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Note Added in Proof: Professor D. N. Kevill has examined 2-adamantyl triflate and has developed a Y_{OTf} scale based on this substrate. We thank Professor Kevill for informing us of his results prior to publication.

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A Novel Dissociative Mechanism in Acyl Group Transfer from Aryl 4-Hydroxybenzoates in Aqueous Solvents†

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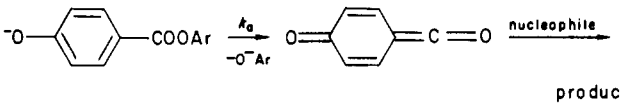
The hydrolysis of aryl 4-hydroxybenzoate esters exhibits the kinetic rate law $k_{obsd} = (k_a + k_b[OH^-])/(1 + [H^+]/K_a)$ where k_b is the second-order rate constant for hydroxide ion attack on the ionized ester and K_a is the ionization constant. The apparent second-order rate constant for the hydrolysis of the 2,4-dinitrophenyl ester (k_aK_a/K_w) is some 340-fold larger than that determined from the Hammett correlation for the alkaline hydrolysis of substituted 2,4-dinitrophenyl benzoates known to possess a $B_{Ac}2$ mechanism. A slightly positive entropy of activation for k_a and aniline trapping experiments for the 2,4-dinitrophenyl ester are consistent with a mechanism where a *p*-oxo ketene intermediate takes the reaction flux.



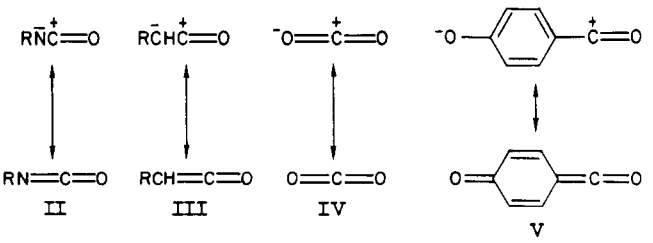
Correlation of k_aK_a/K_w with the pK of the leaving phenol fits the equation $k_aK_a/K_w = 10^{(-1.33pK+9.57)} + 10^{(-0.35pK+3.51)}$ which favors the $B_{Ac}2$ mechanism for poor leaving groups and the E1cB pathway for good leaving groups. There is no reason to postulate a borderline concerted displacement process in this case.

Introduction

We are interested in the factors causing change in mechanisms of acyl group transfer in aqueous solution from associative paths such as the $B_{Ac}2$ process to dissociative mechanisms for example E1cB or S_N1.[1] Whereas the S_N1 route for acyl group transfer (eq 1) is rare in

$$RCOX \xrightarrow{-X^-} \underset{\text{I}}{RCO^+} \xrightarrow{+Y^-} RCOY \qquad (1)$$

aqueous solution because the acylium ion I is unstable, the pathway can be favored if electron-donating features are included in the structure of R which could be RN^-,[2] RC^-H,[3] or O^-.[4] The acylium ion is thus effectively neutralized as isocyanate (II), ketene (III), or carbon dioxide (IV), respectively. One can conceive of many other ways in which



the S_N1 intermediate could be stabilized to yield a species not normally thought of as an acylium ion.[1] We investigate here the possibility that the *p*-oxo ketene V is an E1cB intermediate. Species similar to V have been discussed in the literature and there is matrix isolation trapping evidence that the *o*-oxo ketene has been isolated.[5] A nitrogen analogue (an *o*-imino ketene) has been observed in the mass spectrometer[6] and similar species have been postulated to explain the formation of novel reaction products.[7] Ketenes and thioketenes fused into aromatic rings have been reported.[8] The species are related to quinones and quinone methides which are well-known compounds; they are liable to be much more reactive than these species however because nucleophilic attack at the

† Dedicated to Professor Giuseppe Leandri on the occasion of his 70th birthday.

‡ Instituto di Chimica Organica dell'Università.

§ University Chemical Laboratory.

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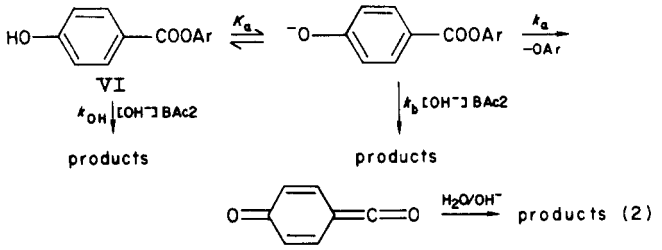
ketene (which is already a reactive function in its own right) can result in aromatization of the nucleus.

We decided to study the alkaline hydrolysis of 4-hydroxybenzoate esters VI which could take place by either $B_{Ac}2$ or E1cB routes (eq 2). The sensitivity of an asso-



ciative pathway to substituent change on the leaving group is very much less than that of the corresponding dissociative path because the leaving bond fission must be very much more advanced in the transition state of the latter mechanism.[1] Results from the literature[9] indicated a "normal" $B_{Ac}2$ mechanism for the alkaline hydrolysis of the 4-nitrophenyl ester (VI, Ar = C_6H_4-4-NO_2) and we therefore studied a range of aryl esters including those of acidic phenols to "force" the E1cB process to occur and to obtain evidence for a possible changeover in mechanism.

Experimental Section

The aryl 4-hydroxybenzoates were prepared by two standard routes. The first, the carbodiimide method,[10] involved treating the mixture of the acid (10 mmol) and phenol (10 mmol) in ethyl acetate (20 mL) with dicyclohexyl carbodiimide (2.06 g). The mixture was stirred for 12 h and then filtered. The filtrate was evaporated and the residue recrystallized from ethanol. Difficulties were obtained with the 4-nitrophenyl ester which could not be completely freed from the urea coproduct despite extensive chromatographic investigation. A product 4-nitrophenyl 4-hydroxybenzoate was finally obtained with mp 172–182 °C which proved to be greater than 90% pure by assay of 4-nitrophenol release in hydrolytic studies. Previous difficulties were reported for this ester.[9]

For phenols of pK greater than that of 4-nitrophenol the carbodiimide method of synthesis was not successful and the following method was employed: the phenol (10 mmol) was heated with 4-hydroxybenzoic acid (1.38 g) and $POCl_3$, (3.06 g) in xylene solvent (20 mL) for 6 h. The solvent was then evaporated under reduced pressure and the residue treated carefully with ice water in an ice–salt bath. The product solidified, was recovered by filtration, and recrystallized from ethanol.

Other esters and the anilides required to standardize the trapping experiments were obtained by the carbodiimide route from commercially available acids. N-Phenyl-4-hydroxybenzamide had mp 194–195 °C (lit.[11] and N-phenyl-2-hydroxy-5-nitrobenzamide had mp 223–224 °C (lit.[12] mp 224 °C). 2,4-Dinitrophenyl 2-hydroxybenzoate was prepared by stirring 2,4-dinitrophenol (1.84 g), salicyloyl chloride (1.57 g, prepared by the method of Kirpal),[13] and triethylamine (1.01 g) with dry $CHCl_3$ (20 mL) at room temperature for 24 h. The chloroform was extracted with dilute HCl, dried, and evaporated to yield a residue which was recrystallized from ethanol. 4-Nitrophenyl 2-hydroxy-5-nitrobenzoate had mp 200 °C (lit.[14] mp 200 °C). and was prepared by the method of Tozer and Smiles.[14]

Other materials were of analytical reagent grade or were recrystallized or redistilled from bench quality reagents. Dioxan was purged of peroxide impurities by passage of the analytical reagent grade material through an activated alumina column; the absence of peroxides was assayed by the KI test. Water used throughout the investigation was deionized and distilled once from glass. ^{18}O-Enriched water was obtained from Prochem Ltd.

Methods. Kinetics. The reactions of the aryl esters in aqueous solutions of buffers were followed spectrophotometrically by using either a Gilford 2400 or a Perkin-Elmer 554 scanning UV instrument fitted with an external recorder. Spectral scanning of a test reaction indicated the best wavelength to use for kinetics. The reaction was initiated by adding an aliquot of the stock solution of ester (ca. 10^{-2} M) in dioxan (25 μL) on the flattened tip of a glass rod to buffer (2.5 μL) in a silica cell in the thermostatted cell compartment of the spectrophotometer set at the appropriate wavelength. The change in absorbance was recorded as a function of time and pseudo-first-order rate constants were obtained from the slopes of linear plots of $A_t - A_\infty$ against time on two cycle semilogarithmic graph paper. Reactions were normally followed over about seven half-lives. The pH of the reactant buffer was measured before and after the reaction with a Radiometer PHM 62 pH meter calibrated to +0.02 pH units with Merck standard buffers. Reaction buffers were prepared by adjusting the pH of a solution of 0.01 M acid or base component in 0.1 M KCl solution. KOH buffers for high pH were prepared by diluting KOH (0.1 M) with KCl (0.1 M) solution.

Measurement of pK values was carried out by spectrophotometric titration of the phenyl 4-hydroxybenzoate. Where these species rapidly hydrolyzed the absorption extrapolated to zero time was employed.

Brønsted and Hammett correlations of the various kinetic parameters were made with a Texas Instruments TI-51 III calculator.

Product Analysis. Thin-layer chromatography and UV spectroscopy were employed to monitor the products of hydrolysis of the phenyl 4-hydroxybenzoates.

The degradation of 2,4-dinitrophenyl 4-hydroxybenzoate was studied by using aqueous aniline buffers under the conditions of the kinetics. The yield of trapped N-phenyl-4-hydroxybenzamide was measured from the absorption of the anilide product at 302 nm (ϵ 24900) where both 4-hydroxybenzoic acid and 2,4-dinitrophenoxide ion absorb only weakly (ϵ_{acid} 4350, $\epsilon_{phenolate}$ 2790). A measure of the total reaction (aminolysis + hydrolysis) was obtained from the absorption at 360 nm (2,4-dinitrophenolate, ϵ 15700); this absorption also indicated whether or not any attack had occurred at the 2,4-dinitrophenyl aromatic nucleus. Kinetics were followed at pH 10.0 with 0.01 M K_2CO_3 buffers with aniline added to the desired concentration. The product of the reaction was made alkaline (to pH 13 approximately) with a pellet of KOH. The excess aniline was extracted with $CHCl_3$ and the absorption of the resulting solutions measured at 302 and 360 nm. Blank experiments were carried out to show that the extraction of the aniline was complete and that none of the ionic species was extracted. Measurements of the absorption at 302 nm were made to check that the anilide is stable under the conditions of the workup.

The position of bond fission was checked by carrying out the hydrolysis of the 2,4-dinitrophenyl ester in ^{18}O-enriched water solvent. A solution of the 4-hydroxybenzoate ester in dioxan (0.1 g in 2 mL) was added slowly with stirring to water (10 mL, 6.20% ^{18}O-enriched) kept at pH 10 with carbonate buffer (0.1 M). After reaction was complete, as judged from TLC analysis, the solution was acidified with concentrated HCl to pH 2 and extracted with $CHCl_3$. The chloroform extract was dried (Na_2SO_4) and evaporated and the residue subjected directly to mass spectral analysis (A.E.I. MS 902 spectrometer carried out under the direction of Dr. J. F. J. Todd). The 2,4-dinitrophenol molecular ion was identified in the recorder trace and the (M + 2)/M percentage obtained from the peak heights.

Results

Kinetics for hydrolysis of aryl 4-hydroxybenzoate esters exhibited excellent pseudo-first-order plots over at least 90% of the total reaction. The products of reaction in non-amine buffers and tris[(hydroxymethyl)amino]-methane at low concentration were found, using TLC and UV analysis, to be 4-hydroxybenzoic acid and the phenol. The kinetics exhibited a slight acceleratory effect in the

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(14) Tozer, B. T.; Smiles, S. *J. Chem. Soc.* **1938**, 1897.

Table I. Hydrolysis of Substituted Phenyl 4-Hydroxybenzoates in Aqueous Solutions at 60 °C[a]

leaving phenol	mp, °C	λ[d]	10^8K_a, M[b]	k_a, s^{-1}	k_b, M^{-1} s^{-1}	N[e]	pH[c]
parent	173–175	320	1.61 ± 0.01	$7.75 \pm 0.17 \times 10^{-6}$	$3.78 \pm 0.06 \times 10^{-2}$	7	7–12
4-chloro	185–187	325	1.79 ± 0.01	$8.80 \pm 0.73 \times 10^{-6}$	$7.15 \pm 0.26 \times 10^{-1}$	8	7–12
4-cyano	192–195	320	2.21 ± 0.05	$2.95 \pm 0.09 \times 10^{-5}$	$2.07 \pm 0.03 \times 10^{-1}$	9	6–12
4-nitro	172–182[g]	400	1.88 ± 0.05	$5.18 \pm 0.17 \times 10^{-5}$	$2.94 \pm 0.06 \times 10^{-1}$	8	7–12
2-nitro-4-chloro	172–173	430	3.21 ± 0.06	$8.06 \pm 0.51 \times 10^{-5}$	$1.64 \pm 0.01 \times 10^{-1}$	11	9–12
2-chloro-4-nitro	132–133	407	3.32 ± 0.05	$3.59 \pm 0.13 \times 10^{-4}$	$2.63 \pm 0.03 \times 10^{-1}$	13	6–12
2,5-dinitro	136–137	445	3.90 ± 0.1[f]	$1.69 \pm 0.16 \times 10^{-3}$	$5.51 \pm 0.03 \times 10^{-1}$	12	5–12
2,4-dinitro	164–165	400	4.24 ± 0.1[f]	$5.55 \pm 0.15 \times 10^{-2}$	$8.05 \pm 0.03 \times 10^{-1}$	12	5–12
2,6-dinitro	147–148	435	3.21 ± 0.14[f]	$6.08 \pm 0.1 \times 10^{-2}$		12	5–12

[a] Ionic strength maintained at 0.1 M with KCl, $K_w = 9.62 \times 10^{-14}$ M^2. [b] Measured spectrophotometrically. These values obey the equation $pK_a = (0.065 \pm 0.018)\ pK^{ArOH} \pm (7.14 \pm 0.08)r = 0.901$. If the 4-nitro and 2,6-dinitro points are omitted the equation becomes $pK_a = (0.074 \pm 0.005)\ pK^{ArOH} + (7.05 \pm 0.04)r = 0.988$. [c] pH range of the kinetic experiments. Buffers: 8.5–9.5, borate; 7.5–8.5, tris[(hydroxymethyl)-amino]methane; 5–7.5, phosphate; 11.5–13, KOH. [d] Wavelength (nm) used for the kinetics. Mostly the release of phenol was observed excepting for the 4-chlorophenyl and 4-cyanophenyl esters where disappearance of substrate was monitored. [e] Number of data points including the duplicates. [f] Values for these esters were also determined from the kinetic equation: 2,5-dinitro, 3.98×10^{-8} M; 2,4-dinitro, 4.47×10^{-8} M; 2,6-dinitro, 3.98×10^{-8} M. [g] See Experimental Section for a discussion of this ester.

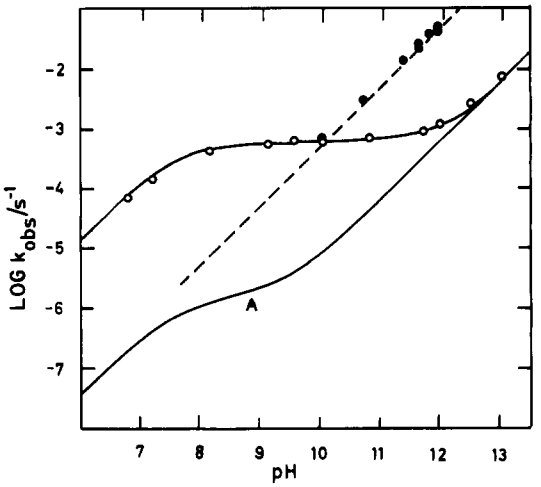

Figure 1. Dependence on pH of the pseudo-first-order rate constants (O) for the hydrolysis of 2,4-dinitrophenyl 4-hydroxybenzoate (25 °C, ionic strength maintained at 0.1 M with KCl). The line is calculated from eq 4 where $k_a = 6.0 \times 10^{-4}$ s^{-1}, $k_b = 6.65 \times 10^{-2}$ M^{-1} s^{-1}, and $K_a = 1.78 \times 10^{-8}$ M. The dashed line (<<ftd) is calculated for the bimolecular attack of hydroxide ion on the 4-methoxybenzoate (Table II). The pH dependence (A) is shown for the hydrolysis of the 4-hydroxybenzoate via hydroxide ion attack on the neutral and anionic esters (see text).

presence of increasing buffer concentrations. This effect is not pursued here and in the main rate constants were determined at 0.01 M in total buffer where there is negligable buffer effect.

The pH dependence of the pseudo-first-order rate constants for hydrolysis of the 4-hydroxybenzoates was found to obey the eq 3. The values of k_a and k_b were obtained

$$k_{obsd} = (k_a + k_b[OH])/(1 + [H^+]/K_a) \qquad (3)$$

from plots of $k_{obsd}(1 + [H^+]/K_a)$ vs. $[OH^-]$. The kinetic pK_a is the intercept on the pH ordinate of a plot of log $k_{obsd}/(k_a - k_{obsd})$ vs. pH; for this purpose k_a was taken to be the average of the values of k_{obsd} in the plateau region of pH (see Figure 1). Parameters for the reactions at 60 °C are collected in Table I. The pH dependence is illustrated in Figure 1 for the hydrolysis of the 2,4-dinitrophenyl ester at 25 °C; the pK_a determined kinetically for this ester (7.75) is very close to that obtained by spectroscopic measurements (7.67). Similar comparisons are seen for some of the esters at 60 °C (Table I).

The hydrolysis of 2,4-dinitrophenyl substituted benzoates was measured spectrophotometrically by using the wavelength 400 nm. The rates obeyed a second-order rate law: rate = $k_{OH}[OH^-][ester]$ and the derived parameters and conditions are recorded in Table II. The value k_{OH}

Table II. Second-Order Rate Constants for Attack of Hydroxide Ion on 2,4-Dinitrophenyl Benzoates at 0.1 M Ionic Strength and 25 °C

benzoate	mp, °C (lit. mp, °C)	k_{OH}, M^{-1} s^{-1} [e,j]	N[h]	pH[g]
4-hydroxy		1070[f]		
4-oxy anion		0.0665[i]		
4-methoxy	132–134 (135–136)[a]	4.28	8	10–12
4-amino	146–148	0.773	5	12–13
3-methyl	117–119 (117–118)[c]	14.1	4	12.2–13
3-chloro	121–123 (123.5–24)[c]	97.6	8	10–11
3-methoxy	111–112	28.7	5	11.4–12.4
4-nitro	138–139 (139–140)[a]	582	4	9–10
3-nitro	157–159 (161)[b]	358	5	9.2–10
3,5-dinitro	154–156	3.36×10^4	6	7.5–9
parent	132–133 (132–133)[d]	18.9	4	11.7–12.5

[a] Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824. [b] Neumann, G. *Chem. Ber.* **1885**, *18*, 3322. [c] Hubbard, C. D.; Kirsch, J. F. *Biochemistry* **1972**, *11*, 2843. [d] Akahori, Y. *Chem. Pharm. Bull. Jpn.* **1965**, *13*, 368. [e] Followed by absorbance change at 400 nm. [f] Apparent second-order rate constant k_aK_a/K_w (see text). [g] Range of pH; for buffers see Table I. [h] Number of data points including duplicates. [i] Equal to k_b (see text). [j] Uncertainty in these values is no more than ±5%.

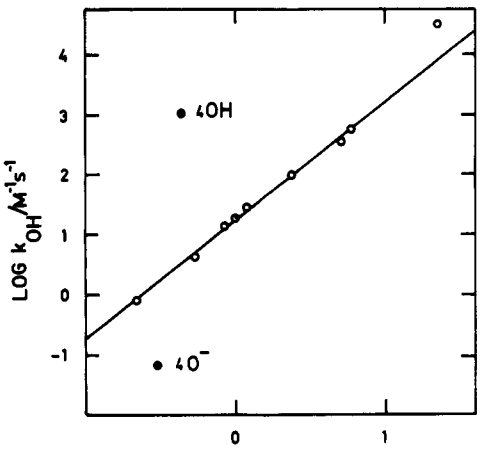

Figure 2. Hammett–σ relationship for the alkaline hydrolysis of 2,4-dinitrophenyl benzoates (data from Table II). The value for the apparent bimolecular reaction of hydroxide ion with the neutral 4-hydroxybenzoate (k_aK_a/K_w) is indicated. The line is calculated from eq 4.

obeys and excellent Hammett correlation (eq 4, Table II, and Figure 2). the term for the 3,5-dinitrobenzoate. If the

$$\log k_{OH} = 1.23 + 1.97\sigma \qquad (r = 0.998) \qquad (4)$$

σ value for 3,5-dinitro (1.35), as determined from the pK of the 3,5-dinitrobenzoic acid,[15] is employed, there is a

Table III. Activation Parameters for the Rate Constant k_a for the Hydrolysis of 2,4-Dinitrophenyl 4-Hydroxybenzoate[a,b]

$k_a \times 10^4$ s^{-1}	T, °C	N[c]	pH
5.65	25.00	3	10.03–10.06
28.6	36.60	3	9.96–10.01
183	51.40	3	9.97–10.02

[a] Ionic strength maintained at 0.1 M with KCl. [b] E_a = 25.3 kcal/mol; $\Delta H^{\ddagger}$ = 24.70 ± 0.1 kcal/mol and $\Delta S^{\ddagger}$ = 9.6 ± 0.4 eu/mol at 25 °C. [c] Number of data points.,

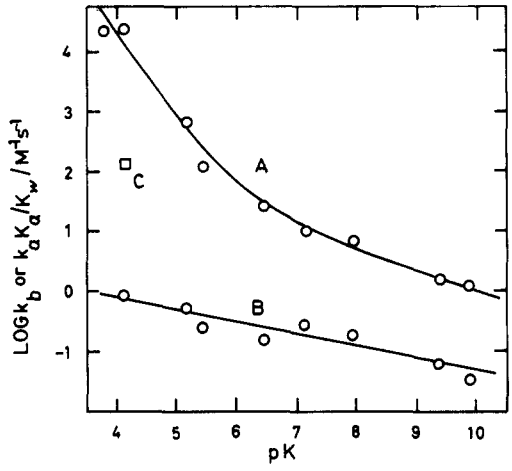

Figure 3. The dependence of k_aK_a/K_w (A) and k_b (B) on the pK of the leaving phenol. The data are from Table I and the lines are calculated from eq 6 and 5 for A and B, respectively. The point C is the value of k_aK_a/K_w calculated for the hydrolysis of the 2,4-dinitrophenyl 4-hydroxybenzoate assuming a BAc2 mechanism (see text).

relatively large deviation and we suggest a value of 1.68 is more appropriate considering the excellence of fit of the other points. We note that the 4-O$^-$ term (k_b for the 4-hydroxybenzoate) is much lower than predicted probably due to an electrostatic effect.

The apparent second-order rate constant for the 2,4-dinitrophenyl 4-hydroxybenzoate (k_aK_a/K_w) is in excess of the rate constant calculated by using eq 4 by about 340-fold as expected for a different mechanism for this species. Using the values estimated for k_{OH} for the 4-hydroxybenzoate (3.17 M^{-1} s^{-1}), K_a (1.78 10^{-8} M) and K_w (10^{-14} M^2), and the observed value of k_b we can calculate a predicted pH dependence from eq 3 for the BAc2 mechanism for the 2,4-dinitrophenyl ester. This is shown in Figure 1 and is clearly orders of magnitude different from the observed kinetics except when the reaction flux is taken by k_b.

Activation parameters for the k_a term were measured by carrying out the reaction of the 2,4-dinitrophenyl 4-hydroxybenzoate at pH 10 at different temperatures. The parameters are collected in Table III.

The parameters for k_b (Table I) obey a good Brønsted relationship (eq 5) against the pK of the leaving phenol. The apparent second-order term (k_aK_a/K_w) followed a nonlinear Brønsted dependence on the pK of the leaving phenol (Figure 3) indicative of a change in mechanism in the pK range studied. The k_aK_a/K_w term obeys eq 6 essentially the "sum" of two linear Brønsted equations for two mechanisms.

$$\log k_b = (-0.20 \pm 0.03)pK + (0.69 \pm 0.23) \quad (5)$$

$$\log k_aK_a/K_w = 10^{(-1.33\pm0.24pK+9.57\pm0.67)} + 10^{(-0.35\pm0.031pK+3.51\pm0.27)} \quad (6)$$

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Table IV. Aniline Trapping of the Intermediate in the Hydrolysis of 2,4-Dinitrophenyl 4-Hydroxybenzoate[a]

[aniline], M	A_{360}[d]	A_{302}	% obsd[b]	% calcd[c]
0.0658	1.592	1.121	10.5	5.1
0.102	1.596	1.275	17.9	7.7
0.161	1.572	1.409	26.5	11.6

[a] 25 °C, pH 10.0, carbonate buffer at 0.01 M, ionic strength maintained at 0.1 M with KCl. [b] Calculated from 100 $(A_{302} - A_2)/(A_1 - A_2)$ where A_1 is the absorbance at 302 nm calculated for complete production of anilide and A_2 is that calculated for complete acid production. [c] Calculated from the second-order rate constant for attack of aniline on the 2,4-dinitrophenyl 4-hydroxybenzoate ion (4.88 × 10^{-4} M^{-1} s^{-1}) and the rate constant for hydrolysis of the anion (K_a = 6.0 × 10^{-4} s^{-1}) with the formula percentage = 100 × 4.88 × 10^{-4}[aniline]/(6.0 × 10^{-4} + 4.88 × 10^{-4}[aniline]). [d] Monitors the amount of 2,4-dinitrophenol released. The value of A_{360} expected for complete phenol release is 1.604.

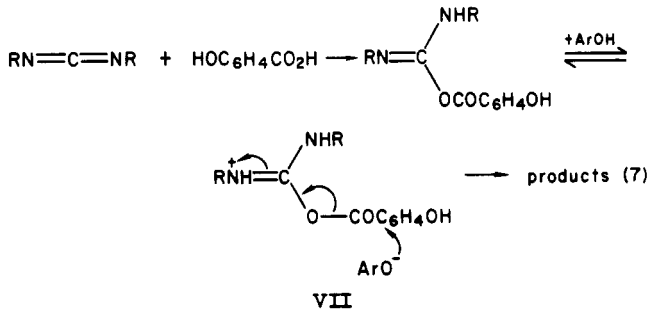
Assuming the limb of lower slope in Figure 3 corresponds to the regular BAc2 mechanism we can compute a rate constant for the bimolecular attack of hydroxide ion on the 2,4-dinitrophenyl ester with a completely different method from that already outlined. Substitution of the pK of 2,4-dinitrophenol into the right hand component of eq 6 (corresponding to the limb of lower slope in Figure 3) gives a value of 118 M^{-1} s^{-1} for k_aK_a/K_w. The observed value (Table 2, 2.45 × 10^4 M^{-1} s^{-1}) is thus 207-fold larger than expected. The difference between this ratio and the previous one (340) is ascribed to the different conditions of temperature.

The degradation of 2,4-dinitrophenyl 4-hydroxybenzoate in the presence of aniline at pH 10 indicates a second-order rate constant in aniline (Table IV). The product of the reaction was shown to include *N*-phenyl-4-hydroxybenzamide as well as the acid by UV and TLC analysis. There is no evidence (by TLC) for aniline attack on the 2,4-dinitrophenyl nucleus and this is confirmed by the constancy of the absorption of the product at 360 nm (Table IV) and its agreement with the absorption for total release of 2,4-dinitrophenol. The rate constants for attack of aniline on the conjugate base of the ester predict a percentage yield of anilide substantially less than that observed in the trapping experiments (Table IV). The excess value which is in all cases greater than 100% of the calculated must be due to attack of aniline on an intermediate *after* 2,4-dinitrophenol release.

The observed values of (M + 2)/M × 100 for the 2,4-dinitrophenol derived from the hydrolysis of 4-hydroxy- and 4-methoxybenzoate at pH 10 in ^{18}O-enriched water are 1.242% and 1.222%, respectively. These values agree with that for a naturally obtained phenol of 1.230%. Water at 6.2% ^{18}O-enrichment should give a value 7.43% for the ratio for complete incorporation into the phenol indicating no Ar–O fission.

The reaction of 2,4-dinitrophenyl salicylate gave only the "Smiles" rearrangement product[14] and no evidence was seen for hydrolysis. The 4-nitrophenyl ester of 2-hydroxy-5-nitrobenzoic acid gave only a small percentage of "Smiles" rearrangement product (ca. 13%); experiments with aniline as a trapping agent are consistent with the normal BAc2 mechanism taking the major part of the reaction flux for the hydrolysis component of the reaction.

The failure of the carbodiimide method of synthesis of 4-hydroxybenzoyl esters of the least acidic phenols can be traced to the competition between the hydroxyl group of the phenol and the 4-hydroxyl function of the acid. Reference to previous work with the carbodiimide coupling method[10] indicates that the acidic phenol (eq 7) competes with the 4-hydroxy group for the activated acyl function because it is more ionized under the conditions of the



VII

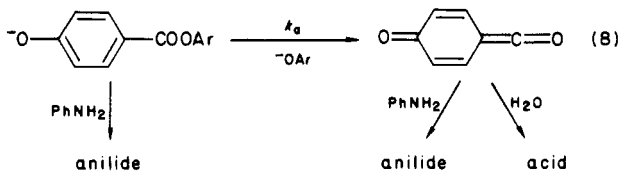
synthesis,; the activated ester is furnished with a crucial proton transfer from the phenol. If the phenol is less acidic than that of the 4-hydroxybenzoyl function (VII) then polymeric species will arise because the preferred phenol will be present in its neutral form and will not compete with the alternative nucleophile (the 4-hydroxy anion).

Discussion

We observe, using two indepenent methods, that the apparent second-order rate constant (k_aK_a/K_w) involving hydroxide ion and neutral 2,4-dinitrophenyl 4-hydroxybenzoate is some 207- and 340-fold larger than that calculated for the $B_{Ac}2$ mechanism. The large difference is illustrated in Figures 1, 2, and 3 and indicates that the mechanism giving rise to the k_a term cannot be a simple $B_{Ac}2$ type process. We propose that the mechanism involves unimolecular decompositon of the conjugate base as in eq 2 and that the $B_{Ac}2$ process (k_{OH}) takes only a small part of the reaction flux.

Figure 3 illustrates a nonlinear dependence of k_aK_a/K_w on the pK of the leaving phenolate ion. This is consistent with a changeover in mechanism taken by the reaction. At low pK values there is a large negative β value which would be predicted by the dissociative mechanism (k_a pathway in eq 2),[1] where C–OAr fission is advanced in the transition state of the rate-limiting step. As the pK of the leaving group increases, the dissociative path gives way to the associative route ($B_{Ac}2$, K_{OH}); the β value for this section of the graph (–0.35) is normal for a regular $B_{Ac}2$ mechanism (–0.25 to –0.55).[16,17] The observed change in mechanism explains why previous workers did not see any exceptional mechanistic behavior with the 4-nitrophenyl ester of 4-hydroxybenzoic acid[9] where we show that most of the reaction flux is through the $B_{Ac}2$ path.

The results of trapping experiments with aniline are also in agreement with a mechanism involving an intermediate *after* the release of the leaving group. The rate constant for release of 2,4-dinitrophenol increases with aniline concentration indicating that a bimolecular mechanism contributes to the reaction. However, the amount of anilide formed is over 100% more than that calculated from the kinetic rate law (Table IV). This is consistent with the concomitant participation of a two-step mechanism where aniline attacks an intermediate after the rate-limiting departure of the phenolate ion (eq 8). Trapping with ^{18}O-enriched water indicates that no Ar–O cleavage is occurring in the reaction.



(8)

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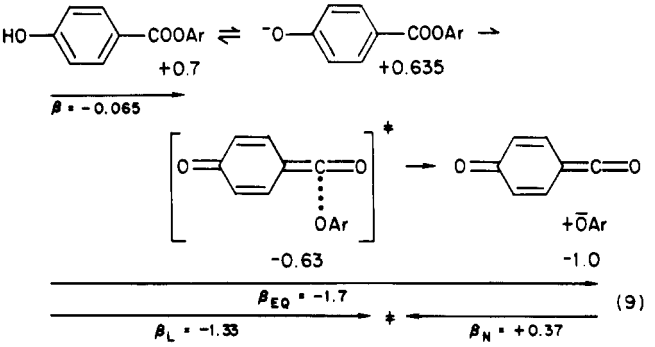
The observation of a positive entropy of activation for the k_a term (Table III) is good supporting evidence for the rate-limiting formation of an intermediate in a unimolecular step.

We have been unable to observe the intermediate directly in the reaction by spectroscopic means but there is no doubt that the dissociative pathway is followed. The *p*-oxo ketene species V is the simplest intermediate consistent with our results. Similar species, although very reactive, have precedent in the literature.[5-8]

The esters hydrolyze in strong alkali through an alternative path corresponding to the k_b term. The mechanism for this term is unambiguous and must involve bimolecular attack of the hydroxide ion on the conjugate base of the ester. This is confirmed by the value of β (–0.2) for a plot of log k_b vs. the pK of the leaving phenol (figure 3) which is close to that expected for a $B_{Ac}2$ process.[1,17]

The change in effective charge on the leaving phenolate ion (eq 9) can be calculated knowing that the overall change in effective charge for a neutral aryl ester is –1.7.[18]



(9)

We require, for this calculation, the change in effective charge on the phenyl oxygen during ionization of the ester (–0.065) and the β_L for the apparent second-order rate constant k_aK_a/K_w for the dissociative process. It is reasonable that the ionization step is not affected much by the substituents in the remote phenyl group. The effective charge on the oxygen in the transition state of the rate-limiting step (–0.63) is indicative of extensive bond cleavage as expected for a fragmentation. The reverse reaction, namely attack of phenolate ion on the ketene, has a β_N of 0.37 and this is lower than the range of selectivities seen for phenolate ion attack on other heterocumulenes such as cyanic acid (0.65)[19] and 3-nitrophenyl isothiocyanate (0.81).[20] We may calculate, using a similar method, the β_N for attack of phenolate ion on another ketene (+0.47) with data for the hydrolysis reaction[21] known to proceed via the ketene as an intermediate. The stereochemistry of the elimination will be dealt with in a future contribution but we believe the reaction occurs from the rotamer of the ester anion where the ester function is perpendicular to the aromatic plane.

The simple eq 6 for the operation of two discrete paths fits the data perfectly leaving little evidence for a smooth transition from one mechanistic type to the other. The leaving groups of low pK are sufficiently well activated by the assistence from *p*-oxy anion as to require no extra assistance from a nucleophile as in VIII which might represent the transition state of an "intermediate" mech-

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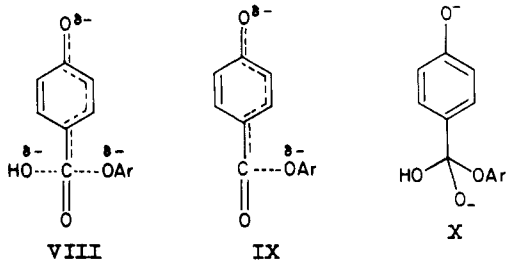

VIII IX X

anism between the two extremes IX and X. The conjugate base of the ester reacts with hydroxide ion through a path involving a tetrahedral intermediate (X) which is more energetically favorable than that represented by (VIII).

At the standard state of 1 M for reactants and hydroxide ion there is significant reaction through both k_a and k_b routes of hydrolysis (structures IX and X, respectively). Changing the pK of the leaving group will only alter the likelihood that the path taken will be one of the two as shown in Figure 3 (A). Change in leaving group basicity cannot lead to the concerted pathway (VIII) taking the major part of the reaction flux.

A preliminary investigation indicates that the *o*-oxo ketene is not formed in either 4-nitrophenyl 2-hydroxy-5-nitrobenzoate or 2,4-dinitrophenyl salicylate hydrolysis. The major competitor of the $B_{Ac}2$ mechanism is the Smiles[14] rearrangement in these cases. The efficiency of other para electron-releasing groups in assisting the S_N1 mechanism was tried; the ester with a 4-amino group has a $B_{Ac}2$ mechanism for its alkaline hyrolysis (Figure 2) indicating that the relatively high pK of the amine does not provide sufficient of the conjugate base for the dissociative mechanism to compete. The 4-acetamido group, although possessing a more acidic nitrogen, does not promote an E1cB mechanism in the hydrolysis of 2,4-dinitrophenyl 4'-acetamidobenzoate.[22]

Acknowledgment. We thank S.E.R.C. (United Kingdom) and CNR (Italy) for the support of this work and N.A.T.O for a travel grant (RF 115.80). Part of this work was carried out during tenure of a Ciba-Geigy Senior Fellowship (A.W.).

Registry No. $PhNH_2$, 62-53-3; $PhNHC(O)$-*p*-C_6H_4OH, 14121-97-2; HO-*p*-$C_6H_4C(O)OPh$, 17696-62-7; HO-*p*-$C_6H_4C(O)$-O-*p*-C_6H_4Cl, 50687-75-7; HO-*p*-$C_6H_4C(O)O$-*p*-C_6H_4CN, 70568-47-7; HO-*p*-$C_6H_4C(O)O$-*p*-$C_6H_4NO_2$, 38597-39-6; ^-O-*p*-$C_6H_4C(O)O$-2,4-$(NO_2)_2C_6H_3$, 94324-03-5; H_2O, 7732-18-5; 2,4-dinitrophenyl 2-hydroxybenzoate, 94324-02-4; 2,4-dinitrophenol, 51-28-5; salicyloyl chloride, 1441-87-8; 2-nitro-4-chlorophenyl 4-hydroxybenzoate, 93749-96-3; 2-chloro-4-nitrophenyl 4-hydroxybenzoate, 93749-97-4; 2,5-dinitrophenyl 4-hydroxybenzoate, 93749-98-5; 2,4-dinitrophenyl 4-hydroxybenzoate, 83187-56-8; 2,6-dinitrophenyl 4-hydroxybenzoate, 93749-99-6; 2,4-dinitrophenyl 4-methoxybenzoate, 24642-86-2; 2,4-dinitrophenyl 4-aminobenzoate, 94324-04-6; 2,4-dinitrophenyl 3-methylbenzoate, 36106-78-2; 2,4-dinitrophenyl 3-chlorobenzoate, 37156-55-1; 2,4-dinitrophenyl 3-methoxybenzoate, 36106-79-3; 2,4-dinitrophenyl 4-nitrobenzoate, 7622-07-3; 2,4-dinitrophenyl 3-nitrobenzoate, 36106-83-9; 2,4-dinitrophenyl 3,5-dinitrobenzoate, 94324-05-7; 2,4-dinitrophenyl benzoate, 1523-15-5; 4-carbonyl-2,5-cyclohexadienone, 94324-06-8.

Supplementary Material Available: Analytical data (1 page). Ordering information is given on any current masthead page.

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On the Amination of Halogenonitropyridines

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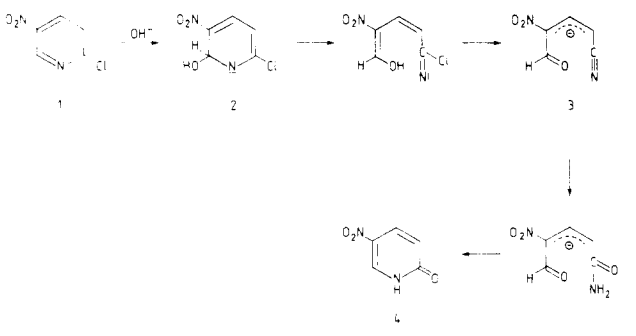
Evidence is presented, based on ^{15}N-labeling experiments and ^1H NMR spectroscopy, that the conversion of 2-chloro-5-nitropyridine (1) into 2-amino-5-nitropyridine by treatment with potassium amide/liquid ammonia proceeds to about 75% according to a sequence of reactions involving addition of the amide ion to C-6, ring-opening, and ring-closure [S_N(ANRORC) mechanism]. On the contrary, 2-chloro-3,5-dinitropyridine (11) is nearly quantitatively aminated by liquid ammonia (containing no potassium amide) into 2-amino-3,5-dinitropyridine according to an S_N(AE) process, thus no ring-opening being involved. As shown by NMR spectroscopy, the position of addition of liquid ammonia to 11 is temperature dependent. At −60 °C the addition takes place at C-4, while at −40 °C the addition at C-6 is strongly favored. Apparently the addition at C-4 is kinetically controlled; the addition at C-6 leads to the thermodynamically more stable adduct. Amination of 11 with liquid ammonia in the presence of potassium permanganate yields mainly 2,6-diamino-3,5-dinitropyridine.

The nucleophilic displacement of halogen in heteroaryl halides can occur according to a number of different pathways. It has been shown that amination of many halogenopolyazaaromatics by potassium amide/liquid ammonia often involves an S_N(ANRORC) mechanism, describing a reaction sequence, which starts by Addition of the Nucleophile (usually at a position meta to the leaving group), and is followed by Ring Opening and Ring Closure.[1]

The occurrence of an S_N(ANRORC) mechanism in nucleophilic substitutions of halogenopyridines has not hitherto been observed. It has been reported that 2-bromopyridine on amination with potassium amide/liquid ammonia does not react with ring opening but gives 2-aminopyridine exclusively according to the S_N(AE) process.[2,3]

Scheme I



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