Kinetics and mechanism of the hydrolysis of 1-aryloxyethyl alkanoates

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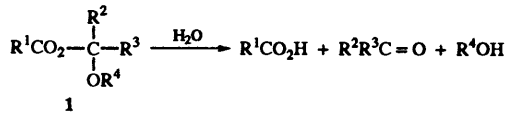
The kinetics and mechanism of the hydrolysis of 1-aryloxyethyl alkanoates are reported. In acidic media, ^{18}O isotope exchange studies, kinetics, activation parameters and substituent effects point clearly to an A_{Al}-1 mechanism with the formation of an alkoxycarbonium ion as the rate-limiting step. In basic media the data indicate a conventional B_{Ac}-2 mechanism through attack of hydroxide ion on the carbonyl carbon. In neutral medium (pH 2.5–8.8) there is a certain amount of conflicting evidence which leads, however, to the proposal that hydrolysis occurs *via* attack of a water molecule on the acyl carbon as the rate-limiting step.

The mechanism of hydrolysis of esters of the type **1** has received attention over the past 30 years since they are of considerable interest as intermediates in enzymic reactions.[1] These esters represent a combination of an ester function with an acetal function and hence, in theory, may hydrolyse by the whole



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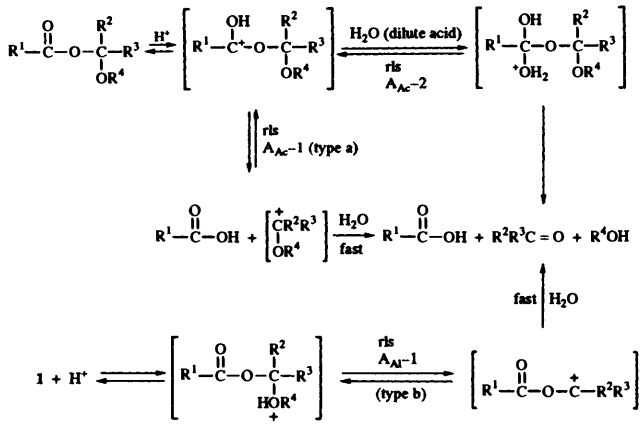
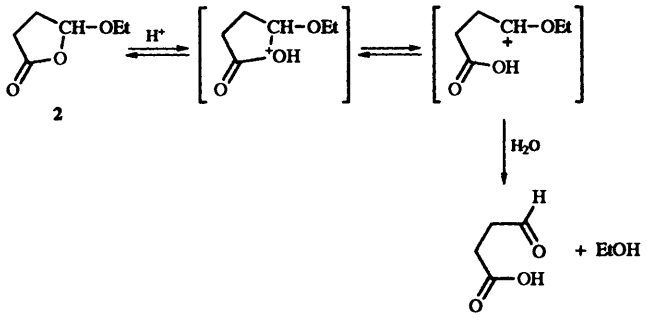
range of mechanisms available to ester or acetals under acidic, neutral or basic conditions.[2] In practice, however, convincing evidence has accumulated to suggest that under acidic conditions hydrolysis of oxyalkyl esters (**1**), where $R^2 = R^3 = H$, occurs *via* an A_{Ac}-2 mechanism in dilute acid with a changeover to an A_{Al}-1 mechanism of type (a) in more concentrated acid media (Scheme 1).[3]



Scheme 1

The alternative A_{Al}-1 mechanism (type b) involving protonation of the acetal alkoxy group was considered unlikely on the basis of several arguments including the fact that methylene diacetate required very strong (78%) sulfuric acid to effect a changeover to the A_{Al}-1 mechanism.[4] The point at which the change in mechanism from A_{Al}-2 to A_{Al}-1 occurs, however, clearly depends upon the structure of the oxyalkyl ester. The competition between the A_{Al}-1 and A_{Ac}-2 mechanism is also evident in the early finding that oxyalkyl esters from formic acid follow the A_{Ac}-2 mechanism whereas analogous esters from acetic acid follow a predominantly A_{Al}-2 mechanism.[5] The



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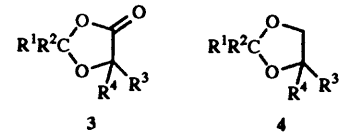
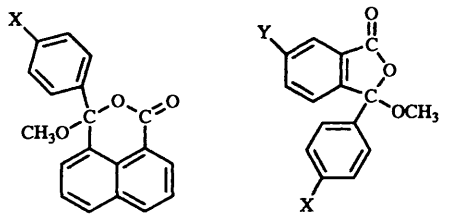
hydrolysis of the cyclic ester (**2**) has also been studied as a function of pH at 30 °C.[6]

At low pH, a specific hydronium-ion catalysed reaction occurred which was ascribed to an A_{Al}-1 reaction proceeding *via* pre-equilibrium protonation followed by rate-limiting unimolecular dissociation of the intermediate. At high pH, hydroxide ion catalysis occurred consistent with the B_{Ac}-2 mechanism, but the pH–rate profile revealed a large plateau between pH 5 and 9 in which the carboxylate ion was thought to act as the leaving group in an S_N1-type reaction. A comparison has also been made between the mechanism of hydrolysis of 1,3-dioxolones **3** and that of the 1,3-dioxolanes **4**; it is clear from



3 **4**

the activation parameters that under acid-catalysed conditions, the dioxolanes were hydrolysed by an A_{Al}-1 mechanism, whereas the dioxolones followed by an A_{Ac}-2 mechanism or A_{Al}-1 mechanism depending upon the substituents (R^1–R^4).[7] The rates of hydrolysis of methyl esters of pseudo-8-aroylnaphthoates (**5**)[8] and 3-methoxy-3-arylphthalides (**6**)[9] have also been studied in aqueous sulfuric acid and/or perchloric acids. The application of criteria such as rate–acidity correlations (Zucker–Hammett, Bunnett and φ), entropy of activation, D_2O solvent isotope effects and Hammett correlations led to the conclusion that in both cases the reactions proceeded *via* a unimolecular mechanism involving an alkoxycarbonium ion. Thus at the extreme ends of the pH scale, the mechanisms of hydrolysis of the oxyalkyl esters (**1**) seem to be quite well established. The mechanistic interpretation in the neutral or pH plateau region, however, is not well defined and the work described below was undertaken with the intention of extending the mechanistic studies into this pH region with a view to creating a more precise mechanistic picture.



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Experimental

General preparation of 1-aryloxyethyl alkanoates

1-Phenoxyethyl propionate. A mixture of phenyl vinyl ether (0.5 mol, 60 g), propionic acid (0.5 mol, 42 g) and anhydrous phosphoric acid (5×10^{-3} mol, 0.5 g) was stirred at room temperature for 30 min. The solution was filtered through a bed of basic alumina to remove excess phosphoric acid and then distilled under reduced pressure to yield 80.5 g (83%) of a colourless liquid, bp 70 °C/1.0 mmHg, M_w = 194.0927 corresponding to a molecular formula, $C_{11}H_{14}O_3$; $\delta_H(CDCl_3)$ 1.10 (3 H, t, CH_3CH_2), 1.64 (3 H, d, CH_3CH), 2.32 (2 H, q, CH_3CH_2), 6.59 (1 H, q, CH) and 6.92–7.31 (5 H, m, Ar); δ_C(DEPT) 8.85 (CH_3CH_2), 20.64 (CH_3CH), 27.64 (CH_3CH_2), 93.38 (CH), 116.66, 122.79, 129.71 (Ar, 5 C), 155.88 [Ar, C(qt)] and 173.46 (C=O).

The method for the preparation of 1-phenoxyethyl propionate was used throughout, but with the appropriate alkanoic acid in place of propionic acid. The physical constants, molecular weights and formulae for the 1-phenoxyethyl alkanoates are given in Table 1.

General preparation of 1-aryloxyethyl propionates[10]

X = *p*-Cl. Lead tetraacetate (11.1 g, 25 mmol), 2-(*p*-chlorophenoxy)propionic acid[11] (5.0 g, 25 mmol) and propionic acid (50 cm^3) were stirred under nitrogen for 2 h at 80 °C. The cooled solution was added to diethyl ether, followed by washing with water (2×200 cm^3) and 10% sodium hydrogen carbonate (2×200 cm^3). The ether extracts were dried ($MgSO_4$) and evaporation of diethyl ether gave the crude product, which was then purified by reduced pressure distillation to yield a colourless liquid (3.3 g, 58%). Physical properties, molecular weights and formulae are given in Table 1.

Preparation of 1-ethoxyethyl propionate

A solution of ethyl vinyl ether (36.1 g, 0.5 mol), propionic acid (37.0 g, 0.5 mol) and anhydrous phosphoric acid (0.5 g, 5×10^{-3} mol) was stirred at room temperature for 30 min. The solution was filtered through a bed of basic alumina to remove excess phosphoric acid and then distilled under reduced pressure, to yield 63.5 g, 87% of a colourless liquid, bp 52–57 °C/15 mmHg, M_w = 149.1852 ($C_7H_{14}O_3$); $\delta_H(CDCl_3)$ 1.12 (3 H, t, $CH_3CH_2C{=}O$), 1.19 (3 H, t, CH_3CH_2O), 1.34 (3 H, d, CH_3CH), 2.34 (2 H, q, $CH_3CH_2C{=}O$), 3.50–3.75 (2 H, d of m, CH_3CH_2O) and 5.95 (1 H, q, CH_3CH); δ_C(DEPT) 9.07 ($CH_3CH_2C{=}O$), 15.08 (CH_3CH_2O), 20.91 (CH_3CH), 27.86 ($CH_3CH_2C{=}O$), 64.61 (CH_3CH_2O), 96.07 (CH_3CH) and 174.22 (C=O).

Kinetic measurements

Rate measurements were carried out on a Hewlett–Packard Diode-Array 8452A spectrophotometer controlled by a Vectra QS/HS computer and fitted with a thermostatted cell compartment regulated to ±0.2 °C by a Grant thermostat water-bath. Stock solutions of the 1-aryloxyethyl propionates were prepared in dry acetonitrile at 10^{-3} mol dm^{-3}, and reactions were initiated by addition of 25 μl (1 μl = 1 mm^3) of each ester solution to pre-equilibrated cuvettes containing 3 cm^3 of aqueous solution. The final concentrations of substrates were in the region of $1–5 \times 10^{-5}$ mol dm^{-3}. Reactions were monitored by following the increase of absorbance at the wavelengths given in Table 2. First-order rate constants were calculated from plots of $\ln(A_\infty - A_t)$ *vs.* time.

At pH values greater than 1.0, rates were measured at a constant ionic strength of 1.0 mol dm^{-3} made up with NaCl. To ensure constant pH within the range of 3.0 to 9.5 the reaction solutions were buffered, using acetate and borate buffers at a concentration of 0.02 mol dm^{-3}.

Results and discussion

The system chosen for study was that of the 1-aryloxyethyl alkanoates (**7**) since their relatively straightforward synthesis allowed a wide range of alkanoic acids (R^1CO_2H) and aryl substituents (X) to be used. Hydrolysis gave the alkanoic acid

$$\underset{\mathbf{7}}{RCO_2CH(Me)OC_6H_4X} \xrightarrow{H_2O} \underset{\mathbf{8}}{RCO_2H} + \underset{\mathbf{9}}{MeCHO} + \underset{\mathbf{11}}{HOC_6H_4X}$$

Table 1 Yields, physical constants, molecular formulae and exact molecular masses for $R^1CO_2CHMeOPh$ and $EtCO_2CHMeOC_6H_4X$

X	Yield (%)	Bp/°C (1 mmHg)	Molecular formula (Molecular weight/ MS)	R^1	Yield (%)	Bp/°C (1 mmHg)	Molecular formula Molecular weight/ MS)
4-MeO	70	132	$C_{12}H_{16}O_4$ (224.1049)	$CH_2{=}CH$	87	68	$C_{11}H_{12}O_3$ (192.0775)
4-Me	74	104	$C_{12}H_{16}O_3$ (208.1098)	$ClCH_2CH_2$	78	112	$C_{11}H_{13}ClO_3$ (^{37}Cl) (^{35}Cl)
4-Cl	58	114	$C_{11}H_{13}ClO_3$ (230.0559 ^{37}Cl) (228.0648 ^{35}Cl)	CH_3CHBr	91	134	$C_{11}H_{13}{}^{81}BrO_3$ (273.9991 ^{81}Br) (272.006 ^{79}Br)
3-Cl	65	116	$C_{11}H_{13}{}^{37}ClO_3$ (230.0552 ^{37}Cl) (228.0656 ^{35}Cl)	CH_2CN	70	137	$C_{11}H_{11}NO_3$ 205.2112
3-NO_2	27	157	$C_{11}H_{13}NO_5$ (239.0778)	CH_3CCl_2	65	151	$C_{11}H_{12}O_3$ (262.0151 ^{35}Cl) (266.0818 ^{37}Cl)
4-NO_2	23	164	$C_{11}H_{13}NO_5$ (239.0780)	CCl_3	57	179	MS not obtained due to instability

Table 2 Wavelength values employed to follow the hydrolysis of 1-aryloxyethyl propionates

X	λ/nm Acid	Base
4-MeO	288	240
4-Me	278	236
H	278	236
4-Cl	280	246
3-Cl	280	240
3-NO_2	340	256
4-NO_2	340	234

(**8**), ethanal and a range of phenols; the latter affording an effective means of monitoring the reaction by UV–VIS spectroscopy.

^{18}O-Labelling experiments

^{18}O-Labelling experiments were carried out at an early stage of the investigation in order to establish the position of bond fission under different pH conditions. The technique used was to carry out the hydrolysis of **7** (R = Et, X = H) in ^{18}O water (90% labelled) and then to observe the ^{18}O-shift on the ^{13}C signals of the carboxyl groups of **8** and **9**.[12] The solvent system employed at 25 °C was a 40:60 mixture of $H_2{}^{18}O$ (90% labelled) and [$^2H_3$]acetonitrile, the latter being necessary in order to achieve the solubility of **7** consistent with obtaining ^{13}C spectra without perturbing the system (*e.g.* by changes of concentration). Under acidic conditions (1 mol dm^{-3} HCl) the ^{18}O label was found in the carbonyl group of the aldehyde **9** in a ratio of 9:1 (^{18}O:^{16}O) identical to that of the solvent. Clearly, the reaction occurs with loss of propionic acid *via* the A_{Al}-1 mechanism (type a or b). Under alkaline conditions (pH 12), however, the ^{18}O label was found in the propionate ion at 184 ppm (in a ratio of 7:3, ^{18}O:^{16}O) † and therefore one may safely conclude that under these conditions, hydrolysis occurs by the expected B_{Ac}-2 route.[13] Unfortunately, under neutral conditions in the medium employed, the hydrolysis occurred too slowly to allow meaningful results to be obtained. Using a more reactive oxyalkyl ester, 1-ethoxyethyl propionate (**11**) however, the ^{18}O label was found in the aldehyde product in a ratio of 9:1

$$\underset{\mathbf{11}}{EtCO_2CH(Me)OEt} \xrightarrow[H^+ \text{ or neutral}]{H_2{}^{18}O\text{–}CD_3CN} EtCO_2H + EtOH +$$

$$MeCH^{18}O\ (\delta\ ^{13}C\ 205.015) + MeCH^{16}O\ (\delta_C\ 205.066)$$

(^{18}O:^{16}O) in both acidic and neutral conditions. It seems therefore, that with more active esters the A_{Al}-1 mechanism definitely persists into the neutral region.

Kinetic data

The rates of hydrolysis of **7** were followed by UV–VIS spectroscopy observing the formation of the phenol (λ_{max} = 268 nm for X = H) and phenoxide ion (λ_{max} = 236 nm for X = H) in the acid and base medium respectively. The rates of hydrolysis of **7** (R^1 = Et, X = H) over a pH range of 1–12 are shown in Table 3 which gives rise to the pH–rate profile of Fig. 1. Clearly, there are three important pH regions in which the reaction is either acid-catalysed, base-catalysed or pH-dependent leading to eqn. (1) as the expression for k_{obs}. The

$$k_{obs} = k_H[H^+] + k_{OH}[HO^-] + k_o \qquad (1)$$

† The amount of ^{18}O in the solvent mixture was reduced to 70% by the introduction of aqueous [^{16}O]sodium hydroxide to raise the pH.

Table 3 Kinetic data for the hydrolysis of $EtCO_2CHMeOPh$ over a range of pH values

pH	k_{obs}/ 10^{-4} s^{-1}	pH	k_{obs}/ 10^{-4} s^{-1}
0.69	260.00	4.38	1.18
0.82	215.00	5.38	1.16
0.98	131.00	6.58	1.01
1.18	99.00	7.82	0.97
1.32	60.00	9.06	1.92
1.58	45.00	10.32	4.15
1.80	27.00	10.90	14.00
1.82	24.00	11.30	30.00
1.90	9.48	11.49	57.00
2.33	2.70	11.85	129.00
3.74	1.60	12.06	219.00
		12.40	401.00

Table 4 Arrhenius data at pH 0.80, 7.0 and 11.32

pH 0.80		pH 7.00		pH 11.32	
T/K	k_{obs}/ 10^{-3} s^{-1}	T/K	k_{obs}/ 10^{-5} s^{-1}	T/K	k_{obs}/ 10^{-3} s^{-1}
303.3	1.39	318.0	3.503	318.0	1.30
310.3	3.00	320.0	4.811	323.0	1.70
315.2	5.80	323.0	5.500	328.0	2.40
320.3	9.61	328.0	8.304	333.0	3.00
326.3	13.89	333.0	11.870		
332.2	28.71				

Table 5 Activation parameters at 303 K for the hydrolysis of $EtCO_2CHMeOPh$ at pH values of 0.8, 7.00 and 11.32

pH	E_A/ kJ mol^{-1}	$\Delta H^‡$/ kJ mol^{-1}	$\Delta G^‡$/ kJ mol^{-1}	$\Delta S^‡$/ J mol^{-1} K^{-1}
0.80	85.6	83.3	87.0	−12 ± 5
7.00	68.4	65.9	102.8	−124 ± 12
11.32	50.2	47.7	82.3	−108 ± 9

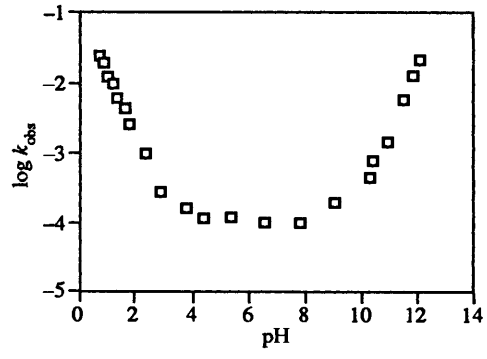


Fig. 1 log k_{obs} *vs.* pH for $EtCO_2CHMeOPh$

average value of k_o for these results is 1.08 × 10^{-4} s^{-1} and plots of k_{obs} *vs.* [H$^+$] [eqn. (2)] and k_{obs} *vs.* [HO$^-$] [eqn. (3)] give

$$k_{obs} = 1.13 \times 10^{-1}[H^+] + 4.45 \times 10^{-4} \qquad (2)$$

$$k_{obs} = 1.58[HO^-] + 2.67 \times 10^{-4} \qquad (3)$$

values of k_H = 1.31 × 10^{-1} dm^3 mol^{-1} s^{-1} and k_{OH} = 1.58 dm^3 mol^{-1} s^{-1}, respectively.

Activation parameters for the reaction were determined in each region of the pH–rate profile by measuring the rate of reaction at several temperatures in the range of 30–60 °C at constant pH. The values of k_{obs} at pH 0.8, 7.00 and 11.32 are shown in Table 4 giving rise to Arrhenius plots represented by eqns. (4)–(6) respectively, which allow the calculation of the activation parameters shown in Table 5.

Table 6 Solvent deuterium isotope effects at 333 K for hydrolysis in each pH region

	k_H/dm^3 mol^{-1} s^{-1}	k_{OH}/dm^3 mol^{-1} s^{-1}	k_o/10^{-4} s^{-1}
H_2O	0.13	1.58	1.01
D_2O	0.37	0.39	0.95
k_H/k_D	0.35	4.0	1.06

Table 7 Rates of hydrolysis of 1-aryloxyethyl propionates

4-MeO		4-Me		4-Cl	
pH	k_{obs}/s^{-1}	pH	k_{obs}/s^{-1}	pH	k_{obs}/s^{-1}
1.61	0.006 5	3.05	0.000 57	1.24	0.001 7
1.31	0.011 5	2.49	0.001 2	1.00	0.002 5
0.96	0.025 9	2.02	0.002 2	0.74	0.004
0.84	0.029 1	1.78	0.003 3	0.43	0.011
0.69	0.046 5	1.50	0.004 7	0.33	0.014 3
0.58	0.070 2	1.27	0.006 2	0.25	0.178 8
0.42	0.084 6	1.04	0.010 16	0.06	0.022 52
		0.97	0.012 5	−0.01	0.027 9
		0.76	0.020 57	−0.15	0.037 72
		0.64	0.027 9		

3-Cl		3-NO_2		4-NO_2	
pH	k_{obs}/s^{-1}	pH	k_{obs}/s^{-1}	pH	k_{obs}/s^{-1}
1.97	0.0001 76 4	0.57	0.000 893 3	1.30	0.000 56
1.69	0.000 350 6	0.47	0.001 224	1.12	0.000 603 6
1.20	0.000 67	0.18	0.001 903	0.66	0.001 1
0.86	0.001 59	−0.18	0.005 381	0.44	0.001 6
0.56	0.004 9	−0.36	0.007 495	−0.14	0.002 5
0.38	0.007 3	−0.51	0.012 32	−0.40	0.004 9
0.28	0.009 17	−0.57	0.013 5	−0.76	0.012 4
0.08	0.015 9	−0.66	0.020 59	−0.90	0.016 52
0.02	0.017 4	−0.74	0.023 53	−0.93	0.018
−0.15	0.027 52	−0.88	0.035 79		
−0.25	0.034 439	−0.98	0.046 49		
−0.40	0.051				

$$\ln k_{obs} = -1.032 \times 10^4 (1/T) + 27.48; r = 0.993 \quad (4)$$

$$\ln k_{obs} = -8.226 \times 10^3 (1/T) + 15.67; r = 0.990 \quad (5)$$

$$\ln k_{obs} = -6.034 \times 10^3 (1/T) + 12.33; r = 0.994 \quad (6)$$

These data provide strong evidence for a dissociative A_{Al}-1 mechanism (or type a or b) in the acid-catalysed region (low values of $\Delta S^{\ddagger}$), but associative mechanisms ($\Delta S^{\ddagger}$ highly negative) in the neutral and base-catalysed regions.[14] It is reasonable to assume that k_{OH} represents the rate coefficient of a conventional B_{Ac}-2 mechanism and similar activation parameters in the neutral region also suggest rate-limiting attack by water on the carbonyl carbon of the substrate. The solvent deuterium isotope effects (Table 6) are entirely consistent with this interpretation since in the acidic region, $k_H/k_D = 0.35$,[15] whereas in the neutral region the value is close to unity. In the basic region, the value of $k_{OH}/k_{OD} = 4.0$, is indicative of general-base catalysis[16] (*vide infra*).

The rates in the acidic and neutral regions were investigated further by variations of the substituents, X, in the *meta*- or *para*-position of the aryl group of **7** for a fixed R^1 and variations of R^1 for X = H. For the former, with R^1 = Et, variations of k_{obs} with pH gave the data shown in (Table 7) which, through plots of k_{obs} *vs.* [H^+] (*e.g.* Fig. 2), afforded the k_H values shown in Table 8 and the resultant Hammett plot against σ of Fig. 3. The ρ value of −2.07 for the acid-catalysed region indicates development of positive charge in the transition state and is consistent with an A_{Al}-1 mechanism of type a in which the developing positive charge is stabilised by electron-donating groups (X) in the phenyl rings, but is insulated from direct conjugation with X by the intervening oxygen atom. It is clear from Fig. 4 that the onset of the A_{Al}-1 mechanism occurs over a pH range from *ca.* 2.5 (X = *p*-MeO) to *ca.* 0.5 for the electron-withdrawing group, X = *p*-NO_2. This is analogous to the data reported by McClelland.[3] for the hydrolysis of aryloxymethyl acetates (**12**) which gave a Hammett plot against σ with a ρ-value of −3.06 except that in this case the onset of the A_{Al}-1 mechanism occurred over an acidity range from 40% (X = H) to 70% (X = *p*-NO_2) H_2SO_4. The slightly greater negative value of the aryloxymethyl acetates is probably due to the fact that in this case all the stabilisation of the incipient carbocation comes from the aryloxy group whereas with the 1-aryloxyethyl

Table 8 Hammett σ data for the hydrolysis of $EtCO_2CHMeO$-C_6H_4X at pH 0.87, 7.14, 11.32

	pH 0.87	pH 7.14	pH 11.32
X	k_H/10^{-3} mol^{-1} dm^3 s^{-1}	k_o/10^{-4} s^{-1}	k_{OH}/10^{-2} s^{-1}
4-MeO	23.213	1.326	2.35
4-Me	11.55	1.190	2.42
H	12.88	1.002	2.79
4-Cl	2.670	0.779	3.15
3-Cl	2.020	0.773	3.74
3-NO_2	0.490	0.557	4.70
4-NO_2	0.241		4.91

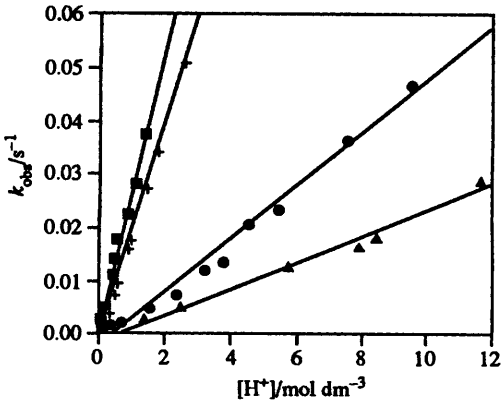


Fig. 2 k_{obs} *vs.* [H^+] for $EtCO_2CHMeOC_6H_4X$; X = 4-Cl (■), 3-Cl (+), 3-NO_2 (●) and 4-NO_2 (▲)

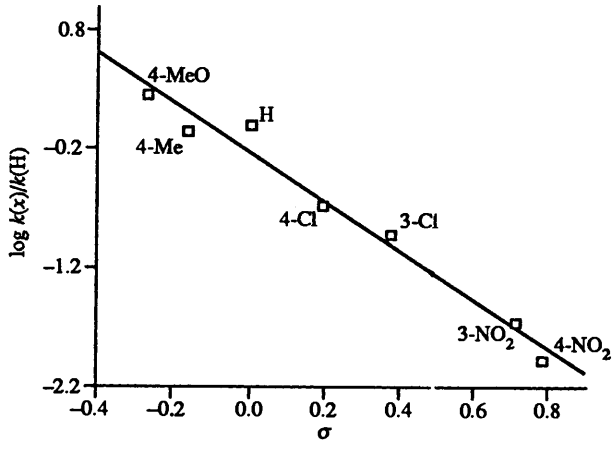


Fig. 3 Hammett σ plot for the acid-catalysed hydrolysis of $EtCO_2CHMeOC_6H_4X$

Table 9 Taft σ^* data for the hydrolysis of $R^1CO_2CHMeOPh$ at pH 0.87 and 7.14

		pH 0.87	pH 7.14
R^1	σ^*	$k_{obs}/10^{-3}$ s^{-1}	$k_{obs}/10^{-4}$ s^{-1}
CH_3CH_2	−0.1	25.50	1.10
CH_2=CH	0.36	20.50	3.91
CH_2ClCH_2	0.385	18.45	4.66
CH_3CHBr	1.00	16.37	27.98
$CNCH_2$	1.3	54.88	410.0
CH_3CCl_2	1.94	9.47	93.49
CCl_3	2.65	8.98	39.60

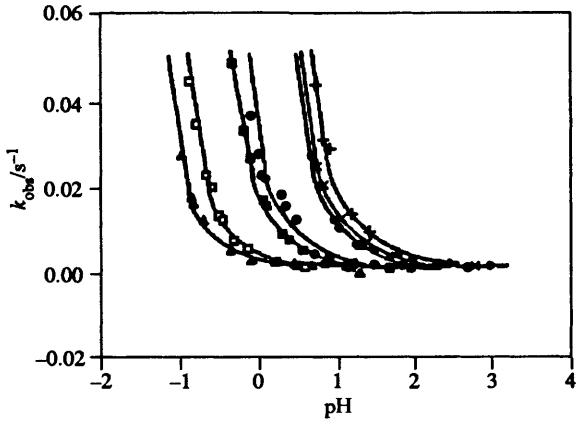


Fig. 4 pH–rate profile for the hydrolysis of 1-aryloxyethyl propionates: X = 4-MeO (+), 4-MeO (◆), H (×), 4-Cl (●), 3-Cl (■), 3-NO_2 (□) and 4-NO_2 (▲)

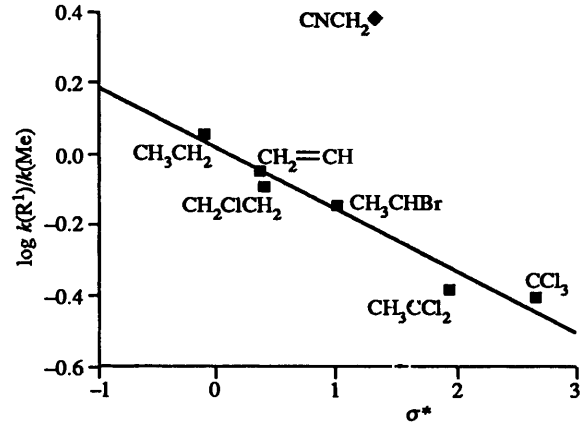


Fig. 5 Taft σ^* plot for acid-catalysed hydrolysis of R^1CO_2CH-MeOPh

propionates, the stabilisation of the incipient carbocation is shared between the aryloxy group and the inductive effect of the methyl group.

$$MeCO_2CH_2OC_6H_4X \xrightarrow{H_2O} \underset{\mathbf{12}}{} MeCO_2H + CH_2O + HOC_6H_4X$$

The proposal of an A-1 mechanism in the acid region received further support from a study of rate variations in the hydrolysis of 7 (X = H) induced by changes in R^1 (Table 9). A Taft plot of log (k_{R^1}/k_{Me}) *vs.* σ^* (Fig. 5) gave a negative slope with $\rho^* = -0.18$ indicating a decrease in rate with electron-withdrawing substituents, but with the cyanomethyl group falling off the line with an unexpectedly high rate of hydrolysis. In the A_{Al}-1 process the ρ^* value is derived from a combination of two factors. The pre-equilibrium protonation of the substrate moves

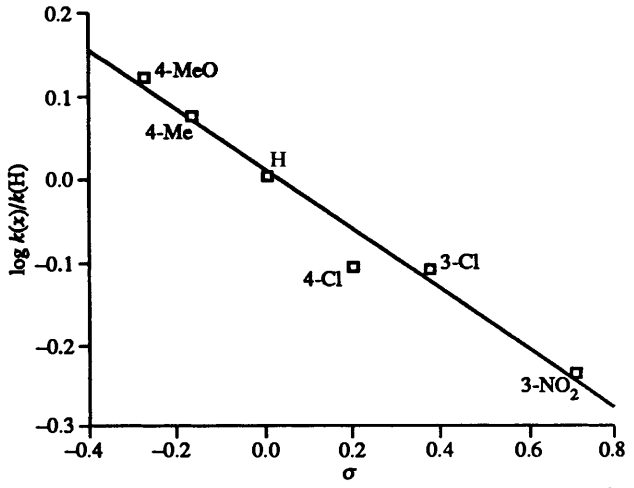
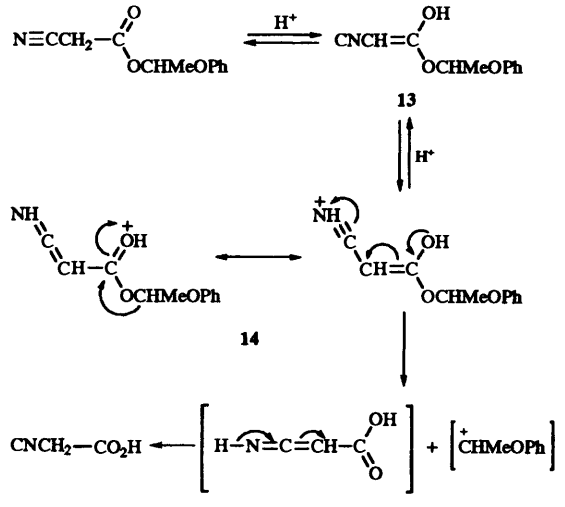


Fig. 6 Hammett σ plot for neutral hydrolysis of $EtCO_2CH$-$MeOC_6H_4X$

towards unprotonated substrate as the substituents become more electron-withdrawing which would give a negative ρ^* value, but the rate of dissociation of the protonated substrate is enhanced by electron-withdrawing substituents to give a positive ρ^* value. For the acid-catalysed hydrolysis of 7 the effect of the electron-withdrawing substituents on the pre-equilibrium outweighs that on the rate of dissociation, resulting in a small negative ρ^* value. Thus, acid catalysis is evident and the unusually high rate with $R^1 = CH_2CN$ may be due to protonation of the enol form **13** on nitrogen to form **14** prior to dissociation (Scheme 2).



Scheme 2

The values of k_o for 7 (R^1 = Et and varying X) which occur over a pH range of *ca.* 2.5–8.0 are also dependent on X (Table 8) giving a ρ-value of −0.36 (Fig. 6). The ρ-value is still negative, but of a much lower magnitude than the acid-catalysed reaction and this indicates a change in mechanism. The negative value of ρ suggests the development of positive charge in the transition state (*i.e.* a dissociative mechanism), but this is not consistent with the bimolecular mechanism indicated by the activation parameters (Table 5). McClelland [3] also reported a negative ρ-value of *ca.* −0.03 for the hydrolysis of **12** in dilute acid and proposed hydrolysis by the A_{Ac}-2 mechanism. The present paradox was resolved by variation of the substituents, R^1, in the substrate 7 which gave the rates shown in Table 9. A Taft plot of log (k_{R^1}/k_{Me}) *vs.* σ^* (Fig. 7) gives a positive slope with $\rho^* = +0.95$ indicating that the rates

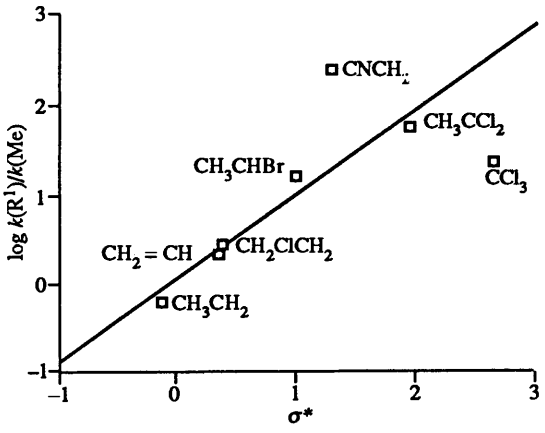
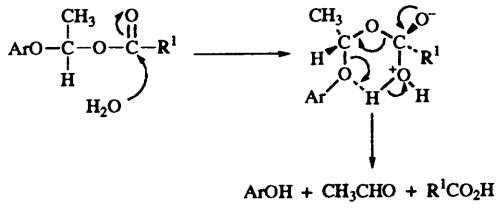


Fig. 7 Taft σ^* plot for the neutral hydrolysis of $R^1CO_2CHMeOPh$

increase as the substituent becomes more electron-withdrawing between R = Et and R = Me_2CCl_2 and pointing to nucleophilic attack by water in the carbonyl carbon as the rate-limiting step. This conclusion was reinforced by the observation that the rate of hydrolysis for R = CCl_3 was much lower than expected presumably due to the bulkiness of the CCl_3 group with the steric effect outweighing the electronegativity of the CCl_3 group. Once again there is an unexpectedly high rate of hydrolysis for R = CH_2CN which may be due to the keto–enol equilibrium and attack of water on the enol form. Thus the mechanism for the hydrolysis of **7** in the neutral region is shown in Scheme 3.



Scheme 3

The negative ρ value is explained by the aryloxy group forming a hydrogen bond with the incoming water molecule so that electron-donating substituents stabilise the intermediate. The products then follow naturally through a six-membered transition state.[17] An apparently conflicting piece of evidence is the lack of general-base catalysis in the neutral region (acetate and imidazole at 1.0 mol dm^{-3}) normally associated with attack of the carbonyl carbon in the pH-independent region (Table 10). Scheme 3 however, reveals *intramolecular* base catalysis by the aryloxy group which presumably outweighs the intermolecular catalysis by buffer. The proposed A_{Ac}-2 mechanism also explains the lack of a solvent isotope effect, k_H/k_D = 1.1, since only *one* molecule of water and no proton transfer is involved in the transition state. Therefore in the pH-independent region all the evidence points towards the A_{Ac}-2 mechanism, but *via* an intramolecular hydrogen-bonded intermediate.

In the base-catalysed region the hydrolysis of the 1-aryloxyethyl propionates (Table 8) gave a linear Hammett plot with ρ = 0.36 (Fig. 8). The rate of hydrolysis increases as the substituents on the aryloxy group become more electron-withdrawing thus indicating the development of a negative charge in the transition state which is consistent with a B_{Ac}-2 mechanism. The unusually low value of ρ compared with base-catalysed ester hydrolysis (benzyl acetates ρ = 0.8,[18] phenyl

Table 10 The effects of buffer concentration on the rate of hydrolysis of 1-phenoxyethyl propionate in the neutral region

Total acetate buffer/mol dm^{-3}	$k_{obs}/10^{-4}$ s^{-1}	Total imidazole buffer/mol dm^{-3}	$k_{obs}/10^{-4}$ s^{-1}
0.02	1.108	0.02	0.987
0.1	1.230	0.1	0.935
0.2	1.092	0.2	1.076
0.5	1.163	0.5	0.965

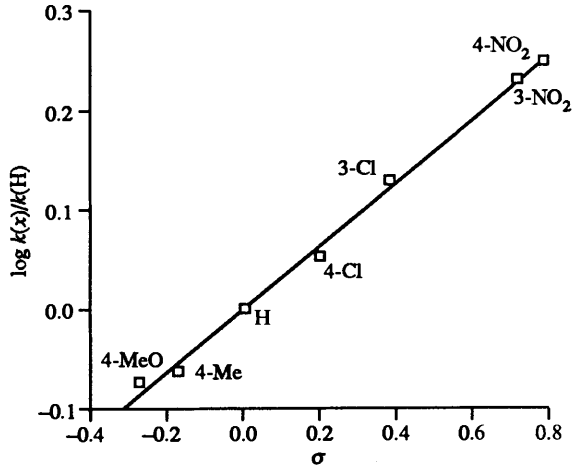
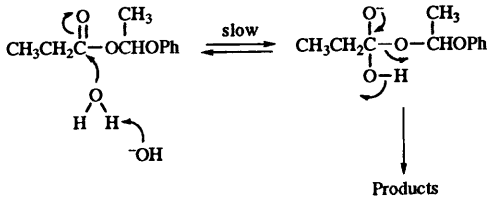


Fig. 8 Hammett σ plot for base-catalysed hydrolysis of $EtCO_2CHMeOC_6H_4X$

acetate ρ = 1.2[18]) has been found for the base-catalysed hydrolysis of aryloxymethyl acetates where ρ = 0.42[3] and is due to the distance of the substituents from the reaction centre. This mechanism is reinforced by the $H_2{}^{18}O$ hydrolysis experiments in the basic region. The unusually high k_H/k_D value in this region may be explained by general-base catalysis (Scheme 4), but this was not substantiated experimentally and may be explored in future work.



Scheme 4

The overall conclusion is that the mechanism of hydrolysis of these esters is A_{Al}-1 in the acid region of the pH–rate profile, probably B_{Ac}-2 in the basic region and A_{Ac}-2 *via* an intramolecular hydrogen-bonded intermediate in the neutral region.

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