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Correlation of the Rates of Solvolyses of 4-Methylthiophene-2-carbonyl Chloride Using the Extended Grunwald-Winstein Equation

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The specific rates of sovolysis of 4-methylthiophene-2-carbonyl chloride (**1**) have been determined in 26 pure and binary solvents at 25.0 °C. Product selectivities are reported for solvolyses of **1** in aqueous ethanol and methanol binary mixtures. Comparison of the specific rates of solvolyses of **1** with those for *p*-methoxybenzoyl chloride (**2**) 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 S_N1 and/or ionization (I) pathway rather than through an associative S_N2 and/or addition-elimination (A-E) pathway.

Key Words : Grunwald-Winstein equation, Selectivity, Z-value, Addition-Elimination (A-E), Ionization (I)

Introduction

For several years, we have been investigating the mechanisms available for the solvolyses of carbonyl halides;[1-6] these reactions offer a model for nucleophilic substitution reactions of carbonyl halides in general, including many other applications.[7]

The Grunwald-Winstein equation (Eq. 1) is a very powerful tool for the mechanistic study of the solvolyses of substrates in various binary mixtures.[8] In Eq. (1), k and k_o 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}[9] and c represents a residual term. However, dispersion into separated lines in the correlation of the specific rates of solvolysis of benzoyl[10] and sulfonyl halides[11] in various aqueous solvents mixtures was documented in early treatments using the Grunwald-Winstein equation, given below.

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

It was realized early[8(b)] that it would be necessary to incorporate a term governed by sensitivity (l) to changes in solvent nucleophilicity N,[12] and equation (2) was proposed for bimolecular solvolysis.[13] 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.[13]

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

Kevill *et al*., recently developed an I scale, designed for the removal of dispersion in Grunwald-Winstein plots of solvolysis of benzylic derivatives and aromatic carbonyl halides. Analyses have been carried out in terms of Equation (3), with use of either the full equation or with omission of one or two terms.[13(a),13(f)] In Equation (3), the symbols are as described in Equation (1) but with the addition of sensitivity (h) to the aromatic ring parameter (I).[13(a),13(f)]

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

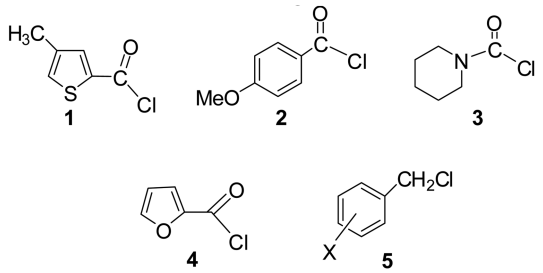
For ionization reactions without nucleophilic assistance, l will be zero and m close to unity. For an addition-elimination (A-E) reaction pathway with extensive nucleophilic assistance, the l value will be greater than 1.5 and the m value will be in the region below 0.5.[14]

When product selectivities (S) are defined by using Equation (3), where the square brackets refer to considerations in moles/liter, product ratios are adjusted for changes in bulk solvent compositions (i.e., ignoring preferential solvation).[15] S values were found to be approximately independent of solvent composition for solvolyses 4-methylthiophene-2-carbonyl chloride (**1**) in methanol/water and ethanol/water at 25 °C.[15,16] We now extend our previous work, and discuss the implications for the effect of preferential solvation on reactivity in alcohol/water mixtures. Solvolytic reactions in alcohol-water mixtures lead to acid and ester products from which the selectivities can be calculated using Equation. (4).[17-19]

$$S = [\text{ester product}]/[\text{acid product}] \times [\text{water}][\text{alcohol solvent}] \quad (4)$$

The effects of solvents with extended Grunwald-Winstein relationships in the solvolysis of alkyl and aromatic acyl halides such as *p*-methoxybenzoyl chloride (**2**),[2,20] 1-piperidinecarbonyl chloride (**3**),[21] furoyl chloride (**4**),[5] and benzyl chlorides (**5**),[14,20(a),22] have received much attention and have been discussed extensively, but little work has been done on the solvent effect on mixed solvents, especially for solvolyses of substituted thiophene-2-carbonyl chlorides. In this work, we determined the rate constants for solvolyses of **1** in aqueous binary solvents of acetone, ethanol and trifluoroethanol (TFE) 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), activation parameters, and product selectivities (*S*).



Results and Discussion

The specific rates of the solvolysis of **1** at 25.0 °C are reported in Table 1. The N_T and Y_{Cl} values are also reported in Table 1. The specific rates of solvolysis for methanol, 90% methanol, ethanol, 80% ethanol, 87% acetone, 97% 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. The product selectivities, *S*, for the solvolyses of **1** in aqueous alcohols are summarized in Table 3.

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 7.78×10^{-5} to 5.41×10^{-1} s^{-1} as *Y* changes

Table 1. Specific rates of solvolysis (k/s^{-1}) of 4-methylthiophene-2-carbonyl chloride (**1**) in binary solvent mixtures at 25 °C

Solvent[a]	N_T[b]	Y_{Cl}[c]	k_{obs}
100% EtOH	0.37	-2.52	7.78×10^{-5}
90% EtOH	0.16	-0.94	2.50×10^{-4}
80% EtOH	0.00	0.00	7.03×10^{-4}
70% EtOH	-0.20	0.78	1.79×10^{-3}
60% EtOH	-0.39	1.38	5.05×10^{-3}
50% EtOH	-0.58	2.02	1.57×10^{-2}
40% EtOH	-0.74	2.75	5.27×10^{-2}
30% EtOH	-0.93	3.53	2.73×10^{-1}
20% EtOH	-1.16	4.09	5.41×10^{-1}
100% MeOH	0.17	-1.17	5.52×10^{-4}
90% MeOH	-0.01	-0.18	1.34×10^{-3}
80% MeOH	-0.06	0.67	3.33×10^{-3}
70% MeOH	-0.40	1.46	7.37×10^{-3}
60% MeOH	-0.54	2.07	2.56×10^{-2}
50% MeOH	-0.57	2.70	5.81×10^{-2}
40% MeOH	-0.87	3.25	1.87×10^{-1}
30% MeOH	-1.06	3.73	3.63×10^{-1}
87% Acetone	-0.34	-1.81	2.83×10^{-5}
80% Acetone	-0.37	-0.83	8.30×10^{-5}
75% Acetone	-0.39	-0.28	1.66×10^{-4}
63% Acetone	-0.54	0.62	3.27×10^{-3}
52% Acetone	-0.68	1.45	8.76×10^{-3}
42% Acetone	-0.81	2.21	1.73×10^{-2}
97% TFE	-3.30	2.83	5.16×10^{-3}
80% TFE	-2.19	2.90	1.33×10^{-2}
50% TFE	-1.73	3.16	8.47×10^{-2}

[a]Volume/volume basis at 25.0 °C, except for TFE-H_2O mixtures, which are on a weight/weight basis. [b]Data from ref. 9. [c]Data from ref. 25(g).

Table 2. Specific rates of solvolysis (k/s^{-1}) for 4-methylthiophene-2-carbonyl chloride (**1**) and activation parameters

Solvent[a]	T (°C)	k (s^{-1})	$\Delta H^{\neq}$ (kcal/mol)[b]	$-\Delta S^{\neq}$ (cal/mol·K)[b]
100% EtOH	25.0	7.78×10^{-5}	17.7	-17.8
	35.0	2.09×10^{-4}		
	45.0	5.12×10^{-4}		
80% EtOH	25.0	7.03×10^{-4}	18.5	-10.8
	35.0	1.87×10^{-3}		
	45.0	5.03×10^{-3}		
100% MeOH	25.0	5.52×10^{-4}	17.7	-14.1
	35.0	1.42×10^{-3}		
	45.0	3.61×10^{-3}		
90% MeOH	25.0	1.34×10^{-3}	17.5	-12.9
	35.0	3.43×10^{-3}		
	45.0	8.62×10^{-3}		
87% Acetone	25.0	2.83×10^{-5}	16.2	-25.0
	35.0	6.68×10^{-5}		
	45.0	1.58×10^{-4}		
97% TFE	25.0	5.16×10^{-3}	16.5	-13.6
	35.0	1.36×10^{-2}		
	45.0	2.97×10^{-2}		

[a]Volume/volume basis at 25.0, 35.0, and 45.0 °C, except for TFE-H_2O mixtures, which are on a weight/weight basis. [b]Obtained from an Eyring plot and using the specific rate constant at 25.0 °C.

Table 3. Selectivities (*S*) for solvolyses of 4-methylthiophene-2-carbonyl chloride (**1**) in alcohol/water mixtures (after one half-life at 25.0 °C)[a]

Alcohol[b,c] %(v/v)	[Ester]/[Acid]	*S*	[Ester]/[Acid]	*S*
	EtOH-H_2O		MeOH-H_2O	
90	3.07	1.1	9.05	2.3
80	1.13	0.91	3.40	1.9
70	0.571	0.79	1.74	1.7
60	0.354	0.76	1.01	1.5
50	0.225	0.73	0.672	1.5
40	0.151	0.74	0.418	1.4
30	0.0950	0.72	0.286	1.5
20	0.0490	0.64	0.164	1.5
10	0.0200	0.59	0.0700	1.4

[a]Determined by duplicate HPLC analyses of two solutions of each solvent composition; average deviation < ± 2%. [b]Volume/volume basis at 25.0 °C. [c]Injected 10 μL of a 1% solution of 4-methylthiophene-2-carbonyl chloride (**1**) in dry acetonitrile into 3 mL of solvent.

Table 4. Rate constants ratios (k_1/k_4) for solvolyses of 4-methylthiophene-2-carbonyl chloride (**1**) and furoyl chloride (**4**) in aqueous alcohol mixtures at 25 °C

MeOH% (v/v)	100	90	80	70	60	50	40	30	20
k_1/k_4	0.681	0.893	1.61	2.87	8.28	16.5	50.4	101	-
EtOH% (v/v)	100	90	80	70	60	50	40	30	20
k_1/k_4	0.489	0.746	1.57	3.20	7.34	18.0	43.6	160	282

from −2.52 (100% EtOH) to 4.09 (20%EtOH-80%H_2O)[12,13] for solvolyses of **5** (representing a 6,950-fold increase). This indicates that the rate is remarkably affected by solvents with higher ionizing power, suggesting that bond breaking in the transition state is importance. The observed first-order rate constants for **2**,[2,20] **3**,[21] and **5**,[14,20(d),22] 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 **1** are very similar to those of the solvolytic reaction of **2**, **3**, and **5**.

We attempt a simple comparison with the solvolysis rate of **1** and **4** in aqueous alcohol solvent mixtures at 25 °C. The reaction mechanism of the solvolysis of **4** is known to proceed through associative S_N2 and/or A-E pathway channels.[9] The rate ratios, k_1/k_4, for the aqueous alcohol mixtures are shown in Table 4. The rate ratio is seen to increase with the water content of the binaries from a value of less than one ($k_1/k_4 < 1.0$) at about 80% co-solvent, to greater than 280 ($k_1/k_4 > 280$) at 20% co-solvent mixtures. This behavior of a higher k_4 in a low polarity solvent reserving to a lower k_4 in a medium with higher polarity than k_1 is also noted with other reactions of two compounds. The reactivity trends confirm that **1** *via* a TS that is much more sensitive to the ionizing power of the solvent compared with that of **4**. This suggests that the reaction route for the two compounds is different: a bond cleavage process in the TS for **1** is important (*i.e.* S_N1 and/or a dissociative S_N2 pathway), whereas **4** has a large polarizable TS that is stabilized preferentially by a softer solvent[23] (indicative of an A-E mechanism).[9]

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,

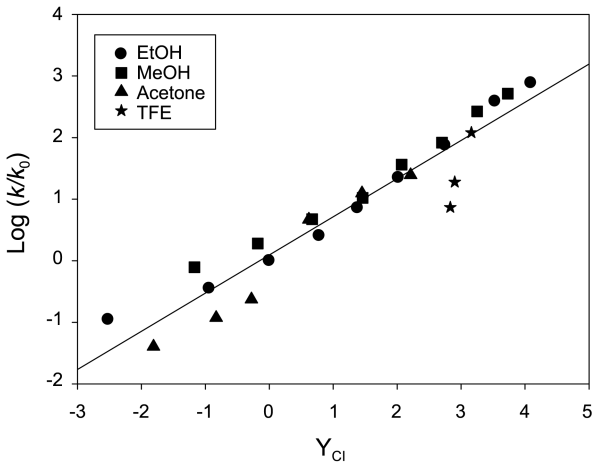


Figure 1. The plot of log(k/k_0) for solvolyses of 4-methylthiophene-2-carbonyl chloride (**1**) against 0.62 Y_{Cl} at 25 °C (r = 0.910).

very good correlations are obtained for aqueous solvent mixtures, with an *m* value of 0.62 ± 0.01 (r = 0.910) for the one-term equation (Figure 1). 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.[11(c),14,24(d),25] The rate ratio in the two solvents that have the 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}]=10.2, EW=ethanol-water).[26] The *m* value (=0.62) and k_{40EW}/k_{97TFE} ratio (=10.2) imply that the solvoly-

Table 5. Coefficients from the extended Grunwald-Winstein correlations of the specific rates of solvolysis of 4-methylthiophene-2-carbonyl chloride (**1**) at 25.0 and a comparison with coefficients from the correlations for other acyl chlorides

Substrate	Mech[a]	n^b	l^c	m^c	l/m	R^d
C_6H_5COCl[e]	I	32	0.47±0.03	0.79±0.02	0.59	0.9895
2[e]	I	37	0.31±0.05	0.81±0.02	0.38	0.9887
p-$NO_2C_6H_4COCl$[e]	A-E	34	1.78±0.08	0.54±0.04	3.3	0.9895
PhOCOCl[f]	A-E	21	1.68±0.10	0.57±0.06	2.9	0.973
2-AdOCOCl[g]	I	19	~0	0.47±0.03	~0	0.970
EtSCOCl[h]	I	19	0.66±0.08	0.93±0.07	0.70	0.961
PhSCOCl[i]	A-E	16	1.74±0.17	0.48±0.07	3.6	0.946
3[j]	I	26	0.51±0.07	0.65±0.03	0.78	0.988
1[k]	I	26	0.46±0.02	0.77±0.02	0.60	0.961

[a]The two reaction channels are designated as addition-elimination (A-E) and ionization (I). [b]Number of solvent systems included in the correlation. [c]With associated standard errors, those associated with the *c* values being the standard errors of the estimate. [d]Correlation coefficient. [e]Data from refs. 2(a), 10, 14, 20(a), 20(c), 20(d), 22(d), and 25(i). [f]Data from ref. 25(j). [g]Data from ref. 25(i). [h]Data from ref. 22(d). [i]Data from ref. 13(d). [j] Data from ref. 21. [k]Data from this work .

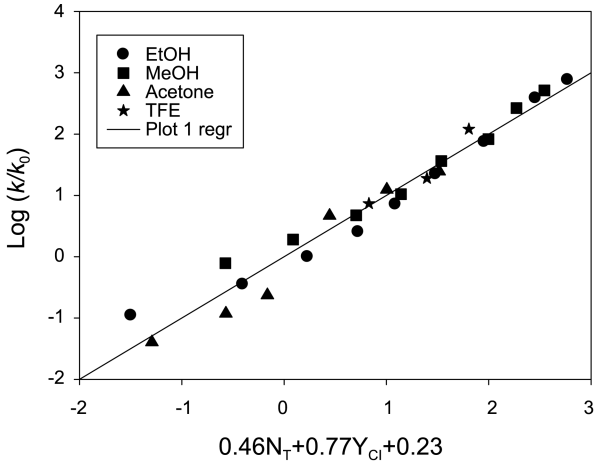


Figure 2. The plot of log(k/k_0) for solvolyses of 4-methylthiophene-2-carbonyl chloride (**1**) 0.46N_T + 0.77Y_{Cl} + 0.23 at 25 °C (r = 0.961).

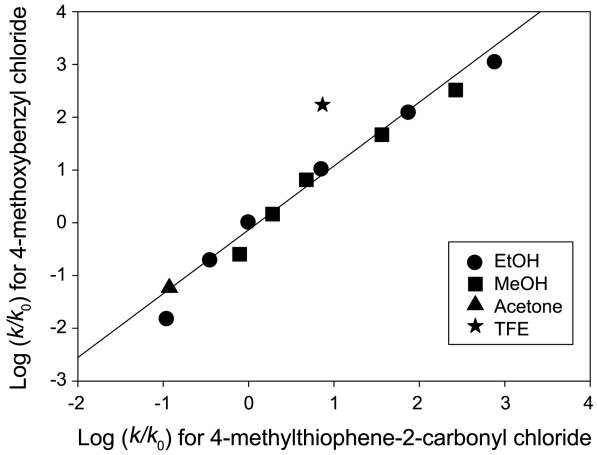


Figure 3. Correlation of logarithms of rate constants for solvolyses of *p*-methoxybenzyl chloride *vs.* solvolyses of 4-methylthiophene-2-carbonyl chloride (**1**) at 25 °C (r = 0.916).

ses of **1** in the binary aqueous solvent mixtures proceeds through S_N1 (I) and/or dissociative S_N2 pathway channels rather than through associative S_N2 and/or A-E pathway channels.[11(c),14,24(d),25]

An analysis using the two-term (or extended) Grunwald-Winstein equation leads to a very good linear correlation, with values of 0.46 ± 0.02 for *l*, 0.77 ± 0.02 for *m*, 0.23 ± 0.02 for *c*, and 0.961 for the correlation coefficient. The results of the correlation are presented in Figure 2 and are reported in Table 5, together with the corresponding parameters of other substrates.[7-13] 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 A-E, values below 0.84 for those believed to represent S_N1(I), and values of 0.84-1.9 for those postulated to represent the borderline [S_N1(I)/(A-E)] mechanism.[13,14] For **1**, the ratio of *l*/*m,* 0.60, is very similar to that observed for the solvolyses of **2**,[2,20] ethyl chloroformate and ethyl chlorothioformate,[1(a)] which have been shown to solvolyze with the ionization step of the ionization pathway being rate determining.[14]

Good correlations showing negligible dispersion can also be seen for solvolyses of **1** *vs* solvolyses of **2**, where the reaction is known to proceed through S_N1(I) and/or a dissociative S_N2 pathway (Figure 3).[7(d),14,22,27]

The plot of the rate of the solvolyses of **1** with the solvatochromic parameter *Z*,[20(d),28] a measure of solvent polarity based on the solvent dependence of the intermolecular charge-transfer transition in prydinium salt, also shows a good correlation, as presented in Figure 4. These results indicate that the solvolyses of **1** proceeds predominantly by S_N1(I) and/or a dissociative S_N2 pathway with an acylium ion pair intermediate or loose S_N2 transition state; the results also support the idea that the acylium ion pair intermediate is stabilized by solvent polarity.

The activation parameters for solvolyses of **1** in aqueous solvents at 25 °C are summarized in Table 2. The relatively small negative $\Delta S^{\neq}$ and large positive $\Delta H^{\neq}$ support the idea

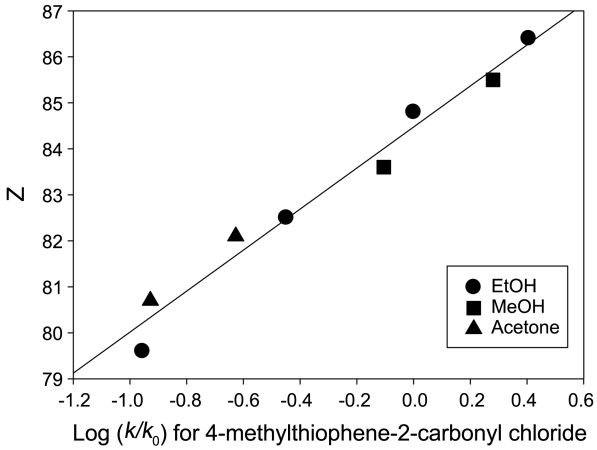


Figure 4. Correlation of Z values *vs*. logarithms of rate constants for solvolyses of 4-methylthiophene-2-carbonyl chloride (**1**) at 25 °C (r = 0.974).

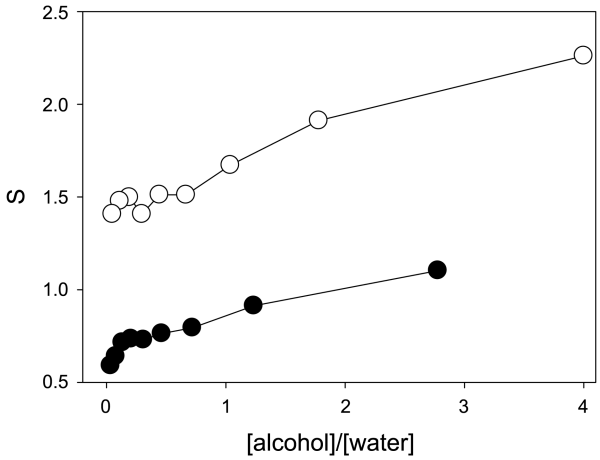


Figure 5. Correlation of S and alcohol-water mole ratio for solvolyses of 4-methylthiophene-2-carbonyl chloride (**1**) (solvent code: ○, methanol; ●, ethanol).

that the solvolytic reaction proceeds though a typical S_N1(I) and/or dissociative S_N2 pathway.[2,22]

The product selectivities, *S*, for the solvolyses of **1** in aqueous alcohols are summarized in Table 3, and are plotted versus the mole of the mixtures, R=[alcohol]/[water], in Figure 5. Examination of Figure 5 reveals that for the solvolyses of **1** in aqueous alcohol mixtures the selectivity increases with an increase in methanol and ethanol; thus, the reactivity-selectivity principle (RSP)[30] is obeyed in ethanol mixtures. The types of selectivity observed in **1** have been shown to be typical for the S_N1(I) and/or a dissociative S_N2 pathway with a loose S_N2 transition state.[4,15,16,19] Product studies in ethanol-water and methanol-water mixtures suggest that product formation occurs at the solvent-separated ion-pair stage ($S < 1$ in ethanol-water and $S \approx 1.5$ in methanol-water solvent mixtures). Because a positive charge is delocalized from the conjugating acylium ion to the thiophene S atom, the transition state is stabilized and a relatively low sensitivity to changes in solvent ionizing power is observed ($m = 0.62$).

Experimental Section

Materials. 4-Methylthiophene-2-carbonyl chloride is of commercial grade (Aldrich GR-grade > 99%). Merck GR-grade (< 0.1% H_2O) acetone, ethanol, methanol, and trifluoroethanol were used without further purification. 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.[3-5] Activation parameters were determined using the Arrehenius and Eyring equations. The solvolyses products were identified by ^{1}H NMR spectra.

Product Selectivity. The solvolysis products, ester and acid, were determined by the HPLC analysis described previously.[2(b),10(c),31] The product selectivities, *S*, were then calculated by Equation (4). The *S* values calculated from the observed peak area ratios of ester and acid yielded the S_{raw} values, which were divided by a response factor to arrive at the true *S* values. For the HPLC response calibrations, area ratios were obtained for pure alcohol and 40% acetonitrile water mixture and the flow rate was adjusted to 1 mL/min. Other details of the apparatus are as described previously.[2(b),10(c),31]

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