

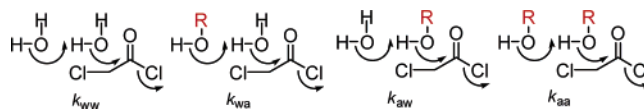
Mechanisms of Solvolyses of Acid Chlorides and Chloroformates. Chloroacetyl and Phenylacetyl Chloride as Similarity Models

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Rate constants and product selectivities ($S = ([\text{ester product}]/[\text{acid product}]) \times ([\text{water}]/[\text{alcohol solvent}])$) are reported for solvolyses of chloroacetyl chloride (**3**) at $-10\text{ }^{\circ}\text{C}$ and phenylacetyl chloride (**4**) at $0\text{ }^{\circ}\text{C}$ in ethanol/ and methanol/water mixtures. Additional kinetic data are reported for solvolyses in acetone/water, 2,2,2-trifluoroethanol(TFE)/water, and TFE/ethanol mixtures. Selectivities and solvent effects for **3**, including the kinetic solvent isotope effect (KSIE) of 2.18 for methanol, are similar to those for solvolyses of *p*-nitrobenzoyl chloride (**1**, $Z = \text{NO}_2$); rate constants in acetone/water are consistent with a third-order mechanism, and rates and products in ethanol/ and methanol/water mixtures can be explained quantitatively by competing third-order mechanisms in which one molecule of solvent (alcohol or water) acts as a nucleophile and another acts as a general base (an addition/elimination reaction channel). Selectivities increase for **3** as water is added to alcohol. Solvent effects on rate constants for solvolyses of **3** are very similar to those of methyl chloroformate, but acetyl chloride shows a lower KSIE, and a higher sensitivity to solvent-ionizing power, explained by a change to an $\text{S}_{\text{N}}2/\text{S}_{\text{N}}1$ (ionization) reaction channel. Solvolyses of **4** undergo a change from the addition/elimination channel in ethanol to the ionization channel in aqueous ethanol (<80% v/v alcohol). The reasons for change in reaction channels are discussed in terms of the gas-phase stabilities of acylium ions, calculated using Gaussian 03 (HF/6-31G(d), B3LYP/6-31G(d), and B3LYP/6-311G(d,p) MO theory).

Introduction

Solvolyses of acid halides in mixtures of aqueous alcohol are nucleophilic substitutions leading to mixtures of acid and ester products. For acyl chlorides, substituent effects, solvent effects, and product selectivities (S , eq 1) can be explained by competing reaction channels.^{1,2} Rate constants for one of the reaction channels (ionization or $\text{S}_{\text{N}}2/\text{S}_{\text{N}}1$) are strongly dependent on the solvent ionizing power (Y): e.g., solvolyses of *p*-

methoxybenzoyl chloride (**1**, $Z = \text{OMe}$).³

$$S = ([\text{ester product}]/[\text{acid product}]) \times ([\text{water}]/[\text{alcohol}]) \quad (1)$$

As Y decreases (e.g., adding alcohol to water) and/or as the substituent become less strongly electron-donating, another reaction channel becomes competitive, a third-order addition/elimination mechanism, much less sensitive to changes in Y : e.g., solvolyses of *p*-nitrobenzoyl chloride (**1**, $Z = \text{NO}_2$),^{4a,b} for which rate constants show an unusual shallow maximum,⁴ and the kinetic solvent isotope effect (KSIE) in water or methanol is relatively

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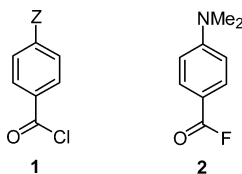
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large (ca. 2).^{4b} The results can be explained by competing third-order addition/elimination mechanisms in which one molecule of solvent acts as a nucleophile assisted by a second molecule of solvent acting as a general base catalyst.⁴

Mechanistic changes due to structural effects (e.g., solvolyses of **1**, Z = OMe and NO₂)^{3,4} are well established. Examples of solvent-induced mechanistic changes are rarer, and more difficult to establish. Solvolyses of *p*-dimethylaminobenzoyl fluoride (**2**) in ethanol/water provide a clear example of mechanistic changes induced simply by adding water to alcohol solvent.^{1a} In more polar solvent compositions, the rates depend strongly on solvent polarity, and the ionization reaction channel is favored. As the solvent polarity decreases, the dominant process is an addition/elimination reaction channel, almost insensitive to solvent polarity. The above interpretation is supported by a recent comparison with solvolyses of benzoyl fluoride, which reacts by an addition/elimination mechanism.^{5a}



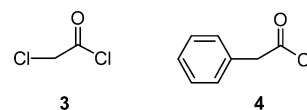
Kinetic data for many acid chlorides^{1–6} and chloroformates (both aryl^{7a} and alkyl^{7b–e}) are consistent with reactions via one or both of these two competing reaction channels (ionization and/or addition/elimination). Clear differences due to mechanism-related charge effects are also observed when rate constants in aqueous anionic and cationic micelles are compared.⁸ However, the mechanistic changes for chlorides are not as clear as those for fluorides, and additional supporting data from *S* values (eq 1) in alcohol/water have been useful in characterizing the two reaction channels, and the region of mechanistic change. For solvolyses of **1**, Z = OMe, *S* values are low and close to constant.³ For solvolyses of **1**, Z = NO₂, *S* increases as water is added to alcohol.⁴ In contrast, solvolyses of **1**, Z = H and Cl, show clear maxima in *S* as water is added to alcohol, consistent with a change in reaction channel.

Solvolyses of acyl chlorides have not yet yielded clear-cut mechanistic conclusions. The scope of kinetic data is limited by the high reactivity of acyl chlorides,^{9–11} so

many previous studies of solvolyses acyl halides have been made in solvents of low polarity, and relatively complex kinetics have been observed.^{9,12} Unlike the systematic studies of electronic effects of para-substituents in acyl chlorides (**1**), substituent effects for acyl chlorides are a combination of electronic and steric effects, with the strong possibility of additional complications from mechanistic changes. Although stereochemical studies provided mechanistic insights into other substitutions at sp² carbon (e.g., oximoyl halides¹³), they are uninformative for substitutions at carbonyl carbon. Leaving group effects (especially fluoride/chloride ratios) are useful broad indicators of mechanistic changes,^{7b,c,12} and kinetic isotope effects provide detailed specific information about individual reactions.¹⁴

Data for solvent effects on rates and products allow us to detect mechanistic changes for solvolyses of acyl chlorides. Solvolyses of acetyl chloride in methanol and in more polar mixtures proceed via the ionization reaction channel; they show a low KSIE (1.3), a low *S*, a high sensitivity to *Y*, and a relatively high sensitivity to solvent nucleophilicity *N*.¹⁰ Except for the latter, these mechanistic features are “similar”¹⁵ to those for solvolyses of **1**, Z = OMe. The high sensitivity to *N* can be explained by S_N2 character or by nucleophilic solvation of a cationic transition state,¹⁰ a proposal recently supported by density functional theory (DFT) calculations of acetyl chloride solvated by up to six methanol molecules.¹⁷

We now report rate and product data for solvolyses of chloroacetyl chloride (**3**) and phenylacetyl chloride (**4**). The solvolyses data for **3** are shown to be very similar to that of **1**, Z = NO₂, and of methyl chloroformate (MeO-COCl). The data for **4** link solvolyses of **3** with those of acetyl chloride and reveal mechanistic changes not previously apparent. Mechanistic interpretations are compared with cation stabilities, obtained by DFT and other MO calculations using Gaussian 03.¹⁸



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TABLE 1. Rate Constants ($k/10^{-3} \text{ s}^{-1}$) for Solvolyses of Chloroacetyl Chloride (3) in Acetone/, Ethanol/ and Methanol/Water at $-10.0 \text{ }^\circ\text{C}^a$

solvent % v/v	acetone	ethanol	methanol
100	101 ± 2^b	260 ± 4^c	
90	33.9 ± 0.3	256 ± 4	551 ± 22
80	73.2 ± 0.5	327 ± 4	765 ± 32
70	103 ± 1	341 ± 3	
60	149 ± 1	366 ± 6	1230 ± 110
50	183 ± 1	378 ± 6	965 ± 46
40	228 ± 1	391 ± 8	755 ± 7
30	254 ± 4	385 ± 2	
20	303 ± 2^d	361 ± 4	

^a Determined conductometrically at least in duplicate; errors shown are average deviations. ^b In agreement with data from ref 9a: $10^3k = 101.6 \pm 8.9 \text{ s}^{-1}$ at $-9.8 \text{ }^\circ\text{C}$. ^c Additional data for MeOD: $k = 119 \pm 5$, so KSIE is 2.18. ^d Extrapolation of the correlation line in Figure 1 gives a value of 0.35 s^{-1} for the rate constant in water.

TABLE 2. Rate Constants ($k/10^{-3} \text{ s}^{-1}$) for Solvolyses of Phenylacetyl Chloride (4) in Acetone/, Ethanol/ and Methanol/Water at $0.0 \text{ }^\circ\text{C}^a$

solvent % v/v	acetone	ethanol	methanol
100		$20.4 \pm 1^{b,c}$	82.7 ± 1.4^d
90	2.45 ± 0.01	44.5 ± 4	126 ± 3
80	4.62 ± 0.12	54.7 ± 2^b	188 ± 1
70	9.38 ± 0.40	77.6 ± 2	273 ± 14
60	16.5 ± 0.7	96.2 ± 1	435 ± 77
50	59.2 ± 1	144 ± 5	
40	139 ± 1	264 ± 24	
30	432 ± 20		

^a As for Table 1. ^b Ref 11a. ^c Data calculated from ref 9a: $10^3k = 17.0 \text{ s}^{-1}$. ^d At $10 \text{ }^\circ\text{C}$, the KSIE (MeOH/MeOD) = $(1.44 \pm 0.05) \times 10^{-1}/(1.03 \pm 0.02) \times 10^{-1} = 1.40$.

Results

Rate constants for solvolyses of **3** and **4** in acetone/, ethanol/, and methanol/water are shown in Tables 1 and 2, respectively, and constants in TFE/water and TFE/ethanol are shown in Table 3. Product selectivities (*S*, eq 1) for ethanol/ and methanol/water are shown in Table 4.

The energetics of reactions of a wide range of acid chlorides (ZCOCl) in the absence of solvent was outlined using Gaussian 03,¹⁸ by comparing the energies of various acylium ions with the acetyl cation in chloride transfer reactions (eq 2, Table 5). Contributions from the stabilization energies of neutral ground states were calculated

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TABLE 3. Rate Constants ($k/10^{-3} \text{ s}^{-1}$) for Solvolyses of Chloroacetyl Chloride (3) at $-10.0 \text{ }^\circ\text{C}$ in Trifluoroethanol (TFE)/Water and TFE/Ethanol^a

%	TFE/water ^b	TFE/EtOH ^c
97	0.070^d	
90	1.03 ± 0.07	1.40 ± 0.01
80	7.54 ± 0.05	6.60 ± 0.04
70	12.5 ± 0.1	12.7 ± 0.3
60	35.1 ± 0.7	23.9 ± 0.3
50	81.5 ± 0.1	43.6 ± 0.1
30	87.1 ± 2.3	

^a As for Table 1. ^b Wt %. ^c Vol %. ^d Calculated by extrapolation of the following data: $10^3k/\text{s}^{-1}$ ($T/^\circ\text{C}$) 0.660 ± 0.001 (20.0); 0.327 ± 0.005 (10.0); 0.157 ± 0.006 (0.0); $\Delta H^\ddagger = 10.9 \text{ kcal/mol}$ and $\Delta S^\ddagger = -36 \text{ eu}$.

TABLE 4. Product (% Ester) and Selectivities (*S*, Eq 1) for Solvolyses of Chloroacetyl Chloride (3) at $-10.0 \text{ }^\circ\text{C}$ and for Phenylacetyl Chloride (4) at $0.0 \text{ }^\circ\text{C}^a$ in Ethanol/ and Methanol/Water

solvent ^a	3		4	
	% ester ^b	<i>S</i> ^c	% ester ^d	<i>S</i> ^c
95EtOH	90.3	1.6	93.0	2.3
90EtOH	84.9	2.0	89.3	3.0
80EtOH	79.8	3.2	81.6	3.6
60EtOH	65.9	4.2	65.4 ^e	4.1
40EtOH	46.8 ^f	4.3	37.6 ^c	2.9
20EtOH			15.7 ^{f,g}	2.4
90MeOH	97.5		94.6 ^f	
80MeOH	91.0	5.7	93.3	7.8
70MeOH	91.5 ^f		88 ^{e,h}	7.1
60MeOH	86.0	9.2	80.4 ^e	6.1
50MeOH	83 ^h	11		
40MeOH			59.9 ⁱ	5.0

^a Solvents are % v/v. ^b Determined by HPLC from at least duplicate analyses of duplicate samples, using an appropriate ester as internal standard; injected $100 \mu\text{L}$ of 4% solution of acid chloride in acetonitrile into 5.0 mL of solvolysis medium; typical average deviations $\pm 1\%$. ^c Calculated from eq 1, and the molarities of the bulk solvent concentrations; see Table 1, footnote a of ref 4a. ^d Calculated from the observed ester/acid area ratios, determined by HPLC from at least duplicate analyses of duplicate samples; injected $40 \mu\text{L}$ of 10% solution of acid chloride in acetonitrile into 5.0 mL of solvolysis medium; typical average deviations $\pm 1\%$. ^e First sample was from 10% solution, but duplicate sample was an injection of $100 \mu\text{L}$ of 4% solution of acid chloride. ^f Determined from a single sample. ^g Precipitate formed at $0 \text{ }^\circ\text{C}$ —analyzed after warming. ^h Average deviation $\pm 2\%$. ⁱ Injected $100 \mu\text{L}$ of 4% solution as first sample and $100 \mu\text{L}$ of 2% solution as “duplicate” sample.

from isodesmic reactions (eq 3, Table 6).



Discussion

Solvolysis Rate Constants and Selectivities. A plot of logarithms of rate constants for solvolyses of *p*-nitrobenzoyl chloride (**1**, $Z = \text{NO}_2$) at $25 \text{ }^\circ\text{C}$ vs solvolyses of chloroacetyl chloride (**3**) at $-10 \text{ }^\circ\text{C}$ is linear with a slope of 0.96 for solvents from 90% to 20% acetone/water, including ethanol/ and methanol/water mixtures (Figure 1); inclusion of data for the much slower solvolyses in TFE/water and TFE/ethanol gives a similar slope (1.09) and shows the high sensitivity of the solvolyses to solvent

TABLE 5. Calculated Energies (kcal/mol) for Chloride Ion Transfer between Acylium Ions (ZCO^+) and Acetyl Chloride (eq 2) at Three Levels of MO Theory^a

Z	HF/6-31G(d) ^b	B3LYP/6-31G(d) ^c	B3LYP/6-311G(d,p) ^d
H	27.5	31.0	30.1
Me	0.0 ^e	0.0 ^e	0.0 ^e
Et	-4.4	-4.7	-4.3
CH ₂ Cl	12.3	11.1	11.5
CH ₂ OMe	1.5	4.0	3.9
CH ₂ SMe	-0.5	-6.4	-5.9
CH ₂ Ph	-10.0	-12.5	-11.5
Ph ^f	-15.5	-17.7	-16.4
HO	30.0	25.7	24.5
MeO	(10.6) ^g	(9.1) ^g	(7.9) ^g
EtO	(-0.6) ^g		
MeS	3.4	0.4	0.9

^a Calculated from the total energies obtained using Gaussian 03, with fully optimized geometries for each level of theory. ^b Total energies (Hartrees) for HF/6-31G(d) calculations of individual species are in Table S1. ^c Total energies (Hartrees) for B3LYP/6-31G(d) calculations of individual species are in Table S2. ^d Total energies (Hartrees) for B3LYP/6-311G(d,p) calculations of individual species are in Table S3. ^e By definition. ^f Experimental thermochemical data give $\Delta H = -15.5 \pm 4.2$ kcal/mol (but see discussion). ^g Bond between the CH₂ and the oxygen atom in the cation is unusually long, so the O-alkyl bond is beginning to break.

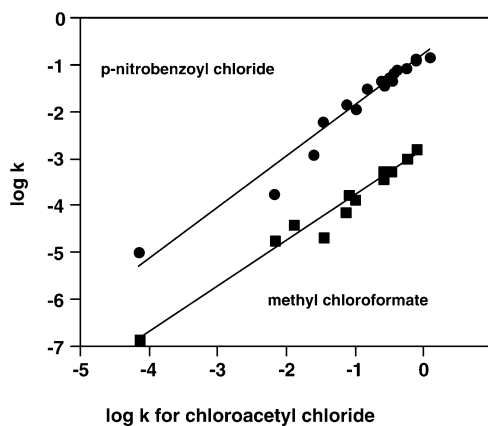
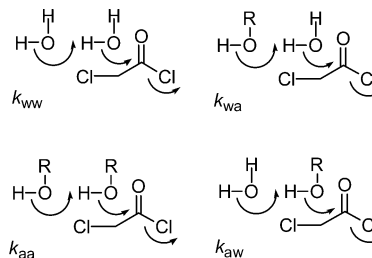
TABLE 6. Calculated Ground-State Stabilization Energies (kcal/mol) from Methyl Transfer between Acid Chlorides (ZCOCl) and Ethane (Eq 3) at Two Levels of Theory^a

Z	HF/6-31G(d) ^b	B3LYP/6-31G(d) ^c
H	-10.0	-10.6
Me	0.0 ^d	0.0 ^d
Ph	0.7	1.8
HO	16.1	15.7
MeO	15.5	14.7
MeS	-0.7	3.3

^a Calculated using Gaussian 03. ^b Total energies (Hartrees) for individual species are in Tables S1 and S4. ^c Total energies (Hartrees) for individual species are in Tables S2 and S4. ^d By definition.

nucleophilicity (N).^{20,21} On the same plot (Figure 1), logarithms of rate constants for solvolyses of methyl chloroformate at 40 °C also give a good linear correlation (slope = 0.98) for solvents including TFE mixtures. These results provide a link between rate constants for solvolyses of aroyl and acyl chlorides (containing electron-withdrawing substituents) and solvolyses of methyl chloroformates, known to react similarly to other chloroformates.^{7c}

Product selectivities (S , eq 1) for solvolyses of **3** are even higher than those for the much more hydrophobic substrate **1**, $Z = NO_2$.⁴ These results support other evidence^{3b} that preferential solvation of hydrophobic substrates by alcohol in alcohol/water mixtures is not the cause of high S values—if the true mole ratio of alcohol to water at the reaction site were significantly greater (e.g., 4-fold) than

**FIGURE 1.** Logarithms of rate constants for solvolyses of *p*-nitrobenzoyl chloride (**1**, $Z = NO_2$) at 25 °C and of methyl chloroformate (MeOCOC(1) at 40 °C vs solvolyses of chloroacetyl chloride (**3**) at -10 °C. For **1**, $Z = NO_2$, slope of the correlation line shown: 1.09 ± 0.05 ; $R = 0.98$, $n = 18$. Excluding the three TFE-containing solvent mixtures: slope = 0.96 ± 0.06 ; $R = 0.98$, $n = 15$; data from Tables 1 and 3 and refs 4b and 19. For methyl chloroformate (data from ref 20): slope = 0.98 ± 0.06 , $R = 0.98$, $n = 12$.**SCHEME 1.** Competing Third-Order Rate Constants for Solvolyses of Chloroacetyl Chloride (**3**) in Alcohol/Water Mixtures^a

^a The first letter of the subscript to the rate constant (k) refers to water (w) or alcohol (a) acting as a nucleophile and the second letter refers to the role of solvent as a general base.

that of the bulk solvent composition, then the true S would be lower (e.g., 4-fold). In contrast, solvolyses of acetyl chloride¹⁰ and **1**, $Z = OMe$,³ show much lower S values in ethanol/ and methanol/water (<2), almost independent of solvent composition for each binary alcohol/water mixture. Consequently, we will now further explore the possibility that variations in S values arise from mechanistic changes.

The relatively high KSIE for **3** in MeOH of 2.18 (Table 1, footnote c) is the same within experimental errors as the values of 1.8–2.3 for **1**, $Z = NO_2$,^{4b} for which a third-order mechanism (second-order in solvent) has been proposed.⁴ A very similar KSIE value in MeOH (2.17 ± 0.03) was observed for *n*-propyl chloroformate.^{7e} If one molecule of solvent acts as a nucleophile, and the other acts as a general base, then there are four possible third-order reactions in binary alcohol/water mixtures, with rate constants k_{ww} , k_{aw} , k_{wa} , and k_{aa} (Scheme 1).

Assuming kinetic control of product formation and third-order rate laws for formation of each product, the product ratio $E/A = [\text{ester}]/[\text{acid}]$ is then given by eq 4, where square brackets refer to molar concentrations. Rearrangement of eq 4 gives eq 5.

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(21) Kinetic data for solvolyses of **1**, $Z = NO_2$, are correlated by the equation: $\log(k/k_0) = 0.54Y_{Cl} + 1.78N_T + 0.1$, for details, see ref 2b. For methyl chloroformate: $\log(k/k_0) = 0.58Y_{Cl} + 1.58N_T + 0.16$ (ref 20). Data for **3** (Tables 1 and 3) are correlated by the equation: $\log(k/k_0) = 0.45Y_{Cl} + 1.54N_T + 0.16$.

$$E/A = \{k_{aw}[\text{alcohol}][\text{water}] + k_{aa}[\text{alcohol}]^2\} / \{k_{wa}[\text{alcohol}][\text{water}] + k_{ww}[\text{water}]^2\} \quad (4)$$

$$f(\text{rates}) = \{(E/A)k_{ww}[\text{water}]^2 - k_{aa}[\text{alcohol}]^2\} / [\text{alcohol}][\text{water}] = -(E/A)k_{wa} + k_{aw} \quad (5)$$

Values of k_{aa} and k_{ww} are obtained from the observed first-order rate constants in a pure solvent divided by the molar concentration of solvent.⁴ Plots of $f(\text{rates})$ vs E/A (eq 5) for ethanolsis of **3** are linear (Figure 2); the slope is $-k_{wa}$ and the intercept is k_{aw} (see legend to Figure 2). The sum of all four terms in eq 4 is the calculated first-order rate constant: e.g. for 40% ethanol/water, in which the rate reaches a maximum, $k_{\text{calc}} = 3.91 \times 10^{-1} \text{ s}^{-1}$ in good agreement with the observed value of $3.84 \times 10^{-1} \text{ s}^{-1}$. The calculations indicate that contributions from k_{aw} and k_{wa} are dominant, in part because the $[\text{alcohol}] \times [\text{water}]$ term is large. The mechanism (Scheme 1) also accounts for two unusual features of solvolyses of **3**: as water is added to alcohol, S increases as reactivity increases, and a rate maximum is reached in ca. 50 vol % alcohol.

The above results strongly support the third-order mechanism (Scheme 1) for solvolyses of **3** in aqueous alcohols. Adapting the same mechanism for solvolyses in acetone/water, values of k_{ww} can be obtained by dividing the observed first-order rate constants by $[\text{water}]^2$; for this calculation, we assume that acetone is a relatively inert solvent and has no significant role as a general base or as a nucleophile (however, it is possible that acetone could act as a weak general base catalyst^{4c}). A plot of the logarithms of calculated third-order rate constants for solvolyses of **3** in acetone/water vs Grunwald–Winstein Y values is linear (Figure 3), with the same slope for the same range of solvents as for solvolyses of **1**, $Z = \text{NO}_2$.^{4a}

If solvolyses of **4** in acetone/water are also assumed (for comparison) to be second-order in water solvent, the calculated third-order rate constants (Figure 3) show a shallow U-shaped curve or two linear regions, with a minimum around $Y = 0$. A very similar result was observed for solvolyses of **1**, $Z = \text{Cl}$,^{1b} for which competing reaction channels were proposed. In addition to the third-order mechanisms (Scheme 1), which are relatively insensitive to changes in solvent ionizing power (Y), there is a competing reaction channel more sensitive to Y . Strong support for the competing mechanism is provided by the maxima in S values observed for solvolyses of **1**, $Z = \text{Cl}$, NO_2 , and H , in alcohol/water mixtures.¹

In contrast to the upward trend in S values for solvolyses of **3**, solvolyses of **4** show a maximum S in ethanol/water and a downward trend in methanol/water (Table 4), consistent with a change in mechanism; a similar but clearer maximum in S values was observed for solvolyses of **1**, $Z = \text{Cl}$.^{1b} Further support for mechanistic change can be obtained by comparing rate profiles for solvolyses of **3** and **4** in ethanol/water with those for solvolyses of acetyl chloride. If $\log(k/k_0)$ is plotted, where k_0 is the rate constant in 80% ethanol/water ($Y = 0$) as in typical Grunwald–Winstein plots,²² corrections are

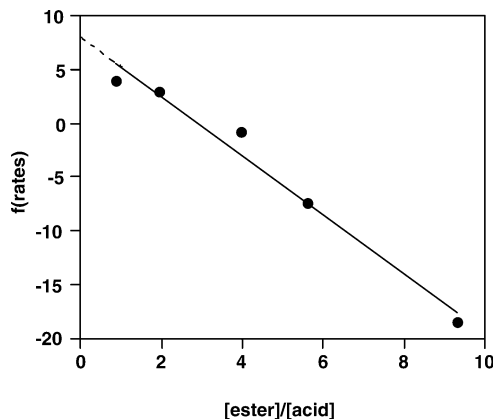


FIGURE 2. Evaluation of k_{wa} and k_{aw} from eq 5, based on the mechanism shown in Scheme 1 for ethanolsis of chloroacetyl chloride (**3**) at -10°C ; solvent concentrations are molarities from ref 4b. From data for pure solvents: $k_{aa} = 1.01 \times 10^{-2}/(17.14)^2 = 3.44 \times 10^{-4} \text{ M}^{-2} \text{ s}^{-1}$ and $k_{ww} = 3.5 \times 10^{-1}/(55.5)^2 = 1.1 \times 10^{-4} \text{ M}^{-2} \text{ s}^{-1}$. From the correlation line: slope (k_{wa}) = $(2.8 \pm 0.3) \times 10^{-4} \text{ M}^{-2} \text{ s}^{-1}$ and intercept (k_{aw}) = $(8.0 \pm 1.3) \times 10^{-4} \text{ M}^{-2} \text{ s}^{-1}$; $R = 0.989$.

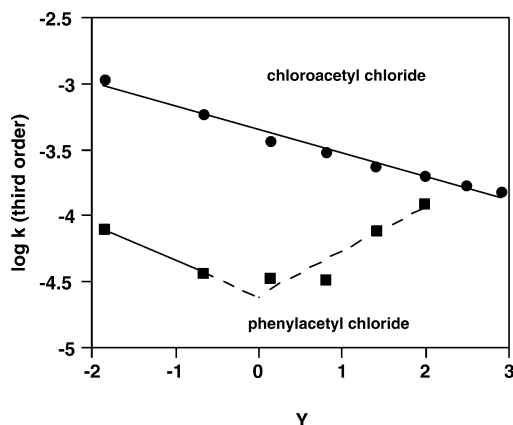


FIGURE 3. Plots of logarithms of calculated third-order rate constants for solvolyses of **3** at -10°C and **4** at 0°C in acetone/water vs Grunwald–Winstein Y values; kinetic data from Tables 1 and 2; Y values from ref 22. For **3**: slope = $m = -0.18 \pm 0.01$, intercept = -3.35 ± 0.02 , $R = 0.990$, $n = 8$.

made for differences in reactivity and the solvent effect on relative rates is obtained. Such plots are particularly useful if, as in the case of **4**, a mechanistic change occurs around $Y = 0$.

Logarithms of observed first-order rate constants for acetyl chloride (selected as a similarity model¹⁵ for the ionization reaction channel for solvolyses of acyl chlorides) give a precise linear plot vs Y (Figure 4), with slope $m = 0.63 \pm 0.02$, showing a larger dependence on solvent-ionizing power. In contrast, rate constants for solvolyses of **3** (selected as a similarity model for the third-order reaction channel for solvolyses of acyl chlorides) vary less than 1.5-fold from 90% to 20% ethanol/water. The rate profile for solvolyses of **4** is almost superimposable on that of **3** from ethanol to 80% ethanol/water ($Y = 0$), but then it diverges and the slope gradually increases until it is similar to that for solvolyses of acetyl chloride (Figure 4).

In the absence of the similarity model (**3**) for the third-order reaction channel, it could appear that there was

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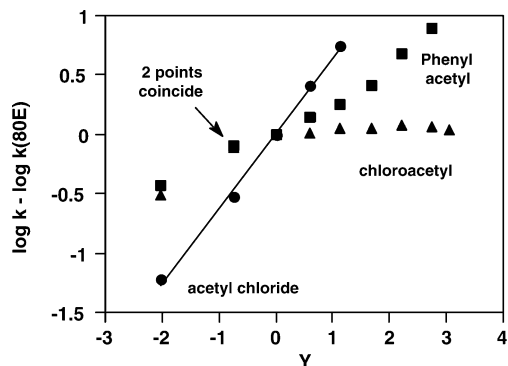


FIGURE 4. Grunwald–Winstein plots for solvolyses of acetyl chloride, chloroacetyl chloride (**3**) and phenylacetyl chloride (**4**) in ethanol ($Y = -2$) and in ethanol/water mixtures; 80E refers to 80% v/v ethanol/water ($Y = 0$); kinetic data from Tables 2 and 3 and ref 10; Y values from ref 22. For acetyl chloride: slope = $m = 0.63 \pm 0.02$, intercept = 0.02 ± 0.02 , $R = 0.998$, $n = 5$.

only one reaction channel for solvolyses of **4**. The plot for **4** (Figure 4) is related linearly to Y over the whole range of alcohol/water solvent compositions ($m = 0.27 \pm 0.02$, $R = 0.98$, $n = 8$); only on closer inspection is the shallow S-shape discernible. We previously reached the conclusion, based on a linear mY plot, that solvolyses of thiomethylacetyl chloride ($\text{MeSCH}_2\text{COCl}$) reacted by a single reaction channel;^{11c} however, the solvent effect is almost identical to that for **4**, except that the change in slope beyond $Y = 0$ is offset by about one unit of Y , and so thiomethyl acetyl chloride probably solvolyses by competing reaction channels in ethanol/water mixtures.

Theoretical Calculations and Gas-Phase Ion Chemistry. Useful mechanistic insights have been obtained by comparing experimental data for gas-phase ion chemistry with solvolytic reactivity. Relative rates of solvolyses of *tert*-butyl and 2-propyl halides are solvent dependent, and in weakly nucleophilic media approach the value of 10^8 expected from the cation stabilities in the gas phase.²⁴ Relative rates of 1-adamantyl and *tert*-butyl solvolyses increase in less nucleophilic media, and 1-adamantyl becomes of comparable or greater reactivity than *tert*-butyl (as expected from gas-phase ion chemistry; contrary to expectations based on “unfavorable” bridgehead cations).²⁵ Increases in relative rates in more nucleophilic media can be explained by nucleophilic solvent assistance (S_N2 character) in 2-propyl solvolyses, and (to a smaller extent) *tert*-butyl solvolyses.^{24,25}

Rates of solvolyses of para-substituted acid chlorides in TFE show about the same substituent effects as the appearance potentials of acylium ions produced by gas-phase fragmentation of acetophenones, so the solvolyses in TFE were thought then to be S_N1 reactions.^{19b} However, later independent theoretical investigations of para-substituted acylium ions by HF/6-31G(d)^{2a} and B3LYP/

TABLE 7. Comparisons of Calculated and Experimental Energies (kcal/mol) for Chloride Ion Transfer from *tert*-Butyl Chloride to the Acetyl Cation (Eq 6)

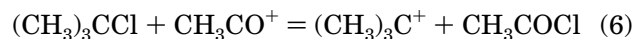
theory/method	calculated	experimental ^a
G3 ^b	-0.3	-1.2 ^c
B3LYP/6-311G(d,p) ^d	-8.0	(3.5 ± 3) ^e
B3LYP/6-31G(d) ^d	-10.7	
HF/6-31G(d) ^d	-5.4	

^a Experimental values are calculated from enthalpies of formation of each of the four species in eq 6. ^b Ref 17. ^c Thermochemical data from ref 10, except for a revised value for the acetyl cation; the previous value of 152 ± 1 kcal/mol (ref 10) was reevaluated (ref 29) to give a new recommended value of 156.7 kcal/mol; this was the value we chose, and it is in good agreement with a recent value of 157.6 ± 0.3 kcal/mol, obtained by threshold photoelectron photoion coincidence (ref 30). ^d This work, using total energies (Tables S1–S4), excluding small corrections for differences in ZPE. ^e Using pre-1996 data in ref 10.

6-311G(d,p)²⁶ DFT methods agreed well but showed greater substituent effects than those observed from appearance potentials; the difference in stability between *p*-OMe and *p*-NO₂ substituted benzoyl cations was 23.75^{2a} or 21.59²⁶ kcal/mol from theory, but only ca. 15 kcal/mol from experiment.^{19b} The discrepancy can be explained (at least in part) by the greater ionization probabilities of electron-rich aromatic compounds, one of the factors not accounted for in the semilog method for measuring appearance potentials.²⁷

Appropriate experimental data were not available for the chloroacetyl cation.²⁸ Consequently, to try to overcome the problems associated with the lack and/or inadequacy of experimental data for acylium ions, theoretical results were obtained (Table 5). A minor difference between the two theoretical treatments^{2a,26} (discussed above) is that only the later one²⁶ included correction for changes in zero-point energies (ZPE); published data²⁶ show that neglect of differences in ZPE introduces small errors (up to 0.3 kcal/mol).

A recent G3 MO calculation¹⁷ giving -0.3 kcal/mol for the enthalpy of chloride ion transfer from *tert*-butyl chloride to the acetyl cation (eq 6) is in good agreement with the latest experimental value of -1.2 kcal/mol (Table 7). These results provide an important reference point for mechanistic discussions of acyl halides because they confirm that the acetyl cation is of comparable stability to the *tert*-butyl cation; consequently, S_N2/S_N1 reaction channels could operate in corresponding solvolyses.^{10,17}



Energies calculated for eq 6 from the three levels of theory we used (Table 5) vary by 5 kcal/mol, and are at least 4 kcal/mol more negative than the best available values (Table 7). Differences in predicted energies between DFT and higher level methods (e.g. MP2) have recently been noted in calculations for cationic intermedi-

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ates involved in the nitration of toluene.³¹ Although similar bonds are present on both sides of eq 7 (isodesmic reactions), the reaction involves changes in hybridization (i.e. it is not homodesmotic).^{26,32} Consequently, caution will be needed in interpreting our calculations (Tables 5 and 6), especially for reactions which are not homodesmotic (e.g. for chloroformates) and/or when different MO methods give significantly different numerical values.

Experimental data for chloride ion transfer from benzoyl chloride to the acetyl cation are available, but data for the benzoyl cation have not been re-examined and corrected for precursor internal energy.²⁹ If we use the older thermochemical data,^{14,10} and we do not correct the data for either acetyl or benzoyl cations, we obtain $\Delta H = -15.5 \pm 4.2$ kcal/mol, in good agreement with the three calculated values ($Z = \text{Ph}$, Table 5). All three calculations indicate that the chloroacetyl cation is about 12 kcal/mol less stable than the acetyl cation ($Z = \text{CH}_2\text{Cl}$, Table 5). As expected, smaller cations (e.g. H-substituted) are less favorable, and larger cations (e.g. Ph-substituted) are favored. The large substituent effect for chloroformates (ROCOCl, e.g. $Z = \text{OH}$, OMe, OEt in Table 5) appears to be associated with fragmentation of the ROCO⁺ cation to R⁺ and CO₂.

The proposal³³ that the low reactivity of chloroformates (ROCOCl) could be due in part to stabilization of the ground state of neutral chloroformates (e.g. by resonance interactions between RO and CO) is now supported by calculations—a stabilization energy of ca. 15 kcal/mol is calculated for $Z = \text{OH}$ and OMe (Table 6).

Replacement of the alkyl-oxygen by sulfur favors the ionization channel,^{7b} as the cation is more favorable (Table 5). Ethyl thiochloroformate (EtSCOCl) is thought to hydrolyze by the ionization reaction channel, and in water at 25 °C is over 100 times more favorable kinetically than the addition–elimination channel for EtOCOCl.^{7b} Although the ground-state effect is calculated to be small for thiochloroformates (Table 6), EtOCOCl is slightly more reactive than EtSCOCl in ethanol.^{7b}

Conclusions

Rates and products of solvolyses of chloroacetyl chloride (**3**) are remarkably similar to those of *p*-nitrobenzoyl chloride (**1**, $Z = \text{NO}_2$) in selectivity (*S*, eq 1), KSIE (MeOH/D), low sensitivity to solvent ionizing power, and high sensitivity to solvent nucleophilicity. Solvolyses of methyl²⁰ and *p*-nitrophenyl chloroformates²³ are also very similar (Figure 1). All of the reactions fit a third-order addition/elimination mechanism, involving attack by a solvent nucleophile assisted by another molecule of solvent acting as a general base (Scheme 1).

Mechanistic changes from addition/elimination (Scheme 1) to S_N2/S_N1 reaction channels can be explained by an

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increase in stability of incipient acylium ions. Nucleophilic attack at carbonyl carbon is favored when the acylium ion is destabilized. The chloroacetyl cation is calculated to be 12 kcal/mol less stable than the acetyl cation (Table 5), and the *p*-nitrobenzoyl cation is 12–15 kcal/mol less stable than the benzoyl cation.^{2a,26} Consequently, an ionization mechanism becomes substantially more favorable in the absence of electron-withdrawing substituents (e.g. Cl or NO₂), and experimental evidence indicates that a change of reaction channel does occur for solvolyses of acetyl (Figure 4)¹⁰ and benzoyl chlorides.^{1,2} Acylium ions (ROCO⁺) from chloroformates (ROCOCl) are susceptible to fragmentation to R⁺ and CO₂, so more electron-donating alkyl groups (R) favor mechanistic change. As the S_N2/S_N1 reaction channel involves direct heterolysis, it is more sensitive to solvent polarity, and so mechanistic changes will also be favored in more polar solvents.

Experimental Section

Materials. Chloroacetyl chloride (**3**, >98%) and phenylacetyl chloride (**4**, >98%) were used as obtained. Solvents for kinetic studies were dried and distilled by standard methods.¹ Solvents for product studies (ethanol and methanol) were AR or HPLC grades respectively, containing 0.01% water. Acetonitrile was a dried HPLC grade, containing 0.006% water. Water was glass-distilled. Solvolysis media were prepared as v/v solutions, mixed at room temperature, except for TFE/water mixtures prepared as % w/w; the water content of 97% w/w TFE/water was checked by Karl Fisher titration using HYDRANAL (5) titrant.

Kinetic Methods. Rate constants were determined using a rapid-injection, conductometric method.^{4b} A freshly prepared, dilute solution of the acid chloride in dry acetonitrile was injected into a rapidly stirred solution of the solvolysis medium. Increases in conductance were monitored automatically, and rate constants were calculated with the Origin 6.0 program, using the Guggenheim equation.^{11a} Traces of acid impurities do not affect the accuracy of measurements of rate constants, monitored from changes in conductance after a set mixing time (additional acid is formed as the reaction proceeds).

Product Studies. Acid chlorides were dissolved in dry acetonitrile, and were stored as stock 10 or 20% solutions for up to a few hours. Equimolar amounts of internal standards were added to the stock solutions for solvolyses of chloroacetyl chloride (methyl propionate for methanolysis and ethyl acetate for ethanolysis). More dilute solutions (4% and 2%—see footnotes to Table 4) were prepared by diluting the stock solutions, and were then used immediately. Experiments were initiated by injecting acetonitrile solutions into the thermostated solvolysis medium (5 mL) in a turbo-stirred apparatus;^{4b} usually multiple injections were made in rapid succession (e.g., 2 × 20 μL, or 2 × 50 μL, or 5 × 20 μL).

Analyses of quenched alcoholysis products were carried out to correct for acid impurities present in the chloroacetyl chloride stock solutions, after manipulations (including storage in dry acetonitrile). For each stock solution, yields of chloroacetyl esters were monitored by comparison of the area ratio with an internal standard and set to 100% for solvolysis in pure alcohols, so correcting for any acid impurities in the solutions of acid chloride in acetonitrile. It was necessary to check the calibrations (area ratios) about every 2 h, and to make small corrections for the changes due to slow decomposition of the acid chloride.

For the phenylacetyl solvolyses, accurate 40 μL aliquots of the 10% stock solutions in acetonitrile were injected into 5.00 mL of ethanol, methanol, or 40% acetonitrile/water to obtain standard solutions of the two ester products and the acid.

These samples were then analyzed immediately by HPLC at least in triplicate to obtain the areas of acid and ester signals (after injecting 10 μL of solution as accurately as possible). Ester/acid area ratios were calculated after correcting for the ca. 3% acid present after manipulations in the stock solutions. Duplicate samples were analyzed several hours later, and it was shown that no significant deterioration of the stock acetonitrile solution occurred. UV responses of the two esters and the acid were identical within ca. 2%.

Product mixtures were analyzed by injecting 10 μL of product solutions onto the HPLC column, as soon as possible after completion of the reaction, because the acid products were esterified in highly alcoholic, relatively acidic solutions. Ester exchange was also minimized in the same way, and also (for chloroacetyl solvolyses) by the choice of appropriate methyl or ethyl ester as internal standard. Additional details are given in the footnotes to Table 4.

The HPLC system comprised a 5 μm , 15 cm Apex Advantage ODS column, a pump (flow rate 1 mL/min), a detector and an integrator/plotter. Chloroacetyl solvolyses were monitored at 210 nm with absorbance FSD = 0.05 (eluent: 18% v/v methanol/water for methanolysis and 30% v/v methanol/water for ethanolysis). Under these conditions, the signal for chloride ion overlapped with that for chloroacetic acid; addition to the eluent of 10^{-2} M ammonium chlorides, or triethylamine hydrochloride was investigated, but did not lead to good quantitative data. Phenylacetyl solvolyses were monitored at 260 nm with absorbance FSD = 0.05 (eluent: 60% v/v methanol/water to which 1% glacial acetic acid was then added).

Calculations. Gaussian 03 calculations¹⁸ were performed at the Rutherford Appleton Laboratory (Columbus service), using the EPSRC National Service for Computational Chemistry software (NSCCS). Linear regressions were performed using Microsoft Excel; errors quoted in statistical analyses are the standard errors. Graphs were plotted using KaleidaGraph (Synergy Software, Reading, PA).

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Supporting Information Available: Total energies (Harteess) calculated by HF/6-31G(d) for acid chlorides (ZCOCl) and corresponding cations (ZCO⁺), Table S1. Total energies (Harteess) calculated by B3LYP/6-31G(d) for acid chlorides (ZCOCl) and corresponding cations (ZCO⁺), Table S2. Total energies (Harteess) calculated by B3LYP/6-311G(d,p) for acid chlorides (ZCOCl) and corresponding cations (ZCO⁺), Table S3. Other total energies (Harteess) required to calculate stabilization energies of neutral acid chlorides, Table S4. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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