Kinetics and mechanism of the hydrolysis of tetrahydro-2-furyl and tetrahydropyran-2-yl alkanoates

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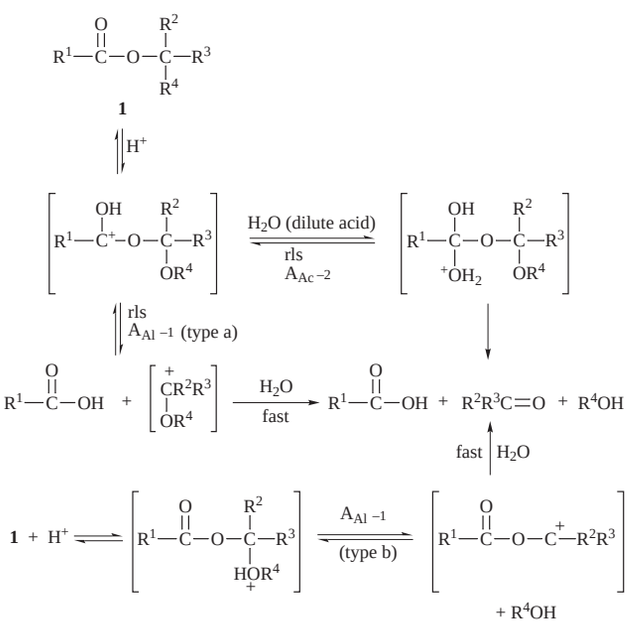
The kinetics and mechanism of the hydrolysis of tetrahydro-2-furyl and tetrahydropyran-2-yl alkanoates in water and water–20% ethanol are reported. In acidic and neutral media, kinetics, activation parameters, ^{18}O isotope exchange studies, substituent effects, solvent effects and the lack of buffer catalysis point clearly to an A_{A1}-1 mechanism with formation of the tetrahydro-2-furyl or tetrahydropyran-2-yl carbonium ion as the rate-limiting step. There is no evidence of a base-promoted B_{AC}-2 mechanism up to pH 12.

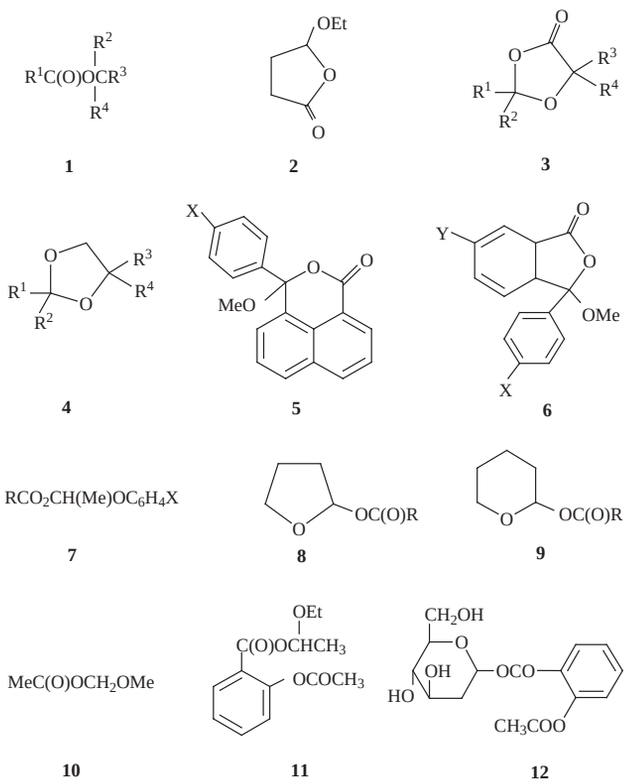
Introduction

The mechanism of hydrolysis of 1-alkoxyalkyl alkanoates (**1**) often referred to by the generic term 'acylals' has received considerable attention over the past 30 years since acylals are of interest as intermediates in enzymic reactions.[1] These compounds contain both an ester function and an acetal function and hence, in theory, may hydrolyse by the whole range of mechanisms available to both functional groups under acidic, neutral or basic conditions.[2] In practice, however, convincing evidence has accumulated to suggest that under acidic conditions, hydrolysis of (**1**, $R^2 = R^3 = H$) occurs *via* an A_{Ac}-2 mechanism in dilute acid with a changeover to a A_{A1}-1 mechanism of type (a) in more concentrated acid media (Scheme 1).[3]



Scheme 1

The alternative A_{A1}-1 mechanism (type b) involving protonation and dissociation 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-1 mechanism.[4] The point at which the change in mechanism occurs, however, depends upon the structure of the oxyalkyl ester. Thus 1-alkoxyalkyl formates follow the A_{Ac}-2 mechanism whereas analogous esters from acetic acid follow a predominantly A_{A1}-1 mechanism.[5]



The hydrolysis of the cyclic acylal (**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-1 reaction proceeding *via* pre-equilibrium protonation followed by rate-limiting unimolecular dissociation of the intermediate. At high pH, a hydroxide ion promoted reaction 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 a 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**) from which it was clear that under acid-catalysed conditions, the dioxolanes hydrolysed by an A-1 mechanism, whereas the dioxolones followed an A_{Ac}-2 mechanism or an A_{A1}-1 mechanism dependent 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, deuterium oxide 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.

We recently reported the kinetics and mechanism of the hydrolysis of 1-aryloxyethyl alkanoates (**7**) which in acidic media (< pH 3) follow the A_{A1}-1 mechanism and in basic media (pH > 9) are hydrolysed by the conventional B_{AC}-2 mechanism. In neutral medium (pH 2.5–9) there was a certain amount of conflicting evidence which led to the suggestion of rate-limiting attack of water on the acyl carbon of (**7**) through an intermediate involving intramolecular hydrogen bonding.[10]

This paper reports the kinetic results associated with the hydrolysis of alkanoates (**8**) and (**9**) derived from 2,3-dihydrofuran and 2,3-dihydropyran respectively.

Experimental

Preparation of tetrahydro-2-furyl propionate (8, R = Et)

2,3-Dihydrofuran (5.00 g, 0.07 mol) was added to propionic acid (5.3 g, 0.07 mol) and the mixture was stirred at room temperature for 15 h. The product was then purified by fractional distillation under reduced pressure to yield 8.6 g (85% yield) of (**8**, R = Et), bp 72–4 °C at 15 mmHg, M = 144.0823 (calc. for $C_7H_{12}O_3$ = 144.0786); δ_H($CDCl_3$) 1.15 (3H, t, CH_3CH$_2$), 1.9–2.1 (4H, m, C–CH$_2$–C), 2.3 (2H, q, CH$_3$CH_2CO), 3.9–4.10 (2H, d of m, CH$_2$O), 6.30 (1H, t, OCHO); δ_C(DEPT) 8.9(+) (*C*H$_3$CH$_2$), 22.9, 32.9(−) (C–*C*H$_2$–C), 27.9(−) (CH$_3$*C*H$_2$CO), 68.9(−) (*C*H$_2$O), 98.8(+) (O*C*HO), 174.0(0) (*C*=O).

General preparation of tetrahydro-2-furyl alkanoates (8)

The reactions were carried out with the appropriate carboxylic acid and 2,3-dihydrofuran in a 1 : 1 molar ratio with dry toluene as the solvent. Thus, for example, 2-bromopropionic acid (5.6 g, 70 mmol) in toluene (5 ml) was added dropwise to a solution of 2,3-dihydrofuran (5.00 g, 70 mmol) in toluene (3 ml) with stirring. For reactions using carboxylic acids with pK_a < 4 the dihydrofuran was cooled in an ice bath. The mixtures were left to stir overnight at room temperature and the solvent was evaporated prior to vacuum distillation. The boiling points, % yields and ^{1}H NMR data are recorded in Table A and the mass spectroscopy and ^{13}C NMR data appear in Table B, both as supplementary information.†

Preparation of tetrahydropyran-2-yl propionate (9, R = Et)

A mixture of 2,3-dihydropyran (5.00 g, 0.06 mol), propionic acid (4.4 g, 0.06 mol) and anhydrous phosphoric acid (0.10 g, 10^{-3} mol) was stirred at room temperature for 30 min. The solution was then filtered through a bed of basic alumina to remove the phosphoric acid catalyst. The product was purified by fractional distillation under reduced pressure to yield 7.3 g (78%) of the title compound, bp 80–82 °C at 15 mmHg, M = 158.1058 (calc. for $C_8H_{14}O_3$ = 158.0943); δ_H($CDCl_3$) 1.18 (3H, t, *C*H$_3$CH$_2$), 1.55–1.93 [6H, m, C–(CH$_2$)$_3$–C], 2.40 (2H, q, CH$_3$*C*H$_2$CO), 3.7–4.0 (2H, d of m, CH$_2$O), 5.98 (1H, t, OCHO); δ_C(DEPT) 9.0(+) (*C*H$_3$CH$_2$), 18.8, 25.0, 29.3 (all −) (C–*C*H$_2$–C), 27.8(−) (CH$_3$*C*H$_2$CO), 63.4(−) (*C*H$_2$O), 92.5(+) (O*C*HO), 173.3 (0) (*C*=O).

General preparation of tetrahydropyran-2-yl alkanoates (9)

The synthesis of tetrahydropyran-2-yl alkanoates followed a similar procedure to that for the tetrahydro-2-furyl alkanoates (*vide supra*). The yields, bps and ^{1}H NMR data are recorded in Table C and the mass spectrometry and ^{13}C NMR data in Table D, again as supplementary information.

† Tables A–I and Figs. A–C are available as supplementary data (SUPPL. NO. 57372, 11 pp.) from the British Library. For details of the Supplementary Publications Scheme, see 'Instructions for Authors' *J. Chem. Soc., Perkin Trans. 2*, available *via* the RSC Web page (http://www.rsc.org/authors).

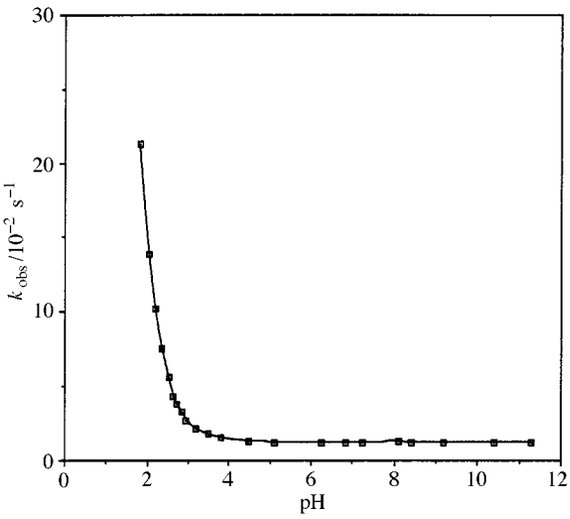


Fig. 1 Plot of $k_{obs}/10^{-2}$ *vs.* pH for the hydrolysis of **8** (R = Et) in H_2O at 20 °C, μ = 0.1 M

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 waterbath. Stock solutions of the substrates (1–5 × 10^{-2} M) were prepared in dry acetonitrile and reactions were initiated by addition of 3 ml of each acylal solution to pre-equilibrated cuvettes containing 3 cm^3 of aqueous solution. The final concentrations of substrates were in the region of 1–5 × 10^{-5} M. At pH values between 6–11 the reactions were carried out in KH_2PO_4–NaOH buffer (0.02 M) and below pH 6 a CH_3CO_2Na–HCl buffer (0.02 M) was used. The pH of each solution was determined before and after each run with a Metrohm 691 pH meter to check the constancy of pH throughout the kinetic run. Buffer solutions were prepared according to the methods reported by Britton[11] and the ionic strength was kept constant at 0.1 M by addition of potassium chloride. The UV spectra of the products (identified by NMR) in the appropriate buffer, were identical to those obtained in the kinetic runs.

Results and discussion

Kinetics and mechanism of the hydrolysis of tetrahydro-2-furyl propionate

The rate of hydrolysis of tetrahydro-2-furyl propionate was monitored by UV–VIS spectrophotometry at λ = 222 nm. The kinetic experiments were carried out at 20 ± 0.2 °C in aqueous buffer, and at 25 ± 0.2 °C for 20% EtOH–H_2O (v/v) buffer. For ease of comparison, it was necessary to use the latter aqueous alcoholic buffer for the hydrolysis of tetrahydro-2-furyl propionate because its analogue (tetrahydropyran-2-yl propionate, *vide infra*) was immiscible with pure aqueous buffer. The hydrolysis reactions were carried out under pseudo-first-order conditions with the concentration of buffer in large excess (2 × 10^{-2} M) relative to the substrate (1–5 × 10^{-5} M) and the rate of hydrolysis was obtained by plotting ln ($A_t - A_\infty$) against time to give a gradient = $-k_{obs}$. An example of a pseudo-first-order plot for the hydrolysis of tetrahydro-2-furyl propionate is shown in Fig. A (supplementary information).

pH–rate profiles. The hydrolysis of tetrahydro-2-furyl propionate was followed in H_2O and in EtOH–H_2O (20% v/v) buffers over a range of pH (2–12) at constant ionic strength (0.1 M). The rate coefficients for hydrolysis in H_2O (T = 20 °C) appear in Table E (supplementary information) and are plotted in Fig. 1. The results for hydrolysis in EtOH–H_2O buffer at 25 °C are summarised in Table F (supplementary data) and again show that there is a region of acid-catalysed hydrolysis (pH 2–4) and

Table 1 Rate coefficients for the hydrolysis of **8** (R = Et)

	k_H/dm^3 s^{-1} mol^{-1}	k_o/10^{-3} s^{-1}
100% H_2O @ 20 °C	13.4	14.0
20% EtOH @ 25 °C	18.2	9.64

Table 2 k_{obs} values for the hydrolysis of **8** (R = Et) as a function of temperature (T) in the acidic region

(a) at pH 2.71 (H_2O)		(b) at pH 3.69 (20% aq. EtOH)	
T/K	k_{obs}/10^{-2} s^{-1}	T/K	k_{obs}/10^{-3} s^{-1}
293.1	3.80	288.0	4.54
300.5	8.33	298.1	12.4
307.7	17.1	304.0	22.9
318.5	43.3	313.1	54.0
		319.5	102

Table 3 k_{obs} values for the hydrolysis of **8** (R = Et) as a function of temperature (T) in the neutral region

(a) at pH 7.25 (H_2O)		(b) at pH 7.50 (20% aq. EtOH)	
T/K	k_{obs}/10^{-2} s^{-1}	T/K	k_{obs}/10^{-3} s^{-1}
293.1	1.24	288.0	2.54
300.5	2.50	298.1	7.08
307.7	5.60	304.0	14.2
318.5	14.8	313.1	34.0
		319.5	67.0

Table 4 Activation parameters for the hydrolysis of **8** (R = Et)

	pH	E_A/kJ mol^{-1}	$\Delta H^‡$/kJ mol^{-1}	$\Delta G^‡$/kJ mol^{-1}	$\Delta S^‡$/J mol^{-1} K^{-1}
100% H_2O @ 25 °C	7.25	77	74	82	−27
	2.71	74	72	65	+22
20% EtOH–H_2O @ 25 °C	7.50	80	77	85	−25
	3.69	76	73	66	+25

a pH-independent or uncatalysed hydrolysis ($4 \geqslant pH \leqslant 12$). The overall rate is therefore described by eqn. (1), where

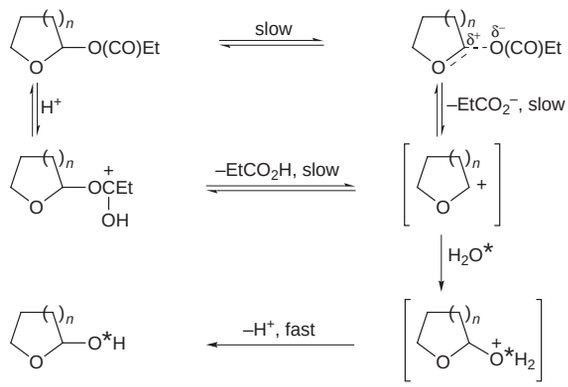
$$k_{obs} = k_H[H^+] + k_o \quad (1)$$

k_H = second-order rate constant for the acid-catalysed hydrolysis, $[H^+]$ = hydronium ion concentration and k_o = rate constant for the uncatalysed hydrolysis. From eqn. (1), the values of k_H and k_o are obtained by plotting k_{obs} *vs.* $[H^+]$ in water (Fig. B, supplementary information). A similar plot is found in EtOH–H_2O and the gradient of each straight line graph gives k_H. The pH-independent region (and the intercept) gives k_o and the values of the parameters in each medium are given in Table 1.

Variation of reaction rate with temperature. The activation parameters for the hydrolysis of each substrate were determined by measuring the rate of reaction in the acid and neutral regions over a temperature range at constant pH. In the acid-catalysed region, the rates were measured at 20, 27, 35 and 45 °C for hydrolysis in H_2O (Table 2a) and at 15, 25, 31, 40 and 46 °C (Table 2b) for hydrolysis in EtOH–H_2O (20% v/v) buffers. In the neutral region, the rates were also measured at 20, 27, 35 and 45 °C (Table 3a) for hydrolysis in H_2O and at 15, 25, 31, 40 and 46 °C (Table 3b) for hydrolysis in 20% EtOH–H_2O.

The values of activation parameters for tetrahydro-2-furyl propionate in H_2O and in EtOH–H_2O (20% v/v) buffer are summarised in Table 4. Although the values of entropy of activation obtained in the neutral region are negative ($\Delta S^‡ = -27$ J mol^{-1} K^{-1} for hydrolysis in H_2O and $\Delta S^‡ = -25$ J mol^{-1} K^{-1} for hydrolysis in EtOH–H_2O) they are comparable with other acylals, which are alleged to react by an S_N1 mechanism in the pH-independent region with larger negative entropy values. For example, the uncatalysed hydrolysis of methoxymethyl acetate (**10**)[5] and γ-ethoxy-γ-butyrolactone (**2**)[6] have $\Delta S^‡$ values of −48.0 J mol^{-1} K^{-1} and −77.0 J mol^{-1} K^{-1} respectively. The slightly negative entropy of activation is probably due to solvent reorganisation in progressing from a neutral ground state to a dipolar transition state in the rate-determining unimolecular (dissociative) process.

In the acid-catalysed region, the values of the entropy of activation are found to be positive, suggesting that the hydrolysis also proceeds *via* a unimolecular mechanism ($A_{AL}1$ or $A_{AC}1$), in which the substrate undergoes pre-equilibrium protonation and then undergoes unimolecular dissociation in the rate-determining step (Scheme 2). Other acylals and acetals



Scheme 2 (n = 1 or 2; * = ^{18}O)

which have been alleged to hydrolyse by the above mechanism include the acid-catalysed hydrolysis of methoxymethyl acetate [(**10**), $\Delta S^‡ = +14$ J mol^{-1} K^{-1}][5,7] and γ-ethoxy-γ-butyrolactone [(**2**), $\Delta S^‡ = -29$ J mol^{-1} K^{-1}].[6]

The solvent effect. Changing the solvent in which a reaction is carried out often produces a profound effect on its rate. Hussain and co-workers[12–14] investigated the hydrolysis of several acylals in the pH-independent region by varying the solvent medium. The same method was employed to determine the effect of solvent dielectric on the hydrolysis of tetrahydro-2-furyl propionate in the neutral region (pH 7.25) at concentrations of 0, 5, 10, 20 and 25% dioxan (v/v) and the results appear in Table G (supplementary data).

If the rate-limiting step is accompanied by an increase in electrical charge on the reactant, a change to a more polar solvent will cause an increase in the rate. The magnitude of the rate acceleration produced by increasing the polarity of the solvent (× 20 from 25% dioxane–H_2O to H_2O) is consistent with a mechanism in which there is a high degree of ionic character in the transition state. The negative slope obtained for the plot (Fig. 2) of k_{obs} *versus* the reciprocal of the relative permittivity,[15] is similar to that found by Hussain[12–14] for the unimolecular S_N1 decomposition of 1-ethoxyethyl 2-acetoxybenzoate (**11**) and 1-(2-acetoxybenzoyl)-2-deoxy-α-D-glucopyranose (**12**).

$H_2{}^{18}O$ labelling. ^{18}O-Labelling experiments were carried out to confirm the proposed mechanism for the hydrolysis of tetrahydro-2-furyl propionate under acidic and neutral conditions. The experiments were carried out using a known ratio of $H_2{}^{16}O$:$H_2{}^{18}O$ and the ^{18}O-isotope effect on the ^{13}C NMR shift was used to identify the labelling in the hydrolysis products[10] and hence to determine whether a particular bond was broken in or before the rate-limiting step of a reaction. The reaction mixture for the labelling experiment contained $H_2{}^{16}O$ and $H_2{}^{18}O$ in an approximate ratio of 6:4 respectively.

The acidic region. The ^{13}C NMR chemical shifts with respect to ^{16}O and ^{18}O bonded carbon appear in Table 5a. The ^{18}O label

Table 5 ^{13}C NMR data for $^{16}O/^{18}O$ shifts

(a) in the acidic region			(b) in the neutral region		
δ_C(C-2)			δ_C(C-2)		
^{16}O	^{18}O	$\Delta\delta_C$ (^{18}O)	^{16}O	^{18}O	$\Delta\delta_C$ (^{18}O)
98.714	98.696	0.018	98.694	98.675	0.019

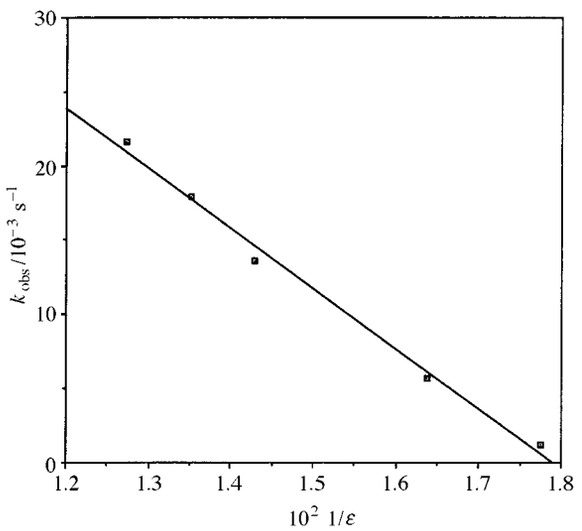


Fig. 2 Plot of $k_{obs}/10^{-3}$ *vs.* $1/\varepsilon$ for the hydrolysis of **8** (R = Et) in H_2O at pH 7.25 and 25 °C

was found attached to the C-2 of 2-hydroxyfuran and an upfield shift $\Delta\delta_C(^{18}O)$ of 0.018 ppm was observed. Integration over ^{16}O–C and ^{18}O–C peaks in the ^{13}C NMR spectrum indicated an isotopic ratio of approximately 6:4, identical to the amount of $H_2{}^{16}O:H_2{}^{18}O$ used in the experiment. Since ^{18}O was found in the hemi-acetal and *not* in the carboxylic acid of the product, hydrolysis of tetrahydro-2-furyl propionate in the acidic region must proceed by loss of propionic acid in the slow rate-determining step.

The neutral region. Under neutral conditions, a similar upfield shift was observed in the ^{13}C NMR spectrum for tetrahydro-2-furyl propionate. The chemical shifts in the ^{13}C NMR spectra for $^{16}O/^{18}O$ are tabulated in Table 5b and the integration ratio of the ^{16}O–C and ^{18}O–C peaks in the ^{13}C NMR spectrum was again in good agreement with the ratio of normal and ^{18}O water employed in the experiment. The upfield shift caused by ^{18}O–C was confirmed by the addition of a known quantity of the hydrolysis product in normal water which enhanced the intensity of the downfield peak. Thus the result of ^{18}O labelling experiment in neutral conditions is very similar to that found for the acidic region which indicates that the hydrolysis proceeds *via* either unimolecular dissociation of the propionate or a bimolecular (S_N2) process involving water. However, the entropy of activation is only slightly negative ($\Delta S^{\ddagger} = -25$ J mol^{-1} K^{-1}) and the results with a range of alkanoates (see below) favours the dissociative mechanism.

Kinetics of the hydrolysis of tetrahydrofuryl alkanoates

The alkanoic acids used in this study were selected over a wide range of pK_a values[16] from 2,2-dimethylpropionic acid (pK_a 5.05) to 2-chloropropionic acid (pK_a 2.88). The rates of hydrolysis of each alkanoate were then studied in the acidic and neutral pH regions.

The acidic region. In this region the rates of hydrolysis of the tetrahydro-2-furyl alkanoates were studied at pH 2.60 in EtOH–H_2O (20% v/v) buffer solution and at 15 °C. The results are shown in Table 6 and the plot of log k_{obs} *vs.* pK_a (Fig. 3) gives a good linear correlation ($\beta_{LG} = -0.92$) with the rate of hydrolysis increasing as the pK_a of the parent acid decreases. The alkanoate substituents may affect the pre-equilibrium protonation of

Table 6 k_{obs} and p$K^{\ddagger}$ values for the hydrolysis of **8** (R = alkyl) at 15 °C

R	pK_a	pH 2.60 $k_{obs}/10^{-2}$ s^{-1}	pH 7.50 $k_{obs}/10^{-3}$ s^{-1}	p$K^{\ddagger}$
CMe_3	5.05	1.22	1.0	3.65
$MeCH_2$	4.87	2.28	2.8	3.45
$PhCH_2CH_2$	4.66	2.85	3.6	3.44
$ClCH_2CH_2$	4.00	11.8	22.5	3.22
$MeCH_2OCH_2$	3.65	26.1	80.1	2.95
MeCHBr	2.97	—	327	—

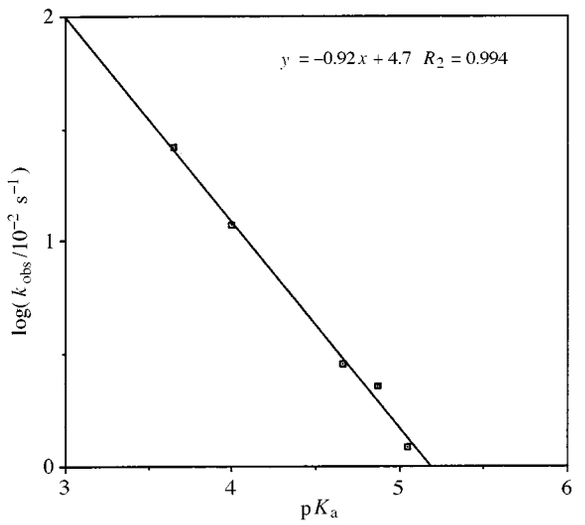


Fig. 3 Plot of log $k_{obs}/10^{-2}$ *vs.* pK_a for the hydrolysis of **8** in H_2O–20% EtOH at pH 2.6 and 15 °C

the acylal and/or the dissociation of the protonated acylal (Scheme 2, $n = 1$). It is reasonable to assume that as R becomes more electron withdrawing, the position of equilibrium (K) between the acylal and the protonated acylal would move to the left, which would give a *positive* slope of log k_{obs} *vs.* pK_a. This was in fact found for the acid catalysed hydrolysis of **7**[10] although the slope was only 0.1. On the other hand, one would expect the rate of dissociation (k_d) of the protonated substrate to be enhanced by electron-withdrawing groups in R which would give rise to a *negative* slope of the same plot. The overall effect of the electron withdrawing substituents on the tetrahydro-2-furyl alkanoates gives a negative slope (Fig. 3) which implies that the effect on k_d is dominant, *i.e.* C–O bond cleavage is extensive in the TS. Support for this contention is provided by the work ‡ of Kankaanperä[17] and also by consideration of the results in the neutral region discussed below.

The neutral region. The results obtained for the hydrolysis of tetrahydro-2-furyl alkanoates in the neutral region are also recorded in Table 6 and plotted in Fig. 4. Thus in the same series of alkanoates, a similar trend to that observed in the acidic region is observed since the rates of hydrolysis increase as the alkanoate becomes a better leaving group, *i.e.* as the pK_a of the parent acid falls. This result again implies that the mechanism involves rate-limiting ionisation if the alkanoate group. The slope (−1.19) agrees remarkably well with the β_{LG} value of 1.18 found for the spontaneous hydrolysis of 2-aryloxytetrahydropyrans,[18] which is considered to occur *via* an A-1 mechanism. The slope of the plot of log k_{obs} *vs.* pK_a in the acid region is composed of a combination of k_H and k_o. When k_H values were calculated (Table 6) from k_{obs} and k_o, a plot of log k_H *vs.* pK_a gave a slope of −0.84 ($r = 0.996$). This contrasts with the positive slope associated with the acid-catalysed hydrolysis of (**7**, *vide supra*) and with the negative ρ value (= −0.92) found for a Hammett plot of log k_H *vs.* σ for the acid-catalysed hydrolysis

‡ We are indebted to a referee for drawing our attention to this analogy.

Table 7 Activation parameters for the hydrolysis of **9** at pH 2.55 and 7.49

pH	E_A/kJ mol^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta G^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
2.55	87	84	68	+54
7.49	93	91	89	+5

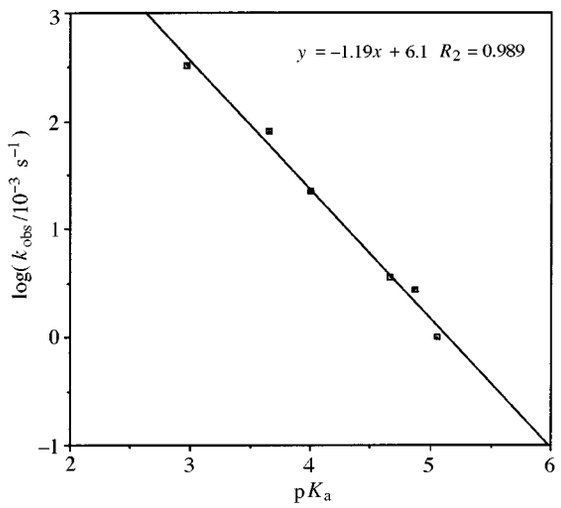


Fig. 4 Plot of log $k_{obs}/10^{-3}$ *vs.* pK_a for the hydrolysis of **8** in H_2O–20% EtOH at pH 7.5 and 15 °C

of 2-aryloxytetrahydropyrans.[19] In the latter case, therefore, partial cancellation of opposing equilibrium (negative ρ) and C–O bond cleavage (positive ρ) effects, results in a negative ρ whereas with the better leaving group (alkanoate) bond cleavage seems to dominate. Calculation of the p$K^{\ddagger}$ values[20] (Table 6) indicates, by comparison with the pK_a values of the alkanoic acids, that C–O bond cleavage is close to completion in the TS. Furthermore, a plot of (pK_a − p$K^{\ddagger}$) *vs.* pK_a is linear ($r = 0.985$) with a positive slope (= 0.6) indicating that bond cleavage increases with increasing leaving group acidity.

Kinetics of the hydrolysis of tetrahydropyran-2-yl propionate

Eliel and Giza[21] considered that an axial proton at C-2 of a tetrahydropyran derivative would give a broad peak at 4.15–4.72 ppm, whereas an equatorial proton would give a sharp peak at 4.53–5.52 ppm in the ^{1}H NMR spectrum. The sharp triplet at 5.90 ppm is therefore consistent with the presence of an equatorial proton at C-2 and consequently the substituent group must be axial. Alkoxy or aryloxy groups at C-2 of tetrahydropyran derivatives apparently prefer the axial position[21] and hence the propionate group of tetrahydropyran-2-yl propionate is almost certainly axial and therefore subject to the anomeric effect.[22]

Kinetic measurements. The rates of hydrolysis of tetrahydropyran-2-yl propionate were monitored by UV–VIS spectrophotometry at $\lambda = 222$ nm. The kinetic experiments were carried out at 25 ± 0.2 °C in 20% EtOH–H_2O (v/v) buffer in order to counteract the solubility problems experienced with pure water.

pH–rate profiles. The kinetics were studied over a range of pH (2–12) at a constant ionic strength ($\mu = 0.1$ M) and the results (Table H, supplementary data) are plotted in Fig. C which reveals an acid-catalysed hydrolysis (pH 2–4), and an uncatalysed hydrolysis or pH-independent ($4 \geqslant$ pH $\leqslant 12$) region. The overall rate of hydrolysis is therefore described by eqn. (2) and a plot of k_{obs} *versus* [H$^+$] gives values of k_H (6.82 dm^3 mol^{-1} s^{-1}) and k_o (1.3×10^{-3} s^{-1}).

$$k_{obs} = k_H[H^+] + k_o \qquad (2)$$

Table 8 ^{13}C NMR data for ^{16}O/^{18}O shifts in hydrolysis of **9** (R = Et)

(a) in acidic region δ_C(C-2) ^{16}O	^{18}O	$\Delta\delta_C$ (^{18}O)	(b) in neutral region δ_C(C-2) ^{16}O	^{18}O	$\Delta\delta_C$ (^{18}O)
95.252	95.237	0.015	95.233	95.281	0.015

Table 9 Rate coefficients for the hydrolysis of **9**, pH 7.49 at 15 °C

R	pK_a	$k_{obs}/10^{-3}$ s^{-1}
CMe_3	5.05	0.33
$MeCH_2$	4.87	1.02
$PhCH_2CH_2$	4.66	1.29
$ClCH_2CH_2$	3.97	7.54
$EtOCH_2$	3.65	31.8
MeCHBr	2.97	103
MeCHCl	2.88	165

Variation of rates with reaction temperature. In the acid-catalysed region, the rates were measured at 16, 20, 25 and 31 °C [Table I(i), supplementary data] and in the neutral (pH-independent) region the rates were measured at 25, 32, 40 and 46 °C [Table I(ii), supplementary data]. The resultant activation parameters are summarised in Table 7. The entropy of activation ($\Delta S^{\ddagger}$) is positive in both regions which is consistent with a unimolecular (dissociative) reaction. The acid-catalysed hydrolysis of 2-ethoxytetrahydropyran (with $\Delta S^{\ddagger} = +33.0$ J mol^{-1} K^{-1})[17,23] is also alleged to react by a unimolecular mechanism.

$H_2{}^{18}O$ labelling. ^{18}O-Labelling experiments were carried out to substantiate the proposed mechanism for the hydrolysis of tetrahydropyran-2-yl propionate under acidic and neutral conditions. As in the case of tetrahydro-2-furyl propionate, a known ratio (6:4) of $H_2{}^{16}O$:$H_2{}^{18}O$ was used and the ^{18}O label was then expected in the hemi-acetal or in the carboxylic acid.

The chemical shifts of the ^{16}O–C and ^{18}O–C labelled acylal carbon for both the acidic and the neutral region are shown in Table 8a and b. In both cases ^{18}O was again found attached to the C-2 of the hemi-acetal in the product and an upfield shift $\Delta\delta_C(^{18}O)$ of 0.015 ppm was observed. Integration over ^{16}O–C and ^{18}O–C peaks indicated an isotopic ratio of approximately 6:4, identical to the isotopic ratio used in the experiment. Thus, hydrolysis of tetrahydropyran-2-yl propionate in both regions occurs by cleavage of the C–O alkanoate bond probably *via* an $A_{AL}1$ mechanism consistent with the positive $\Delta S^{\ddagger}$ values in both regions.

Kinetics of the hydrolysis of tetrahydropyran-2-yl alkanoates

The results obtained for the hydrolysis of tetrahydropyran-2-yl alkanoates in the neutral region are recorded in Table 9 and plotted in Fig. 5. The rates increase as the alkanoic acid becomes more acidic which again indicates formation of the carboxylate anion in the rate-limiting step. The slope of −1.18 again accords with the β_{LG} value found for aryloxytetrahydropyrans[18] and the value of p$K^{\ddagger} = 3.4$ calculated for R = Et, again suggests a high degree of C–O bond cleavage in the TS.

Buffer catalysis in the hydrolysis of tetrahydro-2-furyl and tetrahydropyran-2-yl propionates

The kinetics of the hydrolysis were monitored in the neutral region with three types of buffer (acetate, phosphate and imidazole). The results (Table 10) show no buffer catalysis which again supports the proposal of a unimolecular rate-limiting step for both substrates.

pH-Independent hydrolysis of tetrahydro-2-furyl and tetrahydropyran-2-yl propionates

Tetrahydro-2-furyl propionate and tetrahydropyran-2-yl propionate were found to have a large plateau in the pH–rate

Table 10 Rate coefficients for the hydrolysis of **8** and **9** (R = Et) in three buffers (μ = 0.5 M with KCl at 25 °C)

pH 5.2		pH 8.5		pH 7.5	
[Acetate]/M	$k_{obs}/10^{-3}$ s^{-1}	[Phos]/M	$k_{obs}/10^{-3}$ s^{-1}	[Imid]/M	$k_{obs}/10^{-3}$ s^{-1}
(a) for **8**					
0.02	7.57	0.02	7.67	0.02	7.00
0.10	7.25	0.10	7.29	0.10	7.08
0.35	7.16	0.35	7.52	0.35	7.19
(b) for **9**					
0.02	2.76	0.02	2.62	0.02	2.72
0.10	2.89	0.10	2.73	0.10	2.71
0.35	2.71	0.35	2.68	0.35	2.74

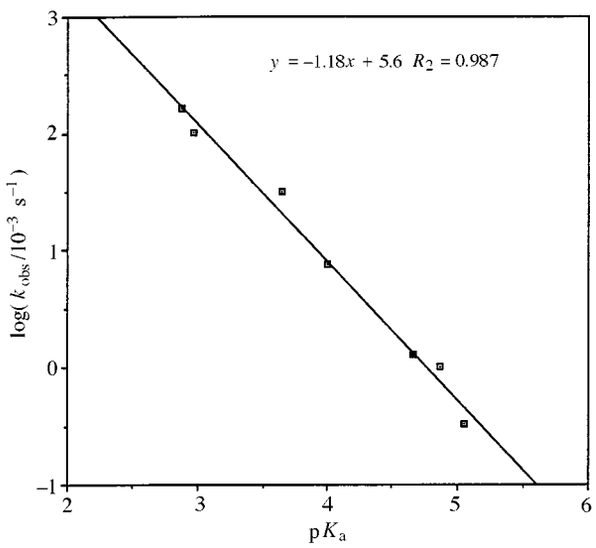


Fig. 5 Plot of log $k_{obs}/10^{-3}$ *vs.* pK_a for the hydrolysis of **9** in H_2O–20% EtOH at pH 7.5 and 15 °C

profile (3 ⩾ pH ⩽ 12). This extensive pH-independent region is almost certainly favoured by the formation of a resonance stabilised cyclic oxycarbonium ion. The pH-independent hydrolysis of 1-β-D-glucopyranosyl benzoate also occurs *via* unimolecular breakdown to an oxycarbonium ion and benzoate ion.[24] In the hydrolysis of γ-ethoxy-γ-butyrolactone,[6] it is very likely that the decomposition on the pH independent region also occurs by a unimolecular reaction to a resonance stabilised oxycarbonium ion. Similar pH-independent unimolecular decompositions are found in the hydrolysis of acylal and acetal analogues having very good leaving groups.[2,18,25–28]

Conclusion

The acidic region

In the acid-catalysed hydrolysis of tetrahydro-2-furyl propionate and tetrahydropyran-2-yl propionate, the unimolecular $A_{AL}1$ mechanism is indicated by the following evidence. (i) The entropy of activation values for tetrahydro-2-furyl propionate and tetrahydropyran-2-yl propionate ($\Delta S^{\ddagger}$ = +25 J mol^{-1} K^{-1} and +54 J mol^{-1} K^{-1} respectively) are both positive, indicating a dissociative process. (ii) The ^{18}O water labelling experiments show that the ^{18}O label remains in the hemi-acetal of the products in both cases which excludes the $A_{AC}2$ and $A_{AC}1$ mechanisms. (iii) The correlation of rate with the pK_a of the leaving group (for the furyl system) is consistent with a unimolecular process.

Thus the mechanism of acid-catalysed hydrolysis of tetrahydro-2-furyl propionate and tetrahydropyran-2-yl propionate is similar to that of A-1 acetal hydrolysis involving pre-equilibrium protonation of the substrate followed by rate-determining alkyl–oxygen dissociation of carboxylic acid to give a stabilised oxycarbonium ion, which reacts with water to form the hemi-acetal. Since tetrahydro-2-furyl and tetrahydropyran-2-yl propionates hydrolyse by an A-1 mechanism, it is likely that all the tetrahydro-2-furyl and tetrahydropyran-2-yl alkanoates also hydrolyse *via* the same mechanism.

The neutral region

In the neutral region the mechanism of the uncatalysed hydrolysis of 2-tetrahydrofuranyl propionate and 2-tetrahydropyranyl propionate also appears to be a unimolecular S_N1 process. The evidence to support the proposed mechanism is as follows. (i) The entropies of activation for tetrahydro-2-furyl propionate and tetrahydropyran-2-yl propionate ($\Delta S^{\ddagger}$ = −25 J mol^{-1} K^{-1} and +5 J mol^{-1} K^{-1} respectively) although negative in the former case, are comparable to the values found for other S_N1 reactions in this pH region. (ii) Experiments in $H_2{}^{18}O$ again resulted in the ^{18}O label being incorporated in the hemi-acetal of the products. This implies either an S_N1 or S_N2 mechanism, but the values of $\Delta S^{\ddagger}$ obtained for both substrates favour the S_N1 decomposition rather than S_N2. (iii) The lack of buffer catalysis is consistent with a unimolecular process. If water was functioning as a nucleophile the presence of more powerful nucleophiles would be expected to affect the rates of reaction and this is not observed. (iv) The reaction is sensitive to the solvent medium and the rate increases as the relative permittivity increases which implies a transition state which is ionic relative to the ground state.

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