

Classical tosylate/chloride leaving group approach supports a tetrahedral transition state for additions to trigonal carbon

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ABSTRACT

The experimentally measured rates of solvolysis of 2-chloroethoxycarbonyl chloride (2-chloroethyl chloroformate, **3**), 2-chloroethoxycarbonyl *p*-toluenesulfonate (**5**), and phenoxycarbonyl *p*-toluenesulfonate (**6**) were followed at 25.0 °C in various pure and binary aqueous-organic solvents with varying degrees of polarity. An analysis of the rate constants for **3**, **5**, and **6**, was carried out using the two-term extended Grunwald-Winstein equation and comparisons are made to the previously published results for ethyl and phenyl chloroformate esters. The $k_{\text{OTS}}/k_{\text{Cl}}$ rate ratios and the Grunwald-Winstein l/m ratios indicate the probability of a dominant bimolecular carbonyl-addition pathway in the more nucleophilic solvents. Nevertheless in **3** and **5**, in the strongly hydrogen-bonding 70% and 50% HFIP mixtures, a side-by-side ionization mechanism is favored.

KEYWORDS: solvolysis, carbonyl-addition, phenyl chloroformate, ethyl chloroformate, 2-chloroethyl chloroformate, 2-chloroethoxycarbonyl *p*-toluenesulfonate, phenoxycarbonyl *p*-toluenesulfonate.

1. INTRODUCTION

Ethyl chloroformate (EtOCOC_l, **1**) and the homologous mono chloro- α -ethyl- (1-chloroethyl-,

2), and β -ethyl- (2-chloroethyl-, **3**) chloroformate esters are inexpensive organic protecting group blocks and alkylating reagents [1-5]. On the other hand, the aryl phenyl chloroformate (PhOCOC_l, **4**) is a common key intermediate in useful synthetic functional group transformations [6-10]. Yet, the (material) safety data sheets for **1-4** (Figure 1) identify them as being acutely toxic and single exposures are reported as being detrimental to human health [11-15].

In the chloroformate esters **1-4**, the lone pair on the ether oxygen provides resonance stabilization [16] and hence, the chloride leaving group is not easily cleaved by an incoming solvent molecule [17-21]. This charge delocalization allows for the solvolysis reactions of **1-4** to be conveniently followed at temperatures at or near 25.0 °C. Extensive solvolytic investigations of other alkyl/aryl chloroformate esters and their related analogs have been carried out and insights into their mechanistic nuances have been summarized as recent peer-reviewed publications [21-28].

Several groups used kinetics, activation parameter measurements, and solvent isotope effect studies, to evaluate the nucleophilic displacements at the acyl sp² (trigonal) carbon [16-35]. For understanding the solvent effects in haloformate esters, we have favored [16-21, 23-25, 28] the use of the dual-term (equation 1) Grunwald-Winstein LFER (Linear Free Energy Relationship).

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

In equation 1, the specific rates of solvolysis in each solvent studied and in 80% ethanol (the

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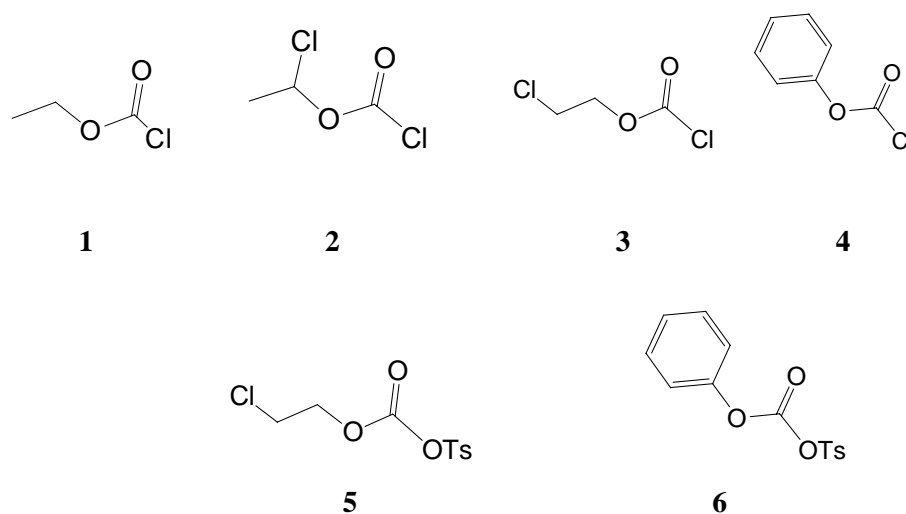
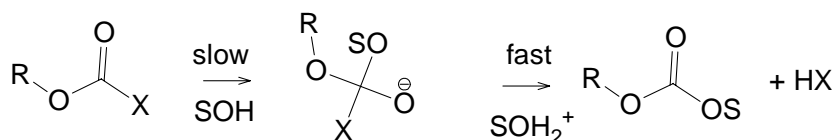


Figure 1. Molecular structures of ethyl chloroformate (**1**), 1-chloroethyl chloroformate (**2**), 2-chloroethoxycarbonyl chloride or 2-chloroethyl chloroformate (**3**), phenoxycarbonyl chloride or phenyl chloroformate (**4**), 2-chloroethoxycarbonyl *p*-toluenesulfonate (**5**), and phenoxycarbonyl *p*-toluenesulfonate (**6**).



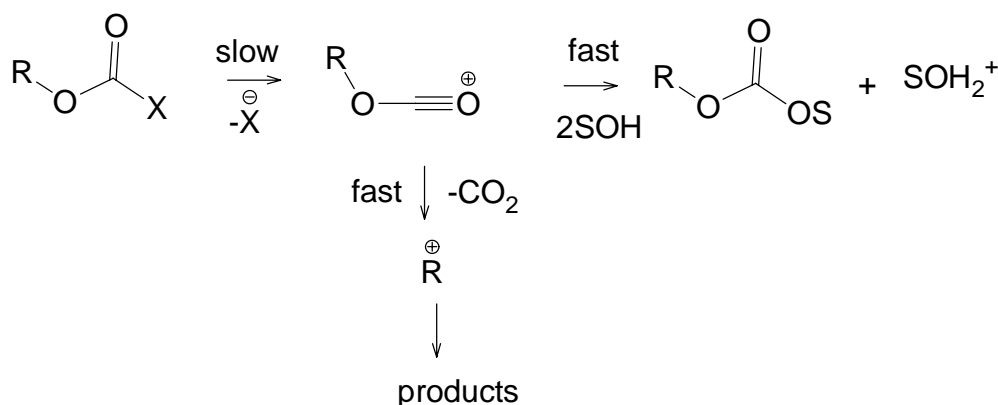
Scheme 1. The bimolecular carbonyl addition process in haloformate (ROCOX) esters.

standard solvent) are represented by k and k_o , respectively. The sensitivity to changes in solvent nucleophilicity (N_T) are approximated by l , while m approximates sensitivity changes to the solvent ionizing power Y_{Cl} , and c is the residual term. For considerations of solvent nucleophilicity, the solvolyses of the *S*-methylidibenzothiophenium ion was used to develop the N_T scale [36, 37], and the solvent ionizing power Y_X scale is based on the solvolysis of 1- or 2-adamantyl derivatives [38-42].

The solvolysis of PhOCOCl (**4**) has been extensively followed [18, 19, 43, 44] in varying pure and binary mixtures that have wide-ranging solvent polarities. For **4** in 49 solvents, the Grunwald-Winstein l (1.66) and m (0.56) values (l/m ratio of 2.96) acquired through the application of equation 1, are recommended [18, 19, 21, 23, 24] as standard indicators for homologous two-step (bimolecular) carbonyl-addition (addition-elimination) processes (Scheme 1).

The experimentally determined specific rates of reaction (k) for octyl chloroformate and octyl fluoroformate were found to be very similar [45]. Since the k_F/k_{Cl} rate ratio is shown to be close to unity [45], the rate law for alkyl haloformate (ROCOX) esters appears to be independent of the breaking of the stronger carbon-fluorine bond and to be simply determined by the slow initial formation of a tetrahedral intermediate (Scheme 1). Similar k_F/k_{Cl} ratios were observed with analogous alkyl and aryl haloformates [21, 24, 25, 46-49] and aryl substituted acyl halides [21, 22, 24-26, 50-54].

Alternatively, in the highly polar, strongly hydrogen-bonding binary aqueous mixtures with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and 2,2,2-trifluoroethanol (TFE), the chloroformates (ROCOCl) tend to follow a concerted solvolysis-decomposition process (Scheme 2) and the resultant structure of the cation formed was shown to be very dependent on the identity of the R group [21, 24, 25].



Scheme 2. Unimolecular solvolytic and decomposition pathways for haloformate esters.

In this project, to further probe the acyl-carbon leaving-group heterolytic bond cleavage, comparison solvolytic studies were carried out between the chloroformates **3** and **4**, and their analogous tosylates, **5** and **6**. A prior comparative analysis of $k_{\text{OTs}}/k_{\text{Cl}}$ solvolytic rate ratios is available for benzoyl substrates [32]. This project will (now) allow for a parallel study of solvent effects on substrates **3**, **5**, and **6**.

2. MATERIALS AND METHODS

The compounds 2-chloroethyl chloroformate (**3**, 97%, Sigma-Aldrich), the phenyl chloroformate (**4**, 99%, Sigma-Aldrich), and the silver tosylate ($\geq 99\%$, Sigma-Aldrich) were used as received. Using literature methodologies [32], 2-chloroethoxycarbonyl *p*-toluenesulfonate (**5**) and phenoxy carbonyl *p*-toluenesulfonate (**6**) were synthesized from additions of silver tosylate to 2-chloroethyl chloroformate and phenyl chloroformate, respectively. A rapid precipitation of silver chloride occurred, and the resulting filtered solution was used directly as the source of the substrate. All the spectroscopic grade organic solvents were purified using methods described elsewhere [17].

For **3**, **5**, and **6**, a substrate concentration in the 0.003-0.009 M range in a variety of solvents was employed. For **3**, **5**, and **6**, the 25.0 mL binary solution mixtures were first allowed to equilibrate in a 25.0 °C constant-temperature water bath and then, the progress of the reaction was monitored by titrating aliquots of the solution using a lacmoid indicator. Rapid kinetic runs were

followed using a conductivity cell containing 15 mL of solvent which was first allowed to equilibrate in a 25.0 °C constant-temperature water bath, with stirring. The specific rates and associated standard deviations, as presented in Table 1, are obtained by averaging all of the values from, at least, duplicate runs. Multiple regression analyses were carried out using the Excel 2016 package from the Microsoft Corporation. The molecular structures (*syn* geometry) presented in Figure 1, were drawn using the KnowItAll® Informatics System 2018, from BioRad Laboratories, Philadelphia, PA.

3. RESULTS AND DISCUSSION

This solvolytic study was undertaken in a variety of pure polar protic solvents and binary aqueous-organic mixtures. The pseudo first-order rates of solvolysis, at 25.0 °C, of 2-chloroethoxycarbonyl chloride (2-chloroethyl chloroformate, **3**), $(k_{\text{Cl}})_3$, and the corresponding 2-chloroethoxycarbonyl *p*-toluenesulfonate (**5**), $(k_{\text{OTs}})_5$, in 19 solvents are shown in Table 1. Also presented in Table 1, are the $(k_{\text{OTs}})_5/(k_{\text{Cl}})_3$ ratios and the N_{T} , Y_{Cl} , and Y_{OTs} values that are needed to compute the necessary bond-making (l value), bond-breaking (m value), and residual (c value) components in equation 1. In Table 2, we list the (pseudo) first-order rate constant for phenoxy carbonyl *p*-toluenesulfonate (**6**) in 21 solvents, at 25.0 °C, and the corresponding $(k_{\text{OTs}})_6/(k_{\text{Cl}})_4$ rate ratios (as noted in Table 2, the 25.0 °C phenyl chloroformate rate constants are available in the literature).

Table 1. Specific rates of solvolysis, at 25.0 °C, of 2-chloroethoxycarbonyl chloride (2-chloroethyl chloroformate, **3**), k_{Cl} , and the corresponding *p*-toluenesulfonate (**5**), k_{OTs} . Also listed with these values are the corresponding literature values for solvent nucleophilicity (N_{T}) and for solvent ionizing power with the chloride or *p*-toluenesulfonate (tosylate) leaving group (Y_{Cl} or Y_{OTs}) and the $(k_{\text{OTs}})_5/(k_{\text{Cl}})_3$ ratios.

Solvent ^a	3 , $10^5 k_{\text{Cl}}$, s^{-1b}	5 , $10^5 k_{\text{OTs}}$, s^{-1b}	$(k_{\text{OTs}})_5/(k_{\text{Cl}})_3$	N_{T}^c	Y_{Cl}^d	Y_{OTs}^e
100% EtOH	22.2 ± 0.3	20.6 ± 0.4	0.93	0.37	-2.50	-1.95
90% EtOH	39.8 ± 0.5	47.7 ± 0.3	1.20	0.16	-0.90	-0.77
80% EtOH	47.8 ± 1.2	58.3 ± 0.4	1.22	0.00	0.00	0.00
100% MeOH	59.4 ± 1.0	61.9 ± 0.4	1.04	0.17	-1.20	-0.92
90% MeOH	113 ± 2	112 ± 1.8	0.99	-0.01	-0.20	-0.05
80% MeOH	136 ± 2	156 ± 3.3	1.15	-0.06	0.67	0.47
90% Acetone	1.53 ± 0.05	1.54 ± 0.09	1.01	-0.35	-2.39	-2.95
80% Acetone	3.92 ± 0.11	5.14 ± 0.13	1.31	-0.37	-0.80	-0.94
70% Acetone	8.92 ± 0.08	9.58 ± 0.08	1.07	-0.42	0.17	0.07
97% TFE (w/w)	0.0112 ± 0.0013	0.0131 ± 0.0013	1.17	-3.30	2.83	1.83
90% TFE (w/w)	0.164 ± 0.004	0.187 ± 0.011	1.14	-2.55	2.85	1.90
50% TFE (w/w)	11.3 ± 0.5	12.5 ± 0.7	1.11	-1.73	3.16	2.14
80T-20E	0.272 ± 0.005	0.380 ± 0.013	1.40	-1.76	1.89	0.98
60T-40E	1.78 ± 0.08	2.20 ± 0.11	1.24	-0.94	0.63	0.21
50T-50E	2.85 ± 0.10	3.92 ± 0.10	1.38	-0.64	0.16	0.14
40T-60E	5.28 ± 0.19	5.62 ± 0.10	1.06	-0.34	-0.48	-0.44
20T-80E	9.06 ± 0.09	11.5 ± 0.6	1.27	0.08	-1.42	-1.18
70% HFIP (w/w)	2.72 ± 0.08	2.78 ± 0.21	1.02	-2.94	3.83	2.40
50% HFIP (w/w)	8.96 ± 0.16	9.19 ± 0.15	1.03	-2.49	3.80	2.26

^aSubstrate concentrations were in the 0.003-0.009 M range and the binary solvent mixtures are on a volume-volume basis at 25.0 °C, except for TFE-H₂O and HFIP-H₂O mixtures which are on a weight-weight basis. T-E represent TFE-ethanol mixtures. ^bWith associated standard deviations. ^cValues from ref 36, and 37. ^dValues from ref 38-42. ^eValues from ref 39 and 54.

For **3-6**, in all of the aqueous-organic mixtures studied, the rate of reaction increases with the increase of water content in the binary mixtures, and in the TFE-ethanol (TFE-EtOH) solvents, the rate increase is directly dependent on the increase in ethanol content (which corresponds to an increase in N_{T} value and a decrease in Y_{Cl} or Y_{OTs} value). These observations are aligned with prior

haloformate ester studies [21, 24-26] where, in a majority of pure and binary aqueous-organic mixtures, it was demonstrated that a typical bimolecular step-wise carbonyl-addition process is occurring (Scheme 1).

Also shown in Tables 1 (in 19 solvents) and 2 (in 21 solvents), are the $(k_{\text{OTs}})_5/(k_{\text{Cl}})_3$ and the $(k_{\text{OTs}})_6/(k_{\text{Cl}})_4$ rate ratios, which in general, are

Table 2. Specific rates of solvolysis of phenoxycarbonyl *p*-toluenesulfonate (**6**) at 25.0 °C, k_{OTs} , and a comparison with literature values for the corresponding chloride (more frequently named as phenyl chloroformate, **4**).

Solvent ^a	6 , $10^5 k_{\text{OTs}}$, s ⁻¹ ^b	$(k_{\text{OTs}})_6/(k_{\text{Cl}})_4$ ^c
100% EtOH	336 ± 2	1.29
90% EtOH	457 ± 2	1.17
80% EtOH	546 ± 2	1.09
100% MeOH	642 ± 1	0.92
90% MeOH	1440 ± 23	1.17 ^d
80% MeOH	2060 ± 27	1.23 ^d
90% Acetone	26.0 ± 0.7	1.09 ^e
80% Acetone	68.4 ± 2.7	0.99
70% Acetone	131 ± 6	1.05 ^d
97% TFE (w/w)	0.0862 ± 0.0030	1.51
90% TFE (w/w)	1.08 ± 0.04	0.94
70% TFE (w/w) ^f	20.4 ± 0.6	1.17 ^e
50% TFE (w/w)	66.8 ± 3.2	1.17 ^e
80T-20E	3.20 ± 0.14	1.32
60T-40E	22.2 ± 1.2	1.27 ^e
40T-60E	75.8 ± 2.2	1.31 ^e
20T-80E	187 ± 1	1.11 ^e
97% HFIP (w/w) ^g	0.00215 ± 0.00015	1.45 ^e
90% HFIP (w/w) ^h	0.217 ± 0.017	1.31
70% HFIP (w/w)	13.6 ± 0.8	1.30
50% HFIP (w/w)	35.2 ± 2.6	1.11

^{a,b}As in table 1. ^cUnless otherwise indicated the k_{Cl} values are from ref 17. ^dThe k_{Cl} values are from ref. 44. ^eThe k_{Cl} values are from ref 23. ^f N_{T} value of -1.98 and Y_{OTs} value of 2.00. ^g N_{T} value of -5.26 and Y_{OTs} value of 3.61. ^h N_{T} value of -3.84 and Y_{OTs} value of 2.90.

slightly higher than unity. Such marginally higher than unity $k_{\text{OTs}}/k_{\text{Cl}}$ rate ratios indicate that changes in bonding to the leaving group are not appreciably involved in the rate-determining step and hence, for substrates **3-6**, a unimolecular solvolysis pathway (Scheme 2) is in all likelihood, unimportant.

A comparison of the specific rates of solvolysis of ethyl chloroformate (**1**) and its 1-chloro- (**2**), 2-chloro- (**3**), and 2,2,2-trichloro-derivatives in four representative solvents is given in Table 3. When compared to **1**, the proximity of the chloro-substituent in **2** to the carbonyl carbon causes a powerful inductive effect and as a result, the rates

Table 3. A comparison of the specific rates of solvolysis ($10^5 k, \text{s}^{-1}$) of ethyl chloroformate and its 1-chloro, 2-chloro, and 2,2,2-trichloro derivatives in four representative solvents at 25.0 °C.

	100EtOH ^{a,b}	80EtOH ^{a,b}	70TFE ^{a,c}	70HFIP ^{a,c}	Ref
CH ₃ CH ₂ OCOCI ^d	2.26	7.31	0.611	0.444	17
CH ₃ CHClOCOCI	543	2260	30.9		20
CH ₂ ClCH ₂ OCOCI	22.2	47.8	1.12 ^e	2.72	This work
CCl ₃ CH ₂ OCOCI	231	711	3.29	6.4 ^f	34

^aOther component water. ^bVolume-volume at 25.0 °C. ^cWeight-weight. ^dValues at 24.2 °C. ^eObtained by interpolation of a plot of low k against weight percentage of TFE in the solvent. ^fThe value at 35.0 °C ($11.7 \times 10^{-5} \text{s}^{-1}$) multiplied by 0.55. The studies [34] in 100% EtOH, 100% MeOH, 80% EtOH, and 70% TFE gave an almost constant k_{25}^0/k_{35}^0 ratio of 0.55 ± 0.03 .

of reaction are approximately 20 times higher in pure ethanol (EtOH), 300 times higher in 80% EtOH, and 50 times higher in 70% TFE. In **3**, this inductive effect significantly diminishes as the chloro-substituent is further removed by one carbon atom and therefore the rates of reaction for **3** are only 10, 7, 2, and 6 times faster than **1** in 100% EtOH, 80% EtOH, 70% TFE, and 70% HFIP, respectively. Increasing the number of chloro-substituents in the 2-position of **1**, as in the 2,2,2-trichloroethyl chloroformate derivative, has no major (inductive) impact and results in a similar 10-fold reaction rate increase in 100% EtOH and 80% EtOH, while 5- and 15-fold rate increases are seen in 70% TFE, and 70% HFIP mixtures, respectively.

Using equation 1, the correlations obtained for the specific rates of solvolysis of 2-chloroethoxycarbonyl chloride (2-chloroethyl chloroformate, **3**), 2-chloroethoxycarbonyl *p*-toluenesulfonate (**5**), and phenoxy carbonyl *p*-toluenesulfonate (**6**) at 25.0°C, are recorded in Table 4. Also indexed within the same table, are the previously published correlations obtained for phenyl chloroformate (PhOCOCI, **4**), benzoyl *p*-toluenesulfonate, and *p*-nitrobenzoyl *p*-toluenesulfonate.

In 49 solvents of widely varying nucleophilicity and solvent ionizing power values, an equation 1 treatment (reported in Table 4) of the rate constants for PhOCOCI (**4**) resulted in a Grunwald-Winstein l/m ratio of 2.96 [18, 19, 21, 23, 24]. This value is extensively quoted as being

typical, for addition to an sp^2 carbonyl reaction center within a principal two-step (bimolecular) addition-elimination process and where, the carbonyl-addition is the slow step (Scheme 1). In ethyl chloroformate (**1**), an l/m ratio of 2.84 was obtained in 28 solvents where the step-wise (tetrahedral transition-state) carbonyl-addition pathway was found to be dominant [17]. In the 7 highly ionizing (and strongly hydrogen bonding) aqueous TFE and HFIP solvents an l/m ratio of 0.84 was obtained, and a side-by-side ionization mechanism with considerable nucleophilic solvation of the incipient (sp) acylium ion was proposed to apply.

Contrarily for benzoyl *p*-toluenesulfonate, Kevill and Ryu obtained [32] an l/m ratio of 0.14 in 36 solvents (Table 4) that had a predominant unimolecular ionization-decomposition process (Scheme 2). Additionally, a value of 2.37 for *p*-nitrobenzoyl *p*-toluenesulfonate was obtained in 37 solvents and on omission of the aqueous-acetone, TFE-EtOH, 100% TFE and 97% HFIP data points (21 solvents), they found an l/m ratio of 1.80 [32]. Hence, they concluded that a dominant bimolecular mechanism was the preferred pathway except in solvents rich in the fluoroalcohols.

In this project, in the 19 solvents studied, an equation 1 application to the specific rates of solvolysis of **3** resulted in, $l = 1.57 \pm 0.21$, $m = 0.61 \pm 0.13$, $c = 0.14 \pm 0.17$, $R = 0.903$, and $F\text{-test} = 35.4$. For **5** (in same 19 solvents), we

Table 4. Correlations at 25.0 °C of the specific rates of solvolysis of 2-chloroethoxycarbonyl chloride (**3**) and *p*-toluenesulfonate (**5**) and of phenoxycarbonyl *p*-toluenesulfonate (**6**) and a comparison with previous correlations of related solvolysis.

Substrate	n^a	l^b	m^b	c^b	R^c	F^d
CH ₂ ClCH ₂ OCOCI	19 ^e	1.57 ± 0.21	0.61 ± 0.13	0.14 ± 0.17	0.903	35.4
	17 ^f	1.62 ± 0.14	0.52 ± 0.08	0.09 ± 0.11	0.965	95.1
	16 ^g	1.72 ± 0.18	0.54 ± 0.09	0.13 ± 0.12	0.943	52.5
CH ₂ ClCH ₂ COOTs	19 ^e	1.25 ± 0.18	0.59 ± 0.14	0.04 ± 0.18	0.885	28.9
	17 ^f	1.40 ± 0.11	0.52 ± 0.09	0.03 ± 0.11	0.965	94.4
	16 ^g	1.39 ± 0.14	0.52 ± 0.09	0.03 ± 0.12	0.939	48.5
PhOCOCI	49 ^e	1.66 ± 0.05	0.56 ± 0.03	0.15 ± 0.17	0.980	568
PhOCOOTS	21 ^e	1.57 ± 0.13	0.77 ± 0.13	0.26 ± 0.13	0.972	150
PhCOOTS ^h	36 ^e	0.11 ± 0.04	0.80 ± 0.04	0.11 ± 0.06	0.978	364
<i>p</i> -NO ₂ C ₆ H ₄ COOTS ^h	37 ^e	0.90 ± 0.09	0.38 ± 0.08	-0.18 ± 0.11	0.880	58
	21 ⁱ	1.19 ± 0.05	0.66 ± 0.06	-0.13 ± 0.06	0.983	265

^aNumber of solvents (data points). ^bFrom eqn. (1), with associated standard errors, using Y_{Cl} or Y_{OTs} as appropriate. ^cCorrelation coefficient ^d F -test value. ^eUsing all available data points (Figure 4). ^fOmitting 70%, 50% HFIP. ^gOmitting 70%, 50% HFIP and 97% TFE. ^hAt -10.0°C. ⁱOmitting acetone-H₂O, TFE-Ethanol, 100% TFE and 97% HFIP data points.

obtained, $l = 1.25 \pm 0.18$, $m = 0.59 \pm 0.14$, $c = 0.04 \pm 0.18$, $R = 0.885$, and F -test = 28.9. For both **3** and **5**, an omission of the highly ionizing 70% HFIP and 50% HFIP mixtures resulted in improved correlation coefficient (R) numbers and higher F -test values. In the remaining 17 solvents, we obtained, $l = 1.62 \pm 0.14$, $m = 0.52 \pm 0.08$, $l/m = 3.12$, $c = 0.09 \pm 0.11$, $R = 0.965$, and F -test = 95.1 for **3**, and $l = 1.40 \pm 0.11$, $m = 0.52 \pm 0.09$, $l/m = 2.69$, $c = 0.03 \pm 0.11$, $R = 0.965$, and F -test = 94.4, for **5**. Furthermore, as shown in Table 4, for **3** and **5**, an extra omission of the strongly hydrogen-bonding 97% TFE value failed to bring any further improvements in the R and F -test values. For **6**, in all 21 solvents studied, $l = 1.57 \pm 0.13$, $m = 0.77 \pm 0.13$, $l/m = 2.04$, $c = 0.26 \pm 0.13$, $R = 0.972$, and F -test = 150.

A plot of $\log(k/k_0)_3$ against $1.62 N_T + 0.52 Y_{Cl}$ in the 19 pure and binary solvents studied is

shown in Figure 2 and in the same set solvents, a plot of $\log(k/k_0)_5$ against $1.40 N_T + 0.52 Y_{OTs}$ is shown in Figure 3. In both figures, the 70% HFIP and 50% HFIP values were not used in the correlation analysis calculations as their omission resulted in considerably higher R and F -test values (Table 4). However, they are added to the Figure 2 and 3 scatter plots to show their clear divergence from the linear regression line. A similar bifurcation was observed for the solvolysis of ethyl chloroformate (**1**) in 100% formic acid, 100% TFE, 97% TFE and 97-50% HFIP [17]. For these 7 solvents, the l/m ratio = 0.84 and thus, a unimolecular (S_N1) mechanism (Scheme 2) that is accompanied by a robust nucleophilic solvation of the developing carbocation was proposed [17]. For such a loose cationic transition state, Bentley prefers the use of the S_N2 - S_N1 (intermediate) terminology [54].

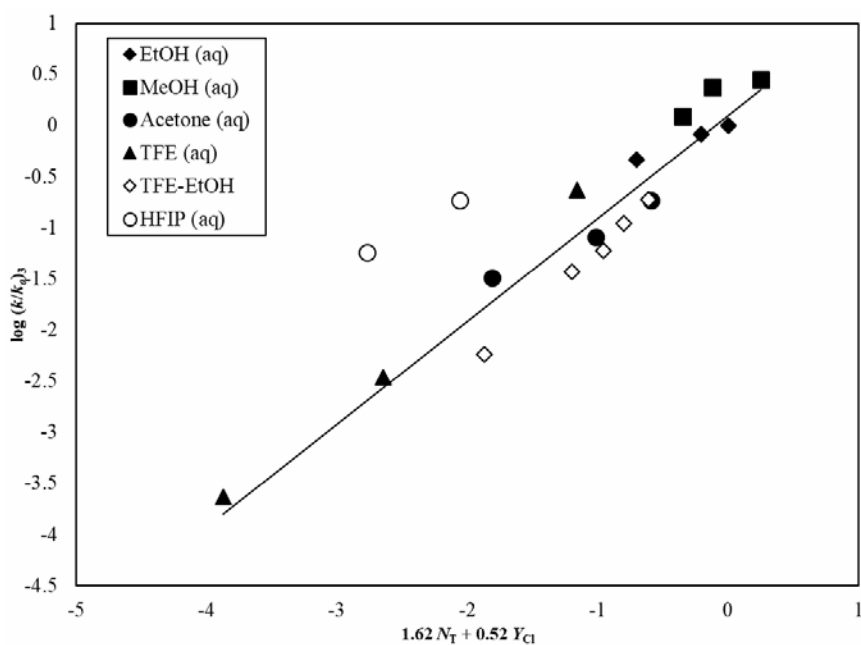


Figure 2. The plot of $\log(k/k_o)$ for 2-chloroethyl chloroformate (**3**) against $1.62 N_T + 0.52 Y_{Cl}$ in the nineteen pure and binary solvents studied. The 70% HFIP and 50% HFIP values were not included in the correlation analysis calculations but were added on the plot to show their deviation.

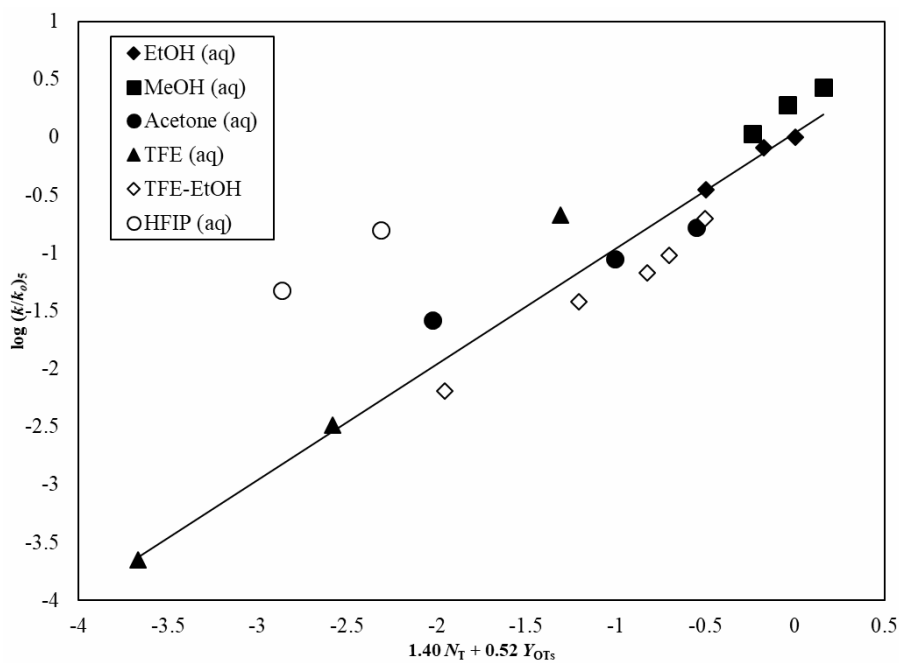


Figure 3. The plot of $\log(k/k_o)$ for 2-chloroethoxyxycarbonyl *p*-toluenesulfonate (**5**) against $1.40 N_T + 0.52 Y_{Ors}$ in the nineteen pure and binary solvents studied. The 70% HFIP and 50% HFIP values were not included in the correlation analysis calculations but were added on the plot to show their deviation.

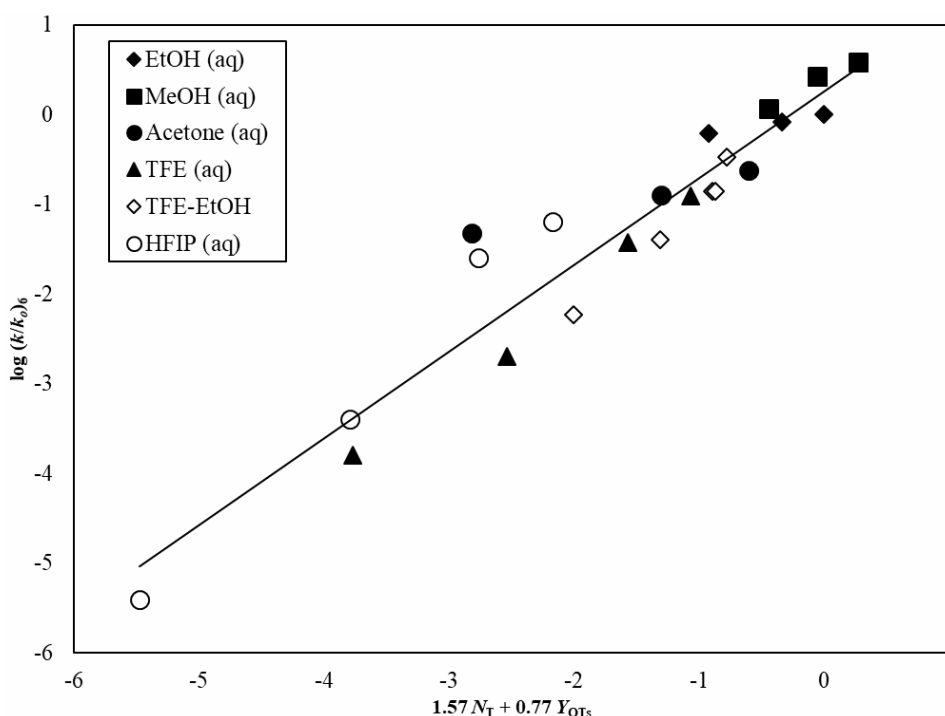


Figure 4. The plot of $\log(k/k_o)$ for phenoxy carbonyl *p*-toluenesulfonate (**6**) against $1.57 N_T + 0.77 Y_{OTs}$ in the twenty-one pure and binary solvents studied.

With equation 1, for both **3** and **5**, the exclusion of the strongly hydrogen bonding 70% and 50% HFIP mixtures, results in appreciable improvements in *R* and *F*-test values. This strongly indicates that the acylium ion formation (Scheme 2) is the favored controlling pathway in these two solvents.

In 17 of the more nucleophilic solvents for **3** and **5**, and for all 21 solvents for **6** (Figure 4), the *l/m* ratios obtained are 3.12, 2.69, and 2.04, respectively. As mentioned earlier, the *l/m* ratio for **4** is 2.96 [18, 19, 21, 23, 24]. Such *l/m* values are consistent with a bimolecular carbonyl addition process where the first step (formation of the tetrahedral transition-state) is rate-determining. This pathway also aligns nicely with the earlier (Table 1 and Table 2) observations that have $(k_{OTs})_5/(k_{Cl})_3$ and $(k_{OTs})_6/(k_{Cl})_4$ ratios only slightly higher than unity. Furthermore, $(l/m)_3 > (l/m)_5$, and $(l/m)_4 > (l/m)_6$. This suggests that the general base catalysis influences decrease in going from **3** to **5** and **4** to **6**.

4. CONCLUSIONS

At an sp^3 hybridized carbon, the superior delocalization of the tosylate leaving group,

relative to a halide leaving group, has been found to have useful applications in the understating of mechanisms that involved an electron-deficient carbon intermediate. This project was a rational extension and used the k_{OTs}/k_{Cl} rate ratio concept to determine the likelihood of acylium ion formation in two common alkyl and aryl carboxylic acid derivatives.

The compounds 2-chloroethoxycarbonyl chloride (2-chloroethyl chloroformate, **3**), 2-chloroethoxycarbonyl *p*-toluenesulfonate (**5**), and phenoxy carbonyl *p*-toluenesulfonate (**6**) were studied at 25.0 °C. To avoid multicollinearity when using the extended Grunwald-Winstein equation (equation 1), the three substrates were studied in solvents of widely differing polarities (with very different N_T and Y_X values). **3** and **5** were studied in 19 solvents, while the pseudo-first order rate constant (*k*) for **6** was obtained in 21 solvents. In addition, the reaction rate constants for **6** were compared to the literature values for phenyl chloroformate (**4**).

In all of the solvents studied, the $(k_{OTs})_5/(k_{Cl})_3$ and $(k_{OTs})_6/(k_{Cl})_4$ rate ratios were found to be slightly

above unity. For typical S_N1 reactions at an sp³ hybridized carbon, tosylate when compared to chloride, has been found to be a much better leaving group. Thus in this study, the observed rate ratio results favor the explanation that the transition state involves a rate-determining carbonyl addition. Evidence to support this bimolecular tetrahedral transition-state formation (within an addition-elimination process) is provided by the *l/m* ratios for **3**, **5**, and **6**. The benchmark for carbonyl-additions is an *l/m* ratio of 2.96 which was observed for **4** in 49 solvents. The *l/m* ratios for **3**, **5**, and **6**, were 3.12, 2.69, and 2.04, respectively. As (*l/m*)₃ > (*l/m*)₅, and (*l/m*)₄ > (*l/m*)₆, this hints that the influence in general base catalysis declines in substrates with the *p*-toulenesulfonate leaving group.

A comparative analyses of the chloro-substituent effect in ethyl chloroformate (**1**) and its 1-chloro- (**2**), 2-chloro- (**3**), and 2,2,2-trichloro-derivatives in four representative solvolyses showed the presence of very strong inductive effects in substrate **2**.

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CONFLICT OF INTEREST STATEMENT

The authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication.

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