Reactions of Carbonyl Compounds in Basic Solutions. Part 30.[1] The Effect of 2-Formyl, 2,6-Diformyl and 2-Trifluoroacetyl Substituents on the Alkaline and Neutral Hydrolysis of Methyl Benzoate and Phenyl Acetate†

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Rate coefficients are measured for the alkaline hydrolysis of methyl 2-formyl-, 2,6-diformyl- and 2-trifluoroacetyl-benzoates and for the alkaline and neutral hydrolysis of 2-formyl-, 2,6-diformyl-4-methyl- and 2-trifluoroacetyl-phenyl acetates in water at several temperatures: the relative rates of hydrolysis and activation parameters demonstrate neighbouring group participation by the acyl-carbonyl groups in the ester hydrolysis.

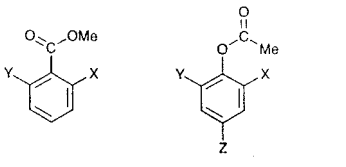
Prodrugs have been designed as reversible derivatives of drugs to eliminate undesirable properties of the drug.[2] While the linkage employed in forming prodrugs has been various, the formation of esters has been common.[3] Esters can be hydrolysed either by enzymes or non-enzymatically to liberate the parent drug. There are clear advantages in using esters whose hydrolysis is facile and can be tuned by comparatively simple structured changes.

Neighbouring group participation by suitably situated carbonyl groups in the alkaline hydrolysis of esters has been recently reviewed.[4] Criteria have been established for the detection and delineation of this behaviour. For powerful facilitation, the acyl group substituent should be electron-withdrawing and have modest steric 'bulk'.[4,5] Thus, the alkaline hydrolysis of methyl 2-formylbenzoate has been studied at 25.0 °C in water[6] and at several temperatures in 70% (*v*/*v*) 1,4-dioxane–water[7] and the alkaline and neutral hydrolysis of 2-formylphenyl acetate at 25.0 °C in water.[8]

We describe here the hydrolysis, under alkaline conditions, of model esters. The esters are methyl benzoates and phenyl acetates *ortho*-substituted with acyl groups designed to achieve high reactivity, *i.e.* 2-formyl, 2,6-diformyl and 2-trifluoroacetyl substituents.

Results

The prepared model compounds were methyl 2-formyl-, 2,6-diformyl- and 2-trifluoroacetyl-benzoate, **1a–c**, and 2-formyl-, 2,6-diformyl-4-methyl- and 2-trifluoroacetyl-phenyl acetates, **2a–c**. The esters **1a** and **2a** were used as reference compounds.[4,7] The alkaline hydrolysis of the methyl benzoates is of first-order both in ester and in hydroxide anion. However, the hydrolysis of the phenyl acetates is of first-order in ester and both zero- and first-order in hydroxide anion. The products of the hydrolysis of all the esters were the corresponding phenol or methanol and the corresponding benzoate or acetate anion. The rate coefficients for the hydrolysis of the esters in water are shown in Table 1 and the activation parameters in Table 2.



1a X = CHO, Y = H
b X ,Y = CHO
c X = C(CF$_3$)O, Y = H

2a X = CHO, Y = Z = H
b X ,Y = CHO, Z = Me
c X = C(CF$_3$)O, Y = Z = H

Table 1 Rate coefficients (k_2) for the alkaline hydrolysis of substituted methyl benzoates and phenyl acetates in water (at constant ionic strength of 0.1 mol dm^{-3})[a,b]

	10^{-2} k_2/dm^3 mol^{-1} s^{-1}			
Methyl benzoates Subst.	at 30.0 °C	at 60.0 °C		λ/nm[c]
2-CHO	19.1	31.1		302
2,6-(CHO)$_2$	475	617		308
2-C(CF$_3$)O	9.30 (1010)[d]	14.6 (1350)[d]		232
	10^{-5} k_2/dm^3 mol^{-1} s^{-1}			
Phenyl acetates Subst.	at 27.0 °C	at 37.0 °C	at 47.0 °C	
2-CHO	1.30 (64.0)[e]	1.87 (102)[e]	2.68 (165)[e]	320
2,6-(CHO)$_2$, 4-Me	11.8 (42.8)[e]	14.8 (64.1)[e]	17.4 (89.7)[e]	354
2-C(CF$_3$)O	10 600 (7.96)[e]	11 000 (14.3)[e]	11 200 (26.5)[e]	268

[a]Rate coefficients are the mean of at least two determinations and were reproducible to within ±3%. [b]1.8% (v/v) 1,4-dioxane–water. [c]Wavelengths used to monitor hydrolysis. [d]10^{-2} k_3/dm^6 mol^{-2} s^{-1}. [e]10^4 k_1/s^{-1} (neutral or water-catalysed reaction).

Table 2 Activation parameters for the alkaline hydrolysis of substituted methyl benzoates and phenyl acetates at 20.0 °C in water[a,b]

Methyl benzoates Subst.	$\Delta H^{\ddagger}$/kcal mol^{-1}[b]	$\Delta S^{\ddagger}$/cal mol^{-1} k^{-1}[b]
2-CHO	2.7	−35
2,6-(CHO)$_2$	1.2	−33
2-C(CF$_3$)O	2.4 (1.4)[c]	−37 (−31)[c]
Phenyl acetates Subst.		
2-CHO	6.3 (8.5)[d]	−14 (−40)[d]
2,6-(CHO)$_2$, 4-Me	3.1 (6.5)[d]	−20 (−48)[d]
2-C(CF$_3$)O	−0.1 (10.9)[d]	−17 (−36)[d]

[a]Values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are considered to be accurate to ±300 cal mol^{-1} and ±2 cal mol^{-1} K^{-1}, respectively. [b]1.8 (*v*/*v*) 1,4-dioxane–water. [c]Using k_3/dm^6 mol^{-2} s^{-1}. [d]Neutral or water-catalysed reaction.

Discussion

Relative Rates.—The rate ratios for the hydrolysis of the esters to that of either methyl benzoate (k_2 at 30.0 °C = 1.28×10^{-1} dm^3 mol^{-1} s^{-1})[9] or phenyl acetate [k_2 (alkaline) and k_1 (neutral) at 27.0 °C = 180 dm^3 mol^{-1} s^{-1} and 9.0×10^{-8} s^{-1}, respectively][9] can be calculated to give the values shown in Table 3. Estimates of the rate ratios for unassisted hydrolysis using the known polar and steric effects of 2-substituents on the alkaline hydrolysis of methyl benzoates and phenyl acetates,[10,11] as well as the Hammett equation[12] and the neutral hydrolysis of phenyl acetates,[13] have been made and are shown in Table 3. In all cases, the rate enhancements, r_e, shown in Table 3, are both significant, *i.e.* ≥ 10, and very large. They all strongly indicate the occurrence of intramolecular catalysis.[4] Mechanistic pathways for the alkaline hydrolysis of the methyl 2-acylbenzoates and 2-acylphenyl acetates have been shown as Scheme 1 for the exocyclic and Scheme 2 for the endocyclic intramolecular catalysis in our review.[4b] A novel pathway for the neutral

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Table 3 Relative rate ratios of the alkaline hydrolysis of the esters in water at 30 °C for **1a–c** and 27 °C for **2a–c**

Ester	Observed	k/k_0 Expected for 'normal' hydrolysis	Enhanced r_e
1a	14 900	5.0	3000
1b	371 000	25	15 000
1c	7270	5.0	1500
2a	722 (7.1×10^4)[a]	5.0 (5.0)[a]	140 (1.4×10^4)[a]
2b	6560 (4.8×10^4)[a]	25 (25)[a]	260 (1.9×10^3)[a]
2c	5.89×10^6 (8.8×10^3)[a]	8.0 (8.0)[a]	7.4×10^5 (1.1×10^3)[a]

[a]Neutral hydrolysis.

hydrolysis of the 2-acylphenyl acetates is shown in Scheme 1.

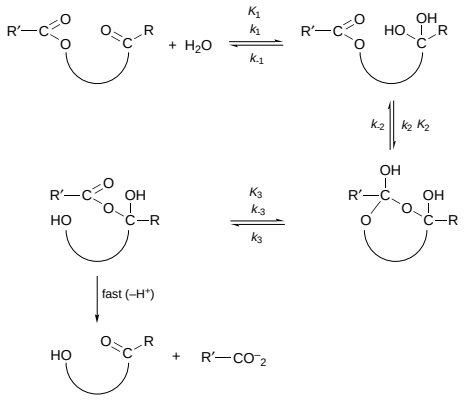
The increased rates of the alkaline reaction hydrolysis of the two 2,6-diformyl esters **1b** and **2b**, relative to those of the 2-formyl esters **1a** and **2a**, are those expected on the basis of the statistical factor, *i.e.* ×2, and of the activating effect of a '*meta*'-formyl group on the formyl group undergoing nucleophilic attack. A combination of an electron-withdrawing effect, *i.e.* $\sigma_1 = 0.40$,[14] and a significant steric 'bulk' effect, *i.e.* $E_s = -2.40$,[12] for the trifluoromethyl substituent would account for the relative rate of the alkaline hydrolysis of **1c**, *cf.* ref. 5. The remarkably rapid rate of reaction for **2c** was unexpected.

Activation Parameters.—For the alkaline hydrolysis of the more reactive methyl esters employing neighbouring group participation, the enthalpies of activation are exceptionally small and are associated with rather large negative entropies of activation.[4] As shown in Table 2, this is true for the methyl esters **1a–c** studied here. The same reaction for the phenyl acetates studied here displays very small enthalpies of activation, but the entropies of activation are normal for a bimolecular reaction. The neutral or water-catalysed reactions of the phenyl esters **2a–c** also have relatively small enthalpies of activation, with very large negative entropies of activation. The latter are very comparable to those found for the neutral hydrolysis of a number of reactive esters.[15] This would appear to be the first observation of intramolecular catalysis by carbonyl groups of neutral or water-catalysis of ester hydrolysis.

Experimental

Materials.—2,6-Diformylbenzoic acid was obtained by bromination of 2,6-dimethylbenzoic acid and subsequent hydrolysis.[16] Oxidation of 4-methyl-2,6-bis(hydroxymethyl)phenol in stages gave 2,6-diformylphenol.[17] 2-Trifluoroacetylbenzoic acid was prepared by the lithiation of 1,2-dibromobenzene and reaction with methyl trifluoroacetate and carbon dioxide.[18] The Fries rearrangement of phenyl trifluoroacetate gave 2-trifluoroacetylphenol.[19] The methyl esters of the acids were prepared from the corresponding acid and diazomethane.[7] The phenyl acetates were prepared by treatment of the corresponding phenol in acetic anhydride with concentrated sulfuric acid or pyridine.[20] The purity of the acids, phenols and esters was monitored by ^{1}H and ^{13}C NMR and IR spectroscopy, as well as mass spectrometry. The mp values of the acids, phenols and esters, after repeated recrystallization and drying under reduced pressure (P_2O_5), was in agreement with literature[6,16–19] values, as was the boiling point of 2-trifluoroacetylphenyl acetate.[21] The following previously unreported esters gave satisfactory elemental analysis. Methyl 2,6-formylbenzoate had mp 65–66 °C and was recrystallised from benzene–hexane. 2,6-Diformyl-4-methylphenyl acetate had mp 110–111 °C and was recrystallised from benzene–hexane. Methyl 2-trifluoroacetylbenzoate had mp 67– 68 °C and was recrystallised from hexane.

Measurements.—Rate coefficients for the alkaline and neutral or water-catalysed hydrolysis were determined spectrophotometrically. The reactions were followed at the wavelengths shown in Table 1. The procedure used was that described previously.[22] The products of the reactions were found to be either the anions of the corresponding carboxylic acids or the phenols in quantitative yield and were further confirmed spectrophotometrically. Rates were extrapolated to zero buffer concentrations. Hydroxide anion concentrations of 1×10^{-3} to 1×10^{-2} mol dm^{-3} were used where required. The hydrolysis of the methyl esters **1a** and **1b** is of first-order in both substrate and hydroxide anion. For the methyl ester **1c**, the reaction is both first- and second-order in hydroxide anion. The hydrolysis of the acetate esters is of first order in substrate and of both zero and first order in hydroxide anion.



Scheme 1

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