

Structure and reactivity in the hydrolyses of aliphatic carboxylic acid esters and chlorides

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ABSTRACT: For hexanoic acid and its seven isomers, relative rates have been determined for acid catalysed esterification with methanol, and compared with those for saponification of the methyl esters. A good correlation between logarithms of relative rates for the two reactions is obtained, and it is suggested that the eight isomers provide a test set of compounds in which steric effects alone act on reactivity at the acyl carbon. A full set of steric parameters (E'_s values) are presented. Rates of solvolyses of the acid chlorides of the isomers have been determined conductometrically in 3:1 wt:wt acetonitrile water. Logarithms of relative rates show a poor correlation with E'_s , and, taking into account the solvent dependence of the rates, the pattern excludes both rate-limiting formation of a tetrahedral intermediate and rate-limiting dissociation of chloride to form acylium ions. The remaining possibilities, a concerted process ($A_N D_N^\ddagger$) and rapid reversible formation of a hydrate followed by rate-limiting dissociation of chloride ($A_N + D_N^\ddagger$) are considered. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: aliphatic carboxylic acids; esters; acid chlorides; hydrolysis; steric and electronic effects; reaction mechanism; kinetics

INTRODUCTION

Mechanisms of hydrolysis of simple esters and amides (RCO.X) usually involve formation and collapse of transient high-energy tetrahedral intermediates,¹ whose lifetimes and protonation states depend on the nature of the leaving group (X) and the acidity of the aqueous medium.² Many of the characteristics of hydrolyses of aliphatic acid chlorides (X=Cl)³ however, are difficult to reconcile with this sequence. Early studies of solvolyses of acetyl chloride, for example, showed that plots of logarithms of rates in dioxan:water⁴ or acetone:water⁵ mixtures against Grunwald–Winstein Y values of the mixtures are linear over a wide range of solvent compositions. A high value ($m=0.81$) for the slopes of the lines is consistent with mechanistic homogeneity across the range of solvent compositions, and with developing positive charge in the acyl portion of the active complex, rather than the reverse. More recent studies by Bentley *et al.* have confirmed the behaviour of acetyl chloride, and shown that selectivities in product formation when solvolyses are carried out in ethanol:water mixtures are only weakly dependent on solvent

composition,⁶ again consistent with a constant mechanism over the solvent range.

For some higher aliphatic acid chlorides, Grunwald–Winstein plots show curvature.⁷ With pivaloyl chloride in acetonitrile:water mixtures, for example, m increases from 0.66 to 1.07 as the water content is increased from 10 to 70% vol:vol. This has been taken to signal mechanistic variation in response to variation in medium, occurring either as a change in rate-limiting step of a multi-step process, or a shift in the balance between competing pathways. The latter interpretation is supported by the observation that, when the solvolysis is carried out in ethanol:water mixtures, product selectivity decreases from 1.94:1 in favour of the ester in 80% ethanol to 1:1 in the more polar 30% ethanol.

Plausible hydrolysis mechanisms include rate-limiting formation of an acylium ion (Fig. 1A), rapid reversible formation of hydrate followed by rate-limiting dissociation of chloride (Fig. 1C), and a loose concerted process (Fig. 1B).

Responses to substituents have been used effectively to probe mechanisms of hydrolyses of acid chlorides in the aromatic series. Variation of reactivity for hydrolyses in the aliphatic series has been less well characterised⁸ although Kevill *et al.*⁹ have examined reactions of acetyl chloride bearing either methyl or chloro substituents with phenol and methanol in acetonitrile, and argue in favour of a concerted mechanism (Fig. 1B with methanol or

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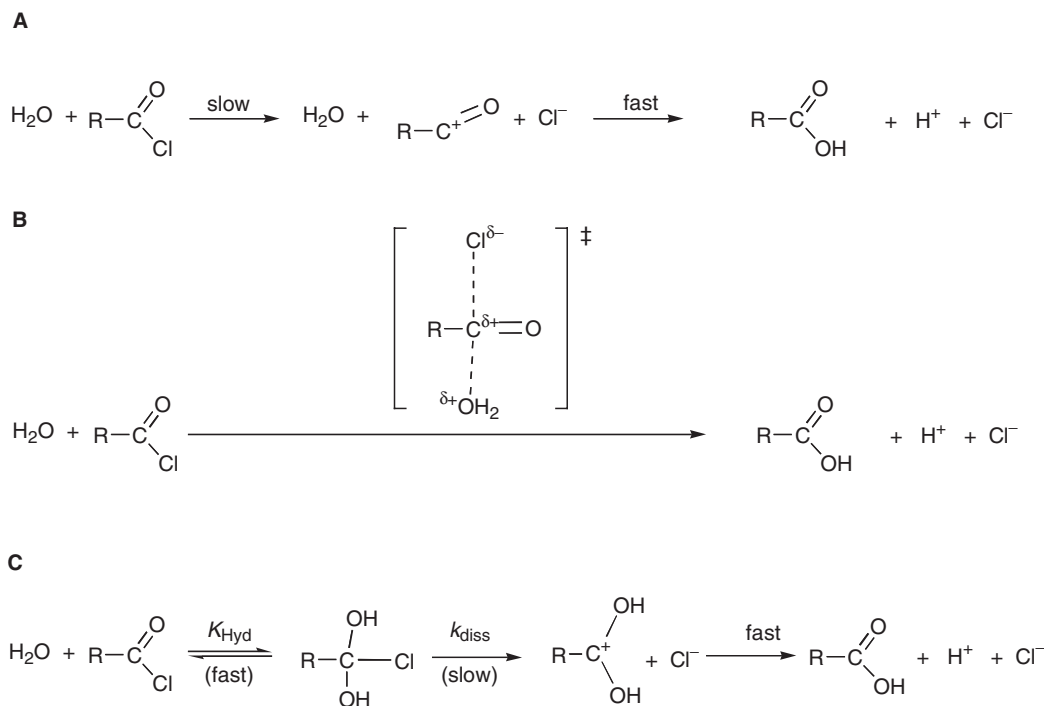


Figure 1. Possible mechanisms for hydrolyses of acid chlorides

phenol rather than water as the nucleophile), with substituents in the alkyl group modulating the tightness of the transition structure. Bentley *et al.*¹⁰ have argued similarly and presented kinetic solvent isotope effects for methanolysis of acetyl chloride and pivaloyl chloride ($k_{\text{MeOH}}/k_{\text{MeOD}} = 1.32$ and 1.46 , respectively at 0°C). They argue that these are too small to be compatible with rapid reversible formation of tetrahedral intermediate (Fig. 1C), although the deuterium fractionation factors¹¹ for hydron attachment to neutral and charged oxygen (1.0 and 0.69, respectively) point to a maximum equilibrium solvent isotope effect, $K_{\text{H}}/K_{\text{D}} = 1.45$, for formation of the protonated carboxylic acid, which is not incompatible with the values given by Bentley. Mechanism C has not found recent favour although Hudson suggested it as a possibility in hydrolysis of acetyl chloride⁴ and it has been considered for hydrolysis of alkylchloroformates¹² and even for hydrolyses of benzoyl chloride.¹³

In this work we examine the hydrolyses of chlorides of hexanoic acid (Fig. 2) and its seven isomers and compare the response to structural variation with that in acid-catalysed formation of their methyl esters and in saponification of these esters.

These compounds sample the basic branching patterns within their alkyl residues, and by working with isomers, we eliminate ponderal effects on relative reactivities, and hope to reduce, and possibly eliminate, contributions which might arise from differential solvation of the hydrocarbon portions of the acids and their derivatives. Variations in rates of formation¹⁴ and cleavage¹⁵ of

methyl esters of the lower straight chain acids, or in esterifications of acetic acid by a range of straight chain alcohols¹⁶ have been associated with these effects. It has been suggested¹⁷ that basicity orders in protonation of simple esters are affected by such solvation differences, and similar effects seem to operate in protonations of ketones.¹⁸ These are likely to be most evident in aqueous solution, and we attempt here to put an upper limit on their contribution within this isomer set.

The detailed description of hydrophobic solvation remains a matter of some controversy,¹⁹ but it seems clear that solvation energies for hydrocarbons in water are linked closely to the surface area of the cavity generated by the hydrocarbon in the medium. The relevant molar volumes are experimental quantities, and application of the empirical group additivity scheme developed by Lepori and Gianni²⁰ for calculation of van der Waal's volumes and partial molar volumes of organic compounds in water shows that both measures are structure invariant (85.02 ± 0.10 and $53.85 \pm 0.06 \text{ cm}^3 \text{ mol}^{-1}$, respectively for the eight isomers). Surface areas are not similarly available from experiment, and estimates rely on calculations using, for example, bond lengths and atomic radii taken from crystallographic sources.²¹ Such calculated surface areas depend on the conformation adopted by the molecule and on the extent of branching. For *n*-pentane for example, calculated molecular surface areas are 286.97 , 280.63 and 273.18 \AA^2 , for conformations with 0, 1, and 2 *gauche* relationships, and for isomeric hydrocarbons, *n*-pentane, 2-methylbutane and

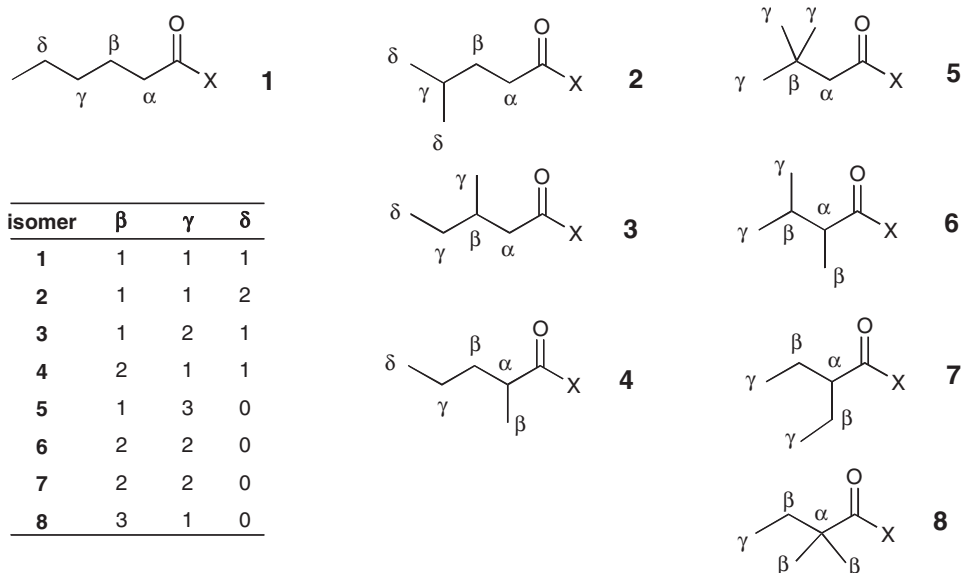


Figure 2. Structures of the isomers of hexanoic acid ($X=OH$) and derivatives ($X=OMe$ or Cl) and numbers of β , γ , and δ carbons in the alkyl residues

neo-pentane, areas range from 286.97 to 269.72 Å², a spread of 16.65 Å². This residual variation is small compared to the average increase in the surface areas of the *n*-alkane series of 31.8 Å² for addition of a single CH₂-group. It has been estimated that the effects of surface area on solvation energies of hydrocarbons in water are *ca.* 0.16 kJ Å⁻² mol⁻¹ so that the differential solvation associated with the isomerism within the C₅ hydrocarbon residues is 2.65 kJ · mol⁻¹. If all of this was expressed in reactivity it might account for a relative rate factor of 3.02, and we consider that eventuality to be extremely unlikely.

FORMATION AND SAPONIFICATION OF THE METHYL ESTERS

Any discussion of the effects of structural variation in the series reasonably starts from the two-term Taft equation,²² which separates steric (E_s) and polar (σ^*) contributions for the alkyl substituents.

$$\log(k/k_o) = \rho^* \sigma^* + \delta E_s \quad (1)$$

Unfortunately, values of E_s and σ^* are not available for all eight of the alkyl groups in the isomer set and where they are, the experimenter is presented with a surfeit of values, often showing some disagreement.²³ Values of these constants are extracted from comparison of reactivities in acid-catalysed esterification or hydrolyses with those in saponification of the esters. Since both acids and esters were available to us, we have made our own measurements on the set of isomers using methyl esters (Fig. 3).

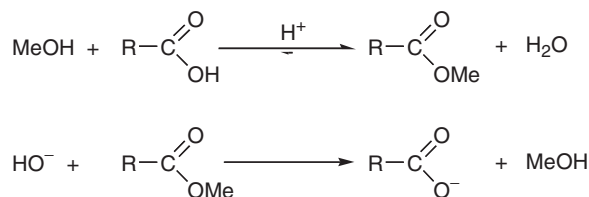


Figure 3. Acid catalysed esterification and saponification of methyl esters

Identical reaction conditions (solvent, catalyst, temperature) across the series were assured by using a mixture of all the acids or esters in the same reaction mixture, equilibrated to 30°C, and monitoring the course of reaction by periodic sampling and GLC analysis on a column previously shown to resolve all eight isomeric esters. For the esterifications, reaction was initiated by adding a drop of concentrated sulphuric acid to a solution of the esters in methanol. For saponification, reaction was initiated by adding a mixture of the esters to a 12-fold excess of potassium hydroxide in 5:95 vol:vol aqueous methanol. For both esterifications and saponifications first order behaviour was found and rate constants and logarithms of rates relative to *n*-hexanoic acid or methyl *n*-hexanoate, isomer **1**, are presented in Table 1.

Taft and Ingold originally suggested that polar effects in acid catalysed esterifications should be minimal, with any effect on the initial reversible protonation step being countered by that on the reactivity of the resultant carbocation in the nucleophilic addition of water. Thus, the esterification reaction defines steric substituent constants, E_s , with $\delta = 1$ in relationship (2).

$$\log(k/k_o) = \delta E_s \quad (2)$$

Table 1. Rate constants for formation and saponifications of methyl esters of the isomeric acids, RCOX (X=Ome or OH) at 30°C and related parameters

RCO.X	Esterifications		Saponifications		Substituent constants	
	$10^4 k_{\text{obs}} \text{ min}^{-1}$	Log k_{rel}	$10^4 k_{\text{obs}} \text{ min}^{-1}$	Log k_{rel}	E'_s ^a	σ^* ^c
1	269 (± 7)	0.000	356 (± 10)	0.000	-0.31	-0.130
2	286 (± 10)	0.027	379 (± 9)	0.027	-0.32	-0.115
3	46.7 (± 1.3)	-0.760	77.1 (± 2.7)	-0.664	-0.97	-0.132
4	41.9 (± 1.0)	-0.808	54.4 (± 1.5)	-0.816	-1.06	-0.157
5	8.18 (± 0.19)	-1.517	20.5 (± 1.1)	-1.240	-1.63	-0.098
6	4.76 (± 0.08)	-1.752	7.70 (± 0.28)	-1.665	-1.82 ^b	-0.192
7	3.86 (± 0.07)	-1.843	5.30 (± 0.15)	-1.827	-2.00	-0.185
8	1.95 (± 0.04)	-2.140	2.74 (± 0.08)	-2.114	-2.28	-0.188

^a From reference 24.^b Calculated in this work, see text.^c σ^* (calc) = (Log k_{rel} (sapon) - E'_s + 0.632)/2.48.

Dubois cogently criticised²⁴ the original set of E'_s parameters, pointing out that they averaged data for hydrolyses and formation of both ethyl and methyl esters under a range of conditions, and were based on an assumption that the various reactions showed the same sensitivity to steric effects. To remedy this, he presented an extensive set of measurements for esterifications of aliphatic carboxylic acids in methanol at 40°C, using these to define a new parameter denoted E'_s . Values are available for all compounds in our isomer set (Table 1) except for **6**, and as might be expected, logarithms of rate relative to **1** (k_{rel}) obtained for those seven acids in this work give a good linear correlation with Dubois' E'_s values, Eqn (3), with $R^2 = 0.998$, which allows us to add a value of $E'_s = -1.82$ for the alkyl group (*i*-PrCHMe) in **6** to Dubois' tabulation.

$$\begin{aligned} \log k_{\text{rel}}(\text{esterification}) \\ = 1.102(\pm 0.021) \times E'_s + 0.336(0.030) \end{aligned} \quad (3)$$

The behaviour of the ester saponifications is remarkably similar. A plot of logarithms of relative rates for the saponifications of the methyl esters against those the acid-catalysed esterification with methanol is shown later in Fig. 6 and a linear least squares fit yields Eqn (4) with $R^2 = 0.988$.

$$\begin{aligned} \log k_{\text{rel}}(\text{saponification}) \\ = 0.963(\pm 0.044) \times \log k_{\text{rel}}(\text{esterification}) \\ + 0.021(\pm 0.056) \end{aligned} \quad (4)$$

The good correlation, near unity of slope and near zero intercept emphasises the small contribution made by the $\rho^* \sigma^*$ term in the Taft equation for this set of compounds in this reaction. A value of $\rho^* = 2.48$ was originally chosen for the ester saponification reactions used to obtain values for σ^* (for comparability with ρ -values for saponification of methyl and ethyl esters of substituted benzoic acids)

and use of that value with our saponification data and Dubois' E'_s constants yields a set of σ^* -values for the alkyl groups in the isomer set, relative to isomer **1**. Taking σ^* for the *n*-pentyl residue to be that same as for *n*-butyl (-0.13)²⁵ from the original set, and $E'_s = -0.31$ permits calculation of $\log(k_{\text{hexanoate}}/k_{\text{acetate}}) = -0.632$ for the ester saponification, in turn permitting scaling to comparability with existing σ^* values. These values are presented in Table 1. We find a rather smaller span ($\Delta\sigma^* = 0.09$) than might have been expected from literature values available for isomeric C₄H₉ alkyl groups ($\Delta\sigma^* = 0.2$) but the trend is similar. Uncertainties in individual σ^* -values²⁶ are comparable with their total span, so that the only safe conclusion here is that the variation of σ^* for these alkyl groups is very small, a conclusion supported by evidence from calorimetry²⁷ on carbocation formation, and from the effects of remote alkyl substitution on solvolytic reactivity of bridgehead halides.²⁸ It seems that steric effects in acidic and basic hydrolyses of methyl esters are indeed equivalent for this set of isomers, one of the basic assumptions of the Taft-Ingold equation, and one which does not seem to hold when alkyl groups are placed at *o*-positions in benzoic acids and their esters.²⁹

We have also analysed the response of reactivity to the branching pattern within the alkyl chain of the isomers in a reduced version of the topological approach used by Dubois.³⁰ For this, we have counted the number of carbon atoms at β -, γ - and δ -positions in each isomer (tabulated in Fig. 2), and then used multiple linear regression to obtain best values for parameters in Eqn (5), which ignores the contribution from the ε -carbon, since only one isomer (hexanoic itself, **1**) has an ε -carbon. Values, standard deviations and correlation coefficients are presented in Table 2.

$$\log k_{\text{rel}} = B\beta + C\gamma + D\delta + \text{Const} \quad (5)$$

This crude treatment affords moderately good correlations ($R^2 > 0.987$) and yields comparably large negative

Table 2. Parameters from multiple regression to Eqn (5)

Reaction	B	C	D	Constant	R ²
Esterifications	-1.111 (±0.083)	-0.853 (±0.083)	0.080 (±0.106)	2.126 (±0.278)	0.991
Saponification	-1.117 (±0.097)	-0.738 (±0.097)	0.080 (±0.106)	2.000 (±0.327)	0.987

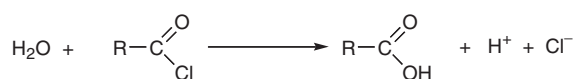
values for both *B* and *C* in both reactions, signalling that branching at both α - and β -positions is strongly rate inhibiting, a pattern compatible with the largely steric origin³¹ of E'_s .

HYDROLYSES OF THE ACID CHLORIDES

For comparability with the studies of Bentley *et al.* we have examined the hydrolyses of the acid chlorides in 3:1 wt:wt acetonitrile:water, that solvent composition being chosen to give easily measurable rates and to exclude complications of slow solution which became evident with these C₆-acid chlorides when the water content approached 50%. Reactions were monitored

conductometrically, a method which effectively follows release of HCl during the hydrolysis (Fig. 4).

With the apparatus available, reactions at 30°C were too fast for us to follow for all but isomer **8**. First order rate constants determined at lower temperatures and activation parameters are collected in Table 3. To avoid uncertainties associated with long extrapolations, rate constants at 10°C have been calculated and included in the table for use in comparisons with the rate

**Figure 4.** Hydrolysis of acid chlorides**Table 3.** Rate constants and activation parameters for hydrolyses of the isomeric acid chlorides in 3:1 wt:wt acetonitrile:water

Compound (X=Cl)	T/C	10 ² k _{obs} ^b s ⁻¹	Activation parameters
1	-1.1	5.49	$\Delta H^\ddagger = 61.5 (\pm 1.8) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -42.4 (\pm 6.6) \text{ JK}^{-1} \text{ mol}^{-1}$
	4.4	9.31	
	9.4	15.5	
	10.0 ^a	16.4 (±1.3)	
2	-0.1	5.79	$\Delta H^\ddagger = 61.6 (\pm 0.5) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -42.3 (\pm 1.6) \text{ JK}^{-1} \text{ mol}^{-1}$
	8.2	13.3	
	13.3	21.6	
	10.0 ^a	15.8 (±0.6)	
3	-0.1	6.33	$\Delta H^\ddagger = 59.2 (\pm 2.0) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -50.4 (\pm 7.0) \text{ JK}^{-1} \text{ mol}^{-1}$
	7.8	14.0	
	15.8	28.0	
	10.0 ^a	16.8 (±1.9)	
4	3.4	2.64	$\Delta H^\ddagger = 57.0 (\pm 0.4) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -68.3 (\pm 1.5) \text{ JK}^{-1} \text{ mol}^{-1}$
	11.5	5.57	
	18.4	9.95	
	10.0 ^a	4.83 (±1.3)	
5	-1.6	8.96	$\Delta H^\ddagger = 59.4 (\pm 3.4) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -45.3 (\pm 12.2) \text{ JK}^{-1} \text{ mol}^{-1}$
	5.5	18.8	
	10.4	28.3	
	10.0 ^a	27.8 (±3.8)	
6	1.1	2.34	$\Delta H^\ddagger = 58.9 (\pm 1.3) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -60.7 (\pm 4.6) \text{ JK}^{-1} \text{ mol}^{-1}$
	8.0	4.40	
	15.7	9.09	
	10.0 ^a	5.40 (±0.30)	
7	5.5	2.10	$\Delta H^\ddagger = 53.5 (\pm 4.3) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -84.4 (\pm 14.9) \text{ JK}^{-1} \text{ mol}^{-1}$
	12.3	4.01	
	18.4	6.09	
	10.0 ^a	3.16 (±0.64)	
8	9.4	1.00	$\Delta H^\ddagger = 60.3 (\pm 0.6) \text{ kJ mol}^{-1}$ $\Delta S^\ddagger = -69.4 (\pm 2.1) \text{ JK}^{-1} \text{ mol}^{-1}$
	17.7	2.13	
	25.5	4.26	
	10.0 ^a	1.06 (±0.13)	

^a Calculated values and 90% confidence limits.

^b Values are the means of at least two determinations whose values differed by less than 5%.

data for formation and saponifications of the methyl esters.

While mechanisms for the esterification and ester saponification are expected to be invariant to structural variation for this series, the same may not be assumed for the hydrolyses of the acid chlorides. The activation parameters give no obvious indication of mechanistic change but we note that entropies of activation (see Table 3) are similar for isomers which do not have branching at the α -carbon, with an average value of ΔS^\ddagger for **1**, **2**, **3** and **5** of $-45.1(\pm 3.8) \text{ J K}^{-1} \text{ mol}^{-1}$, while those for **4**, **6**, **7**, and **8** are significantly more negative and have larger spread with an average of $-70.7(\pm 9.9) \text{ J K}^{-1} \text{ mol}^{-1}$. We return to this point later. The possibility of significant mechanistic variation was further tested by examining the dependence on solvent polarity of rates of hydrolysis of three of the acid chlorides, **5**, **7**, and **8** ($\text{X}=\text{Cl}$), representative of the different branching situations at the α -carbon. Rates were determined in four acetonitrile:water mixtures over the composition range 9:1 to 6:4 (vol:vol) acetonitrile:water. The data are presented in Table 4 and Fig. 5 shows plots of logarithms of rate constants against the Grunwald–Winstein Y values for these solvents determined by Bentley *et al.*³² The behaviour closely resembles that found by Bentley *et al.*⁷ for solvolyses of pivaloyl chloride, with linearity ($R^2 > 0.999$) and high slopes ($m = 0.67, 0.68, \text{ and } 0.70$ for **5**, **7**, and **8**, respectively) for the three least aqueous mixtures, and indication of upward curvature in the 60:40 mixture. Since the Y values are based on the solvolyses of *t*-butyl chloride, they incorporate a component from solvent nucleophilicity as well as ionising power. However, solvent nucleophilicities, as measured by N_T ³³ or N_1 ³⁴ parameters are very similar over the range examined, and slopes therefore do indeed provide a measure of response to ionising power.³⁵ The evidence does not support any major shifts in the nature of charge development within the series, although we note the weak increasing trend in values of m with decreasing reactivity. In the case of **5**, a reaction was also run in a 3:1 wt:wt acetonitrile:D₂O for product analysis which established a complete absence of deuterium incorporation in the recovered acid.

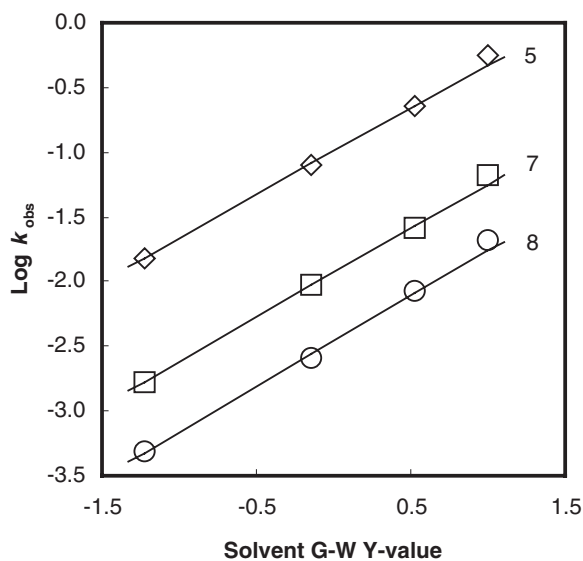


Figure 5. Plot of logarithms of rate constants for solvolyses of representative acid chlorides **5**(◇), **7**(□), and **8**(○) in 9:1, 8:2, 7:3 and 6:4 (vol:vol) acetonitrile:water mixtures at -1.7°C against solvent Y values. Solid lines are the lines of best fit for the first three points

DISCUSSION

Consideration of the data in Table 3 reveals clear differences between behaviour of the acid chlorides and ester formations and saponifications. Firstly, while the least reactive isomer is 2,2-dimethylbutanoyl **8** for all three reactions, and hexanoyl **1** and 4-methylpentanoyl **2** are equally most reactive in the ester formations and saponifications, the most reactive acid chloride is 3,3-dimethylbutanoyl **5** being *ca.* 1.7-fold more reactive than hexanoyl chloride **1**. Since the corresponding acid was less reactive than hexanoic acid by a factor of 0.03 in esterifications, a factor of 53 separates the effects of this alkyl residue in the two different reactions. Secondly, the span of reactivities of the acid chlorides is much reduced, being only 26-fold from **5** to **8** ($\text{X}=\text{Cl}$) as opposed to 140-fold in the acid esterifications.

Table 4. Rate constants for solvolyses of acid chlorides of **5**, **7**, and **8** in acetonitrile:water mixtures at -1.7°C

Solvent ^a AN:water	Y^b	$10^2 k_{\text{obs}} \text{ s}^{-1}$		
		5	7	8
9:1	1.23	1.53×10^{-2}	1.66×10^{-3}	4.84×10^{-4}
8:2	0.14	8.01×10^{-2}	9.62×10^{-3}	2.59×10^{-3}
7:3	0.53	2.30×10^{-1}	2.62×10^{-2}	8.34×10^{-3}
6:4	1.00	5.54×10^{-1}	6.71×10^{-2}	2.10×10^{-2}

^a Volume:volume at 25°C before mixing.

^b From reference 7.

More quantitatively, correlation between logarithms of rates for the acid chloride hydrolysis and E'_s (or logarithms of relative rates of the saponifications) is very poor ($R^2 = 0.455$, Eqn 6). Correlation with both E'_s and σ^* yields Eqn (7) with marginally improved correlation, $R^2 = 0.797$, showing, apparently, a weak dependence on the steric contributions and a very large positive value of $\rho^* = 10.302$.

$$\begin{aligned} \log k_{\text{rel}}(\text{chloride}) \\ = 0.431(\pm 0.192) \times E'_s + 0.217(\pm 0.284) \end{aligned} \quad (6)$$

$$\begin{aligned} \log k_{\text{rel}}(\text{chloride}) \\ = 0.104(\pm 0.171) \times E'_s + 10.302(\pm 3.543)\sigma^* \\ - 1.334(\pm 0.429) \end{aligned} \quad (7)$$

This relationship serves only to re-emphasise the absence of correlation with the steric parameter, and the very small variation of the polar parameter within the series. In fact, large negative values of ρ^* would be anticipated. Indeed, Kreevoy and Taft³⁶ have reported $\rho^* = -3.7$ for acid catalysed acetal hydrolysis, and Kwart and Price³⁷ report $\rho = -2.2$ for lyonium ion catalysed hydrolyses of aromatic ortho esters, both reactions in which positive charge development occurs at the central carbon. Kevill and Kim³⁸ have noted that the Taft equation does not yield chemically sensible correlations for rates of ethanolyse of a range of acid chlorides. Figure 6 compares the good linear correlation of logarithms of relative rates for saponifications with the acid-catalysed esterification and the poor correlation of logarithms of relative rates for the chloride solvolyses with the same data set.

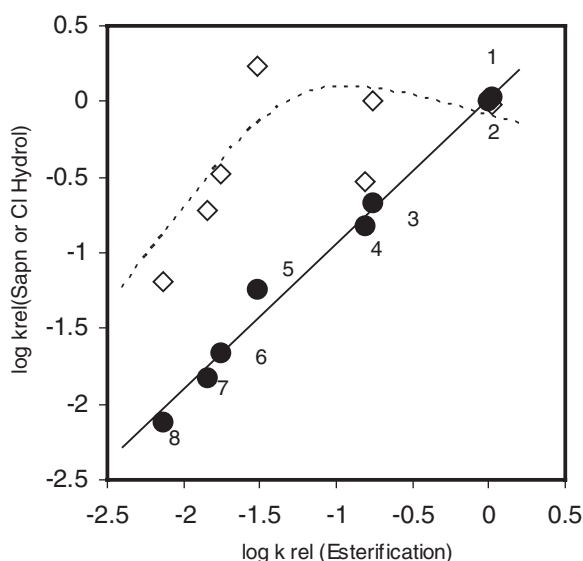


Figure 6. Plot of logs of relative rates for saponification of methyl esters at 30°C (●) and for hydrolyses at 10°C of acid chlorides (◇) against logs of relative rates for acid-catalysed formation of the methyl esters at 30°C

Before proceeding further, we re-emphasise the small span (27-fold; $\Delta\Delta G^\ddagger = 8.3 \text{ kJ} \cdot \text{mol}^{-1}$) of reactivities to be explained.

The absence of correlation with E'_s is difficult to reconcile with a common mechanism involving rate limiting addition to form a tetrahedral intermediate (as is the observed solvent dependency). Given the weight of evidence that alkyl groups are weakly electron donating in their polar interactions, the pattern also excludes the mechanism involving rate-limiting formation of acylium ions (Fig. 1A) across the series. In that case, the ordering of reactivities should be reversed, with both steric and residual polar effects favouring the dissociation of the chloride with increased branching next to the acyl group.

Again, as noted earlier, mechanism C, the ($A_N + D_N^\ddagger$) process, has not found recent favour, but we explore the possibility that the reactivity pattern (i.e. the substituent effect on reactivity and the dependence on medium) is consistent with it.

We note firstly that rapid reversible formation of a hydrate followed by rate limiting dissociation of chloride is qualitatively consistent with the reduced span of reactivities. Steric effects from the variation of the alkyl group will operate in opposite senses on the two separate steps of the reaction, and a reduced span requires only that the sensitivity for formation of the hydrate is larger than for its dissociation. This could not alone account for the very poor correlation shown in Fig. 6, but we have already noted a possible distinction, based on activation parameters, between the group of isomers which do not have branching at the α -carbon (**1**, **2**, **3** and **5**) and those which do (**4**, **6**, **7** and **8**) and note now that the pattern of rates also supports this separation. For isomers **1**, **2**, **3** and **5**, rates are relatively close, (average is $1.11 \pm 0.31 \text{ s}^{-1}$ at 30°C), while for **4**, **6**, **7**, and **8**, the range is from 6.16 to 30.0 s^{-1} , a factor of 4.8. This separation might be reconciled with mechanism of Fig. 1C if the nature of the analytical method used to follow the reaction is taken into account. Conductometry monitors appearance of HCl, and the reaction stoichiometry requires that this equals the amount of carboxylic acid. Covalently bound forms of chloride, that is, the acid chloride and its hydrate are not distinguished and the method can only give an indication of their total loss as reaction proceeds. If an initial equilibration of acid chloride and its hydrate (governed by K_{Hyd}), is sufficiently fast compared to the dissociation of chloride from the hydrate, governed by k_{diss} , then the pseudo-first order rate constant measured by the conductometry is given by Eqn (8). In the extremes, if $K_{\text{Hyd}} \gg 1$ then $k_{\text{obs}} = k_{\text{diss}}$ and if $K_{\text{Hyd}} \ll 1$, the $k_{\text{obs}} = K_{\text{Hyd}} \cdot k_{\text{diss}}$.

$$k_{\text{obs}} = \left(\frac{K_{\text{Hyd}}}{1 + K_{\text{Hyd}}} \right) k_{\text{diss}} \quad (8)$$

If our first group of isomers (**1**, **2**, **3** and **5**) are those where K_{Hyd} is sufficiently large for $k_{\text{obs}} \approx k_{\text{diss}}$, then the

observed small rate change in the series represents a response to branching at more remote positions, that is, in the equation $\log k_{\text{diss}} = \delta_{\text{diss}} E'_s$, δ_{diss} has a small negative value. For the second group, the α -branching reduces K_{Hyd} . Relative reactivities continue to depend weakly on k_{diss} , but this will be countered by the effect of steric bulk of the alkyl group on the formation of the hydrate, that is, in the equation $\log K_{\text{Hyd}} = \delta_{\text{Hyd}} E'_s$, δ_{Hyd} has a positive value, but its contribution is also variable because of the form of the Eqn (8) so the relationship between logarithms of relative rates and E'_s will be curved rather than linear. For illustration only, the dashed curved line in Fig. 6 was generated assuming values of $k_{\text{diss}} = 16.4 \times 10^{-2} \text{ s}^{-1}$ and $K_{\text{Hyd}} = 50$ and for hexanoyl chloride with $\delta_{\text{Hyd}} = 1.7$ and $\delta_{\text{diss}} = -0.3$. As a qualitative description, this has possibilities, but difficulties remain arriving at a fully quantitative treatment using the tabulated values of E'_s , the most important of which, evident in Fig. 6, is the overlap between the two groups which occurs with isomers **5** ($E'_s = -1.63$) and **4** ($E'_s = -1.06$). If E'_s values were simply expressed in the equilibrium formation of a hydrate, then **4** should belong to the first group and **5** to the second, rather than the reverse. There is no easy way out of this contradiction, but we note that E'_s values reflect relative energies of transition structures in the formation of tetrahedral adducts, rather than of the adducts themselves. Steric demand is unlikely to be identical, and branching at the β -positions, which we have shown earlier to contribute significantly to E'_s , may be more important in transition structures than in the adducts.

For the ($A_N + D_N^\ddagger$) mechanism to be viable there also must be reasonable indication a) that equilibria for hydrate formation are moderately favourable, b) that the initial equilibrium is established sufficiently quickly, and finally, c) that reversion of hydrate to acid chloride might be competitive with dissociation of chloride from the hydrate to yield product.

We can find no directly relevant experimental studies yielding values for the equilibrium constant for hydrate formation, but note that a recent computational study³⁹ found the addition of methanol to acetyl chloride to yield 1,1-dihydroxyethyl chloride in the gas phase was exothermic by $4.4 \text{ kcal} \cdot \text{mol}^{-1}$. This is hardly strong support, but we also draw attention to hydration behaviour of ketones and aldehydes.⁴⁰ Equilibrium constants respond to electron deficiency in the carbonyl substituents by increasing from 1.4×10^{-3} for acetone to 35 for 1,1,1-trifluoroacetone⁴¹, with rate constants for the spontaneous addition of water ranging from 8.5×10^{-6} to 9.1 s^{-1} .⁴² Effects for aldehydes are even more pronounced. Hydrate formation for trichloroacetaldehyde has $K = 2.8 \times 10^4$,⁴³ and a rate constant of 450 s^{-1} .⁴⁴ These are for reactions in water, and a true comparison with the behaviour of hexanoyl chloride and its isomers would require extrapolations of both temperature and solvent composition, both of which introduce large uncertainties.

A less extreme extrapolation of Hudson's data⁴ gives $k = 1100 \text{ s}^{-1}$ for the hydrolysis of acetyl chloride. This is not an isomer of hexanoic acid and the unquantified effects of differential hydration complicate interpretation, but it is difficult to reconcile this rate with the available data for hydration of ketones. The C—Cl bond in acid chlorides is, however, rather longer than the C—C bond in ketonic models so that steric hindrance to nucleophilic attack at the carbonyl of an acid chloride is reduced, and their hydration behaviour may be closer to that of aldehydes than ketones in which case the discrepancy between reactivities is much reduced.

Reversibility of the hydration is testable by O^{18} incorporation in recovered acid chloride when reactions are run in H_2O^{18} . To our knowledge, experiments of this type have not been run on aliphatic acid chlorides, but Bunton *et al.*⁴⁵ measured O^{18} incorporation during the hydrolyses of benzoyl, *p*-toluyl and mesitoyl chlorides in dioxan-water mixtures. Incorporations are low, but not vanishingly small. For example for benzoyl chloride in 33% water, $k_{\text{hyd}}/k_{\text{ex}} = 18$. Bunton offers no estimates of uncertainties, but is able to state with certainty when no incorporation is found (for example in acid catalysed hydrolysis of benzamide). It is not clear to us how measurements on the aromatic series relate to the behaviour of aliphatic compounds, but the finding of any incorporation challenges mechanisms **A** and **B**. We suggest that neither this experiment, nor the comparison with the behaviour of acetyl chloride absolutely exclude a mechanism involving hydrate formation.

The more difficult point concerns the partitioning of hydrate between water loss (in reverting to acid chloride), and dissociation of chloride ion. The rate constants found for hydrolysis of hexanoyl chloride are $k = 0.16 \text{ s}^{-1}$ (10°C) or 0.64 s^{-1} (25°C). With an ($A_N + D_N^\ddagger$) mechanism operating as considered above, these would be identifiable with rate constants of dissociation of chloride ion from the hydrate. For *t*-butyl chloride in 80:20 vol:vol acetonitrile:water,³² $k = 6.6 \times 10^{-6} \text{ s}^{-1}$, so that the acid chloride is about 10^5 more reactive than *t*-butyl chloride. Even with some correction for the nucleophilic component in the *t*-butyl chloride solvolysis, the ratio would largely arise from the effect on carbocation stability of replacing two methyl groups at the reactive site by two hydroxyl groups. It is difficult to anticipate the effect of such a structural change on carbocation stability, but values of σ^* for hydroxyl group around 1.4²³ so that, if effects are additive, the value of ρ^* required to reproduce the rate ratio is only 1.8. This seems much too low, and we note that Steenken and McClelland⁴⁶ have found $\rho^* \approx 4.4$ for capture of water by dialkoxyalkyl cations. If applicable to chloride loss from an acid chloride hydrate, the predicted rate ratio is over 10^{10} . The discrepancy is difficult to reconcile with the intermediacy of dihydroxyalkyl cation.

As noted earlier, the bimolecular, concerted process (mechanism Fig. 1B), is currently accepted for solvolyses

of simple aliphatic acid chlorides. Our observations do not challenge this view. The distinct difference in steric requirements of tetrahedral intermediate formation (nucleophilic attack perpendicular to the trigonal plane) and concerted displacement at trigonal carbon (nucleophilic attack in the trigonal plane), might account for the poor correlation of logarithms of rates with E'_s , especially if the transition structure is a loose one, and we suspect that any computational method could be parameterised to reproduce the result.

CONCLUSIONS

We have presented evidence that the relative reactivities of derivatives of hexanoic acid and its isomers reflect only steric effects associated with the structural variation of the alkyl groups. Since these readily available isomers offer a representative sample of alkyl branching patterns, they may be regarded as a test set in examination of mechanisms of reactions at acyl carbon, complementing the purely electronic effects probed by reactivity of *p*- and *m*-substituted benzoic acids.

This 'C₆-isomer probe' has been applied to hydrolyses of acid chlorides. The poor correlation of logarithms of relative rates with E'_s , and solvent dependence of the rates excludes both rate-limiting formation of a tetrahedral intermediate ($A_N^\ddagger + D_N$) and rate-limiting dissociation of chloride to form acylium ions ($D_N^\ddagger + A_N$). The possibility of a rapid reversible formation of a hydrate followed by rate-limiting dissociation of chloride ($A_N + D_N^\ddagger$) has also been considered and is most improbable. A concerted process ($A_N D_N^\ddagger$) is believed to be compatible with the observations.

EXPERIMENTAL SECTION

The compounds

With the exception of 2,3-dimethylbutanoic acid **6** (X = OH) which was prepared by the method of Ikan *et al.*,⁴⁷ all carboxylic acids were commercially available. All acids were distilled before use and exhibited spectroscopic properties consistent with their structures and >99% purity. *Acid chlorides* were prepared by reactions of the acids with oxalyl chloride⁴⁸ and purified by bulb-to-bulb distillation at atmospheric pressure.

Authentic samples of *methyl esters* for GLC analysis were prepared by dissolving a little of the acid chloride in anhydrous methanol.

Kinetics of esterifications with methanol

The acids (100 μ l of each) and toluene (100 μ l) were mixed in a capped vial. A portion (200 μ l) of this mixture

was then added to anhydrous methanol (5 ml) in a capped vial in the block of a thermostat maintained at 30°C. Reaction was initiated by addition of conc. sulphuric acid (10 μ l). Samples were taken periodically and quenched for analysis as follows. A sample (100 μ l) was added to a mixture of pentane (1 ml) and saturated NaHCO₃ solution (0.5 ml) in a capped vial, which was shaken vigorously for 60 s. The NaHCO₃ layer was separated and replaced by distilled water (0.2 ml), then the sample shaken and the aqueous layer separated. This process was repeated with fresh water, and then solid sodium sulphate added to dry the pentane layer. After standing for 5 min the supernatant pentane solution was transferred to a clean vial for analysis by GLC on a 30 \times 0.25 mm polydimethylsiloxane capillary column (*Restek* RTX-1, order of elution **5**, **8**, **6**, **7**, **4**, **3**, **2** and **1**). At least 12 points were collected over 3 half-lives. Growths of ester peak areas relative to toluene were first order and rate constants were extracted by non-linear least squares fitting of $X_{\text{calc}} = X_{\text{inf}} - \Delta X e^{-kt}$ to the data using X_{inf} , ΔX , and k as adjustable parameters.

Kinetics of saponification of the methyl esters

A solution of KOH in 95:5 (vol:vol) methanol:water (5 ml of 0.81 M) was placed in a capped vial in the block of a thermostat maintained at 30°C. Reaction was initiated with addition of the esters and toluene (40 μ l) of an approximately equimolar mixture. Samples were taken periodically and quenched for analysis as follows. A sample (100 μ l) was added to a mixture of pentane (1 ml) and saturated NaH₂PO₄ solution (0.5 ml) in a capped vial, which was shaken vigorously for 60 s. The NaH₂PO₄ layer was separated and replaced by distilled water (0.2 ml), then the sample shaken and the aqueous layer separated. This process was repeated with fresh water, and then solid sodium sulphate added to dry the pentane layer. After standing for 5 min the supernatant pentane solution was transferred to a clean vial for analysis by GLC as described above. Decays of peak areas for the esters relative to toluene were first order and rate constants were extracted by non-linear least squares fitting of $X_{\text{calc}} = \Delta X e^{-kt}$ to the data using ΔX , and k as adjustable parameters.

Kinetics of solvolysis of the acid chlorides

The solvent mixtures were made up by mixing acetonitrile (distilled from P₂O₅) with distilled water. The cell and fast-response conductivity bridge have been described elsewhere.⁴⁹ Reactions were initiated by injecting the neat liquid acid chloride (1 μ l) into solvent (*ca.* 10 ml) in the stirred cell, so that concentrations were *ca.* 0.0005 M. The lowest temperature used, was -1.6°C, below which the solvent mixtures began to freeze. Voltages proportional to conductance were logged

directly via a 12-bit AD converter, taking at least 50 points over 5 half-lives. For the fastest reactions, half-lives were *ca.* 5 s, and our apparatus permitted sampling every second. Rate constants reported were extracted by non-linear least squares fitting of $X_{\text{calc}} = X_{\text{inf}} - \Delta X e^{-kt}$ to the data using X_{inf} , ΔX , and k as adjustable parameters for points taken 2 s after injection of the acid chloride. For individual runs, good fits were obtained ($R^2 > 0.995$) and rates were reproducible to better than $\pm 5\%$ for duplicate runs. Some lack of reproducibility was shown in the first 1 or 2 s, behaviour attributed to relatively slow solution of the acid chlorides in the medium, a feature which became more pronounced as the water content of the medium increased.

As check on the method, reactions of pivaloyl chloride were also determined. In the 3:1 wt:wt AN:water mixture at 0°C, $k_{\text{obs}} = 6.3 \times 10^{-3} \text{ s}^{-1}$, with $\Delta H^\ddagger = 54.4 \text{ kJ mol}^{-1}$ and $\Delta S^\ddagger = -87.1 \text{ J} \cdot \text{K}^{-1} \text{ mol}^{-1}$ in agreement with the data of Bentley *et al.*^{6,7}

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