Reactions of Carbonyl Compounds in Basic Solutions. Part 12.[1] The Mechanism of the Alkaline Hydrolysis of 3-Substituted Phenyl 2-Acetyl- and 2-Benzoyl-benzoates

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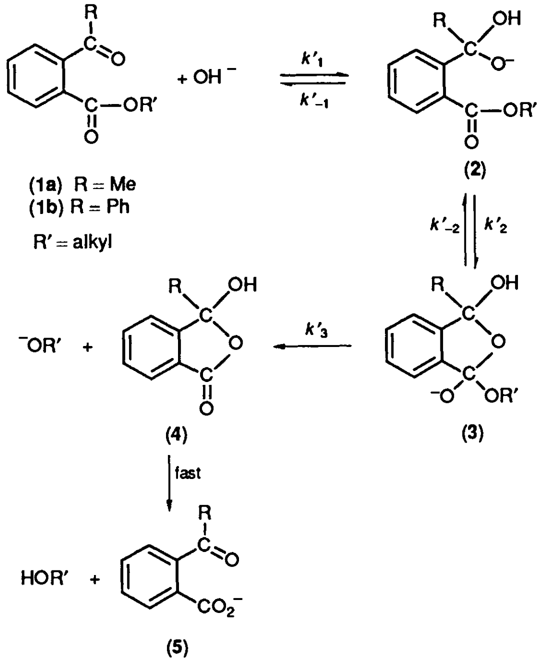
Rate coefficients have been measured for the alkaline hydrolysis of 3-substituted phenyl 2-acetyl- and 2-benzoyl-benzoates in 70% (v/v) dioxane–water at several temperatures. The enthalpies and entropies of activation have been evaluated. The effects of substitution have been assessed by means of the Hammett equation. Comparison of the reaction constants with those for model systems, as well as the relative rates and activation parameters, indicate that the rate-determining step for the 2-acetyl esters is attack by hydroxide anion at the keto-carbonyl group and for the 2-benzoyl esters it is the intramolecular attack on the ester-carbonyl group, which follows equilibrium addition of the hydroxide anion at the keto-carbonyl group.

The participation by suitably oriented neighbouring keto and formyl groups in the alkaline hydrolysis of esters has been observed.[2] The general mechanism is shown in Scheme 1[3,4] for an *ortho*-acyl-(**1a**) or -aroyl-benzoate (**1b**) system. This is shown as proceeding with discrete intermediates, although concerted reactions could occur. However, the nature of the rate-determining step has yet to be determined with confidence. The entropies and enthalpies of activation have been tentatively used in an assignment of the rate-determining step by Bowden *et al.*[3,4] Bhatt *et al.*,[5] extended the observations of Bowden and Taylor[4] regarding the insensitivity of rates to the nature of the leaving group in the 2-benzoylbenzoate systems and suggested that the rate-determining step for these esters is the formation of the adduct,[2] *i.e.*, k'_1 in Scheme 1. A study[6] by Klotz's group of the alkaline hydrolysis of *O*-acetylsalicylaldehyde in $H_2{}^{18}O$ was considered to indicate that hydrolysis occurred by rate-determining hydration of the aldehyde. A recent investigation by Washburn and Cook[7] of the alkaline hydrolysis of non-enolisable acetoacetate esters using kinetic and ^{18}O-labelling studies was judged to indicate that, for different esters, the rate-determining step was either the formation of the adduct or the intramolecular cyclisation step.



Scheme 1.

Studies of series of *meta*-substituted phenoxy substrates have been used as a mechanistic probe.[8] A similar technique has been employed here to delineate the mechanistic pathway. In the present study, the kinetics of the alkaline hydrolysis of a series of 3-substituted phenyl 2-acetyl- and 2-benzoyl-benzoates has been investigated. The effects of substitution, relative rates and activation parameters are discussed in terms of a detailed mechanism.

Results and Discussion

The alkaline hydrolysis of the phenyl esters is of first-order both in ester and hydroxide anion. Rate coefficients for the 3-substituted phenyl esters in 70% (v/v) dioxane–water at several temperatures are shown in Table 1. The activation parameters are shown in Table 2. Three criteria of mechanism are discussed here, *i.e.* relative rates, substituent effects and activation parameters.

Relative Rates.—The rates of alkaline hydrolysis of phenyl esters are, in general,[9] *ca.* 4 times faster than the corresponding methyl esters. Comparison of the rates of alkaline hydrolysis of the phenyl esters in the study with those of the corresponding methyl esters previously studied[3,4] indicates that the phenyl esters are only *ca.* 1.3 times faster than the corresponding methyl esters. The 2-keto esters show a reduced rate enhancement because the seat of the original attack for both 2-keto esters is not directly bonded to the phenoxy group, as it is in normal ester hydrolysis. This insensitivity of rate to the leaving group can be considered diagnostic for neighbouring group participation by carbonyl groups[4,5] for both esters. A very significant rate enhancement of 6400 was estimated previously[4] for the methyl 2-acetyl ester and a value of 2100 can be similarly estimated for the corresponding phenyl ester. A rate enhancement of only 5.6 was estimated for the methyl 2-benzoyl ester,[4] which would reduce to *ca.* 2 for the corresponding phenyl ester. Only in the former case can the result be considered diagnostic.

Table 1. Rate coefficients (k_2) for the alkaline hydrolysis of 3-substituted phenyl 2-acetyl- and 2-benzoyl-benzoates in 70% (v/v) dioxane–water.[a]

3-Substituent	k_2/dm^3 mol^{-1} s^{-1}		
	30.0 °C		50.0 °C
2-Benzoylbenzoates			
H	0.155		0.655
Me	0.126		0.477
Cl	0.433		1.48
NO_2	1.96		6.43
	k_2/dm^3 mol^{-1} s^{-1}		
	20.2 °C	30.0 °C	40.0 °C
2-Acetylbenzoates			
H	8.20	13.3	22.9
Me	6.40	11.6	19.1
Br	11.6	20.4	33.4
NO_2	17.1	29.3	48.3

[a] Rate coefficients are reproducible to within ±3%.

Table 2. Activation parameters for the alkaline hydrolysis of 3-substituted phenyl 2-acetyl- and 2-benzoyl-benzoates in 70% (v/v) dioxane–water at 30.0 °C.[a]

3-Substituent	$\Delta H^\ddagger$/kcal mol^{-1}	$\Delta S^\ddagger$/cal mol^{-1} K^{-1}
2-Benzoylbenzoates		
H	13.5 (13.7)[b]	−18 (−18)[b]
Me	12.3	−22
Cl	11.4	−23
NO_2	11.0	−21
2-Acetylbenzoates		
H	8.9 (8.4)[b]	−24 (−26)[b]
Me	9.4	−23
Br	9.2	−22
NO_2	9.0	−22

[a] Values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ are considered accurate to within ±300 cal mol^{-1} and ±2 cal mol^{-1} K^{-1}, respectively. [b] Values for corresponding methyl esters.[4]

Table 3. The Hammett reaction constants (ρ) for the alkaline hydrolysis of 3-substituted phenyl 2-acetyl- and 2-benzoyl-benzoate in 70% (v/v) dioxane–water at 30.0 °C.[a]

System	ρ	log k_0	r	s	n
2-Acetylbenzoates	0.504	1.110	0.998	0.002	4
2-Benzoylbenzoates	1.48	−0.828	0.989	0.155	4

[a] s is the standard deviation, r the correlation coefficient and n the number of substituents studied.

Substituent Effects.—The effect of substituents in the phenyl ring of the phenoxy group has been assessed using the Hammett equation with *meta*-σ values,[10] as shown in Table 3. Three relevant studies for the purposes of comparison are those of the alkaline hydrolysis of methyl 2-(3- or 4-substituted benzoyl)-benzoates [ρ at 30 °C for 70% (v/v) dioxane–water, 2.07],[3] of 3-substituted phenyl acetates [ρ at 1 °C for 56% (w/w) acetone–water, 1.77],[11] and of 3-substituted phenyl benzoates [ρ at 25 °C for 56% (w/w) acetone–water, 1.73].[12]

If the three limiting or intermediate states in Scheme 1 are considered, *i.e.* (**1**), (**2**) and (**3**), it is possible to estimate the ρ values that can be expected for their formation. For (**2**), the known ρ value for the hydrolysis of methyl benzoates under the same conditions (ρ 2.20)[3] and the transmission coefficients tabulated by Bowden[13] would give an estimate for ρ of *ca.* 0.3. An alternative to this is to use a relevant model process, the alkaline hydrolysis of several series of 2-(3-substituted phenoxyl)phthalides under the same conditions (ρ 0.66–0.97),[14] which would give an estimate for ρ of *ca.* 0.8. For (**3**), an estimate for ρ of *ca.* 1.4 is given based on transmission, and of *ca.* 1.7, based on the hydrolysis of phenyl acetates and benzoates. For (**4**), the ρ value for the ionisation of phenols (ρ 2.6 in 50% aqueous ethanol at 25 °C)[15] would give an estimate for ρ of *ca.* 2.7. Thus, the observed ρ value of *ca.* 0.5 for the hydrolysis of phenyl 2-acetylbenzoates is consistent with a rate-determining attack of hydroxide anion to the keto-carbonyl group, k'_1 in Scheme 1, followed by a rapid intramolecular cyclisation. The observed value of *ca.* 1.5 for the hydrolysis of phenyl 2-benzoylbenzoates indicates a rate-determining cyclisation step, following pre-equilibrium addition of hydroxide anion to the keto-carbonyl group. This approach corresponds to that developed by Williams[8] in assigning 'effective' charges. The latter could be simply calculated as the ratio of the observed ρ value to that for the ionisation of phenols under identical conditions.

Activation Parameters.—The enthalpies of activation, shown in Table 2, of both the phenyl and methyl 2-acetyl esters are much lower than those for both the corresponding 2-benzoyl esters. This appears to characterise these two detailed pathways, as was previously noted.[2,4,16] The entropies of activation, in this study, do not show such significant differences as those previously noted for several methyl 2-acyl esters.[4]

Proposed Mechanisms.—The alkaline hydrolysis of all the simple phenyl 2-acetyl and 2-benzoylbenzoates proceed by a mechanism involving initial hydroxide anion at the keto-carbonyl group. In the transition state for the 2-acetyl esters, negative charge is being developed on the keto-carbonyl oxygen as the hydroxide anion develops its bond to the carbonyl carbon. In the transition state for the 2-benzoyl esters, negative charge on the keto-carbonyl oxygen is commencing transfer to the ester carbonyl oxygen as the intramolecular attack proceeds; but this is an early transition state without significant collapse towards the second tetrahedral intermediate (**3**) in Scheme 1. These considerations agree with the evidence from substitution in both the phenoxy and benzoyl phenyl groups, as well as the insensitivity to the nature of the leaving group.

Experimental

Materials.—The phenyl esters were prepared by coupling the acid and phenol with *N*,*N*-dicyclohexylcarbodiimide (DCC).

Phenyl 2-Acetylbenzoate.—A mixture of 2-acetylbenzoic acid (2.0 g, 6.1 mmol), phenol (0.57 g, 6.1 mmol), toluene-*p*-sulphonic acid (0.3 g, 1.6 mmol) and DCC (2.5 g, 12.1 mmol) in dry pyridine (30 cm^3) was stirred overnight at room temperature. The precipitate of urea was filtered off and pyridine was removed under reduced pressure. The residue was dissolved in methylene dichloride and the solution was filtered. After being washed with aq. hydrochloric acid (1 mol dm^{-3}) and water, the solution was dried ($MgSO_4$), filtered, and evaporated to yield the crude ester. Repeated recrystallisation yielded the pure ester (0.1 g, 10%), m.p. 70–71 °C.

3-*Substituted Phenyl* 2-*Acetylbenzoates.*—These esters were prepared by the method described above.

Phenyl 2-*Benzoylbenzoate.*—A mixture of 2-benzoylbenzoic

Table 4. The physical constants of the 3-substituted phenyl 2-acetyl- and 2-benzoyl-benzoates.

			Found (%)			Required (%)			
3-Substituent	M.p./°C	Formula	C	H	Other	C	H	Other	Recrystallisation solvent[a]
2-Acetylbenzoates									
H	70–71	$C_{15}H_{12}O_3$	75.3	5.1		75.0	5.0		Light petroleum–benzene
Me	36–39	$C_{16}H_{14}O_3$	75.4	5.6		75.6	5.6		Light petroleum–benzene
Br	73–75	$C_{15}H_{11}BrO_3$	56.7	3.5	25.0 (Br)	56.5	3.5	25.0 (Br)	Cyclohexane–isopropyl alcohol
NO_2	97–99	$C_{15}H_{11}NO_5$	63.4	3.9	4.9 (N)	63.2	3.9	4.9 (N)	Cyclohexane–benzene
2-Benzoylbenzoates									
H	81–83	$C_{20}H_{14}O_3$	79.4	4.8		79.5	4.7		Diethyl ether
Me	35–37	$C_{21}H_{16}O_3$	79.6	5.2		79.7	5.1		Diethyl ether
Cl	85–87	$C_{20}H_{13}ClO_3$	71.0	3.9	10.2 (Cl)	71.3	3.9	10.5 (Cl)	Light petroleum–benzene
NO_2	103–104	$C_{20}H_{13}NO_5$	69.0	3.8	3.9 (N)	69.2	3.8	4.0 (N)	Light petroleum–benzene

[a] Light petroleum (b.p. 60–80 °C).

acid (5.0 g, 22.1 mmol), phenol (2.1 g, 22.3 mmol) and DCC (4.7 g, 22.8 mmol) in dry methylene dichloride (70 cm^3) was stirred for 24 h at room temperature. The precipitate of urea was filtered off and the filtrate evaporated. The residue was dissolved in diethyl ether. The solution was cooled to 0 °C and filtered again. After cooling to −40 °C, the ester crystallised out (2 g, 30%), m.p. 81–83 °C.

3-*Substituted Phenyl* 2-*Benzoylbenzoates*.—The esters were prepared by the method described above.

Attempts to synthesise the phenyl 2-formylbenzoates, 8-formyl- and 8-benzoyl-1-naphthoates were not successful. For the 2-formylbenzoates, the methods above gave a product which was a mixture of the normal and pseudo esters. Upon standing or crystallisation, this mixture gave the pseudo esters quantitatively. For the naphthoates, only the pseudo esters resulted from a slow reaction with the predominately cyclic acids.

All the products had IR, ^{1}H and ^{13}C NMR and mass spectra in accord with the stated structures. The phenyl 2-acetylbenzoates and 2-benzoylbenzoates have keto and ester carbonyl frequencies at 1680–1686, 1735–1743 cm^{-1} and at 1669–1673, 1725–1730 cm^{-1}, respectively. The m.p.s, elemental analyses and recrystallisation solvents of the esters are shown in Table 4.

The solvents for the kinetic studies were prepared as previously described.[3]

Measurements.—Rate coefficients for the alkaline hydrolysis of the esters were determined spectrophotometrically by use of a Unicam SP 8000 and a Pye Unicam SP8-100 spectrophotometer. The reactions were followed at 290–300 nm (2-acetyl esters) and at 230–245 nm (2-benzoyl esters). The procedure used was that described previously.[2] The products of the reactions were found to be the anions of the corresponding acids and phenols in quantitative yield in all cases, and were further confirmed spectrophotometrically by comparison of the spectrum of the acid and phenol in base with that of the reaction product.

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