Intramolecular Participation by an Amide Group in Ester Hydrolysis

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The rate coefficient for hydrolysis of 1-acetoxy-8-acetylaminonaphthalene to 1-hydroxy-8-acetyl-aminonaphthalene in aqueous sodium hydroxide shows a curved dependence on hydroxide ion concentration. Similar results are observed for the 3,6-disulphonate and five substituted 1-benzoyloxy-8-benzoylamino-3,6-disulphonates. In the proposed mechanism the ester group undergoes intermolecular attack by hydroxide ion in competition with intramolecular attack by the amide group. The latter generates an imide intermediate in equilibrium with the ester *via* a rapid acyl transfer, and since the imide is hydrolysed slowly to product its formation inhibits the ester hydrolysis.

Examples of intramolecular participation by amide groups in the hydrolysis of esters are relevant to enzymic reactions.[1] The amide may be reactive in its neutral or ionised form and participation of the amide oxygen or nitrogen may be involved. For example, in the hydrolysis of phenyl *N*-acetylanthranilate to *N*-acetylanthranilic acid in alkaline solution, a benzoxazinone intermediate is generated by intramolecular nucleophilic attack of the amide oxygen on the ester.[2] The amide reacts in the ionised form which is present in low concentration. Hydrolysis of the benzoxazinone is the slow step in the overall reaction, which is estimated to occur *ca.* 50-fold more rapidly than reaction involving intermolecular attack of hydroxide ion on the ester carbonyl. Under acidic conditions the carbonyl oxygen of the neutral amide is the intramolecular nucleophile and the rate of hydrolysis of the benzoxazinone is greater than its rate of formation. The hydrolysis of aryl 2-(acylamino)benzene-sulphonates occurs through an intermediate benzoxathiazine *S,S*-dioxide formed by intramolecular nucleophilic attack of the oxygen of the ionised amide.[3] Formation of the intermediate is slow compared with its subsequent hydrolysis but the intramolecular assistance by the amide group is estimated to lead to a 1 000-fold enhancement in rate as compared with intermolecular reaction of the sulphonate ester with hydroxide ion. Large rate enhancements by a neighbouring amide group are observed in the hydrolysis of the benzyl esters of *N*-benzyloxycarbonyl peptides occurring through imide intermediates formed by nucleophilic attack of the nitrogen of the ionised amide on the ester carbonyl.[4] A similar mechanism applies to amide assistance in the hydrolysis of sterically hindered *O*-acylsalicylamides.[5] However in the hydrolysis of methyl *N*-phenylphthalamide and *O*-acetylsalicylamide, the presence of the neighbouring amide group leads to a reduction in the rate of hydrolysis because the imide intermediates are less reactive towards solvolysis than the original esters.[6]

In the present work, the effect of a neighbouring amide group on the alkaline hydrolysis of substituted 1-acyloxy-8-acyl-aminonaphthalenes (1)—(7) has been investigated [reaction (i)]. Rate coefficients for reaction by attack of hydroxide ion on the ester carbonyl and for reaction by a mechanism involving intramolecular nucleophilic attack by the amide on the ester carbonyl have been measured, and the factors which determine the relative efficiencies of the two routes are discussed.

Experimental and Results

Preparations.—1-*Acetoxy*-8-*acetylaminonaphthalene*. A crude sample of 8-amino-1-naphthol was prepared[7] by fusion of 8-aminonaphthalene-1-sulphonic acid with a mixture of NaOH and KOH at 260 °C. The solid from the surface of the melt was

RCONH OCOR → (OH⁻) → RCONH ⁻O (i)
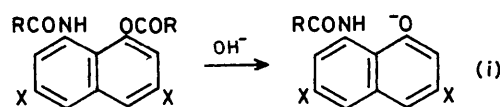
(1) X = H, R = Me
(2) X = SO₃⁻, R = Me
(3) X = SO₃⁻, R = Ph
(4) X = SO₃⁻, R = 4-MeOC₆H₄
(5) X = SO₃⁻, R = 4-ClC₆H₄
(6) X = SO₃⁻, R = 4-NCC₆H₄
(7) X = SO₃⁻, R = 4-NO₂C₆H₄

collected and treated with a mixture of acetic anhydride and acetic acid[8] at room temperature for 1 h. After washing with water, the solid product was recrystallised from ethanol to give 1-acetoxy-8-acetylaminonaphthalene, m.p. 153—154 °C; m/z (chemical ionisation) 244 ($[M + 1]^+$); $\nu_{max.}$ (Nujol) 3 330, 1 760, 1 600, 1 540, and 1 205 cm⁻¹; δ_H[(CD₃)₂SO; 250 MHz] 9.88 (s, 1 H, NH), 7.88—7.19 (m, 6 H, arom.), 2.35 (s, 3 H, CH₃COO), and 2.11 (s, 3 H, CH₃CON); δ_C [(CD₃)₂SO; 62.896 MHz] 169.20 (CH₃COO), 168.46 (CH₃CON), 145.74—122.65 (quat. arom.), 126.69—120.37 (tert. arom.), 23.27 (CH₃COO), and 20.91 (CH₃CON).

1-*Acyloxy*-8-*acylaminonaphthalene*-3,6-*disulphonates*. Concentrated solutions of compounds (2)—(7) were prepared by acylation of a solution of 1-hydroxy-8-aminonaphthalene-3,6-disulphonate (*ca.* 0.01 mol dm⁻³) in the presence of sodium hydrogen carbonate (0.1 mol dm⁻³). In the preparation of (2) the acylating agent, present in excess, was acetic anhydride, but (3)—(7) were prepared by use of the appropriate acid chloride. Acylation was carried out in aqueous solution except for (4), (6), and (7) for which 20% (v/v) dioxane–water was used. Concentrated solutions of (2)—(7) prepared in this way were diluted *ca.* 300-fold for use in kinetic and equilibrium studies.

1-*Acetylaminonaphthalene and* 1-(*diacetylamino*)*naphthalene*. Heating 1-naphthylamine with an equimolar amount of acetic anhydride under reflux for 1 h gave a solid which after recrystallisation from ethanol was identified as 1-acetyl-aminonaphthalene, m.p. 161—162 °C; $\nu_{max.}$ (Nujol) 3 275, 1 660, 1 545, and 1 340 cm⁻¹; δ_H[(CD₃)₂SO; 60 MHz] 10.01 (s, 1 H, NH), 8.30—7.57 (m, 7 H, arom.), and 2.22 (s, 3 H, CH₃). A sample of 1-(diacetylamino)naphthalene was prepared by refluxing 1-aminonaphthalene with a four-fold molar excess of acetic anhydride for 4 h. Distillation left a solid which was recrystallised from ethanol to give the product (m.p. 120—121 °C); $\nu_{max.}$(Nujol) 1 720 and 1 700 cm⁻¹; δ_H [(CD₃)₂SO; 60 MHz] 8.40—7.57 (m, 7 H, arom.) and 2.28 (s, 6 H, CH₃).

1-Acetoxynaphthalene was a commercial sample and was recrystallised from light petroleum.

Identification of the Product of Hydrolysis.—A concentrated aqueous solution of 1-acetoxy-8-acetylaminonaphthalene slowly precipitated a fine crystalline solid which was identified (see later) as 1-hydroxy-8-acetylaminonaphthalene. The u.v. spectra of aqueous solutions of the solid were investigated at different pH values in the range pH 6.5—8.5. The solutions obtained at the completion of the kinetic runs involving hydrolysis of 1-acetoxy-8-acetylaminonaphthalene were treated in the same way and identical behaviour was observed. The change in the spectrum of 1-hydroxy-8-acetylaminonaphthalene with pH is due to dissociation of the hydroxy proton (see under Equilibrium Studies). The isolated product was identified as 1-hydroxy-8-acetylaminonaphthalene, m.p. 140—141 °C; m/z (chemical ionisation) 202 ($[M + 1]^+$); $\nu_{max.}$(Nujol) 3 400br 1 655, 1 550, and 1 350 cm^{-1}; δ_H[(CD$_3$)$_2$SO; 250 MHz] 11.4 (s, 1 H, NH), 8.43—6.87 (m, 6 H, arom.), and 2.15 (s, 3 H, CH$_3$); δ_C[(CD$_3$)$_2$SO; 62.896 MHz] 167.53 (CO), 154.15—115.23 (quat. arom.), 126.27—110.06 (tert. arom.), and 25.22 (CH$_3$). Under the conditions used for kinetic studies, further hydrolysis of 1-hydroxy-8-acetylaminonaphthalene did not occur.

Equilibrium Studies.—Equilibrium and kinetic studies were carried out in aqueous solution at 25.0 °C. The ionic strength was kept at 0.2 mol dm^{-3} by addition of sodium chloride.

The spectra obtained when the substrates (1)—(7) were introduced into aqueous sodium hydroxide were found to depend on the concentration of hydroxide ion. This is later explained (see Discussion section) in terms of a rapid reaction of the substrate to give an imide with which it is in equilibrium; the position of equilibrium depends on the hydroxide ion concentration, $K = $ [imide]/[substrate][OH$^-$]. After a few seconds (or minutes, depending on the particular substrate and hydroxide ion concentration) the spectrum was then observed to change with time, corresponding to hydrolysis by reaction (i). The rapid equilibration with imide was studied in detail for (2) and (3) using a Hewlett Packard Diode Array spectrophotometer and a Hi-Tech rapid-mixing device (SFA-11). Spectra were thereby obtained within 0.1 s after the introduction of substrate and before appreciable hydrolysis had occurred. For solutions containing 1.1 × 10^{-5} mol dm^{-3} of (2) or (3), spectra were recorded with hydroxide ion concentrations in the range 0.001—0.1 mol dm^{-3} and good isosbestic points were observed. Complete conversion into the imide was obtained in the presence of 1 mol dm^{-3} NaOH and negligible conversion was obtained with 0.001 mol dm^{-3} HCl. From the spectra corresponding to intermediate degrees of conversion, values for the equilibrium constant between substrate and imide were obtained, $K = 280 \pm 30$ and 20.4 ± 0.9 dm^3 mol^{-1} for (2) and (3), respectively.

The spectrum of the product of hydrolysis, 1-hydroxy-8-acetylaminonaphthalene, in aqueous solution depends on the pH of the solution because of acid dissociation of the hydroxy group. Following hydrolysis in alkaline solution, the pH was adjusted into the range 6.5—8.5 by addition of phosphate buffers with different buffer ratios [H$_2$PO$_4$$^-$]/[HPO$_4$$^{2-}$]. Spectrophotometric measurements were made with solutions containing 5.0 × 10^{-5} mol dm^{-3} 1-hydroxy-8-acetylaminonaphthalene or the 3,6-disulphonate and pK values 7.9 ± 0.1 and 7.1 ± 0.1 were obtained, respectively. These results refer to 25 °C and ionic strength 0.2 mol dm^{-3}.

Kinetic Studies.—Reaction (i) with substrates (1)—(7) was followed spectrophotometrically. The slow liberation of product is accompanied by a change in spectrum over the range 250—400 nm and excellent isosbestic points were observed. In a
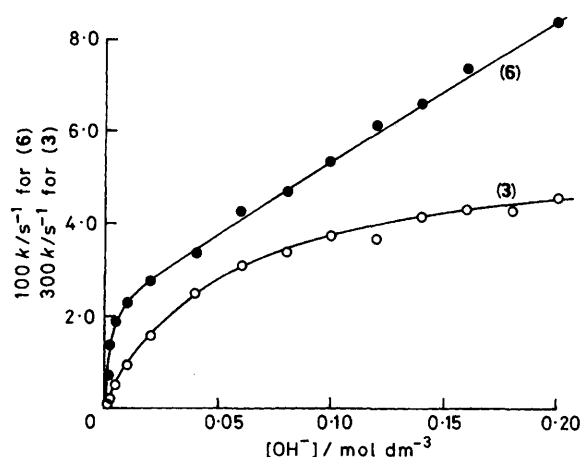

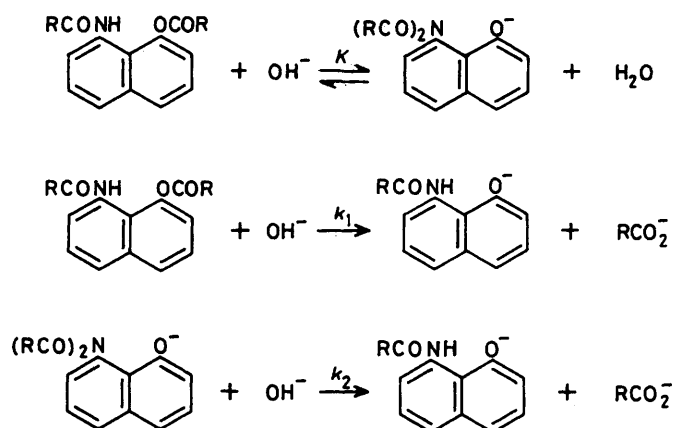**Figure 1.** Dependence of first-order rate coefficient (k) on hydroxide ion concentration

typical kinetic run, the reaction was begun by introducing a small volume of a concentrated aqueous solution of substrate [(2)—(7)] into aqueous sodium hydroxide contained in a thermostatically controlled quartz cuvette. The reaction of (1) was initiated by introducing a small volume of a solution of substrate in Me$_2$SO. Initial reactant concentrations were *ca.* 1—7 × 10^{-5} mol dm^{-3} and the hydrolysis was studied with hydroxide ion concentrations in the range 0.001—0.20 mol dm^{-3}. The change in absorbance at 350 nm with time was used to calculate values for the first-order rate coefficient (k). The reactions were accurately first-order over at least three half-lives and the dependence of k on hydroxide ion concentration for (3) and (6) is given in Figure 1. For the hydrolysis of (1) and (4), a curved dependence similar to that shown for (3) was found, and for (2), (5), and (7) the results were similar to the data given for (6) in Figure 1.

The hydrolysis of 1-(diacetylamino)naphthalene to 1-acetylaminonaphthalene was studied under the conditions used for studies of (1)—(7). With solutions containing initially 1.2 × 10^{-4} mol dm^{-3} of the imide, the first-order formation of product was observed by following the increase in absorbance at 300 nm. The spectrum of product was identical with the spectrum of an independently prepared sample of 1-acetylaminonaphthalene. The dependence of the first-order rate coefficient on hydroxide ion concentration was accurately rectilinear and a second-order rate coefficient of 3.15 ± 0.7 dm^3 mol^{-1} s^{-1} was calculated. In neutral aqueous solution it was observed that the spectrum of 1-(diacetylamino)naphthalene changed to a negligible extent over 4 hours. From this it was deduced that the rate coefficient for spontaneous hydrolysis has a value less than *ca.* 2 × 10^{-6} s^{-1}.
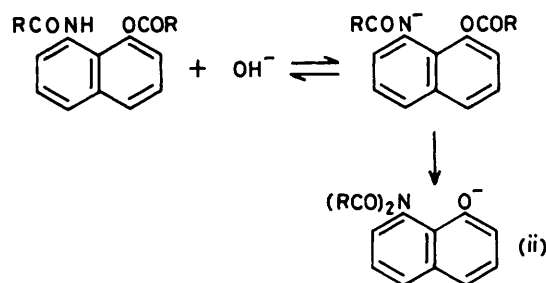
The kinetics of the alkaline hydrolysis of 1-acetoxynaphthalene were studied under the same conditions as used for (1)—(7). The reaction to 1-hydroxynaphthalene and acetate was followed at 331 nm for solutions with an initial concentration of ester of 1 × 10^{-4} mol dm^{-3}. A value for the second-order rate coefficient of 1.47 ± 0.03 dm^3 mol^{-1} s^{-1} was found from measurements at hydroxide ion concentrations in the range 0.005—0.20 mol dm^{-3}.

Discussion

Several experimental observations are important in identifying the mechanism of reaction (i). When the substrates (1)—(7) are introduced into basic solution, a rapid equilibrium with hydroxide ion to give a new species is observed. The equilibrium was studied in detail for (2) and (3) and equilibrium

Scheme 1.

(ii)

Table. Rate coefficients and equilibrium constant for the individual steps in Scheme 1

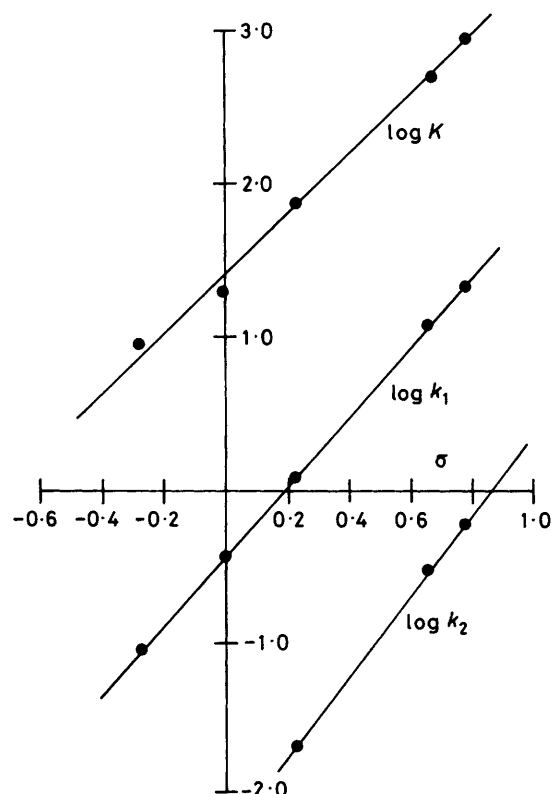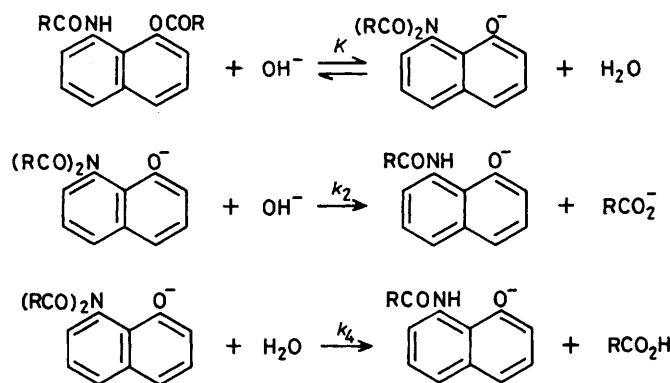| Substrate	$K/dm^3\ mol^{-1}$	$k_1/dm^3\ mol^{-1}\ s^{-1}$	$k_2/dm^3\ mol^{-1}\ s^{-1}$
(1)	2.13 ± 0.1	1.33 ± 0.01	
(2)	257 ± 30	5.16 ± 0.4	0.0488 ± 0.006
(3)	19.3 ± 2	0.366 ± 0.01	
(4)	9.19 ± 0.4	0.0935 ± 0.003	
(5)	75.4 ± 10	1.20 ± 0.2	0.0216 ± 0.015
(6)	495 ± 60	12.0 ± 1	0.305 ± 0.01
(7)	900 ± 400	22 ± 11	0.609 ± 0.02

Figure 2. Hammett $\sigma\rho$ plots for individual steps in Scheme 1

constants of 280 ± 30 and $20.4 \pm 0.9\ dm^3\ mol^{-1}$, respectively, were obtained. These equilibria do not correspond to dissociation of the amide protons in (2) and (3) since under the conditions of the experiment very low concentrations of the amide anions would be present. Formation of the product of hydrolysis is accompanied by spectral changes as a function of time with good isosbestic points, showing that no further intermediates are produced in appreciable concentrations. Non-linear plots of first-order rate coefficient against hydroxide ion concentration are observed and the shape of the plots varies with substituents along the series (1)—(7).

$$k = k_1[OH^-]/(1 + K[OH^-]) + k_2K[OH^-]^2/(1 + K[OH^-]) \quad (1)$$

The mechanism in Scheme 1 provides a satisfactory explanation of the experimental results and leads to equation (1) for the hydroxide ion dependence of the first-order rate coefficient (k). Rapid formation of an imide intermediate is involved and this is likely to occur by the acyl transfer in reaction (ii). For the reactions of (1), (3), and (4) the second term in equation (1) is small and the kinetic data are well fitted by use of the first term. The data for (1), (3), and (4) were plotted in the form $1/k$ against $[OH^-]$ and the resulting linear plots were treated by least-squares analysis to give the values for k_1 and K shown in the Table. The solid line in Figure 1 through the data for (3) was constructed using the values of k_1 and K given in the Table. The value of K for (3) determined by separate equilibrium measurements (20.4 ± 0.9) is in good agreement with the value (19.3 ± 2) obtained by fitting the kinetic results. The value of k_1 deduced for (1) is $1.33 \pm 0.01\ dm^3\ mol^{-1}\ s^{-1}$ and this result is close to the value of the rate coefficient for alkaline hydrolysis of 1-acetoxynaphthalene ($1.47 \pm 0.03\ dm^3\ mol^{-1}\ s^{-1}$).

The full expression in equation (1) is needed to account for the dependence of k on hydroxide ion concentration observed

for (2), (5), (6), and (7). From the linear dependence of k against $[OH^-]$ at high hydroxide ion concentrations (Figure 1) values of k_2 and k_1/K were obtained as the gradient and extrapolated intercept, respectively. These results were used to plot the data in the form of equation (2), obtained by rearrangement of equation (1). Plots of $(1 + k_2K[OH^-]/k_1)/k$ against $[OH^-]^{-1}$

$$(1 + k_2K[OH^-]/k_1)/k = 1/k_1[OH^-] + K/k_1 \quad (2)$$

were accurately linear and values of k_1 and K were calculated by least-squares analysis. The results are given in the Table. For (2) the value of K determined from equilibrium measurements ($280 \pm 30\ dm^3\ mol^{-1}$) is compatible with the value (257 ± 30) found from the kinetic data. The value of k_2 (0.0488 ± 0.006 $dm^3\ mol^{-1}\ s^{-1}$) found for (2) refers to the rate coefficient for alkaline hydrolysis of the imide 1-hydroxy-8-(diacetylamino)-naphthalene-3,6-disulphonate. A much higher value (3.15 ± 0.7 $dm^3\ mol^{-1}\ s^{-1}$) was measured for the rate coefficient for alkaline hydrolysis of 1-(diacetylamino)naphthalene. The difference is in

Scheme 2.

undergoes spontaneous hydrolysis as well as reaction with hydroxide ion, and intermolecular reaction of the ester with hydroxide ion is considered to be unimportant. This mechanism (Scheme 2) leads to equation (3). In equation (1), the first term refers to attack of hydroxide ion on the ester carbonyl, whereas in equation (3) the first term arises from spontaneous hydrolysis

$$k = k_4 K[OH^-]/(1 + K[OH^-]) \\ + k_2 K[OH^-]^2/(1 + K[OH^-]) \quad (3)$$

of the imide intermediate. The second terms in the two equations are identical and correspond to attack of hydroxide ion on the imide. Analysis of the kinetic results in terms of equation (3) yields values for the rate coefficient k_4 for (3)—(7). If the values are treated in the form of a $\sigma\rho$ plot, the result $\rho = +0.33$ is obtained. This appears rather low in comparison with the ρ values for the spontaneous hydrolysis of other carboxylic acid derivatives.[10,11] For the hydrolysis of (1), the result $k_4 = 0.624$ s^{-1} is obtained, to be compared with the value ca. 2×10^{-6} s^{-1} deduced as the upper limit for the rate coefficient for spontaneous hydrolysis of 1-(diacetylamino)naphthalene (see Experimental section). This difference could be explained by assuming that the ionised hydroxy group is involved as an intramolecular base catalyst in assisting the attack of water, and rate enhancements as large as this have been observed previously.[13] Although no firm evidence is available to provide a choice between the mechanisms in Schemes 1 and 2, Scheme 1 is preferred on the basis that attack of hydroxide ion on the ester carbonyl is expected to occur and the value of the rate coefficient deduced for this process from Scheme 1 and equation (1) is very similar to the directly measured value for 1-acetoxynaphthalene. The two Schemes could be distinguished by product analysis studies of the hydrolysis of a mixed ester amide but our attempts to prepare a pure sample of 1-benzoyloxy-8-acetylaminonaphthalene have so far been unsuccessful.

the expected direction to be explained by electron release from the ionised hydroxy group in 1-hydroxy-8-(diacetylamino)-naphthalene-3,6-disulphonate and by a small steric and charge effect which hinders the attack of hydroxide ion.

The results in the Table for the benzoyl-substituted 1-benzoyl-8-benzoylaminonaphthalene-3,6-disulphonates can be used to calculate ρ values for the individual steps in the proposed mechanism. Plots of log k_1, log k_2, and log K against the Taft σ values[9] are given in Figure 2. In Scheme 1 the rate coefficient k_1 refers to the hydroxide-ion-promoted hydrolysis of an ester and a ρ value of 2.28 is found. This result is typical[10] of the values observed for the hydrolysis of other esters. A similar result ($\rho = 2.49$) is found for the hydroxide-ion-promoted hydrolysis of the imide intermediates and this is a reasonable result in view of the values which have been obtained for the alkaline hydrolysis of amides.[11,12] The observed value of ρ (1.96) for the equilibrium between substrate and imide is unexpectedly high. A substantial field effect involving the ionised hydroxy group and the imide nitrogen may be responsible. In the case of (1), (3), and (4), since the contribution of the second term in equation (1) was undetectable, values of k_2 could not be measured. However if the $\sigma\rho$ plot of the k_2 values for (5), (6), and (7) in Figure 2 is extrapolated, k_2 values of 5.0×10^{-3} and 1.0×10^{-3} dm^3 mol^{-1} s^{-1} may be estimated for (3) and (4), respectively. The relative magnitude of the first and second terms in equation (1) is determined by the ratio $k_1/k_2 K[OH^-]$. The estimated values of k_2 and the measured values of k_1 and K can be used to show that for (3) and (4) the second term in equation (1) contributes ca. 5 and 2%, respectively, to the value of k at a hydroxide ion concentration of 0.2 mol dm^{-3}. At lower hydroxide ion concentrations the contributions are lower still. Hence the failure to observe contributions from the second term in equation (1) for the reactions of (3) and (4) is compatible with the observed substituent effects along the series (3)—(7). For (5), (6), and (7) the second term in equation (1) makes contributions of 20, 72, and 83%, respectively, at a hydroxide ion concentration of 0.2 mol dm^{-3}. Along the series (3)—(7) the first term in equation (1) is determined by the substituent effect on k_1, whereas the second term depends on the product of effects on k_2 and K. Since the values of k_1, k_2, and K are all increased to a similar extent by electron-withdrawing substituents, the second term begins to dominate for strongly electron-withdrawing groups. Thus for (6) and (7), hydrolysis occurs predominantly through the imide intermediate because, at a particular hydroxide ion concentration, there is a greater proportion of the imide present and it is hydrolysed more rapidly. In the hydrolysis of (3), reaction occurs predominantly by attack of hydroxide ion at the ester group.

The kinetic results can also be explained by a mechanism similar to that in Scheme 1, but in which the imide intermediate

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