ($0.932 \rightarrow 0.936$) as well as a sharp drop of the *F*-test value ($137 \rightarrow 56.5$), as listed in Table 3, all indicate a statistically low confidence level for the relevance of the *h*_l term.

Consequently, the results outlined above provide strong support for the validity of inclusion of the *h*_l term in analyses of the solvolyses of **4** and use of the three-term GW parameter correlation analysis (equation 3). In the case of **2**, indication are that the two-terms GW parameter correlation (excluding the *h*_l term; equation 2) is the most suitable for evaluation of the solvent effect on the reactivity and mechanism of the solvolyses.

It is appropriate to be cautious when interpreting the results of multi-parameter equations.³² In order to confirm our interpretations, we have measured the kinetic solvent

Table 5. First order rate constants (k/s^{-1}) in methanol, kinetic solvent isotope effect (KSIE) and values for the solvolysis rate ratio, $[k_{40\text{E}}/k_{97\text{T}}]_{\text{Y}}$, in 40(v/v)% ethanol/water compared with 97(w/w)% trifluoroethanol/water^a

Compound	MeOH	MeOD ^b	$(k_{\text{H}}/k_{\text{D}})^c$	$[k_{40\text{E}}/k_{97\text{T}}]_{\text{Y}}^d$
1 ^e (25 °C)	$(1.08 \pm 0.05) \times 10^{-3}$	$(1.05 \pm 0.05) \times 10^{-3}$	1.03	27
2 ^e (50 °C)	$(4.65 \pm 0.05) \times 10^{-4}$	$(3.85 \pm 0.25) \times 10^{-4}$	1.21	5.3
3 (25 °C)	—	—	—	109 ^f
4 (50 °C)	$(3.51 \pm 0.05) \times 10^{-3}$	$(3.06 \pm 0.05) \times 10^{-3}$	1.15	2.4 ^g
5 ^h (10 °C)	$(1.64 \pm 0.04) \times 10^{-1}$	$(1.10 \pm 0.05) \times 10^{-1}$	1.49	240 ^e
6 ^h (10 °C)	$(1.57 \pm 0.03) \times 10^{-1}$	$(9.36 \pm 0.01) \times 10^{-2}$	1.68	215
PhCH ₂ COCl (0 °C)	$(1.44 \pm 0.05) \times 10^{-1}$	$(1.03 \pm 0.02) \times 10^{-1}$	1.40 ⁱ	87 ^j
MeCOCl ^h (0 °C)	$(1.09 \pm 0.03) \times 10^{-1}$	$(8.21 \pm 0.08) \times 10^{-2}$	1.32	320

^aDetermined conductimetrically at least in quadruplicate. ^bMeOD was Aldrich (> 99.5% D). ^cKinetic solvent isotope effect; $k_{\text{H}}/k_{\text{D}} = k_{\text{MeOH}}/k_{\text{MeOD}}$. ^dSubscripted Y symbol means essentially identical ionizing power (*Y*_{Cl}) but different nucleophilicity (*N*_T) (due to two solvents differing by only 0.08 for *Y*_{Cl} value but by 2.56 for *N*_T value between 40 (v/v)% ethanol/water and 97 (w/w)% trifluoroethanol/water). ^eTable 4 of ref. 24. ^f $[k_{40\text{E}}/k_{97\text{T}}]_{\text{Y}} = (6.89 \pm 0.09) \times 10^{-2} \text{ s}^{-1}/(6.30 \pm 0.01) \times 10^{-4} \text{ s}^{-1}$ in Table 1. ^g $[k_{40\text{E}}/k_{97\text{T}}]_{\text{Y}} = (7.98 \pm 0.05) \times 10^{-4} \text{ s}^{-1}/(3.36 \pm 0.05) \times 10^{-4} \text{ s}^{-1}$ in Table 2. ^hTable 1 in ref. 25. ⁱAt 10 °C, footnote of Table 2 in ref. 4. ^j $[k_{40\text{E}}/k_{97\text{T}}]_{\text{Y}} = (2.64 \pm 0.02) \times 10^{-1} \text{ s}^{-1}/(3.04 \pm 0.01) \times 10^{-3} \text{ s}^{-1}$; kinetic data for 40(v/v)% ethanol/water at 0 °C from Table 2 of ref. 25 and kinetic data for 97 (w/w)% trifluoroethanol/water at 0 °C from Table 1 of ref. 2.

isotope effect in methanol and the value of solvolysis rate ratios, $[k_{40E}/k_{97T}]_Y$, in 40 (v/v)% ethanol/water compared with 97 (w/w)% TFE/water as an indication of the extent of nucleophilic solvent interaction solvolyses of **3** and **4** and the various other substrates related to this work (see Table 5). For substrates (such as **1**, **2**, **3** and **4** respectively), capable of reacting via a positive polar-TS stabilised by the S-atom, the low KSIE results in methanol of 1.03–1.15,^{41,42} and the low $[k_{40E}/k_{97T}]_Y$ ratio-values of less than 30-fold, indicate that the reaction channel has a loose (polar)-TS compared to other substrates²⁵ (KSIE in methanol: 1.32–1.68 and $[k_{40E}/k_{97T}]_Y$: 215–320) known to solvolyse by bimolecular (S_N2) type). These results confirm that our interpretation of the multiple parameter GW treatments for solvolytic reaction of substrates (relevant to the RS-group) discussed so far in this work is reasonable.

Conclusions

Taking the results as a whole, the mechanism and reactivity for the solvolytic reactions of **3** and **4** appear to be mainly determined by the effect of the activating influence of the -SR group, leading to a positive polar-TS, compared with a smaller effect of the -RCO group resulting from inductive and/or steric effects.³¹

Solvolysis of **4**, with the *p*-OCH₃ substituent as a strong electron donating group, are analyzed in terms of equation 3 with incorporation of an hI term for aromatic ring solvation effects; the high h-value obtained of 1.14 ± 0.24 may be indicative of the possibility for the ionization pathway through the mesomeric cation development caused by the electronic effect of the *p*-OCH₃ substituent contained within the PhS-group present at the sp^3 -hybridized reaction center. The validity for the inclusion of the aromatic ring effect is confirmed by a probability that the hI term was not statistically significant of only 0.00013 in multiple regression analysis and by the goodness of fit parameters. The values of the rates-ratios, $k_{SPh}(\mathbf{8})/k_{S-Ph-Cl}(\mathbf{9})$, at 0 °C for chloromethyl-phenyl sulfide (PhSCH₂Cl; **8**) and chloromethyl-4-chlorophenyl sulfide (4-ClPhSCH₂Cl; **9**) with **9** containing an electron withdrawing group also support the conclusions discussed above.

The $m = 0.73$ ($l = 0.54$) using equation 3 for solvolyses of **4**, indicates a substantial dependence on solvent ionizing power and it is remarkably similar to m -values for solvolyses of other substrates with an -SR group discussed in this work ($m = 0.7$ for **1** and 0.71 for **3**, respectively). Solvolyses of **2** were described previously as involving competing reaction channels.²⁴ This observation provides convincing evidence for the central role of the S-atom of -SR group as an activator leading to the positive polar TS, independent of whether the -COPh or -COCH₃ group is also attached to the α -carbon.

Experimental

Materials. The 2-chloro-2-(methylthio)acetone (**3**)³⁵ was

prepared from the reaction of α -(methylthio)acetone (4.16 g, 0.040 mole) in 30 mL of carbon tetrachloride (CCl₄) with *N*-chlorosuccinimide (NCS; 5.88 g, 0.044 mole) at room temperature for 6 hours. The product was purified by distillation under reduced pressure (b.p: 91 °C/15 mmHg) after filtering the residue (succinimide) [analytical data obtained; oil phase, ¹H-NMR(CDCl₃) δ : 2.19 (3H, s, SCH₃), 5.42 (1H, s, CH), 2.19 (3H, s, CH₃)]. The 2-(4-methoxyphenylthio)-acetophenone (**4**)³⁶ was similarly prepared from the reaction of α -(4-methoxyphenylthio)acetophenone (7 g, 0.026 mole) in CCl₄ (30 mL) with NCS (3.8 g, 0.028 mole) and then the crystalline product extracted was recrystallized from CCl₄ [analytical data obtained; mp. 94.7–96.2 °C, ¹H-NMR (CDCl₃) δ : 3.78 (3H, s, CH₃), 4.12 (1H, s, CH), 6.77–7.89 (9H, m, ArH)].

The *N*-chlorosuccinimide (NCS) was the Aldrich reagent (AR: 99.6%) and it was used without distillation and/or recrystallization

All solvents used for kinetics in this work were dried and distilled by standard methods with the exception of Aldrich reagents 1,1,1,3,3,3-hexafluoro-2-propanol (AR: 99%) and methanol-*d* ($>99.5 \pm \% D$) which were used without distillation.

Kinetic Methods. The specific rate constants for the solvolytic reaction performed under the condition of pseudo first order reaction were determined by the rapid-injection conductimetric method^{37,38} and the values were calculated using a method in which the data is monitored automatically by the Origin 6.0 program incorporating the Guggenheim equation.³⁹

Analytical Methods. The ¹H NMR measurements were made using a Hitachi FT/NMR R-1500 (60Hz) spectrometer and the Karl Fischer titration for measurement of water content in aqueous fluorinated solvent was carried out as previously described.²⁵

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