Rapid Solvolyses of 2,6-Dimethyl- and 2,4,6-Trimethyl-benzoyl Chlorides: Model Systems for Solvent Effects on the Reactivity of Acid Chlorides

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Rates of solvolyses of 2,6-dimethyl- and 2,4,6-trimethyl-benzoyl (mesitoyl) chlorides are reported for aqueous binary mixtures with acetone, ethanol, and methanol. These data are compared with those obtained for solvolyses of *p*-methoxybenzoyl (anisoyl) chloride. A consistent definition of selectivity is proposed to remove ambiguities in published values. Selectivities (*S*) for formation of ester relative to acid in alcohol–water mixtures are almost independent of solvent composition and are inverse for ethanol mixtures; methanol mixtures show higher *S* values. Acid catalysis does not appear to be significant. The results show that, for solvolyses of acid chlorides, a solvation effect and possibly a mass law effect increase the reaction rates in methanol–water mixtures as compared with those in ethanol–water mixtures having the same *Y* value. Differences between the mechanisms of solvolyses of mesitoyl and anisoyl chlorides are revealed by rate enhancements with added *m*-nitroaniline, and by a comparison of *m* values. Experience of recent conductimetric studies of a wide range of relatively rapid solvolytic reactions is summarised.

Rate–rate profiles can provide comparisons of reactions under investigation with suitably chosen, 'well understood' model reactions, *e.g.* solvolyses of t-butyl chloride, from which the original *Y* scale of solvent ionising power was defined.[1] Later it was established that adamantyl model systems have advantages over t-butyl in that elimination and rear-side nucleophilic attack cannot occur.[2] Rate–rate profiles of solvent effects give indications of mechanistic changes and/or solvation effects. To probe mechanistic changes, comparisons are best restricted to systems having the same leaving group. For the S_N1 solvolyses of 1- and 2-adamantyl systems, Y_X scales of solvent ionising power have recently been defined,[2] where X refers to the leaving group. A range of Y_X scales is necessary to avoid an increase in the number of freely adjustable solvent parameters required to correlate a single set of data.

These ideas have been developed and tested in the general area of aliphatic nucleophilic substitution.[3] As an extension of this work, we compared solvolyses of benzoyl chloride and *p*-substituted derivatives with solvolyses of both t-butyl and 1-adamantyl chlorides.[4] New mechanistic insights into the reactivity of acid chlorides were obtained, along with some unexplained observations which may be due to differences in solvation between alkyl chlorides (*e.g.* t-butyl and 1-adamantyl) and carboxylic acid chlorides. To explore these problems further we chose new model systems, based on 2,6-dimethylbenzoyl chloride (**1**; Z = H). This study required us to establish the upper limit of rate constants determined using a convenient conductimetric method for studying relatively fast solvolytic reactions.[4a] In this paper we also summarise the scope and limitations of this experimental method.

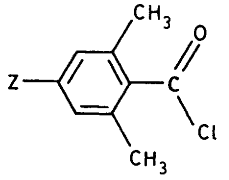
Results

The experimental techniques were developed by investigating a solvolysis previously examined in a flow system, *viz.* kinetic data for triphenylmethyl (trityl) chloride in 90% v/v acetone–water. For this solvolysis, it was hoped that dissolution of the substrate would be more rapid than for our previous studies of more highly aqueous media.[4a] In addition to data obtained by G. E. Carter using a chart recorder for data collection,[4a] we have now done over 30 kinetic runs using computer-aided data collection of up to 30 precision readings per second. The best results (Table 1) were obtained by injecting a freshly prepared dilute solution (*ca.* 1%) of trityl chloride in acetone into the rapidly stirred, thermostatically controlled solvent. Dioxane, a suitably inert alternative dried solvent, may mix more slowly with the aqueous media, particularly at lower temperatures (dioxane freezes at 12 °C).

Table 1. Rate constants (*k*) for solvolyses of triphenylmethyl (trityl) chloride in 90% v/v acetone–water[a]

	k/s^{-1}		
T/°C	Ref. 5	Ref. 4*a*	This work
−20.0	0.044	0.052	0.052 ± 0.002
10.0		0.94	1.08 ± 0.01
25.0	1.83	1.9	2—4[b]
25.0[c]	3.4[d]	3.0	3.9[e]

[a] Determined conductimetrically at least in duplicate; errors shown for this work are average deviations. [b] Range of ten attempted measurements in the 15-ml apparatus; mixing time 0.8 s; none of the individual measurements of *k* were of acceptable precision. [c] Calculated from experimental data at lower temperatures. [d] Our calculation from published data obtained using a flow system at −20 to −40 °C. [e] Activation parameters: $\Delta H^{\ddagger}$ = 13.9 kcal mol^{-1}; $\Delta S^{\ddagger}$ = −9.4 cal mol^{-1} K^{-1}.



(1)

The same experimental method was then applied to the solvolyses of 2,4,6-trimethylbenzoyl (mesitoyl) chloride (**1**; Z = Me) (see Table 2). These solvolyses were very rapid so, to confirm the results and to extend the range of data, we examined

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Table 2. Rate constants (k) for solvolyses of 2,4,6-trimethylbenzoyl (mesitoyl) chloride (**1**; Z = Me)[a]

Solvent[b]	T/°C	k/s^{-1}	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
EtOH	25.0^{e}	$(4.13 \pm 0.15) \times 10^{-1}$		
90E	-10.0	$(1.13 \pm 0.03) \times 10^{-1}$		
	0.0	$(3.20 \pm 0.06) \times 10^{-1}$	14.4	-8.0
	25.0^{c}	3.2		
80E	-20.1^{d}	$(1.31 \pm 0.09) \times 10^{-1}$		
	-10.1	$(4.69 \pm 0.05) \times 10^{-1}$	16.4	2.6
	25.0^{c}	21		
70E	-25.0^{e}	$(1.90 \pm 0.07) \times 10^{-1}$		
	-15.0^{d}	$(7.54 \pm 0.30) \times 10^{-1}$	17.1	7.6
	25.0^{c}	77		
MeOH	-10.0^{d}	$(2.70 \pm 0.03) \times 10^{-1}$		
	0.0^{f}	$(7.79 \pm 0.11) \times 10^{-1}$	14.6	-5.4
	25.0^{c}	8.1		
90M	-28.2^{g}	$(1.91 \pm 0.04) \times 10^{-1}$		
	-20.2	$(5.00 \pm 0.1) \times 10^{-1}$	14.4	-2.8
	25.0^{c}	45		
80M	-27.3^{d}	$(9.7 \pm 0.2) \times 10^{-1}$		
	25.0^{h}	180		
95A	25.0	$(6.9 \pm 0.1) \times 10^{-3}$		
90A	10.0^{i}	$(2.1 \pm 0.1) \times 10^{-2}$		
	25.0^{d}	$(7.9 \pm 0.2) \times 10^{-2}$	14.2	-15.9
80A	-9.9	$(4.12 \pm 0.03) \times 10^{-2}$		
	0.0	$(1.18 \pm 0.02) \times 10^{-1}$	14.6	-9.2
	25.0^{c}	1.23		
70A	-20.0	$(9.45 \pm 0.2) \times 10^{-2}$		
	-10.0	$(3.01 \pm 0.05) \times 10^{-1}$	14.9	-4.2
	25.0^{c}	9.6		
60A	-25.0^{g}	$(3.76 \pm 0.2) \times 10^{-1}$		
	-20.1	$(6.96 \pm 0.01) \times 10^{-1}$	15.2	1.0
	-15.0^{d}	1.28 ± 0.10		
	25.0^{c}	78		

[a] Determined conductimetrically in duplicate except where noted otherwise; errors shown are average deviations. [b] Solvent codes: E = % v/v ethanol–water; M = % v/v methanol–water; A = % v/v acetone–water. [c] Calculated from data at other temperatures. [d] Triplicate measurement of rate constant. [e] Quadruplicate measurement of rate constant. [f] Mean of ten measurements under various conditions including change of conductivity cell and protection from atmospheric carbon dioxide. [g] The same result was obtained using both 3-ml and 15-ml cells. [h] Estimated assuming $\Delta H^{\ddagger} = 14$ kcal mol^{-1}. [i] Six measurements of rate constant for which the initial substrate concentration was varied tenfold from *ca.* 1×10^{-4}M to 1×10^{-3}M.

Table 3. Rate constants (k) for solvolyses of 2,6-dimethylbenzoyl chloride (**1**; Z = H)[a]

Solvent[b]	T/°C	k/s^{-1}	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
EtOH	0.1^{d}	$(3.47 \pm 0.2) \times 10^{-3}$		
	10.0	$(1.06 \pm 0.05) \times 10^{-2}$	15.6	-12.7
	25.0^{d}	$(4.18 \pm 0.08) \times 10^{-2}$		
90E	0.0	$(3.19 \pm 0.05) \times 10^{-2}$		
	10.1	$(8.88 \pm 0.08) \times 10^{-2}$	15.0	-10.3
	25.0^{e}	3.54×10^{-1}		
80E	0.0^{d}	$(1.26 \pm 0.04) \times 10^{-1}$		
	10.1	$(3.77 \pm 0.13) \times 10^{-1}$	16.1	-3.6
	25.0^{c}	1.66		
70E	-20.0	$(3.90 \pm 0.11) \times 10^{-2}$		
	0.0	$(3.94 \pm 0.04) \times 10^{-1}$	16.3	-0.2
	10.0	1.42 ± 0.03		
	25.0^{c}	6.0		
60E	-20.0	$(1.23 \pm 0.12) \times 10^{-1}$		
	-10.0	$(4.30 \pm 0.03) \times 10^{-1}$	16.1	1.0
	25.0^{c}	18		
MeOH	-10.1	$(2.05 \pm 0.01) \times 10^{-2}$		
	0.0	$(6.46 \pm 0.02) \times 10^{-2}$	16.0	-5.3
	10.0	$(1.93 \pm 0.06) \times 10^{-1}$		
	25.0^{c}	8.4×10^{-1}		
90M	-10.1	$(1.11 \pm 0.01) \times 10^{-1}$		
	0.0^{d}	$(3.04 \pm 0.1) \times 10^{-1}$	14.6	-7.2
	10.0	$(8.7 \pm 0.1) \times 10^{-1}$		
	25.0^{c}	3.3		
80M	-20.0	$(1.27 \pm 0.02) \times 10^{-1}$		
	-10.0	$(4.39 \pm 0.03) \times 10^{-1}$	14.5	-4.9
	0.0	1.13 ± 0.04		
	25.0^{c}	12		
70M	-20.0^{d}	$(5.41 \pm 0.04) \times 10^{-1}$		
	-15.1	$(9.35 \pm 0.22) \times 10^{-1}$	14.0	-4.2
	25.0^{c}	42		
90A	25.0	$(1.05 \pm 0.04) \times 10^{-2}$		
80A	10.0	$(3.35 \pm 0.06) \times 10^{-2}$		
	25.0^{d}	$(1.42 \pm 0.03) \times 10^{-1}$	15.6	-10.2
70A	-15.0	$(1.62 \pm 0.02) \times 10^{-2}$		
	-5.0	$(5.33 \pm 0.23) \times 10^{-2}$	15.3	-7.2
	0.0	$(8.7 \pm 0.1) \times 10^{-2}$		
	25.0^{c}	1.03		
	25.0^{e}	1.08		
60A	-15.0	$(1.29 \pm 0.06) \times 10^{-1}$		
	-5.0	$(4.42 \pm 0.13) \times 10^{-1}$	16.4	1.3
	25.0^{c}	11		
50A	-20.0	$(4.23 \pm 0.17) \times 10^{-1}$		
	-15.0	$(7.57 \pm 0.23) \times 10^{-1}$	14.6	-2.2
	25.0^{c}	40		

[a–d] As Table 2. [e] Single measurement of rate constant.

solvolyses of 2,6-dimethylbenzoyl chloride (**1**; Z = H) (see Table 3). Additional kinetic data for solvolyses of *p*-methoxybenzoyl (anisoyl) chloride are given in Table 4, and some aminolysis data in methanol are given in Table 5. Product selectivities (S) in alcohol–water mixtures, defined by equation (1), are shown in Tables 6 and 7.

$$\text{Selectivity}\,(S) = [\text{ester}]_{\text{prod.}} \times [\text{water}]_{\text{solv.}}/[\text{acid}]_{\text{prod.}} \times [\text{alcohol}]_{\text{solv.}} \quad (1)$$

Discussion

Reliability of Data.—The results in Table 1 and other results[4] indicate that our current experimental method could give reliable k values up to 2 s^{-1}, but unsatisfactory results when $k > 2$ s^{-1}. Extrapolations of three sets of data (Table 1) to 25 °C from data at lower temperatures strongly suggest that two previous direct measurements[4a,5] at 25 °C are unreliable; these two include an early version of our current method, which we suspected had been pushed beyond its limit of reliability,[4a] but also a study made using a flow system.[5] A modern stopped-flow system may give better results, but modifications would be required to extend this work to alcohol–water mixtures to avoid extensive solvolysis before mixing of the two flowing streams.

Some of the solvolyses in Tables 2 and 3 have been investigated by others. In a pioneering study of the kinetics of solvolyses of various acid chlorides examined conductimetrically, it was reported that ethanolysis of 2,6-dimethylbenzoyl chloride at 0 °C was too fast to be measured.[6a] Later conductimetric studies at lower temperatures (-20 to -50 °C) of hydrolyses of carboxylic acid chlorides in acetone–water mixtures included rate constants up to 9×10^{-1} s^{-1}.[6b] However, the problem of dissolving the substrate sufficiently rapidly is illustrated by the observation that mesitoyl chloride (0.04M) in *ca.* 60% acetone–water reacts less than twice as fast as in *ca.* 80% acetone–water.[6b] In contrast by investigating much more dilute solutions (*ca.* 10^{-4}M), we find a rate increase of over fifty-fold (Table 2). The quality control checks necessary to avoid

Table 4. Additional rate constants for solvolyses of *p*-methoxybenzoyl (anisoyl) chloride at 25.0 °C[a]

Solvent[b]	k/s^{-1}	Solvent	k/s^{-1}
EtOH	$(9.86 \pm 0.05) \times 10^{-4}$	70E	$(6.52 \pm 0.07) \times 10^{-2}$
90E	$(5.96 \pm 0.03) \times 10^{-3}$	90A	$(2.06 \pm 0.08) \times 10^{-4}$

[a,b] As Table 2.

Table 5. Rate constants for aminolysis (RNH_2 = *m*-nitroaniline) and methanolysis of 2,4,6-trimethylbenzoyl (mesitoyl) chloride and *p*-methoxybenzoyl (anisoyl) chloride

Substrate	$[RNH_2]/\text{M}$	k/s^{-1}[a]	$T/°\text{C}$
Mesitoyl	0[b]	$(2.70 \pm 0.03) \times 10^{-1}$	−10.0
	0.01	$(2.82 \pm 0.07) \times 10^{-1}$	−10.0
	0.05	$(2.85 \pm 0.05) \times 10^{-1}$	−10.0
Anisoyl	0[c]	$(1.07 \pm 0.01) \times 10^{-2}$	25.0
	0.01	$(1.29 \pm 0.02) \times 10^{-2}$	25.0
	0.05	$(2.28 \pm 0.02) \times 10^{-2}$	25.0

[a] Determined conductimetrically in duplicate; errors shown are average deviations. [b] As Table 2. [c] Ref. 4*b*.

Table 6. Product ratios and product selectivities for solvolyses of *p*-methoxybenzoyl (anisoyl) chloride in alcohol–water mixtures at 25 °C[a]

	Ethanol		Methanol	
% Alcohol (v/v)	[ester]/[acid]	S^b	[ester]/[acid]	S^c
98	8.5[d]	0.56	27[d]	1.3
95	4.28	0.73	12[d]	1.4
90	1.95	0.71	5.43	1.36
80	0.78	0.64	2.33	1.31
70	0.51	0.71		
60	0.32	0.70	0.82	1.23
50	0.22	0.72		
40	0.15	0.73	0.399	1.35
30	0.098	0.75		
20	0.059	0.77	0.159	1.43

[a] Determined by h.p.l.c. analyses of *ca.* 10^{-4}M-solutions at least in duplicate; values quoted are the averages of results obtained by injecting the acid chloride as a freshlyprepared 10% solution in acetonitrile; similar results (except for 20% v/v MeOH) were obtained by injecting the neat liquid acid chloride to give a 10^{-3}M-solution. [b] Calculated from equation (1), the product ratios, and the following molar concentrations of ethanol and water: 98E, 16.79, 1.11; 95E, 16.28, 2.78; 90E, 15.42, 5.55; 80E, 13.71, 11.10; 70E, 11.99, 16.65; 60E, 10.28, 22.20; 50E, 8.57, 27.75; 40E, 6.85, 33.31; 30E, 5.14, 38.86; 20E, 3.43, 44.41. [c] Calculated from equation (1), the product ratios, and the following molar concentrations of methanol and water: 98M, 24.21, 1.11; 95M, 23.47, 2.78; 90M, 22.23, 5.55; 80M, 19.76, 11.10; 70M, 17.29, 16.65; 60M, 14.82, 22.20; 50M, 12.35; 27.75; 40M, 9.88, 33.31; 20M, 4.94, 44.41. [d] Corrected for 0.3% acid impurity in the starting material.

Table 7. Product ratios and product selectivities for solvolyses of 2,6-dimethylbenzoyl chloride (**1**; Z = H) in alcohol–water mixtures[a]

% Methanol (v/v)	[ester]/[acid][d]	[ester]/[acid][e]	[ester]/[acid][f]	$S^{b,c,f}$
90	6.15	4.64	5.37	1.34
80	3.11	2.25	2.35	1.32
70	1.99	1.43	1.43	1.38
60	1.41	1.04	0.85	1.27
50	1.06	0.80	0.50	1.12
% Ethanol (v/v)				
90			2.61	0.94
80			1.11	0.90
70			0.69	0.96
60			0.48	1.04
50			0.38	1.23

[a] Determined by h.p.l.c. analyses at least in duplicate. [b,c] As Table 6. [d] A 30% solution of acid chloride in acetonitrile (15 µl) was injected into the kinetics apparatus (turbo-stirrer and 3 ml of solvent) at 0 °C; very similar results were obtained by direct injection of 15 µl of acid chloride into a sample tube containing 2 ml of solvent at 25 °C. [e] A 10% solution of acid chloride in acetonitrile (5 × 2 µl) was injected into a sample tube containing 2 ml of solvent in an ultrasonic bath at 40 °C. [f] A 10% solution of acid chloride in acetonitrile (5 × 2 µl) was injected into the kinetics apparatus (turbo-stirrer and 3 ml of solvent) at 0 °C.

Table 8. Relative rates of solvolyses of mesitoyl (**1**; Z = Me) and 2,6-dimethylbenzoyl (**1**; Z = H) chlorides and comparison of activation enthalpies[a]

	Rate ratios[c]		
Solvent[b]	25 °C	−20 °C	$\Delta\Delta H^{\ddagger d}$
EtOH	9.9		
90E	9.0	11.1	−0.6
80E	12.7	11.9	+0.3
70E	12.8	9.8	+0.8
MeOH	9.6	14.5	−1.4
90M	13.6	14.8	−0.2
(80M)[e]	(15)	(17.4)	(−0.5)
90A	7.5		
80A	8.7	11.5	−1.0
70A	9.1	10.6	−0.4
60A	7.1	10.5	−1.2
Average (8)	10.4	11.8	−0.5

[a] Data from Tables 2 and 3. [b] Solvent codes as in Table 2. [c] For mesitoyl/2,6-dimethylbenzoyl chloride at 25 °C and at −20 °C. [d] Difference in enthalpy of activation (kcal mol^{-1}) for mesitoyl and 2,6-dimethylbenzoyl chlorides. [e] Rate constant for mesitoyl chloride (Table 2) not firmly established.

inadvertently incorporating the rate of dissolution of substrate into the observed solvolysis rate constant have been discussed elsewhere.[4a,7]

Results from a substantial number of attempts to measure these rate constants (Tables 2 and 3) were rejected, usually because unsatisfactory mixing was readily apparent. However, kinetic data for 2,6-dimethylbenzoyl chloride in 60% v/v acetone–water at −20 °C gave apparently satisfactory data in duplicate [$k = (5.76 \pm 0.07) \times 10^{-2}\ \text{s}^{-1}$]; when these were compared with data at −15 °C a surprisingly high $\Delta H^{\ddagger}$ value was calculated. The substrate may have been dissolving during the kinetic run, and data at −5 °C were obtained to give the results reported (Table 3), from which a higher rate constant (6.7×10^{-2}) at −20.0 °C could be calculated. Extrapolations of rate constants from −20 to +25 °C greatly increase experimental uncertainties. When experimental data over a very limited range of temperatures are available, an error of only 5% at −20 °C could be magnified about ten-fold on extrapolation to 25 °C. Also, extrapolated results tend to be too high because accurate Arrhenius plots are non-linear.[8]

Further evidence for the reliability of the data is shown in Table 8, where comparisons are made between the data given in Tables 2 and 3. It should be emphasised that these data are *independent*, being measured on different compounds in different batches of solvent by different workers at different times (about 1 year apart). If the rate ratio of mesitoyl and 2,6-dimethylbenzoyl chlorides in the various solvents were constant, at a particular temperature, we could conclude that the experimental errors are up to about 20% (larger for 80% v/v methanol–water). The average rate ratio of 10.4:1 at 25 °C (Table 8) agrees with the published value of 10.5 for 99% v/v acetonitrile–water.[9a] However it seems likely that the rate ratio will be slightly solvent dependent. If a constant difference in $\Delta H^{\ddagger}$ were assumed, we could conclude that quoted values of $\Delta H^{\ddagger}$ are reliable to about 1 kcal mol^{-1}. In view of the experimental difficulties, the results in Table 8 show the remarkably good consistency of the rate data in Tables 2 and 3. Further support for the overall reliability of the results is provided by the correlations given in Figures 1 and 2 (discussed later); only the solvolysis of 2,6-dimethylbenzoyl chloride in 60% v/v acetone–water at 25 °C appears to be seriously inconsistent (*ca.* 30%) with other data.

Product studies under various mixing conditions showed that insufficiently rapid dissolution of the acid chloride could lead to erroneously high *S* values [equation (1)]. A possible explanation is that if these solutions are not homogeneous during the early part of the reaction, a microphase of acid chloride attracts an excess of alcohol molecules to that phase or to its interface with the bulk solution. This problem was most readily apparent for the product studies of 2,6-dimethylbenzoyl chloride (**1**; Z = H) in the more aqueous media, and it is conceivable that slightly lower *S* values would be obtained if mixing were even more rapid (Table 7). Product studies by reverse-phase h.p.l.c. (Tables 6 and 7) involve direct analyses of very dilute solutions (10^{-3}—10^{-4}M). In previous studies of selectivities of adamantyl substrates (discussed later), product studies typically involved much higher substrate concentrations (about 0.1M), and reactions in a microphase may sometimes have occurred.

In a preliminary study of mesitoyl chloride (**1**: Z = Me), it was established that addition of 0.01M-perchloric acid did not significantly change *S* values for solvolyses in 90% v/v methanol–water and 80% v/v ethanol–water (neither did acid catalysis up to *ca.* 10^{-3}M affect the rates: see Table 2, footnote *i*). In 99% v/v acetonitrile–water, solvolyses of mesitoyl chloride are acid-catalysed.[9a]

Choice of Model Substrate.—We wish to compare the rate profiles for S_N1 solvolyses of 1-adamantyl and t-butyl chlorides with those for S_N1 solvolyses of acid chlorides. Hence, ideally, we require an acid chloride so encumbered by alkyl groups that it is forced to react by an S_N1 mechanism. One possibility is 2,6-di-t-butylbenzoyl chloride, but this would be difficult to synthesise and it would probably not dissolve very rapidly.

Structural features of both anisoyl and 2,6-dimethylbenzoyl derivatives are well suited to our purpose. All these solvolyses show the accelerating effects of increasing electron donation, *e.g.* rates of solvolyses of *p*-methoxy- as compared with *p*-methylbenzoyl chloride (Figure 2 of ref. 4*b*) and rates of solvolyses of mesitoyl chloride as compared with solvolyses of 2,6-dimethylbenzoyl chloride (Table 8). Strong electron donation by the *p*-methoxy group reduces the need for nucleophilic assistance to substitution in anisoyl chloride. With further electron donation even solvolyses of fluorides (*e.g. p*-dimethylaminobenzoyl fluoride in water) show common-ion rate depression.[10] However, the presence of small quantities of *m*-nitroaniline in methanol adds a second-order term to the rate law for anisoyl chloride (Table 5). The rate constant (k_{am}) is 0.246 ± 0.005 l mol^{-1} s^{-1} (ignoring medium effects[4a]), as expected lower than for the corresponding aminolysis of benzoyl chloride (k_{am} = 1.5 l mol^{-1} s^{-1}).[4c] It appears that solvolyses of anisoyl chloride may be weakly susceptible to nucleophilic solvent assistance.[4b]

Our other choices of model substrate also have limitations. The 2- and 6-methyl groups would prevent S_N2 attack at the carbonyl group if it remained in the plane of the benzene ring. However, rotation is known to occur,[11] and the high reactivity of mesitoyl chloride is associated with the smaller resonance stabilisation of the ground state.[9a] Also, molecular models indicate that nucleophilic attack is then possible. The effect of added *m*-nitroaniline on the methanolysis of mesitoyl chloride is almost too small to be detectable (Table 5), but any small corrections for the medium effect of the added non-electrolyte[4a] would tend to increase k_{am}. Also, *m*-nitroaniline is a relatively bulky nucleophile. A wide range of amines, but particularly n-butylamine, accelerate solvolyses of mesitoyl chloride in 89.1% v/v acetone–water at −40 °C.[6b] Under more basic conditions, hydroxide ion substantially accelerates reactions of mesitoyl chlorides,[9a,12] and electron-withdrawing groups then increase the reaction rate ($\rho = +1.2$).[9a] The reactions with hydroxide ion probably proceed by a carbonyl addition mechanism.[9a,12]

However, under neutral conditions in 99% v/v acetonitrile–water, solvolyses of mesitoyl chloride gave a ρ^+ value of −3.8 and showed a common-ion rate depression, consistent with the formation of an acylium ion intermediate.[9] Although this cation could be stabilised by weak rear-side nucleophilic solvation, mesitoyl chloride appears to be a good choice of model substrate. For our work 2,6-dimethylbenzoyl chloride was also studied in detail, because it was possible to obtain kinetic data for a wider range of solvents.

Product Selectivities.—Typical studies of nucleophilic reactivity of anions have been investigated in water as solvent and k_N/k_{H_2O} values have been obtained.[13] Trapping of carbocations by azide ion has been studied by plotting k_N/k_{H_2O},[14] and earlier product studies of solvolyses in ethanol–water mixtures established k_E/k_W ratios.[15] The definition of selectivity [equation (1)][4a] for reactions of carboxylic acid chlorides could also be expressed as k_{ROH}/k_{H_2O}; unfortunately, for solvolyses of adamantyl halides and related sulphonates it has become common practice more recently to express selectivities as the *inverse* of equation (1).[3d,g,16] As well as ignoring historical convention,[13–15] this definition yields *lower S* values when typical alcohols (*e.g.* ethanol and methanol) show *greater* reactivity than water,[4a] as expected from their higher nucleophilicity.[3b,13b,17]

An additional useful proposal for studies of selectivities in mixtures of two alcohols is to obtain $S = k_{ROH}/k_{R'OH}$, where ROH is the more nucleophilic alcohol.[18] However, it is confusing to allow[18] this to take precedence over $S = k_{ROH}/k_{H_2O}$, because for studies of trifluoroethanol (TFE)–water mixtures the inverse of equation (1) would then be required. In earlier work k_{TFE}/k_{H_2O} values were quoted,[4a,19] consistent with equation (1). It may not always be clear or generally agreed which is the more nucleophilic component, and a definition of selectivity relative to water (if possible) is consistent and unambiguous.

The use of k_E/k_W[15] shows clearly which way round the selectivity values are defined, but it has not been widely adopted because products may be formed by several pathways.[20] Also the early definition of *S* as log (k_E/k_W)[15] has not been continued: the dynamic range of *S* values defined by equation (1) is not large and the term *inverse selectivity* (water more reactive than alcohol) is more descriptive that 'negative selectivity',[19,21] which arises if logarithms are evaluated under these circumstances. Plots involving log *S* [*S* defined by equation (1)] may still be useful,[15] and the situation when *S* = 1 (unselective) becomes log *S* = 0; zero selectivity could describe this situation, rather than zero log (selectivity).

Many studies of the solvolyses of adamantyl substrates, with a wide range of leaving groups, have established that *S* is almost constant in various ethanol–water mixtures and that attack by water is preferred.[3d,g,16,19] Our results for anisoyl chloride (Table 6) in ethanol–water show no clear trends for variations in

S; these results are also close to constant and the average *S* value of 0.70 is similar to that for 1-adamantyl bromide at 100 °C [*S* from equation (2) is 0.5 (refs. 16*a* and *b*) or 0.8 (ref. 22)], and for

$$S = [\text{ether}]_{\text{prod.}} \times [\text{water}]_{\text{solv.}}/[\text{alcohol}]_{\text{prod.}} \times [\text{alcohol}]_{\text{solv.}} \quad (2)$$

1-adamantyl chloride[16a] ($S = 0.5$). Despite the experimental difficulties in the product studies for solvolyses of 2,6-dimethylbenzoyl chloride in alcohol–water mixtures (Table 7), an approximately constant $S = 1.0$ is apparent (Table 7) for ethanol–water. These results contrast with those for solvolyses of benzoyl chloride for which *S* decreased from 2.3 in 80% v/v ethanol–water to 1.0 in 30% v/v ethanol–water.[4a]

An accepted explanation[15,16,19,22,23] of inverse selectivity for solvolyses in ethanol–water is that a large amount of the product is formed by front-side collapse from a solvent-separated ion pair. Hence solvent properties other than nucleophilicity (*e.g.* electrophilicity and bulk[22,23]) would be important in determining the product. Presumably this argument could also be applied when $S = 1$ because that value is also lower than expected from solvent nucleophilicities.[3b,17] Further dissociation of a solvent-separated ion pair is also possible, and this could account for the common-ion rate depression: solvolysis rate was halved on addition of 10^{-2}M-$Bu_4N^+Cl^-$ in 99% v/v acetonitrile–water.[9a] Under these conditions the maximum water concentration is only 0.55M and a significant proportion of this may be required to solvate the ions, leaving less available for nucleophilic attack. Also if the ions are separated by acetonitrile (relatively unreactive), there is an increased chance of further dissociation to free ions, which can then show common-ion rate depression. A small common-ion rate depression was observed in 95% v/v acetone–water,[9b] and no rate depression effect in 80% v/v alcoholic acetone.[12b]

Relatively little work has been published on product selectivities in methanol–water mixtures. For solvolyses of 1-adamantyl bromide, $S = 1.0$,[22] *i.e.* 25% higher for methanol–water than for ethanol–water. Our results show a similar effect for 2,6-dimethylbenzoyl chloride (average *S* increases from 1.0 to 1.29; Table 7) but a larger effect for anisoyl chloride (average *S* increases from 0.70 to 1.31; Table 6). Solvolyses of benzoyl chloride in methanol–water gave *S* values double those for ethanol–water in the less aqueous solvent compositions (*e.g.* 80% alcohol).[4a] In this case, ion pair intermediates are not involved and the higher *S* values for methanol than for ethanol are unexpected, because these two alcohols have very similar nucleophilicities.[3b,17]

Solvent Effects on Reactivity.—The correlation of rate data for 2,6-dimethylbenzoyl chloride *versus* Y_{Cl} (Figure 1) can be compared with previous results for solvolyses of *para*-substituted benzoyl halides;[4b] a direct comparison with solvolyses of anisoyl chloride is given in Figure 2. Solvolyses of mesitoyl chloride are very similar to those of 2,6-dimethylbenzoyl chloride (Table 8).

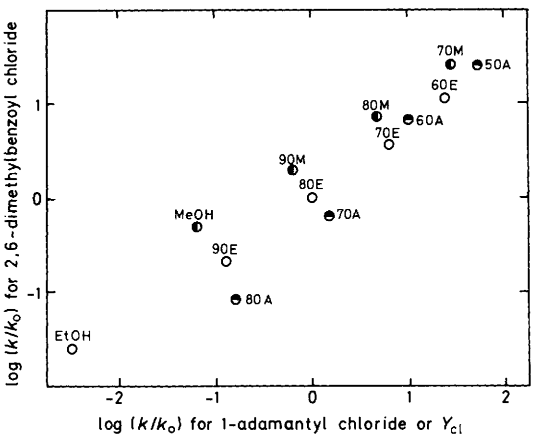

Figure 1. Correlation of logarithms of solvolysis rates for 2,6-dimethylbenzoyl chloride (**1**; Z = H) relative to 80% v/v ethanol–water (k_0) at 25 °C *versus* Y_{Cl} (kinetic data and solvent codes given in Table 3; Y_{Cl} data from ref. 2*c*)

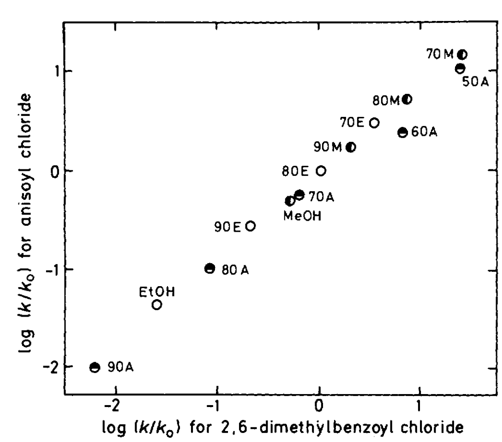

Figure 2. Correlation of logarithms of solvolysis rates for anisoyl chloride relative to 80% v/v ethanol–water (k_0) at 25 °C *versus* corresponding data for 2,6-dimethylbenzoyl chloride (kinetic data and solvent codes given in Tables 3 and 4 and ref. 4*b*); slope 0.839, correlation coefficient 0.995

The slope of the correlation line for acetone–water (80–50%) is 1.0 (Figure 1), in agreement with ideal expectations: S_N1 solvolyses of various tosylates give slopes of similar plots very close to 1.0.[24] However, the relatively large dispersion of data points for the three different aqueous binary mixtures (Figure 1) is unexpected; also the ethanol–water points fit a shallow curve. Solvolyses in pure methanol are over ten times faster than expected from an ideal Y_{Cl} plot, for which dispersion is assumed to be absent. In practice, all such correlations show some dispersion,[2c,25] and solvolyses of α-phenylethyl chloride also show greater dispersion for methanol–water mixtures than for ethanol–water mixtures.[25] The results may be explained at least in part by small differences in solvation, *e.g.* between solvolyses of substrates containing aryl and carbonyl groups and the aliphatic substrates used to define *Y* or Y_{Cl} values. There may also be a contribution from mass law effects because, as already discussed, solvolyses in methanol–water are more selective towards methanol than solvolyses in ethanol–water are towards ethanol. However, the product data correspond to rate ratios showing a preference for methanol over ethanol of only 1.3 (Table 7), whereas the dispersion corresponds to a rate ratio of about 3. Also the *S* values can be explained (see before) by product-determining steps occurring independently of the rate-determining step.

The foregoing discussion should be considered within the mechanistic framework of Ingold, in which mechanistic changes are associated with molecules 'necessarily undergoing covalency change'.[26] This implies that solvation effects can be separated from mechanistic changes, and we regard this concept as a very useful approximation.[27] A more complete description of reaction mechanisms would include increasing numbers of solvent molecules, and this approach is currently being developed in gas-phase ion chemistry,[28] and theoretically with inclusion of over two hundred solvent molecules.[29]

The good correlation between kinetic data for solvolyses of anisoyl and 2,6-dimethylbenzoyl chlorides (Figure 2) is consistent with similar mechanisms. If the slope of Figure 2 (0.839) is mechanistically significant, it may indicate weak nucleophilic solvent assistance for solvolyses of anisoyl chloride. A wider range of kinetic data is available and accessible for solvolyses of anisoyl chloride, so this will be a useful model substrate.[30] Comparison of a previous correlation of kinetic data for anisoyl chloride *versus* Y_{Cl}[4b] with Figures 1 and 2 suggests that the plot for methanol–water in Figure 1 would curve slightly upwards as Y_{Cl} increases.

Conclusions

Reaction *via* solvent-separated ion pairs accounts for the inverse and constant S values for solvolyses of 2,6-dimethylbenzoyl (**1**; Z = H) and anisoyl chlorides (Tables 7 and 8) in ethanol–water, which are similar to those for S_N1 solvolyses of 1-adamantyl substrates;[15,16,19,22,23] solvent effects on reactivity for acetone–water mixtures are also closely similar to solvolyses of 1-adamantyl chloride (Figure 1). However, the dispersion of correlation lines (Figure 1) for the three binary aqueous mixtures (with acetone, ethanol, and methanol) is *not* a reliable characteristic of the carbonyl addition mechanism, contrary to proposals based on earlier work.[4a] The experimental data now available do *not* support the conclusion[4b] that solvolyses of anisoyl chloride in less aqueous methanol–water mixtures may occur by a carbonyl addition mechanism; the experimental evidence is consistent with a weakly nucleophilically solvent-assisted S_N2 mechanism. Kinetic data for unusually fast solvolytic reactions can be obtained by the convenient conductimetric method described.

Experimental

Materials.—Anisoyl and mesitoyl chlorides were commercial samples; 2,6-dimethylbenzoyl chloride was prepared from the corresponding acid (Fluka) by reaction with thionyl chloride and was purified by distillation under reduced pressure; b.p. 50 °C (*ca.* 0.5 mmHg) [lit.,[9a] 90—91 °C (5 mmHg)]. Ethyl 2,6-dimethylbenzoate (Lancaster Synthesis) was distilled under reduced pressure. Ethyl and methyl *p*-methoxybenzoates and methyl 2,6-dimethylbenzoate were prepared from the acid chlorides and were purified and characterised by standard methods. The acid chlorides and esters were shown to be pure (>99.5%) by h.p.l.c. analyses of methanolysis products. Solvents for kinetic studies were prepared as described previously.[4a]

Kinetic Methods.—Most of the results were obtained using the 3-ml stirred conductivity cell and the conductivity amplifier described previously.[4b] The kinetic technique was also as before: the acid chloride was usually injected as a *ca.* 1% solution in acetone, which appears to be preferable to dioxane particularly at low temperatures. Acetonitrile was also found to be a useful co-solvent, but stock solutions slowly decomposed, possibly because of solvolysis by acetonitrile.[31] The timing of fast kinetic runs was controlled by a BBC Model B and later by a BBC Master Series microcomputer using a BASIC computer program. The accuracy of each of the required time intervals was established using a calibrated triangular voltage–time (4 V s^{-1}) wave produced by a Wavetek model 114 sweep/trigger signal generator. The microcomputer controlled the Solartron 7066 storage voltmeter; the most refined version of the computer program also selected appropriate settings for the voltmeter and provided a countdown to the time when injection of the sample was required. Up to 30 precision readings per second were obtained at 1 200 baud (50 per second at 9 600 baud), well suited to our target of obtaining 8—12 readings (see Table 5, ref. [4a] in the first half-life of the reaction; at the upper limit, a rate constant of 2 s^{-1} corresponds to a half-life of 0.33 s, which is accessible with a mixing time of 0.4 s.[4b]

Liquid Chromatography and Product Studies.—The apparatus and eluting solvents described previously,[4a] with a 5 μm Spherisorb ODS2 chromatography column, was operated with the addition of a Perkin-Elmer ISS 101 autosampler, which also triggered the start of the HP3390A integrator/plotter. A suitable wavelength maximum was selected for product analyses from each substrate; the high ε values for *p*-methoxybenzene derivatives permitted very convenient studies at concentrations as low as 10^{-4}M, and other studies were at concentrations from 10^{-4}M to *ca.* 2×10^{-3}M. Linear calibration plots of ester–acid ratios of concentration and integrated peak areas were established over the whole of the required range and response factors were thus obtained; esters gave a slightly greater (*ca.* 1.1) signal than the corresponding acids.

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References

1 E. Grunwald and S. Winstein, *J. Am. Chem. Soc.*, 1948, **70**, 846.
2 (*a*) D. J. Raber, R. C. Bingham, J. M. Harris, J. L. Fry, and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1970, **92**, 5977; (*b*) D. N. Kevill, K. C. Kolwyck, D. M. Shold, and C. Kim, *ibid.*, 1973, **95**, 6022; (*c*) T. W. Bentley and G. E. Carter, *ibid.*, 1982, **104**, 5741.
3 (*a*) F. L. Schadt, T. W. Bentley, and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1976, **98**, 7667; (*b*) T. W. Bentley and G. E. Carter, *J. Org. Chem.*, 1983, **48**, 579; (*c*) B. Allard and E. Casadevall, *Nouv. J. Chim.*, 1983, **7**, 569; (*d*) D. N. Kevill, M. S. Bahari, and S. W. Anderson, *J. Am. Chem. Soc.*, 1984, **106**, 2895; (*e*) T. W. Bentley, G. E. Carter, and K. Roberts, *J. Org. Chem.*, 1984, **49**, 5183; (*f*) X. Creary and S. R. McDonald, *ibid.*, 1985, **50**, 474; (*g*) D. N. Kevill and S. W. Anderson, *ibid.*, p. 3330.
4 (*a*) T. W. Bentley, G. E. Carter, and H. C. Harris, *J. Chem. Soc., Perkin Trans. 2*, 1985, 983; (*b*) T. W. Bentley and H. C. Harris, *ibid.*, 1986, 619; (*c*) T. W. Bentley and A. E. Freeman, *ibid.*, 1984, 1115.
5 C. G. Swain and A. Maclachlan, *J. Am. Chem. Soc.*, 1960, **82**, 6095.
6 (*a*) J. F. Norris and V. W. Ware, *J. Am. Chem. Soc.*, 1939, **61**, 1418; (*b*) I. Ugi and F. Beck, *Chem. Ber.*, 1961, **94**, 1839.
7 T. W. Bentley and K. Roberts, *J. Org. Chem.*, 1985, **50**, 4821.
8 R. E. Robertson, *Prog. Phys. Org. Chem.*, 1967, **4**, 213.
9 (*a*) M. L. Bender and M. C. Chen, *J. Am. Chem. Soc.*, 1963, **85**, 30; (*b*) R. F. Hudson and G. Moss, *J. Chem. Soc.*, 1964, 2982.
10 B. D. Song and W. P. Jencks, *J. Am. Chem. Soc.*, 1987, **109**, 3160.
11 D. Leibfritz, *Chem. Ber.*, 1975, **108**, 3014.
12 (*a*) C. A. Bunton and T. A. Lewis, *Chem. Ind. (London)*, 1956, 180; (*b*) E. R. A. Peeling, *J. Chem. Soc.*, 1959, 2307.
13 (*a*) C. B. Swain and C. B. Scott, *J. Am. Chem. Soc.*, 1953, **75**, 141; (*b*) C. D. Ritchie, *Acc. Chem. Res.*, 1972, **5**, 348; (*c*) J. Koskikallio, *Acta Chem. Scand.*, 1972, **26**, 1201.
14 (*a*) C. B. Swain, C. B. Scott, and K. H. Lohmann, *J. Am. Chem. Soc.*, 1953, **75**, 136; (*b*) R. A. Sneen, J. V. Carter, and P. S. Kay, *ibid.*, 1966, **88**, 2594; (*c*) D. J. Raber, J. M. Harris, R. E. Hall, and P. von R. Schleyer, *ibid.*, 1971, **93**, 4821; (*d*) J. P. Richard, M. E. Rothenberg, and W. P. Jencks, *ibid.*, 1984, **106**, 1361; (*e*) R. Ta-Shma and Z. Rappoport, *ibid.*, 1983, **105**, 6082.
15 J. M. Harris, D. C. Clark, A. Becker, and J. F. Fagan, *J. Am. Chem. Soc.*, 1974, **96**, 4478.
16 (*a*) Y. Karton and A. Pross, *J. Chem. Soc., Perkin Trans. 2*, 1978, 595; (*b*) P. R. Luton and M. C. Whiting, *ibid.*, 1979, 646; (*c*) D. N. Kevill and S. W. Anderson, *J. Am. Chem. Soc.*, 1986, **108**, 1579.
17 D. N. Kevill and G. M. L. Lin, *J. Am. Chem. Soc.*, 1979, **101**, 3916.
18 B. Allard and E. Casadevall, *Nouv. J. Chim.*, 1985, **9**, 725.
19 J. Kaspi and Z. Rappoport, *J. Am. Chem. Soc.*, 1980, **102**, 3829.
20 (*a*) C. D. Ritchie, *J. Am. Chem. Soc.*, 1971, **93**, 7324; (*b*) D. J. McLennan and P. L. Martin, *J. Chem. Soc., Perkin Trans 2*, 1982, 1099.

21 A. Pross, *Adv. Phys. Org. Chem.*, 1977, **14**, 99.

22 S. P. McManus and S. E. Zutaut, *Isr. J. Chem.*, 1985, **26**, 400.

23 T. Ando and S. Tsukamoto, *Tetrahedron Lett.*, 1977, 2775.

24 T. W. Bentley, C. T. Bowen, D. H. Morten, and P. von R. Schleyer, *J. Am. Chem. Soc.*, 1981, **103**, 5466.

25 A. H. Fainberg and S. Winstein, *J. Am. Chem. Soc.*, 1957, **79**, 1597.

26 C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' 2nd edn., Cornell University Press, New York, 1969, pp. 427—428.

27 T. W. Bentley and H. C. Harris, *J. Org. Chem.*, 1988, **53**, 724.

28 D. K. Bohme, A. B. Rakshit, and G. I. Mackay, *J. Am. Chem. Soc.*, 1982, **104**, 1100.

29 J. D. Madura and W. J. Jorgensen, *J. Am. Chem. Soc.*, 1986, **108**, 2517.

30 T. W. Bentley and I. S. Koo, *J. Chem. Soc., Chem. Commun.*, 1988, 41.

31 D. N. Kevill and C. B. Kim, *Bull. Soc. Chim. Fr.*, 1988, in the press.

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