Nucleophilic Substitution at Trigonal Carbon. Part 4.[1] Substituent Effects in the Reactions of Aliphatic Acyl Chlorides with Methanol and Phenol in Acetonitrile

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A previous study of the methanolysis and phenolysis of acetyl chloride in acetonitrile has been extended to the influence of the substitution of up to two chlorine atoms or up to three methyl groups into the acetyl chloride. For each of the substrates so obtained, the methanolysis continues to exhibit pathways with both second- and third-order kinetics. The introduction of up to two methyl groups has only a minor influence but an appreciable fall in the magnitude of both rate coefficients is observed upon introduction of the third methyl group. The introduction of chlorine atoms leads to fairly large accelerations, and a tightening of the loose S_N2 transition state or, possibly, a change to an addition–elimination mechanism. The phenolysis reactions, in the presence of methyl substituents, can be described at fairly low phenol concentrations in terms of second-order rate coefficients, which fall off slightly in value as methyl groups are introduced. In contrast to methanolysis, the phenolysis shows a large decrease in rate on introduction of an electron-withdrawing chlorine substituent; this reduction is consistent with a retardation of the electrophilically assisted ionization mechanism proposed for phenolysis of the parent substrate.

We have previously[1] reported our studies of the methanolysis and phenolysis of acetyl chloride in acetonitrile. It was proposed that both reactions proceeded through activated complexes with considerable carbocationic character. The methanol attacks as a nucleophile and the interaction is subject to general-base catalysis, either by a second molecule of methanol or by added chloride ion.[2] A loose transition state with a concerted S_N2 attack at the rearside of the carbon–chlorine bond was postulated. The phenol attacks initially as an electrophile[3] and assistance to chloride ion removal leads to a $(CH_3CO)^+$ $(ClHOPh)^-$ ion pair; collapse at the oxygen of the anion leads to ester formation. The attack by phenol was retarded by added chloride ion because the electrophilic capacity of phenol was destroyed by complexation.

The present communication considers the influence, upon the kinetics, of replacing the hydrogens of acetyl chloride by chloro or methyl substituents. The reactions of methanol with dichloroacetyl, chloroacetyl, propanoyl (propionyl), methylpropanoyl (isobutyryl), and dimethylpropanoyl (pivaloyl) chlorides and of phenol with chloroacetyl, propionyl, isobutyryl, and pivaloyl chlorides are described. The catalytic activity of chloride ion in the methanolysis of pivaloyl chloride has been investigated.

Earlier investigations of substituent effects upon the kinetics of acetylation reactions have been carried out under one standard condition, either of a constant concentration of alcohol[4,5] or phenol[6] in a relatively inert solvent or of solvolysis.[7–9] In contrast, we have studied each system over a range of methanol or phenol concentration and, for methanolysis, the second- and third-order rate coefficients for the formation of acid [equation (1)] have been considered separately [equation (2)].

$$\mathrm{RCOCl + MeOH \xrightarrow{CH_3CN} RCOOMe + HCl} \quad (1)$$

$$\mathrm{d[HCl]/d}t = k_2\mathrm{[RCOCl][MeOH]} + k_3\mathrm{[RCOCl][MeOH]}^2 \quad (2)$$

An attempt has been made to rationalize the substituent effects, with particular attention to the extent to which the mechanisms previously proposed[1] for methanolysis and for phenolysis of the parent acetyl chloride must be modified in the presence of substituents.

Results

The kinetics of acid production during the reactions of 0.02—0.48M-methanol with 0.04M-chloro- or -methyl-substituted acetyl chloride have been studied in acetonitrile at 0 °C. For each methanol concentration, experimental integrated second-order rate coefficients (k_2') were found to be constant over the extent of reaction followed (>40%); all the values from duplicate runs were averaged to give those reported, together with standard deviations, in Table 1. For each studied substrate, the initial specific rates of background solvolysis corresponded to <3% of the overall specific rates of acid formation in the presence of 0.04M-methanol. In one instance, reaction of chloracetyl chloride with 0.04M-methanol, it was shown that reducing the concentration of the acyl chloride by a factor of up to four did not significantly change the values for the second-order rate coefficient.

For each substrate, the experimental second-order rate coefficients (Table 1) increased linearly with methanol concentration and an analysis was carried out in terms of the concurrent operation of second- and third-order rate coefficients [equation (2)]; these rate coefficients (corresponding to the intercept and slope of the plot of experimental second-order rate coefficients against methanol concentration) are reported, together with those for acetyl chloride,[1] in Table 2. For the methyl-substituted series, the methanol concentration could be varied over a sufficiently wide range (up to 0.48M) for accurate determination of both k_2 and k_3 values. For the chloro-substituted series, the considerably faster reactions led to an upper limit for the methanol concentration of 0.16M, and the associated standard errors are much more pronounced.

For the reaction of 0.04M-pivaloyl chloride with 0.04M-methanol at 0.0 °C, a study was made of the effect of added tetraethylammonium chloride (0.005—0.08M). A large acceleration was observed and the integrated third-order rate coefficients [equation (3)], calculated assuming production of

$$\mathrm{d[HCl]/d}t = k_3\mathrm{[(CH_3)_3CCOCl][MeOH][NEt_4Cl]} \quad (3)$$

Table 1. Experimental second-order rate coefficients for the reactions of 0.0400M-acyl chlorides with methanol, in acetonitrile at 0.0 °C

	$10^4 k'_2$/l mol^{-1} s^{-1} as a function of R in RCOCl				
[MeOH]/M	Cl_2CH	$ClCH_2$	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$
0.0200	252 ± 13				
0.0400	261 ± 19	13.3 ± 0.8[a]	1.84 ± 0.04	1.97 ± 0.04	0.450 ± 0.016
0.0800	289 ± 18	13.6 ± 1.0	1.93 ± 0.04	2.03 ± 0.07	0.485 ± 0.010
0.120	385 ± 56				
0.160	408 ± 58	20.4 ± 1.4	2.20 ± 0.02	2.48 ± 0.06	0.572 ± 0.018
0.320			2.91 ± 0.04	3.22 ± 0.03	0.768 ± 0.017
0.480			3.49 ± 0.05	4.21 ± 0.08	0.904 ± 0.017
$10^7 k_1$/s^{-1} [b]	*c*	6.6 ± 0.8	0.90 ± 0.08	0.65 ± 0.06	0.50 ± 0.04
% Background[d]		1.24	1.22	0.83	2.78

[a] Values of 12.3 ± 0.5 and 14.1 ± 0.6 were obtained with 0.01 and 0.02M-$ClCH_2COCl$, respectively. [b] Specific rate of acid production in the absence of methanol. [c] Background solvolysis found to be much slower than rate of reaction in presence of methanol, but not studied quantitatively. [d] Percentage contribution from background solvolysis towards the overall rate of acid production in the presence of 0.0400M-methanol.

Table 2. Second- and third-order rate coefficients[a] for the reactions of 0.0400M-acyl chlorides (RCOCl) with methanol in acetonitrile at 0.0 °C

R in RCOCl	$10^4 k_2$/l mol^{-1} s^{-1}	$10^4 k_3$/l^2 mol^{-2} s^{-1}	k_3/k_2/l mol^{-1}
Cl_2CH	216 ± 18	1 227 ± 180	5.68 ± 0.96
$ClCH_2$	9.90 ± 2.03	62.9 ± 19.2	6.35 ± 2.35
CH_3[b]	1.68 ± 0.05	4.37 ± 0.18	2.60 ± 0.13
CH_3CH_2	1.64 ± 0.04	3.86 ± 0.12	2.35 ± 0.09
$(CH_3)_2CH$	1.67 ± 0.07	5.14 ± 0.25	3.08 ± 0.20
$(CH_3)_3C$	0.41 ± 0.01	1.06 ± 0.04	2.61 ± 0.12

[a] Calculated from $k'_2 + k_2 + k_3$[MeOH], using the data of Table 1; with associated standard errors. [b] From ref. 1.

Table 3. Experimental third-order rate coefficients[a] (l^2 mol^{-2} s^{-1}) for the reaction of 0.0400M-pivaloyl chloride with 0.0400M-methanol in acetonitrile at 0.0 °C, in the presence of tetraethylammonium chloride, plus values (k'_3) after correction for background rates of solvolysis[b] and values (k''_3) after additional correction for unassisted reaction[c]

[NEt_4Cl]	$10^2 k_3$	$10^2 k'_3$	$10^2 k''_3$
0.0050	6.57 ± 0.09	5.97	5.09
0.0100	5.23 ± 0.09	4.96	4.52
0.0200	4.96 ± 0.05	4.84	4.61
0.0400	4.28 ± 0.04	4.16	4.05
0.0800	3.42 ± 0.06	3.28	3.22

[a] d[HCl]/dt = k_3[$(CH_3)_3CCOCl$][MeOH][NEt_4Cl], with associated standard deviations. [b] Indicated concentration of salt present, but no methanol. [c] Reaction with 0.04M-methanol, in the absence of salt (from Table 1).

Table 4. Second-order rate coefficients for the reactions of 0.0400M-acyl chlorides with phenol, in acetonitrile at 0.0 °C

	$10^6 k'_2$/l mol^{-1} s^{-1} [a]		
[PhOH]/M	CH_3CH_2COCl	$(CH_3)_2CHCOCl$	$(CH_3)_3CCOCl$
0.960	9.48 ± 0.14 (9.43)	4.24 ± 0.04 (4.00)	0.63 ± 0.02 (0.58)
0.640	7.36 ± 0.09 (7.28)	3.69 ± 0.09 (3.34)	0.52 ± 0.02 (0.44)
0.480	6.45 ± 0.24 (6.34)	3.46 ± 0.12 (2.99)	0.48 ± 0.01 (0.38)
0.320	5.69 ± 0.10 (5.53)	3.66 ± 0.08 (2.95)	0.58 ± 0.02 (0.42)
0.160	5.18 ± 0.12 (4.86)	4.20 ± 0.08 (2.78)	0.71 ± 0.03 (0.39)
0.080	5.05 ± 0.18 (4.41)	5.73 ± 0.05 (2.89)	1.04 ± 0.07 (0.39)
$10^7 k_1$/s^{-1} [b]	0.51 ± 0.06	2.27 ± 0.34[c]	0.52 ± 0.03

[a] Values in parentheses are after subtraction of a contribution corresponding to background solvolysis (see footnote *b*). [b] Specific rate of acid production in the absence of phenol. [c] Runs with $(CH_3)_2CHCOCl$ were carried out using a batch of acetonitrile which had been purified several weeks earlier.

Table 5. Specific rates of acid production from 0.0400M-chloroacetyl chloride in acetonitrile at 0.0 and 25.0 °C in the presence of phenol[a]

[PhOH]/M	$10^7 k_1^{0\,°C}$/s^{-1}	$10^7 k_1^{25\,°C}$/s^{-1}
0.000	10.6 ± 0.5	21.6 ± 1.1
0.080	9.7 ± 1.4	
0.160	12.5 ± 1.4	22.8 ± 0.8
0.320	11.3 ± 2.2	23.8 ± 1.3
0.480	9.6 ± 2.1	30.7 ± 3.3
0.640	10.9 ± 2.5	29.5 ± 2.2
0.960	11.9 ± 0.8	36.4 ± 4.1

[a] Average values given; a slight fall off was observed as reaction progressed.

acid removes one entity of each reactant,[1] were constant for up to at least 50% of stoicheiometric reaction. Values reported in Table 3 are mean values using all of the determinations from duplicate runs. Especially for the lower concentrations of salt, the third-order rate coefficients were reduced slightly after corrections for background solvolysis and for unassisted methanolysis; these corrected values are also reported in Table 3.

Mean values for the experimental second-order rate coefficients for reaction of 0.04M-methyl-substituted acetyl chlorides with varying concentrations of phenol (0.08—0.96M), obtained by averaging all the integrated values from duplicate runs, are reported in Table 4. Values corrected for background solvolysis, which makes an appreciable contribution at the lower phenol concentrations, are also reported. Corresponding studies with chloroacetyl chloride, at 0.0 and 25.0 °C, are reported in Table 5. Especially at 0 °C, the addition of phenol causes little increase in the specific rate of acid formation above that observed in its absence.

Table 6 reports experimental second-order rate coefficients for reaction, in acetonitrile at 0.0 °C, of 0.04M-methanol with 0.04M-α-methylated acetyl chlorides in the presence of 0.04—0.96M-phenol. Values after subtraction of the component to be expected from reaction with the phenol alone (from Table 4) are also reported.

Discussion

Methanolysis.—Both the second- and third-order rate coefficients for methanolysis (Table 2) show appreciable increases as chlorine atoms are introduced into the methyl group of acetyl

Table 6. Second-order rate coefficients (k'_2)[a] for the reactions of 0.0400M-acyl chlorides with 0.0400M-methanol in the presence of phenol, in acetonitrile at 0.0 °C, and values (k''_2) after subtraction of the estimated component[b] due to reaction with phenol alone

(i) CH_3CH_2COCl

[PhOH]/M	0.0400	0.160	0.480	0.960
$10^4 k'_2$/l mol^{-1} s^{-1}	2.27 ± 0.05	2.57 ± 0.05	3.68 ± 0.14	7.00 ± 0.21
$10^4 k''_2$/l mol^{-1} s^{-1}	2.16	2.27	2.70	4.10

(ii) $(CH_3)_2CHCOCl$

[PhOH]/M	0.0400	0.0800	0.160	0.320
$10^4 k'_2$/l mol^{-1} s^{-1}	2.39 ± 0.04	2.43 ± 0.07	2.64 ± 0.03	2.86 ± 0.04
$10^4 k''_2$/l mol^{-1} s^{-1}	2.31	2.32	2.47	2.57

(iii) $(CH_3)_3CCOCl$

[PhOH]/M	0.0400	0.0800	0.160	0.320
$10^4 k'_2$/l mol^{-1} s^{-1}	0.494 ± 0.010	0.560 ± 0.005	0.579 ± 0.005	0.637 ± 0.016
$10^4 k''_2$/l mol^{-1} s^{-1}	0.476	0.539	0.551	0.591
[PhOH]/M	0.480	0.640	0.960	
$10^4 k'_2$/l mol^{-1} s^{-1}	0.678 ± 0.006	0.797 ± 0.005	0.863 ± 0.007	
$10^4 k''_2$/l mol^{-1} s^{-1}	0.620	0.714	0.711	

[a] d[HCl]/dt = k'_2[RCOCl][MeOH]. [b] Estimated from the data of Table 4.

Table 7. Relative specific rates of nucleophilic substitution reactions of acyl chlorides (RCOCl)

	R in RCOCl						
System[a]	Cl_3C	Cl_2CH	$ClCH_2$	CH_3	CH_3CH_2	$(CH_3)_2CH$	$(CH_3)_3C$
A		129	5.9	1.00	0.98	0.99	0.244
B		281	14.4	1.00	0.88	1.18	0.243
C		>50	24	1.00			
D			7.0	1.00	1.01	0.98	0.150
E			8.3	1.00	1.02	1.07	0.158
F	32.7	4.5	1.48	1.00	0.78	0.74	0.110
G		2 844	18.6	1.00	0.69	0.41	0.068
H		0.74	0.78		1.00		
I		3.15	2.93		1.00		
J	2.72	1.29	1.00				
K	130	52.3	16.7		1.00		
L				1.00	1.17		
M			5.8	1.00	0.94	0.63	0.117
N			<0.03		1.00	0.66	0.088
O		$<10^{-5}$	*ca.* 0.000 13	1.00	0.54		

[a] A, second-order process for methanolysis in CH_3CN at 0 °C (this study); B, as A but for third-order process (this study); C, 60% ether–40% ethanol at 25 °C (ref. 7); D, 1M-benzyl alcohol in dioxane at 25 °C (ref. 4); E, 1M-cyclohexanol in dioxane at 25 °C (ref. 4); F, 2M-2-chloroethanol in dioxane at 25 °C (ref. 4); G, 89.1% acetone–10.9% water at −20 °C (ref. 8); H, 0.45M-(L)-menthol in chloroform at 25 °C (ref. 5); I, 0.45M-(L)-menthol in benzene at 25 °C (ref. 5); J, 0.45M-(L)-menthol in liquid SO_2 at 25 °C (ref. 5); K, 0.45M-(L)-menthol in tetrahydrofuran at 25 °C (ref. 5); L, 0.45M-(L)-menthol in acetonitrile at 25 °C (refs. 10 and 11); M, ethanol at 25 °C (ref. 9); N, 0.08M-phenol in CH_3CN at 0 °C (this study); O, 0.01M-β-naphthol (CH_3CH_2COCl comparison) or *p*-methoxyphenol ($ClCH_2COCl$ comparison) in CH_3CN (ref. 6).

chloride. Upon replacement of the hydrogens by methyl groups, the values remain almost unchanged for the introduction of one or two groups, and then an approximately four-fold fall-off occurs upon introduction of the third methyl group.

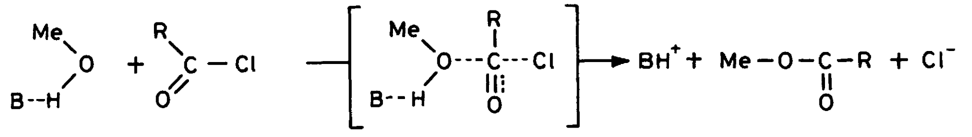
The data are expressed as relative rates within Table 7 (entries A and B), together with closely related data[4,5,7–11] from the literature (entries C—M). In particular, the relative rates are similar to those previously obtained for ethanolysis (entry M). Since the specific rates of ethanolysis correlated poorly with the two-term Taft equation (4),[9] it is not to be expected that the

$$\log(k/k_0) = \rho^*\sigma^* + \delta E_s \qquad (4)$$

equation will satisfactorily correlate the present data. When data do not conform to the equation, this is suggestive[9] of a mechanism, for at least some of the substrates, differing from the addition–elimination mechanism postulated for the reactions used as standards: nucleophilic substitution reactions of esters.[12–14] However, the polar (σ^*) and steric (E_s) substituent constants can be useful in qualitative considerations. The other symbols in equation (4) are k for the appropriate rate coefficient for reaction of a member of the series, k_0 for the corresponding rate coefficient for reaction of the standard substrate, ρ^* for the polar reaction constant, and δ for the steric susceptibility constant.

Entries A—M (hydrolysis or alcoholysis) of Table 7 all show the same general characteristics for the influence of α-methyl substituents: a small decrease in rate (occasionally a small increase) on introduction of one or two methyl groups, followed by a more pronounced, but still modest, decrease on introduction of a third methyl group.

It must be considered how these observations relate to the



(5)

loose S_N2 transition state [equation (5)] which has been proposed for the methanolysis of the parent compound, acetyl chloride.[1] For the series RCOCl, the methyl derivative has, by definition, polar and substituent constants of 0. As one goes across the α-methylated series both types of constant become increasingly negative; the σ^* values[12–14] fall off regularly (− 0.100, −0.190, and −0.300) and the E_s values[12,13] fall off with increasing intervals (−0.07, −0.47, and −1.54). The influence on the reaction rates of α-methyl substitution can be explained on the basis of favourable electronic and unfavourable steric effects being approximately balanced for the introduction of up to two methyl groups, followed by a dominant decelerating steric effect when R is the bulky t-butyl group.

The question arises why if a loose transition state, with considerable carbocation character, is involved do the rates not show a larger favourable polar influence on the introduction of electron-supplying methyl groups. While the answer to this question is not obvious, two studies do exist which show that, for reactions in which the acyl carbocation is actually produced, the influence of α-methyl substitution is small and unpredictable. Both studies are of the rates of cleavage of protonated carboxylic acids $(RCO_2H_2)^+$ in a solvent of high polarity and very low nucleophilicity. The relative rates as R varies from methyl to ethyl to isopropyl to t-butyl are, for reaction in FSO_3H–SbF_5–SO_2 at −24 °C,[15] 1.00:1.46:1.23:0.56 and, for reaction in HF–BF_3 at −26 °C,[16] 1.00:1.87:2.47:2.07. In both systems, the relative rates pass through a maximum and are falling off with introduction of the third methyl group.

The trends of relative rates observed amongst the data of Table 7 for hydrolysis and alcoholysis reactions (entries A—M) upon introduction of α-chloro substituents is much less uniform. With one exception (entry H), the introduction leads to an increase in rate. For these substitutions, since steric factors will become less favourable (E_s values[12,13] of −0.24 for $ClCH_2$, −1.54 for Cl_2CH, and −2.06 for CCl_3), the reactions must be assisted by having electron-withdrawing groups attached to the site of attack within the acyl chloride (σ^* values[12–14] of 1.05 for $ClCH_2$, 1.94 for Cl_2CH, and 2.65 for CCl_3). This direction for the polar effect suggests an increase in the electron density at the carbonyl carbon in going to the activated complex. This could involve either a tightening of the S_N2 transition state or a change over to an addition–elimination reaction, two possibilities previously discussed for the ethanolyses of these substrates.[9] The influences of substituents are reminiscent of those for reactions of benzoyl chlorides. The solvolyses of the parent, benzoyl chloride, have been proposed to involve a loose S_N2 transition state in highly aqueous solvents and an addition–elimination mechanism in less aqueous solvents.[17] In most studies, increases in rate have been observed upon introduction of *meta*- or *para*-electron-withdrawing groups,[7,8,18–21] and this is believed to be associated with an increased tendency towards the addition–elimination pathway.[21] Also, in several studies,[18–21] a faster reaction was observed for the *p*-methoxybenzoyl chloride than for the *meta*- or *para*-methyl derivative, indicating acceleration by electron-supplying groups in this region, consistent with large carbocation character at the transition state.

The relative rates of reaction of dichloroacetyl chloride relative to acetyl chloride vary from 2 844 for solvolysis in 89.1% aqueous acetone[8] to 0.74 for reaction with (L)-menthol in chloroform;[5] a general trend can be seen of a reduced value for the ratio as the size and complexity of the attacking nucleophile increases along the series: water, methanol, 2-chloroethanol, (L)-menthol. Polar and steric factors are opposed on introduction of chlorine atoms into acetyl chloride and the rate trends can be rationalized by assuming that polar effects dominate for fairly small nucleophiles, but the opposing steric factors are of increasing importance as the size and complexity of the attacking molecule increases. Akiyama and Tokura showed[5] that, for reaction with (L)-menthol, the isokinetic temperature was usually low; depending upon the solvent, it lies slightly below or slightly above room temperature. They considered the isokinetic temperature (and hence the low rate ratios) to be a consequence of the bulk and complexity of (L)-menthol: the same conclusion as reached by the present qualitative consideration in terms of the Taft equation.

The data for the reactions with (L)-menthol in tetrahydrofuran[5] (Table 7, entry K) deserve special attention. For this system, the rate ratios are quite different from those for the identical reaction in chloroform, benzene, or liquid sulphur dioxide, and they more resemble those for reaction with methanol or ethanol (entries A—C). It is possible that, for this system, the reaction is initially with the solvent to give an oxonium ion intermediate, which then reacts rapidly with (L)-menthol to give the ester. A related cyclic ether, dioxane, has been found to be able to act this capacity within aqueous dioxane[22] and Kivinen[23] has previously proposed such a scheme for reactions of acyl chlorides in dioxane-containing solvents.

The reactions of *p*-nitrobenzoyl chloride[2] and acetyl chloride[1] with methanol in acetonitrile have previously been shown to be subject to a very powerful general-base catalysis by added chloride ion (as the tetraethylammonium salt). It has been found (Table 3) that the corresponding methanolysis of pivaloyl chloride is also subject to such a catalysis. Throughout each kinetic run, the previously observed[1,2] third-order kinetic form was followed [equation (6)] and, as before, the value for

$$d[HCl]/dt = k_3[(CH_3)_3CCOCl][MeOH][NEt_4Cl] \quad (6)$$

the third-order rate coefficient fell slightly with increasing initial salt concentration.

Phenolysis.—The rates of phenolysis in acetonitrile at 0 °C are modestly reduced, by a factor of about two, on going from propionyl chloride to isobutyryl chloride, followed by a further reduction by a factor of about seven on going to pivaloyl chloride (Table 4). Appreciable adjustments for background solvolysis are needed for phenol concentrations of $<$*ca.* 0.3M. The adjusted second-order rate coefficients rise slightly with concentration but the magnitude of the rise is appreciable only in the region of high phenol concentration; accordingly, the rise could well be a consequence of medium effects, and it cannot be assumed that it reflects contributions of order above unity in phenol. If the mechanism proposed[1] for the phenolysis of the parent acetyl chloride [equation (7)] is accepted, then the changes in rate of acid formation from the phenolysis reaction as the group R is varied will be determined not only by the relative rates of the slow step but also by the position of the pre-equilibrium and by the relative rates of attack upon the cation of the ion pair by the chlorine and the oxygen of the ambident anion.

$$\mathrm{RCOCl} + \mathrm{HOPh} \underset{\text{fast}}{\overset{\text{fast}}{\rightleftharpoons}} \mathrm{RCOCl}\cdots\mathrm{HOPh} \underset{\text{fast}}{\overset{\text{slow}}{\rightleftharpoons}} (\mathrm{RCO})^{+}(\mathrm{ClHOPh})^{-} \xrightarrow{\text{fast steps}} \mathrm{RCOOPh} + \mathrm{HCl} \qquad (7)$$

Indeed, since one might expect the phenol to co-ordinate preferentially with the oxygen of the carbonyl, there is probably a more complex pre-equilibrium than that shown in equation (7), involving co-ordination with oxygen as well as with chlorine. The possibility also exists of a concerted transfer from oxygen to chlorine coupled with cleavage to the ion pair, a pathway parallel to the one mentioned as a possibility in the cleavage of protonated acids.[15] Based on studies of the cleavage of protonated acids,[15,16] one can reasonably expect rather small and unpredictable influences of α-methyl substitution upon the kinetics of the phenol-catalysed acylium ion formation.

Consideration of the partitioning, at the ion-pair stage, between internal return and product formation by attack at oxygen will be complicated by a dependence on the (unknown) geometry of the ion pair at the time of attack by the ambident anion; this geometry may or may not be thermodynamically determined, dependent upon the rates of reaction relative to the rate of equilibration. As the R group becomes bulkier, a preference in the equilibrated structure for closer approach to the site of attack by the chlorine rather than the oxygen of the bulkier phenoxy group could contribute towards the fall-off in rates of ester formation.

Briody and Satchell[6] have previously shown that, for reaction with *p*-methoxyphenol in acetonitrile, introduction of chlorine atoms into acetyl chloride leads to large rate decreases. Indeed, the influence of two chlorine substituents was so great that only an upper limit of 10^{-5} could be given[6a] for the rate ratio (Table 7, entry O). It was postulated that these retardations were a consequence of an ionization mechanism, which was severely retarded by the electron-withdrawing chlorines. We have suggested[1] that the detailed mechanism proposed by Briody and Satchell should be modified to one in which the electrophilic assistance is by the phenol itself [equation (7)] and not (initially) by adventitious hydrogen chloride.

A study of the reaction of phenol with chloroacetyl chloride in acetonitrile (Table 5) confirms the previously observed[6] retardation. Even with 0.96M-phenol, the rate of acid production at 25 °C or, especially, at 0 °C is only slightly greater than the rate of background solvolysis. Further, such small increases could be to a large degree a consequence of a medium effect upon the background rate of solvolysis rather than from reaction with phenol itself. Accordingly, in entry N of Table 7, which refers to the present phenolysis study, only an upper limit of 0.03 for the reactivity of chloroacetyl chloride relative to acetyl chloride is given.

The radical difference in the responses of methanolysis and phenolysis towards the introduction of chloro-substituents gives excellent support for the two distinct mechanisms [equations (5) and (7)] previously proposed largely on the basis of the opposite responses of the reaction with acetyl chloride towards added chloride ion.[1] The observation[6a] that phenolysis rates continue to fall on introduction of a second chlorine atom suggests that the very slow phenolysis reaction of chloroacetyl chloride remains primarily ionic [equation (7)].

It was previously shown[1] that additions of up to 0.16M-phenol to methanolysis reactions of acetyl chloride led to only modest rate increases and, to a close approximation, the overall rate could be considered as the sum of a major contribution from methanolysis and a minor contribution from phenolysis. This pattern is repeated for propionyl, isobutyryl, and pivaloyl chlorides in the present study (Table 6). Further, the range of phenol concentrations has been extended to 0.96M. It is found at these higher concentrations that, even after subtraction of the predicted phenolysis component (Table 4), the second-order rate coefficients for acid formation from the reaction of 0.04M-acyl chloride with 0.04M-methanol continue to rise with initial phenol concentration. This could either represent a medium effect upon the rate of methanolysis or it could indicate the introduction of a termolecular (or higher order) component involving participation by both methanol and phenol.

Leaving-group Effects.—Since traditional stereochemical probes are not possible in studies of acylation mechanisms, leaving-group effects are of increased importance. A collection of values from the literature[4,6,8,24—26] for acylations by aliphatic acyl halides are presented in Table 8. The general trends for hydrolysis (systems A, C, and E), alcoholysis (systems B and D), or phenolysis (systems F and G) are identical, with relative rates in the order RCOI > RCOBr > RCOCl > RCOF. This is also the order observed for both S_N1 and S_N2 nucleophilic substitution reactions at a saturated carbon atom[27] and it is the opposite of that to be expected if the addition step of an addition–elimination mechanism is rate determining. The observed order could also follow from the second step of an addition–elimination mechanism being rate determining; these factors have been reviewed in the context of nucleophilic substitution reactions taking place at a sp^2-hybridized carbon of an aromatic system;[28] this explanation has been put forward to explain the identical pattern of leaving-group effects in the reactions of benzoyl halides with secondary amines in cyclohexane.[29]

Aliphatic acyl iodides are extremely reactive[30] and only one (approximate) RCOI–RCOCl ratio is included in Table 8. The three RCOBr–RCOCl ratios for hydrolysis or alcoholysis are in

Table 8. Leaving-group effects in nucleophilic substitution reactions of acyl halides

		Relative rates of reaction				
System[a]	R	RCOI	RCOBr	RCOCl	RCOF	Ref.
A	CH_3	*ca.* 6 400	322	1.0	Very slow	8
B	CH_3		231	1.0		4
C	CH_3			1.0	1.3×10^{-4}	24
D	$n\text{-}C_3H_7$		524	1.0	1.6×10^{-4}	25
D	$n\text{-}C_4F_9$			1.0	0.045	25
E	CH_3		27	1.0		26
F	CH_3		90	1.0		6
G	CH_3		15	1.0	$< 1.4 \times 10^{-4}$	26

[a] A, 89.1% acetone–10.9% water at −20 °C; B, 2M-2-chloroethanol in dioxane at 15 °C; C, 75% aqueous acetone at 25 °C; D, propan-2-ol at 25 °C; E, 0.05—0.1M-H_2O in acetic acid at 40 °C; F, 0.01M-β-naphthol in CH_3CN at 25 °C; G, 0.01M-β-naphthol in acetic acid at 40 °C.

the range 230—530, quite narrow considering the very different reaction conditions. The RCOF–RCOCl ratios of 1.3×10^{-4} for hydrolysis and 1.6×10^{-4} for alcoholysis are also very similar.

For isopropanolysis at 25 °C, perfluoropentanoyl chloride reacts 7 000 times faster than butanoyl chloride[25] and the RCOF–RCOCl ratio increases to 4.5×10^{-2}. This increase is consistent with our proposal of a loose S_N2 transition state (with extensive breaking of the bond to the leaving group) becoming tighter (reduced breaking of the bond to the leaving group) upon halogen substitution within the acyl halide. However, a change over to an addition–elimination mechanism of the type proposed by Bender and Jones[29] must be regarded as a plausible alternative explanation of the increased ratio.

The entries in Table 8 for phenolysis are from studies of reactions of a large excess of acetyl halide with 0.01M-β-naphthol. In acetonitrile, the RCOBr–RCOCl ratio of 90 is somewhat lower than the range of values reported for hydrolysis and alcoholysis reactions. For phenolysis, the situation is more complex in that the reactant is RCOX ··· HOPh,[31] formed in a pre-equilibrium; not only will this modify the leaving group but a higher concentration of the hydrogen-bonded complex is to be expected for the chloride than for the bromide, favouring the observed lower RCOBr–RCOCl ratio.[32]

Conclusions.—The kinetics of the methanolysis of substituted acetyl chlorides in acetonitrile at 0 °C can be analysed in terms of concurrent operation of second- and third-order processes [equation (2)], which vary with substituent in approximately the same way. Introduction of one or two methyl groups has very little effect but a noticeable drop in value occurs upon introduction of the third methyl group; these reactions are believed to occur *via* a loose S_N2 transition state, as previously proposed[1] for acetyl chloride itself. Acceleration by chlorine atom substituents requires an accumulation of negative charge at the carbonyl carbon during reaction and a tightening of the S_N2 transition state or, possibly, a change to an addition–elimination mechanism.

For moderate concentrations, the second-order rate coefficients for phenolysis increase only slightly with phenol concentration. Introduction of methyl substituents into the acetyl chloride leads to modest rate decreases, which (as for methanolysis) are most pronounced on introduction of the third methyl group. On the basis of the ionization mechanism proposed for phenolysis of acetyl chloride,[1] one would predict an appreciable fall-off in rate upon introduction of electron-withdrawing chlorine atoms (in sharp contrast to methanolysis); such a fall-off is indeed observed.

A comparison of the present methanolysis study with other studies of hydrolysis or alcoholysis indicates very similar behaviour upon introduction of methyl groups. Introduction of chlorine atoms almost always leads to rate increases but the rate ratios are quite variable; the variations can be rationalized on the basis of a balance between favourable polar and unfavourable steric effects.

Leaving-group effects, drawn from several literature sources, are consistent with extensive carbon–halogen bond fission at the transition state of the rate-determining step. Data for the isopropanolysis of butanoyl and perfluoropentanoyl halides[25] are consistent with our proposal of a tightening of the transition state upon introduction of halogen substituents.

Experimental

Materials.—The acyl chlorides were purified by fractional distillation, a late middle fraction was collected and the purity was checked by analytical vapour-phase chromatography. Methanol,[1] phenol,[2] acetonitrile,[33,34] and tetraethylammonium chloride[1] were purified as previously described.

Kinetic Methods.—The kinetic runs were carried out as described previously.[2] For the kinetic runs involving chloroacetyl chloride and dichloroacetyl chloride, normal red to blue end-points were observed after complete reaction in the presence of excess of methanol. However, for portions of reactant solution removed during kinetic runs, the end-point was indicated by a red to greenish yellow to yellow colour change. It appears that the neutral blue form of Resorcinol Blue (Lacmoid) indicator reacts rapidly with the chloro-substituted acetyl chlorides, under the conditions of titration, to give yellow derivatives.

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