S_N2 Mechanism for Alcoholysis, Aminolysis, and Hydrolysis of Acetyl Chloride

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First-order solvolysis rate constants are reported for solvolyses of acetyl chloride in methanol and MeOD, and in binary aqueous mixtures with acetone, acetonitrile, ethanol, methanol, and trifluoroethanol at 0 °C. Product selectivities (S = [MeCOOR]/[MeCOOH] × [water]/[alcohol]) are reported for solvolyses in ethanol/ and methanol/water at 0 °C. Solvolyses of acetyl chloride show a high sensitivity to changes in solvent ionizing power, consistent with C−Cl bond cleavage. As the solvent is varied from pure ethanol (or methanol) to water, S values and rate−rate profiles show no evidence for the change in reaction channel observed for solvolyses of benzoyl and trimethylacetyl chlorides. However, using rate ratios in 40% ethanol/water and 97% trifluoroethanol/water (solvents of similar ionizing power but different nucleophilicities) to compare sensitivities to nucleophilic attack, solvolyses of acetyl chloride are over 20-fold more sensitive to nucleophilic attack than benzoyl chloride. The solvent isotope effect of 1.29 (MeOH/MeOD) for acetyl chloride is similar to that for *p*-methoxybenzoyl chloride (1.22) and is lower than for benzoyl chloride (1.55). Second-order rate constants for aminolyses of acetyl chloride with *m*-nitroaniline in methanol at 0 °C show that acetyl chloride behaves similarly to *p*-methoxybenzoyl chloride, whereas benzoyl chloride is 40-fold more sensitive to the added amine. The results indicate mechanistic differences between solvolyses of acetyl and benzoyl chlorides, and an S_N2 mechanism is proposed for solvolyses and aminolyses by *m*-nitroaniline of acetyl chloride (i.e. these reactions are probably not carbonyl additions, but a strong sensitivity to nucleophilic attack accounts for their high rates).

S_N2 reactions at sp^2 carbon have recently been highlighted by calculations indicating that inversion at vinylic carbon may be feasible in solution.[1] Also, a concerted mechanism (necessarily with retention of stereochemistry) has been proposed from experimental studies of nucleophilic aromatic substitition at sp^2 carbon in (aryloxy)triazines.[2] Although the classical test for inversion cannot be applied to reactions at acyl sp^2 carbon, kinetic[3−6] and theoretical[7] evidence for concerted mechanisms is accumulating, especially for nucleophilic substitutions at acyl carbons having good leaving groups. Concerted mechanisms at acyl carbon may be further classified as either S_N2 or carbonyl addition[6,7] and usually occur when the tetrahedral intermediate becomes too unstable to exist,[3b] i.e. the reactions are carbonyl additions (with development of negative charge on the carbonyl oxygen). We now report rate and product data in support of an S_N2 mechanism (involving in-plane nucleophilic attack and development of positive charge on the carbonyl oxygen) for alcoholysis, aminolysis, and hydrolysis of acetyl chloride.

As acetyl chloride is relatively unhindered, it may have been expected that substitution would occur via tetrahedral intermediates.[4,8,9] Having only a methyl group as substituent, acetyl chloride would not be expected to be influenced by the cation-stabilizing effects which are known to lead to dissociative reactions of aroyl halides (mesitoyl chloride,[10,11] *p*-methoxybenzoyl chloride[11] and *p*-(dimethylamino)benzoyl fluoride[12]), and of carbamoyl chlorides (*N*,*N*-dimethylcarbamoyl chloride[13] and *N*,*N*-diphenylcarbamoyl chloride[14]).

However, solvolyses of acyl chlorides in the presence of an electrophilic catalyst such as phenol may proceed via an ion pair $(CH_3CO)^+$ $(ClHOPh)^-$, and solvolyses in methanol were thought to proceed via a loose S_N2 transition state with high carbocation character.[5c,d] Also, earlier work using Grunwald−Winstein Y values to compare rates of solvolyses in aqueous mixtures with those for corresponding solvolyses of *tert*-butyl chloride, led to the surprising conclusion that acetyl chloride hydrolyzed by an "ionization" mechanism.[4] In this and many other early studies of solvolyses in mixed solvents, acetone/water and dioxan/water mixtures were chosen, and so only one stable product was observed.[4,15]

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Table 1. Solvolysis Rate Constants (k/s^{-1}) for Acetyl Chloride in Binary Aqueous Mixtures at 0.0 °C[a]

composn (% v/v)	cosolvent			
	acetone	acetonitrile	ethanol	methanol
100			1.83×10^{-2} [b]	$(1.08 \pm 0.02) \times 10^{-1}$
90	6.02×10^{-3} [d]	$(1.52 \pm 0.01) \times 10^{-2}$	$(9.31 \pm 0.18) \times 10^{-2}$	$(2.36 \pm 0.05) \times 10^{-1}$
80	$(4.71 \pm 0.18) \times 10^{-2}$	$(1.34 \pm 0.01) \times 10^{-1}$	$(3.05 \pm 0.10) \times 10^{-1}$	$(5.99 \pm 0.18) \times 10^{-1}$
70	$(2.17 \pm 0.10) \times 10^{-1}$	$(4.73 \pm 0.05) \times 10^{-1}$	$(7.9 \pm 0.1) \times 10^{-1}$	1.54 ± 0.06
60	7.6×10^{-1} [c,e]	1.25 ± 0.08[f]	1.7[c,g]	3.3[c,h]
50	2.9[c,i]			

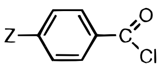
[a] Determined conductimetrically at least in duplicate, except where stated otherwise; errors shown are average deviations; for values in 2,2,2-trifluoroethanol/water, see Table 5. [b] Reference 21. [c] Calculated from data at lower temperatures. [d] Interpolated from data given in ref 15a. [e] Kinetic data at other temperatures (T/°C, k/s^{-1}): −15.0, $(1.64 \pm 0.1) \times 10^{-1}$; −10.0, $(2.77 \pm 0.2) \times 10^{-1}$; −5.0, $(4.66 \pm 0.23) \times 10^{-1}$; $\Delta H^{\ddagger} = 13.8$ kcal/mol, $\Delta S^{\ddagger} = -8.2$ cal/mol deg. [f] Quadruplicate measurement. [g] Kinetic data at other temperatures (T/°C, k/s^{-1}): −20.0, $(2.43 \pm 0.18) \times 10^{-1}$; −10.0, $(6.58 \pm 0.05) \times 10^{-1}$; $\Delta H^{\ddagger} = 12.6$ kcal/mol, $\Delta S^{\ddagger} = -11.2$ cal/mol deg. [h] Kinetic data at other temperatures (T/°C, k/s^{-1}): −15.0, $(7.1 \pm 0.2) \times 10^{-1}$; −10.0, 1.21 ± 0.05; $\Delta H^{\ddagger} = 13.9$ kcal/mol, $\Delta S^{\ddagger} = -5.2$ cal/mol deg. [i] Kinetic data at other temperatures (T/°C, k/s^{-1}): −10.0, 1.02 ± 0.02; −5.0, 1.73 ± 0.10; $\Delta H^{\ddagger} = 14.3$ kcal/mol, $\Delta S^{\ddagger} = -4.0$ cal/mol deg.

More recently, using new mechanistic criteria, considerable progress has been made by investigating solvolyses in alcohol/water mixtures: e.g., studies of trifluoroethanol/water mixtures have led to a better understanding of the role of solvent as nucleophile in heterolytic reactions,[16] and studies of product selectivities in alcohol/water mixtures have provided evidence of competing reaction mechanisms for solvolyses of both carboxylic acid chlorides[17a,c] and sulfonyl chlorides.[17d,e] Also, improved linear free energy relationships are now sensitive probes of nucleophilic solvent assistance even for predominantly dissociative reactions.[13b,14b] Solvent isotope effects in methanol are also proving useful for assessing the role of alcohol solvent as general base catalyst,[18] paralleling previous work with H_2O/D_2O mixtures in organic solvents.[19]

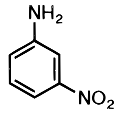
These new mechanistic criteria have not previously been applied to solvolyses of acetyl chloride. We now report kinetic solvent isotope effects in methanol and rate and product data for solvolyses of acetyl chloride in alcohol/water mixtures. We then compare mechanistic criteria based on these data with corresponding data for solvolyses of trimethylacetyl (**1**), benzoyl (**2**, Z = H), and *p*-methoxybenzoyl chloride (**2**, Z = OMe). To gain some insights into the influence of stronger nucleophiles, aminolyses by *m*-nitroaniline (**3**) are also investigated.

$(CH_3)_3CCOCl$

(1)



(2)



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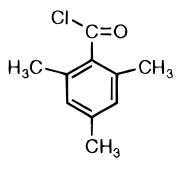

(4)

Results

First-order rate constants were determined by the fast response conductimetric method, in which conductance changes are monitored immediately after injecting microliter amounts of the substrate in dilute solution in a relatively inert solvent such as acetonitrile into milliliter amounts of the rapidly-stirred, thermostated solvolysis medium.[17a] Data for solvolyses in acetone/, acetonitrile/, ethanol/, and methanol/water mixtures are given in Table 1. Activation parameters for some of these solvolyses are given in footnotes to Table 1 and are similar to those previously reported.[15a]

Products of solvolyses of acetyl chloride (MeCOCl) in alcohol/water are the ester (MeCOOR) and the acid (MeCOOH). Product analyses were performed using reverse phase high performance liquid chromatography (HPLC) to determine the % yield of ester, and the % yield of acid was then determined by difference. We were unable to obtain a satisfactory separation of acetic acid from the solvent peaks either by ionization suppression or by ion pair chromatography.[20] Product selectivities (defined by eq 1, based on molar concentrations of products and solvents) for solvolyses of acetyl chloride are given in Table 2.

$$S = [\text{MeCOOR}]/[\text{MeCOOH}] \times [\text{water}]/[\text{alcohol}] \qquad (1)$$

Our S value for solvolyses in 50% ethanol/water is 20% higher than a value we calculated from the literature (Table 2, foootnote b). These reactions are so rapid that there may be some dependence on the method of mixing, as we have observed earlier for solvolyses of mesitoyl chloride (**4**).[11] However, acetyl chloride is much more readily soluble than mesitoyl chloride, so mixing problems are less likely to be significant.

Pseudo-first-order rate constants for reactions of acetyl chloride and benzoyl chloride with *m*-nitroaniline in

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Table 2. Selectivity Values (eq 1) for Solvolyses of Acetyl Chloride in Alcohol/Water Mixtures at 0 °C[a]

cosolvent (% v/v)	alcohol	
	ethanol	methanol
90	1.05 ± 0.03	1.50 ± 0.14
80	1.08 ± 0.05	1.79 ± 0.07
70	1.04 ± 0.02	1.87 ± 0.06
60	0.98 ± 0.01	2.08 ± 0.13
50	1.17 ± 0.04^{b}	1.86 ± 0.13
40	1.20 ± 0.05	1.99 ± 0.03
30	1.16 ± 0.03	2.02 ± 0.07
20	1.30 ± 0.05	2.02 ± 0.07
10	1.35 ± 0.01	2.03 ± 0.05

[a] Calculated from the molar ratios of solvents given in Table 1 of ref 22, and from the ester/acid molar ratios determined by HPLC analyses of 10^{-2} M solutions; measurements were made by duplicate analyses of at least two independent solutions and errors shown are average deviations. [b] A value of $S = 0.98$ can be calculated from the fraction of ester (0.233) obtained from the difference between titrations for acid and for chloride ion (ref 21).

Table 3. Pseudo-First-Order Rate Constants (k/s^{-1}) for Aminolysis by *m*-Nitroaniline of Acetyl and Benzoyl Chlorides in Methanol at 0.0 °C[a]

[amine]/M	MeCOCl[b]	PhCOCl
0	$(1.08 \pm 0.02) \times 10^{-1\,c}$	$(4.66 \pm 0.04) \times 10^{-4}$
3.92×10^{-3}	$(1.24 \pm 0.02) \times 10^{-1}$	$(2.78 \pm 0.01) \times 10^{-3}$
6.5×10^{-3}	$(1.43 \pm 0.01) \times 10^{-1}$	$(4.34 \pm 0.13) \times 10^{-3}$

[a] Determined conductimetrically in duplicate with amine in at least 10-fold excess; errors shown are average deviations; calculated second-order rate constants are given in Table 5. [b] Additional data at other amine concentrations (k/s^{-1}, [amine]/M): $(1.21 \pm 0.01) \times 10^{-1}$, 3.15×10^{-3}; $(1.31 \pm 0.01) \times 10^{-1}$, 5.02×10^{-3}; $(1.40 \pm 0.01) \times 10^{-1}$, 6.21×10^{-3}; $(1.47 \pm 0.01) \times 10^{-1}$, 8.16×10^{-3}; $(1.70 \pm 0.02) \times 10^{-1}$, 12.23×10^{-3}; $(1.90 \pm 0.01) \times 10^{-1}$, 16.0×10^{-3}. [c] From Table 1.

Table 4. Solvent Dependence of Rate Constants for Aminolysis by *m*-Nitroaniline of Benzoyl Chloride in Methanol/Water Mixtures at 0.0 °C[a]

solvent[b]	[amine]/M	k/s^{-1}	k_{am}/M^{-1} s^{-1}
MeOH[c]	0	$(4.66 \pm 0.04) \times 10^{-4}$	0.60 ± 0.01
80% MeOH	0	$(1.25 \pm 0.01) \times 10^{-3}$	1.41 ± 0.01
	3.98×10^{-3}	$(6.83 \pm 0.10) \times 10^{-3}$	
	6.12×10^{-3}	$(9.9 \pm 0.2) \times 10^{-3}$	
60% MeOH	0	$(2.73 \pm 0.02) \times 10^{-3}$	4.17 ± 0.12
	3.98×10^{-3}	$(1.86 \pm 0.01) \times 10^{-2}$	
	7.13×10^{-3}	$(3.25 \pm 0.03) \times 10^{-2}$	
50% MeOH	0	$(4.66 \pm 0.04) \times 10^{-3}$	7.4 ± 0.3
	3.96×10^{-3}	$(3.27 \pm 0.06) \times 10^{-2}$	
	6.04×10^{-3}	$(4.97 \pm 0.12) \times 10^{-2}$	
40% MeOH	0	$(7.82 \pm 0.02) \times 10^{-3}$	13.1 ± 0.4
	3.91×10^{-3}	$(6.14 \pm 0.05) \times 10^{-2}$	
	7.36×10^{-3}	$(1.04 \pm 0.02) \times 10^{-1}$	
20% MeOH	0	$(2.72 \pm 0.08) \times 10^{-2}$	27.8 ± 0.7
	3.84×10^{-3}	$(1.37 \pm 0.03) \times 10^{-1}$	
	5.70×10^{-3}	$(1.85 \pm 0.20) \times 10^{-1}$	

[a] Pseudo-first-order rate constants (k/s^{-1}) determined conductimetrically in duplicate with amine in at least 10-fold excess; errors shown are average deviations; second-order rate constants (k_{am}/ M^{-1} s^{-1}) are calculated from the slope of a plot k vs amine concentration. [b] Solvents are % v/v methanol/water. [c] Data from Table 3.

methanol at 0 °C are given in Table 3, and the solvent dependence of this reaction is investigated for benzoyl chloride (Table 4). Additional kinetic data for solvolyses of acetyl chloride in MeOD and in trifluoroethanol/water are given in Table 5.

Table 5. Comparisons of Kinetic Data and Mechanistic Criteria for Solvolyses and Aminolyses with *m*-Nitroaniline of Acetyl and Benzoyl Chlorides at 0.0 °C

parameter	MeCOCl[b]	PhCOCl
k (MeOH)/s$^{-1\,a}$	$(1.08 \pm 0.02) \times 10^{-1}$	$(4.66 \pm 0.04) \times 10^{-4}$
k (MeOD)/s$^{-1\,b}$	$(8.34 \pm 0.03) \times 10^{-2}$	
k (MeOH)/k (MeOD)	1.29 ± 0.03	1.55^{c}
k (97% TFE)/s$^{-1\,b,d}$	$(5.73 \pm 0.10) \times 10^{-2}$	
k (70% TFE)/s$^{-1\,b,d}$	1.44 ± 0.11	
k (40% EtOH)/s^{-1}	18^{e}	
k (97% TFE)/ k(40% EtOH)	3.2×10^{2}	13.2^{f}
k_{am}/M^{-1} s$^{-1\,g}$	5.23 ± 0.2	0.60 ± 0.01
k_{am}/k (MeOH)	48.4	1.29×10^{3}

[a] From Table 3. [b] Determined conductimetrically in duplicate. [c] Data at 25 °C from ref 18c. [d] Solvent is % w/w 2,2,2-trifluoroethanol/water. [e] Extrapolated using the ethanol/water data shown in Table 6. [f] Calculated for 25 °C from data given in ref 5a. [g] Calculated for methanol as solvent from data given in Table 3.

Discussion

Intrepretation of *Y* and *S* Values. Solvent effects on reaction rates depend on solvation changes between initial and transition states, and rates can be correlated with solvolyses of model substrates such as *tert*-butyl chloride in the case of *Y* values,[23] or with solvent parameters derived from spectroscopic measurements.[24] Solvation of initial states (obtained from solubility data) includes the work required to make the substrate's cavity in the solvent. Detailed analyses of solvent effects on rates for *tert*-butyl halides indicate that the solubility parameter contributes almost equally to initial and transition state solvation.[24] Hence, as might have been expected,[25] there is substantial cancelation of solvation effects present in both initial and transition states. A single reaction parameter (e.g., *Y*) can be used to compare solvolyses of substrates of interest with solvolyses of well understood model compounds or similarity models[26] (e.g., *tert*-butyl chloride in the case of *Y* values).

Initial state solvation of larger molecules such as adamantyl halides would be expected to show greater cavity or hydrophobic effects, but solvation effects remote from the reaction site would not be expected to interfere with those close to the reaction site; i.e. the tendency for initial and transition state effects to cancel[24] would be even greater for larger molecules, and the dominant effect would still be solvation changes (desolvation/resolvation) which occur close to the reaction site during the reaction. According to this model the size of the substrate is not a major factor in determining polar solvent effects on reactivity, and no unusual polar effects would be expected for solvolyses of a relatively small molecule such as acetyl chloride. However, smaller molecules are more susceptible to nucleophilic attack (see later).

S values (eq 1) are complimentary to *Y* values in that they monitor the product-determining step at the reaction site. For a wide range of substrates (adamantyl,[27] mesitoyl,[11] *p*-methoxybenzoyl,[11] and diphenylcarbamoyl derivatives[14b]), which react via solvent-separated ion pair intermediates, *S* values are almost constant over the range of solvent compositions from 10 to 90% ethanol and

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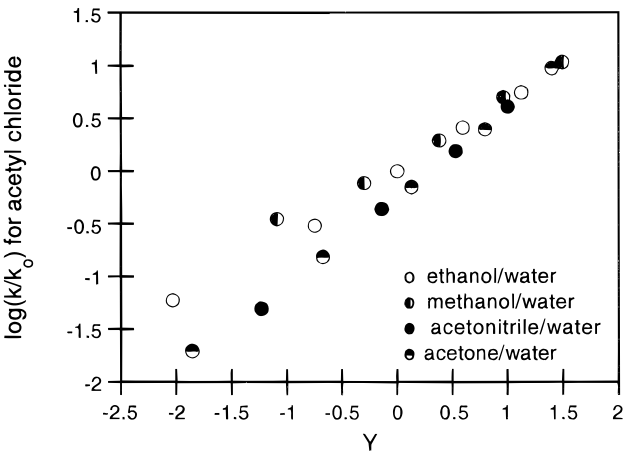

Figure 1. Correlation of logarithms of rate constants for solvolyses of acetyl chloride (relative to rate constants in 80% ethanol/water) at 0 °C vs *Y* values; kinetic data from Table 1 and *Y* values from refs 23a and 30a; the correlation line for acetone/water (slope, 0.90 ± 0.02, intercept, −0.28 ± 0.03, *r* = 0.999) was used to predict rate constants in 20% dioxane and water (see text).

methanol/water. These results imply that for these solvents, there are unlikely to be selective solvation effects close to the reaction site (for the betaine dye on which the $E_T(30)$ spectroscopic solvent polarity scale is based, preferential solvation of parts of the molecule is established for several binary solvents[28]).

Comparisons with Similar Solvolyses. Solvolyses of trimethylacetyl chloride (**1**)[17c] and benzoyl chloride (**2**, Z = H)[17d] in ethanol and methanol/water mixtures show maxima in plots of *S* (eq 1) *vs* solvent composition, and plots of logarithms of rate constants *vs* Grunwald Winstein *Y* values are nonlinear.[5b,17c,d] Also, a plot of log *k* for solvolyses of *p*-(dimethylamino)benzoyl fluoride shows a sharp "break"*vs* *Y* or Y_{Cl}.[12] These results are interpreted in terms of competing reaction channels;[5a,b,12,17c,d] one channel has a high sensitivity to solvent-ionizing powers involves a dissociative mechanism, and is favored in more highly aqueous media; the second may be a carbonyl addition process. In the dissociative process, heterolysis is favored if electron-donating groups are present, positive charge may be stabilized by the adjacent oxygen atom, and heterolysis may also be assisted by nucleophilic attack by solvent in the COCl plane. The second channel is favored by solvents of lower polarity and by electron-withdrawing groups;[5a,12,17d] nucleophilic attack may occur approximately perpendicular to the COCl plane, and a negative charge may develop on the oxygen atom; calculations indicate that departure of a good leaving group such as Cl^- may occur without the formation of a tetrahedral intermediate.[7b]

Grunwald−Winstein plots for solvolyses of acetyl chloride *vs* *Y* (Figure 1) or log (k/k_o) for *p*-methoxybenzoyl chloride (Table 6) show linear rate−rate profiles for each binary mixture, consistent with solvolyses via a single reaction channel for this range of solvents. Extrapolation of the data in acetone/water to 20% dioxane/water gives a rate constant of *ca.* 60 s^{-1} at 0 °C (*ca.* 600 s^{-1} at 27 °C) in fair agreement with the previously reported value of 292 s^{-1} in 24% dioxane/water at 27 °C, determined directly by stopped flow kinetics.[4] Our extrapolated value for solvolyses in pure water at 0 °C is *ca.* 220 s^{-1}. The various binary mixtures show "dispersion" into separate correlation lines for each solvent pair, attributed to minor differences in solvation adjacent to the reaction site for acetyl chloride and *tert*-butyl chloride.[18a,30]

Table 6. Correlation of log(k/k_0) for Solvolyses of Acetyl vs *p*-Methoxybenzoyl (2, Z = OMe) Chlorides in Aqueous Binary Mixtures[a]

cosolvent (n)[b]	slope	intercept	r
acetone (5)[c]	0.88 ± 0.01	0.07 ± 0.01	0.9999
acetonitrile (3)[d]	1.01 ± 0.02	−0.15 ± 0.01	0.9999
ethanol (5)[e]	0.87 ± 0.02	−0.03 ± 0.02	0.999
methanol (5)[f]	0.79 ± 0.03	−0.24 ± 0.03	0.998

[a] Kinetic data for acetyl chloride from Table 1; k_0 refers to solvolyses in 80% ethanol/water. [b] Number of data points (n). [c] Log(k/k_o) values for *p*-methoxybenzoyl chloride in acetone/water are 90A, −2.02; 80A, −0.99; 70A, −0.25; 60A, 0.39; 50A, 1.02; data from refs 11 and 29. [d] Log(k/k_o) values for *p*-methoxybenzoyl chloride in acetonitrile/water are 90An, −1.15; 80An, −0.22; 60 An, 0.76; data from ref 18a. [e] Log(k/k_o) values for *p*-methoxybenzoyl chloride in ethanol/water are EtOH, −1.34; 90E, −0.56; 80E, 0.00; 70E, 0.48; 60E, 0.94 (interpolated); data from refs 11 and 29. [f] Log(k/k_o) values for *p*-methoxybenzoyl chloride in methanol/water are MeOH, −0.31; 90M, 0.22; 80M, 0.71; 70M, 1.16; 60M, 1.60; data from ref 29.

Solvolyses of *p*-methoxybenzoyl chloride (**2**, Z = OMe) show no evidence for the dual reaction channels found for solvolyses of less electron rich aroyl chlorides in aqueous ethanol and aqueous methanol.[17d] Correlations with solvolyses of **2**, Z = OMe give slopes close to unity (Table 6), showing that solvolyses of acetyl chloride and **2**, Z = OMe, have similar high responses to changes in solvent-ionizing power, consistent with the polar S_N1-S_N2 reaction channel.[17d]

S values for acetyl chloride (Table 2) are approximately constant, tending to increase in more highly aqueous media. Solvolyses of **2**, Z = OMe, give constant *S* values about 30% smaller than for acetyl chloride, whereas *S* values for solvolyses of trimethylacetyl (**1**), *p*-methylbenzoyl (**2**, Z = Me), and benzoyl chlorides decrease from 80% alcohol to water. These results support deductions from rate−rate profiles (Figure 1) that there is *not* a change in reaction channel for solvolyses of acetyl chloride over this solvent range.

Other mechanistic criteria can be applied to further characterize the reactions of acetyl chloride. Solvolyses in trifluoroethanol are relatively slow (Table 5); choosing 40% ethanol/water as the nucleophilic solvent of almost the same ionizing power as 97% trifluoroethanol (deduced from solvolyses of adamantyl substrates for which solvent nucleophilicity is unimportant [16d]), the rate ratio *k* (40% EtOH)/*k* (97% TFE) is over 20-fold larger for acetyl chloride than for benzoyl chloride (Table 5). These results show that, in relatively polar solvents, solvolyses of acetyl chloride are over 20-fold more sensitive to solvent nucleophilicity than solvolyses of benzoyl chloride (*tert*-butyl chloride has a similar sensitivity to benzoyl chloride,[5b] and even **2**, Z = OMe, is slightly sensitive to solvent nucleophilicity[11]).

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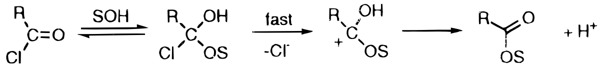
Acetyl chloride solvolyses about 10-fold faster than trimethylacetyl chloride (**1**)[15] and 150-fold faster than **2**, Z = OMe,[2a] but all are highly reactive. One possible explanation of the high reactivity is that reaction occurs via prior addition of solvent to the carbonyl group;[13a,31] fast addition followed by slow heterolysis seems unlikely,[8a] and alternatively the hydrated acid chloride (**5**, R = Me) may be formed in a slow step and may then dissociate rapidly to the highly stabilized cation (**6**),[31] but counterarguments are given below.



(**5**) (**6**)

We have calculated[5a] from the enthalpy of chloride ion exchange in the gas phase (R = Ph, eq 2) that direct heterolysis of benzoyl chloride to give the benzoyl cation is more favorable by 13 ± 7 kcal/mol than heterolysis of *tert*-butyl chloride to give the *tert*-butyl cation (a recent substantially revised value for ΔH_f of the *tert*-butyl cation[32] would increase this to 20 kcal/mol.). Hence, the 100-fold greater solvolytic reactivity of benzoyl chloride compared with *tert*-butyl chloride[5a,23b] parallels the stabilities of the corresponding carbocations, and a hydration mechanism via **5** is not necessary to explain the results.

A similar calculation for chloride ion exchange between acetyl chloride and *tert*-butyl chloride (R = Me, eq 2) gave $\Delta H = -3.5 \pm 3$ kcal/mol,[33] so heterolysis to give the acetyl cation is probably more favorable than heterolysis of *tert*-butyl chloride (or the same, considering experimental uncertainties). As solvolyses of acetyl chloride (e.g., in water at 0 °C) are over 10^5-fold faster than corresponding solvolyses of *tert*-butyl chloride,[4,23b] gas phase cation stabilities also parallel solvolysis rates in this case. Because the acetyl cation has fewer atoms over which to delocalize and stabilize charge,[37] solvolyses of acetyl chloride would probably benefit more than *tert*-butyl chloride from general solvation.

$$\mathrm{RCOCl} + (\mathrm{CH_3})_3\mathrm{C}^+ \rightleftharpoons \mathrm{RCO}^+ + (\mathrm{CH_3})_3\mathrm{CCl} \qquad (2)$$

The possibility that solvolyses of acetyl chloride proceed via a hydrate **5** can be excluded because the kinetic solvent isotope effect (e.g., MeOH/MeOD of 1.29, Table 5) is small and is similar to the value of 1.22 observed for solvolyses of *p*-methoxybenzoyl chloride (**2**, Z = OMe).[18a] Both S_N1 and S_N2 solvolyses give low solvent isotope effects,[18a,d,19b] but reactions involving hydration of a carbonyl group would be expected to show larger isotope effects (as observed for hydrolyses of chloroformates[3e,31a]).

An additional explanation of the high reactivity of acetyl chloride is nucleophilic solvent assistance to carbocation formation. Solvolyses in acetic acid[38] and trifluoroethanol (Table 5) are 50- and 300-fold slower, respectively, than solvolyses in more nucleophilic aqueous media having the same ionizing power, and from these data we estimate a large l value (*ca.* 0.8) for the sensitivity of solvolyses of acetyl chloride to solvent nucleophilicity.[39−42] An l value of 0.8 is similar to that for solvolyses of ethyl tosylate (solvolyses of methyl tosylate have $l = 1.0$ by definition).[40b] Solvolyses of dimethylcarbamoyl chloride are also strongly sensitive to both solvent nucleophilicity ($l = 0.6$ using the N_T scale) and solvent-ionizing power.[13b] A preliminary hydration mechanism via **5** would also be expected to show a high sensitivity to solvent nucleophilicity, but would not be so sensitive to solvent-ionizing power (Table 6).

Third-order kinetics has been observed for solvolyses of acetyl chloride in 95−99% acetone/water,[15b] and the mechanism may involve the second reaction channel with one solvent molecule acting as a general base catalyst to deprotonate the attacking nucleophile.[17a,22,43] Such catalysis can be detected from the increased solvent isotope effects;[18,19] the low MeOH/MeOD value of 1.29 for acetyl chloride (Table 5) is consistent with our proposal that solvolyses of acetyl chloride in alcohol/water mixtures involve only the dissociative reaction channel. As solvent-ionizing power is decreased, it would be expected that contributions from the second reaction channel would increase (e.g., in 95−99% acetone/water[15b,19c]).

Aminolyses. The mechanism of aminolysis will depend on substrate, solvent, and amine, and it is known that mechanistic changes can occur as the amine is varied because of changes in the the stabilities of tetrahedral intermediates.[9,44] However, aminolyses of benzoyl fluoride in water appear to be mechanistically very similar to solvolyses,[45] so there is a strong mechanistic link between solvolyses and aminolyses. The results discussed here refer primarily to mechanisms for *m*-nitroaniline (a relatively weak nucleophile) in relatively polar solvolysis media.

Aminolyses by *m*-nitroaniline (**3**) in methanol gave second-order rate constants, k_{am}, from the rate enhance-

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[33] Gas phase thermochemical data, ΔH_f/kcal/mol: CH_3COCl, −58.0 + 0.2 (ref 34); $(CH_3)_3C^+$, 170 ± 1 (refs 32 and 35), CH_3CO^+ 152 ± 1 (ref 36); $(CH_3)_3CCl$, −43.5 ± 0.6 (ref 34).

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[39] The l value may be estimated by assuming that major deviations from the mY equation are caused by solvent nucleophilicity (see the appendix and Table 5 of ref 40a). If Y_{Cl} is chosen as the most appropriate Y scale,[16d] the deviation for 97% trifluoroethanol is 320-fold (by comparison with data for 40% ethanol, Table 5). For acetic acid, the observed[38] rate constant at 25 °C of 8.5×10^{-3} s^{-1} is first corrected to 0 °C by dividing by 10; the Y_{Cl} value of acetic acid is −1.6,[16d] corresponding to *ca.* 95% ethanol/water, in which the rate constant for solvolysis of acetyl chloride is *ca.* 4×10^{-2} s^{-1} (interpolated from data in Table 1); hence, the deviation for acetic acid is 50-fold. If solvent nucleophilicity is represented by the N_{OTs} scale,[40b] l values of 0.89 and 0.72 are then obtained from the deviations of 320 and 50, respectively, i.e. the average l value of 0.8 would slightly underestimate the deviation for trifluoroethanol, as occurs for other solvolyses.[40b]

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[41] Alternatively, for solvolyses in acetic acid, 97% trifluoroethanol and six other aqueous and/or alcoholic solvents, using the $mY_{Cl} + lN_T$ eq,[42] $m = 0.68 \pm 0.03$ and $l = 0.86 \pm 0.04$ (we thank M. J. D'Souza for this result).

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ment caused by added amine (as <0.01 M of **3** is required, the medium effect of the amine is probably negligible[5a]). Kinetic data for aminolysis of benzoyl chloride in methanol/water mixtures show that, for a given solvent, the numerical values of the second-order aminolysis rate constants are consistently 1000−2000 times greater than the first-order methanolysis rate constants from methanol to 20% methanol/water (Table 4), showing that aminolysis rate constants closely follow the trend of solvolysis rate constants and that addition of the relatively weakly nucleophilic amine does not induce mechanistic change. Hence, rate enhancements caused by addition of small concentrations (<0.01 M) of **3**) to solvolysis media provide a useful guide to sensitivity of acid chlorides to nucleophilic attack.

In 50% dioxane/water at 25 °C, ratios of second-order rate constants for reaction of benzoyl chloride with aniline and water are 500-fold larger than corresponding values for acetyl chloride.[4] The rate constant, k_{am}, can be divided by the rate constant for methanolysis to correct for differences in reactivity between the various acid chlorides. Our k_{am}/k_{MeOH} ratios show that benzoyl chloride is over 26-times more sensitive to added amine than acetyl chloride in methanol at 0 °C (Table 5). The larger MeOH/MeOD solvent isotope effect of 1.55 for solvolyses of benzoyl chloride (Table 5), rate-rate profiles and product selectivities,[17d] are all consistent with a mechanistic change to the second reaction channel in methanol, and rates for benzoyl chloride in this reaction channel appear to be strongly sensitive to added amines.

In contrast, the k_{am}/k_{MeOH} value of 48 for acetyl chloride at 0 °C is similar to the value of 23 for *p*-methoxybenzoyl chloride (**2**, Z = OMe) at 25 °C,[11] and is much greater than the value of 1.1 for mesitoyl chloride at −10 °C.[11] The softer amine nucleophile appears to discriminate less than hydroxylic solvents between acetyl and *p*-methoxybenzoyl chlorides.

Conclusions

Linear rate−rate profiles (Figure 1), and the increase in product selectivities (S, Table 2) for solvolyses of acetyl chloride as the water content increases for aqueous ethanol/ and methanol/water mixtures are consistent with substitution via a single reaction channel. Our results provide a good opportunity for a detailed investigation of this reaction channel over a wide solvent range, in contrast to solvolyses of trimethylacetyl (**1**) and benzoyl chlorides which are much more complex, showing nonlinear rate−rate profiles and maxima in *S* attributed to dual S_N2-S_N1 and carbonyl addition reaction channels.[17c,d] *S* values (Table 2), k_{am}/k_{MeOH} and k_{MeOH}/k_{MeOD} (Table 5), and the high sensitivity to solvent-ionizing power (Table 6) for solvolyses of acetyl chloride are similar to those for *p*-methoxybenzoyl chloride (**2**, Z = OMe), which solvolyzes by an essentially S_N1 mechanism.[11,12] Hence, solvolyses of acetyl chloride occur by the polar S_N2-S_N1 reaction channel, rather than the carbonyl addition channel.

In significant contrast to solvolyses of *p*-methoxybenzoyl chloride, solvolyses of acetyl chloride show a large dependence on solvent nucleophilicity: e.g., solvolyses of acetyl chloride and of ethyl tosylate[40b] show similar sensitivities to solvent nucleophilicity ($l = 0.8$). The acetyl cation is of comparable stability to the *tert*-butyl cation and is significantly less stable than the benzoyl cation, judging by chloride exchange thermochemistry in the gas phase. However, in polar solvolytic media, acetyl chloride is more sensitive than benzoyl or *tert*-butyl chlorides to changes in solvent nucleophilicity and so is much more reactive. An S_N2 mechanism involving extensive cleavage of the C−Cl bond, accompanied by nucleophilic attack by solvent, is consistent with the experimental evidence for solvolyses in methanol and ethanol and in more polar solvents.

Addition of *m*-nitroaniline does not appear to induce mechanistic changes, and rate ratios k_{am}/k_{MeOH}, involving *m*-nitroaniline as nucleophile, provide an additional useful measure of the sensitivity of acid chlorides to nucleophilic attack.

Experimental Section

Chemicals. Acetyl chloride was distilled before use, but NMR showed about 0.5% of acid impurity (by comparison of the signal for MeCOOH with the ^{13}C satellite of MeCOCl). It was found previously that freshly-distilled acetyl chloride is partially hydrolyzed (up to 4%) during manipulations.[21] Ethyl and methyl acetates were distilled. *m*-Nitroaniline (mp 112−114 °C) was recrystallized from 30% ethanol−water.[46] Acetonitrile (Fisons HPLC grade) was dried and stored over molecular sieves. Ethanol for kinetics was distilled over magnesium ethoxide, methanol was dried and distilled (Fisons), and MeOD was obtained from Aldrich. AR methanol was used for HPLC.

Product Studies. From fresh 20% stock solutions of acetyl chloride in dry acetonitrile were injected 20.0 μL aliquots into 5.00 mL of solvolysis medium in a turbostirred vessel (*ca.* 10^{-2} M substrate).[17a] Injections into pure alcohols gave standard solutions of esters, and the integrated area of the chromatographic signal was assumed to represent 100% ester; hence the presence of traces of acid in the acetyl chloride (see above) is allowed for in the calibration. The area of the ester signal was then determined for other solvent compositions, and the % ester was calculated from (ester area for solution)/(ester area for pure alcohol) × 100. The % acid formed during solvolysis (excluding the trace of acid initially present) was assumed to be 100 − % ester. Product stability was established for solvolyses in 20 and 90% ethanol/water, for which the % ester was unchanged over several hours at 0 °C. Also, as negligible ester was detected after 2 h at 0 °C when acetic acid was added to 20, 50, and 90% alcohol/water mixtures containing 10^{-2} M HCl, a rapid equilibration can be excluded. An extra chromatographic peak of shorter retention time than the ester was reduced in size by sonication; possibly, the peak is due to carbon dioxide, although it was not completely removed from the methanol even by a reflux of 5 h.

Chromatography was carried out on a Spherisorb S5 ODS2 RP HPLC column (15 cm × 1/4 in.), having about 8000 plates. Eluents were 30% methanol/water for ethyl acetate and 10% methanol/water for methyl acetate, and the flow rate was 1 mL/min. The detector was set at 210 nm ($A = 0.02$). Each solution was prepared in duplicate, and HPLC analyses were determined in duplicate by injections of 20.0 μL of solvolysis medium using a Rheodyne Model 7125 injection valve. The detector was a Spectromonitor 3200, the pump was a Constametric 3200, and the integrator was a Hewlett Packard 3395.

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