Participation of an Extended *p*-Oxo Ketene Intermediate in the Dissociative Alkaline Hydrolysis of Aryl 4-Hydroxycinnamates

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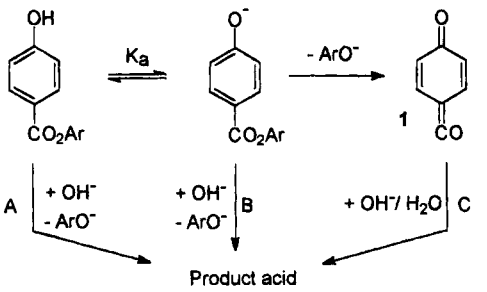
The alkaline hydrolysis of 4-hydroxycinnamate esters of acidic phenols follows an E1cB mechanism and involves the participation of an "extended" *p*-oxo ketene intermediate. The apparent bimolecular rate constant (k_aK_a/K_w) for the hydrolysis of the 2,4-dinitrophenyl ester is some 2500-fold larger than that determined from the Hammett relationship for the $B_{Ac}2$ alkaline hydrolysis of substituted 2,4-dinitrophenyl cinnamates. The positive value of the entropy of activation for the hydrolysis of 2,4-dinitrophenyl 4'-hydroxycinnamate and trapping experiments with nitrogen nucleophiles are consistent with the dissociative pathway. A change from a E1cB to a $B_{Ac}2$ mechanism is expected for esters with leaving groups having pK_a higher than *ca.* 6.7. The higher E1cB reactivity of 2,4-dinitrophenyl 4'-hydroxycinnamate compared to that of the corresponding 4'-hydroxybenzoate is due to the vinylene group that further favors the dissociative route, probably increasing the stability of the unsaturated intermediate.

Our previous studies on acyl transfer reactions involving aryl esters of 4-hydroxybenzoic acid have provided evidence that alkaline hydrolysis occurs through either associative ($B_{Ac}2$) or dissociative (E1cB) mechanisms, depending on the basicity of the leaving group.[1] Indeed, while the usual $B_{Ac}2$ route (path A in Scheme 1) is followed by esters with leaving groups having pK_a higher than about 6.5, esters possessing leaving groups with lower pK_a values hydrolyze through the E1cB mechanism *via* the unprecedented *p*-oxo ketene intermediate **1** (path C).

Our conclusions on the E1cB hydrolysis of 2,4-dinitrophenyl 4'-hydroxybenzoate have been successively confirmed by other researchers who found positive volumes of activation for this reaction.[2] More recently, the same workers have reported that the volume of activation for the alkaline hydrolysis of 2,4-dinitrophenyl 4'-hydroxycinnamate (a vinylogue of 4-hydroxybenzoate) is large and negative, thus suggesting an associative $B_{Ac}2$ pathway for this reaction.[3]

With the aim to extend our knowledge on the factors able to control the reaction flux (associative *vs* dissociative) in ester hydrolysis (*inter alia,* stability of the putative unsaturated intermediate) and to shed more light on the mechanism of hydrolysis of 2,4-dinitrophenyl 4'-hydroxycinnamate, we have undertaken a study on the alkaline hydrolysis of a number of aryl esters of 4-hydroxycinnamic acid including the 2,4-dinitrophenyl derivative. In a recent paper[4] we have reported our preliminary results of such work: kinetic evidence and trapping experiments strongly support the intervention of a dissociative, E1cB-type mechanism in the hydrolysis of 2,4-dinitrophenyl 4'-hydroxycinnamate. This conclusion is in contrast with that stemming from the use of volumes of activation as a mechanistic criterion.

Scheme 1



In this paper we wish to report our results in greater detail together with new data relative to more 4-hydroxycinnamates supporting our proposal[4] of a changeover from a E1cB to a $B_{Ac}2$ mechanism in the alkaline hydrolysis of aryl 4-hydroxycinnamates as the pK_a of the leaving phenol increases.

Experimental Section

General. Starting reagents and solvents were purified and/or distilled before use. Buffer materials were of analytical reagent grade. Dioxane was purged of peroxides by passage of the analytical-grade product through an activated alumina column; the absence of peroxides was checked by the KI test. Water was double distilled and preboiled to free it from dissolved carbon dioxide.

Synthesis. The 2,4-dinitrophenyl esters of 4-hydroxycinnamic and cinnamic acid were prepared as reported in the literature: they had, respectively, mp 141–142 °C (lit.[3] mp 141 °C) and mp 129–130 °C (lit.[5] mp 128–129 °C). The remaining esters were prepared by the carbodiimide method: equimolar amounts of *trans*-4-hydroxycinnamic acid or *trans*-cinnamic acid and phenol were dissolved in anhydrous ethyl acetate (containing a few percent of pyridine as catalyst) and treated with a slight excess of dicyclohexyl carbodiimide. The resulting solution was stirred for several hours at room temperature and then filtered to remove the dicyclohexylurea. The filtrate was washed with diluted hydrochloric acid, water, and phosphate buffer at pH ≅ 7, dried over anhydrous sodium sulfate and evaporated. The crude materials were purified by column chromatography (silica gel, 9:1 dichloromethane–diethyl ether) and finally recrystallized to constant mp. As

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the 2,6-dinitrophenyl ester decomposed on silica gel it could not be purified by chromatography; it was obtained pure (although in very low yield) after several crystallizations from the following solvents: toluene, ethanol, toluene and (twice) a toluene–ligroin mixture. The ^{1}H-NMR spectra were recorded with a Varian Gemini 200 spectrometer (200 MHz) with TMS as internal standard and acetone-d_6 as solvent. The characteristics of the esters were as follows (Ar and Ar′ are the aromatic rings of the phenolic and acylic mojeties of the ester, respectively). **4-Nitrophenyl 4′-hydroxycinnamate**: mp 174–175 °C from ligroin; δ 8.35 (d, 2, J = 8.9 Hz, Ar*H*), 7.87 (d, 1, J = 16.0 Hz, −C*H*=CHCOOAr), 7.69 (d, 2, J = 8.1 Hz, Ar′*H*), 7.53 (d, 2, J = 9.1 Hz, Ar*H*), 6.95 (d, 2, J = 8.0 Hz, Ar′*H*), 6.60 (d, 1, J = 16.0 Hz, −CH=C*H*COOAr). Anal. Calcd for $C_{15}H_{11}NO_5$: C, 63.2; H, 3.9; N, 4.9. Found: C, 63.5; H, 4.0; N, 4.8. **2-Chloro-4-nitrophenyl 4′-hydroxycinnamate**: mp 151–152 °C from ligroin; δ 8.44 (s, 1, Ar*H*), 8.33 (d, 1, J = 8.9 Hz, Ar*H*), 7.92 (d, 1, J = 16.0 Hz, −C*H*=CHCOOAr), 7.51 (m, 3, Ar*H* + Ar′*H*), 6.96 (d, 2, J = 6.7 Hz, Ar′*H*), 6.62 (d, 1, J = 16.0 Hz, −CH=C*H*COOAr). Anal. Calcd for $C_{15}H_{10}NO_5Cl$: C, 56.4; H, 3.2; N, 4.4. Found: C, 57.5; H, 3.3; N, 4.1. **4-Chloro-2-nitrophenyl 4′-hydroxycinnamate**: mp 145–146 °C from chloroform; δ 8.18 (s, 1, Ar*H*), 7.86 (m, 2, −C*H*=CHCOOAr + Ar*H*), 7.69 (d, 2, J = 8.6 Hz, Ar′*H*), 7.55 (d, 2, J = 8.8 Hz, Ar*H*), 6.95 (d, 2, J = 8.7 Hz, Ar′*H*), 6.61 (d, 1, J = 15.9 Hz, −CH=C*H*COOAr). Anal. Calcd for $C_{15}H_{10}NO_5Cl$: C, 56.4; H, 3.2; N, 4.4. Found: C, 55.9; H, 3.3; N, 4.6. **2,6-Dinitrophenyl 4′-hydroxycinnamate**: mp 157–158 °C (see above); δ 8.5 (d, 2, J = 8.2 Hz, Ar*H*), 7.92 (d, 1, J = 15.9 Hz, −C*H*=CHCOOAr), 7.86 (t, 1, J = 8.3 Hz, Ar*H*), 7.73 (d, 2, J = 8.9 Hz, Ar′*H*), 6.96 (d, 2, J = 8.8 Hz, Ar′*H*), 6.65 (d, 1, J = 16.0 Hz, −CH=C*H*COOAr). Anal. Calcd for $C_{15}H_{10}N_2O_7$: C, 54.6; H, 3.1; N, 8.5. Found: C, 55.2; H, 3.3; N, 8.3. **Phenyl 4-hydroxycinnamate**: mp 135–136 °C from ligroin; δ 7.80 (d, 1, J = 16.1 Hz, −C*H*=CHCOOAr), 7.65 (d, 2, J = 8.2 Hz, Ar′*H*), 7.44 (m, 2, Ar*H*), 7.23 (m, 3, Ar*H*), 6.94 (d, 2, J = 8.0 Hz, Ar′*H*), 6.58 (d, 1, J = 16.0 Hz, −CH=C*H*COOAr). Anal. Calcd for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found: C, 75.0; H, 5.1. **2-Methyl-4,6-dinitrophenyl 4′-hydroxycinnamate**: mp 174–175 °C from toluene; δ 8.76 (d, 1, J = 2.6 Hz, Ar*H*), 8.61 (d, 1, J = 2.6 Hz, Ar*H*), 7.95 (d, 1, J = 16.0 Hz, −C*H*=CHCOOAr), 7.73 (d, 2, J = 8.8 Hz, Ar′*H*), 6.96 (d, 2, J = 8.6 Hz, Ar′*H*), 6.70 (d, 1, J = 15.8 Hz, −CH=C*H*COOAr), 2.50 (s, 3, −C*H*$_3$). Anal. Calcd for $C_{16}H_{12}N_2O_7$: C, 55.8; H, 3.5; N, 8.1. Found: C, 56.5; H, 3.7; N, 7.9. **4-Nitrophenyl cinnamate**: mp 144–145 °C from toluene; δ 8.36 (m, 2, Ar*H*), 7.96 (d, 1, J = 16.0 Hz,C*H*CHCOOAr), 7.82 (m, 2, Ar*H* Ar′*H*), 7.53 (m, 5, Ar*H* Ar′*H*), 6.83 (d, 1, J = 16.1 Hz, Ar′CHC*H*). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.9; H, 4.1; N, 5.2. Found: C, 67.2; H, 3.8; N, 5.2. **3-Nitrophenyl cinnamate**: mp 107–108 °C from toluene; δ 8.21 (m, 2, Ar*H*), 7.96 (d, 1, J = 16.0 Hz,C*H*CHCOOAr), 7.70 (m, 4, Ar*H* Ar′*H*), 7.50 (m, 3, Ar*H* Ar′*H*), 6.83 (d, 1, J = 15.9 Hz, Ar′CHC*H*). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.9; H, 4.1; N, 5.2. Found: C, 67.1; H, 4.3; N, 5.2. **4-Chloro-2-nitrophenyl cinnamate**: mp 91–92 °C from toluene; δ 8.21 (d, 1, J = 2.5 Hz, Ar*H*), 7.95 (d, 1, J = 16.1 Hz,C*H*CHCOOAr), 7.85 (m, 3, Ar*H* Ar′*H*), 7.55 (m, 4, Ar*H* Ar′*H*), 6.84 (d, 1, J = 16.0 Hz, Ar′CHC*H*). Anal. Calcd for $C_{15}H_{10}NO_4Cl$: C, 59.3; H, 3.3; N, 4.6. Found: C, 57.6; H, 3.4; N, 4.2.

The amides required to standardize the trapping experiments were prepared as follows. 4-Hydroxycinnamamide was obtained heating a methanolic solution of methyl 4-hydroxycinnamate[6] saturated with gaseous ammonia at 90 °C for 3 days. After recrystallization from water it had mp 191–192 °C (lit.[7] mp 193–194 °C). ***N*-(4-Methylphenyl) 4′-hydroxycinnamamide** was obtained by the carbodiimide route (see above): mp 212–213 °C from toluene; δ 7.55 (m, 5, Ar*H* + Ar′*H* + C*H*=CHCONHAr), 7.12 (d, 2, J = 8.0 Hz, Ar*H*), 6.87 (d, 2, J = 6.6 Hz, Ar′*H*), 6.65 (d, 1, J = 15.5 Hz, Ar′CH=C*H*). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.9; H, 6.0; N, 5.5. Found: C, 75.5; H, 5.8; N, 5.4.

Methods. Product Analysis. TLC analysis and UV–vis spectroscopy were routinely employed to ascertain that the acid and the phenol were the sole products of hydrolysis of the esters.

Kinetics. The hydrolyses of the esters in 40% v/v dioxane–water solvent were followed spectrophotometrically by monitoring, at the appropriate wavelength, either the disappearance of the substrate or the release of the phenol, depending on the ester and on the pH of the single kinetic run. This alternative is due to the fact that in runs carried out at pH higher than the pK_a of the hydroxycinnamate under examination the ionization of the hydroxyl group caused a marked bathochromic shift (near to 400 nm) in the UV maximum. Typically, the buffered solution (2.5 mL) was equilibrated to the required temperature (±0.1 °C) in a 1-cm path-length quartz cell placed in the thermostated cell holder of a Kontron Uvikon 941 spectrophotometer. The reaction, initiated by adding 10 μL of a stock solution of the substrate (*ca.* 0.01 M in dioxane) to the buffer, was followed for at least 7 half-lives. Reactions were carried out with potassium hydroxide at different concentrations, and with phosphate, carbonate, ammonia, borate, and Tris buffers. In all cases at least three different buffer concentrations, at constant pH, were employed: buffer effects were sometimes observed, and in such cases the rate constants at zero buffer concentration were obtained by extrapolation. The ionic strength was kept at 0.1 M with KCl. The pH of the buffered solutions was measured before and after the reaction with a Radiometer PHM 62 pH meter, calibrated to ±0.02 pH units with Merck standard buffers, equipped with a glass electrode. Calculations of the pseudo-first-order rate constants were performed by standard methods. Tables of the primary kinetic data are collected in the supplementary material.

Ionization Constants. Determination of pK_a values was carried out by spectrophotometric titration of the aryl 4-hydroxycinnamates, extrapolating the absorption to zero time for the more reactive esters; however, the exceedingly high reactivity of the 2,6-dinitrophenyl ester did not allow the spectrophotometric determination of its pK_a.

Trapping. The hydrolysis of 2,4-dinitrophenyl 4′-hydroxycinnamate in 0.04 M carbonate buffer (fraction of base = 0.5, 40% dioxane, ionic strength kept at 0.1 M with KCl, pH 11.28) was kinetically investigated in the presence of variable amounts of added *p*-toluidine: no effect on the rate of hydrolysis was observed when the amine concentration was varied in the range 0–0.03 M at constant pH. A large scale reaction was then carried out employing 20 mL of this buffer solution containing 0.025 M *p*-toluidine and the ester (6.25×10^{-3} M). After completion of the reaction (*ca.* 30 min) the solution was acidified to pH 1 with concd HCl and evaporated to dryness under reduced pressure. The residue was dissolved in 0.1 M HCl, and the resulting solution was repeatedly extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated. The ^{1}H-NMR spectrum of the residue clearly showed the characteristic signals of 2,4-dinitrophenol, which was usefully employed as an internal standard, together with those of 4-hydroxycinnamic acid and of *N*-(4-methylphenyl) 4′-hydroxycinnamamide (see above). In particular, the doublet assigned to the α vinylenic hydrogen of the acid (centered at δ 6.33) is decidedly separate from the doublet of the corresponding hydrogen atom of the amide (δ 6.65) thus enabling an easy integration of the signals and therefore a quantitative assessment of the products.

Trapping of the intermediate was also investigated by using ammonia buffers. The reaction was followed kinetically by using concentrations from 0.1 to 1 M in total ammonia buffer (fraction base = 0.9, 40% dioxane, ionic strength kept at 0.1 M with KCl, pH 10.12). The following rate law was obtained

$$k_{obs}\,(s^{-1}) = 1.81 \times 10^{-2} + (2.63 \times 10^{-3})[B]$$

which was employed to calculate the theoretical amount of amide product relative to the total phenol. A large scale reaction was then carried out, as described above, employing 1 M ammonia buffer. The ^{1}H-NMR doublets of the vinylenic hydrogen atom of acid (δ 6.33) and amide (δ 6.53) were used to check the yields of these products.

(6) Schimdt, H.; Karrer, P. *Helv. Chem. Acta* **1945**, *92*, 722.
(7) Fischer, E.; Nouri, T. *Ber. der Deut. Chem. Gesel.* **1917**, 619.

Table 1. Hydrolysis of Aryl 4-Hydroxycinnamates in 40% Dioxane at 25 °C and μ = 0.1 (pK_w = 15.00)

leaving substituted phenoxide	pK_{LG}[a]	$10^{10}K_a$, M	λ,[b] nm	k_a, s^{-1}	k_b, M^{-1} s^{-1}	N[c]	pH[d]
2,6-dinitro	3.71[e]	5.01[f]	400	$(1.2 \pm 0.1) \times 10^{-2}$		7	8.84–13.95
2,4-dinitro	4.11	(4.95 ± 0.06)	400	$(2.2 \pm 0.1) \times 10^{-2}$		14	7.49–13.92
6-methyl-2,4-dinitro	4.35[e]	(4.55 ± 0.04)	390	$(4.1 \pm 0.1) \times 10^{-3}$		10	8.16–13.99
2-chloro-4-nitro	5.45	(3.98 ± 0.03)	385	$(5.1 \pm 0.4) \times 10^{-5}$	$(3.76 \pm 0.01) \times 10^{-2}$	10	10.47–13.97
4-chloro-2-nitro	6.46	(3.62 ± 0.03)	385	$(4.4 \pm 0.7) \times 10^{-6}$	$(1.72 \pm 0.01) \times 10^{-2}$	7	11.04–13.87
4-nitro	7.14	(3.60 ± 0.02)	385	$(1.9 \pm 0.2) \times 10^{-6}$	$(3.34 \pm 0.01) \times 10^{-2}$	9	10.41–13.97
parent	9.99	(2.31 ± 0.02)	373		$(2.10 \pm 0.02) \times 10^{-3}$	3	11.22–13.90

[a] Jencks, W. P.; Regestein, J. *Handbook of Biochemistry and Molecular Biology*, 3rd ed.; Fasman, G., Ed.; Chemical Rubber Co.: Cleveland, 1976. [b] Wavelength for kinetic runs. [c] Number of data points, not including duplicates. [d] pH range employed. [e] Kortum, G.; Vogel, W.; Andrussov, K. *Dissociation Constants of Organic Acids in Aqueous Solution*; Butterworths: London, 1961. [f] Kinetically determined.

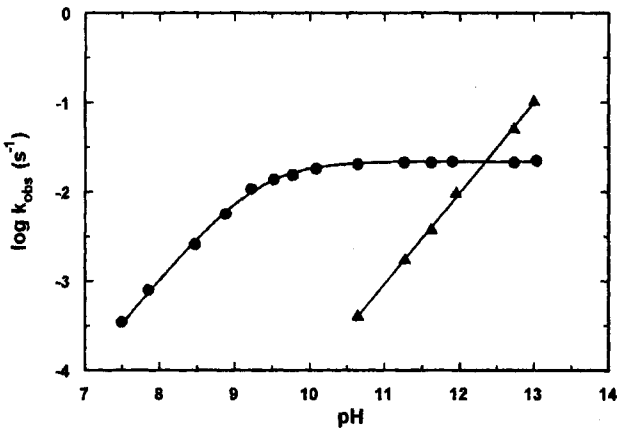


Figure 1. Dependence on pH of the hydrolysis of 2,4-dinitrophenyl 4′-hydroxycinnamate (●) and 2,4-dinitrophenyl cinnamate (▲) in 40% (v/v) dioxane/water at 25 °C and 0.1 M ionic strength made up with KCl. Lines are calculated from eqs 1 and 2 from parameters in Tables 1 and 2.

Blank experiments were performed in both cases to ascertain that the recovery of the products was complete.

Results and Discussion

The pH dependence of the pseudo-first-order rate constants for hydrolysis, in 40% v/v dioxane–water solvent at 25 °C, of 2,4-dinitrophenyl 4′-hydroxycinnamate and 2,4-dinitrophenyl cinnamate obey eqs 1 and 2, respectively, and are illustrated in Figure 1.

$$k_{obs} = k_a/(1 + a_H/K_a) \quad (1)$$

$$k_{obs} = k_{OH}K_w/a_H \quad (2)$$

In eq 1 k_a is the pseudo-first-order rate constant in the plateau region of pH, depicted in Figure 1, and K_a is the ionization constant of the hydroxyl group of the ester. It is not pointless to note that the value of K_a (5.00×10^{-10} M) obtained from kinetic data by iterative nonlinear curve-fitting performed with the Fig.P program,[8] resulted to be identical to the one determined spectrophotometrically (4.95×10^{-10} M). Table 1 collects the values of k_a and K_a for the 2,4-dinitrophenyl ester together with parameters and conditions relevant to the hydrolyses of the remaining aryl 4-hydroxycinnamates (see below). In eq 2 K_w is the ionic product of water, and a value of 15.00 was assessed for the pK_w (at 25 °C) of the medium employed in this work; k_{OH} is the second-order rate constant related to the $B_{Ac}2$ attack of hydroxide ion on 2,4-dinitrophenyl cinnamate. The alkaline hydrolyses of the aryl cinnamates here investigated obey eq 2, and the parameters are recorded in Table 2.

Table 2. Second-Order Rate Constants for the Hydrolysis of Aryl Cinnamates in 40% Dioxane at 25 °C and μ = 0.1

leaving substitd phenoxide	pK_{LG}[a]	λ, nm[b]	N[c]	k_{OH}, M^{-1} s^{-1}
2,4-dinitro	4.11	400	6	10.64 ± 0.29
4-chloro-2-nitro	6.46	400	4	1.31 ± 0.01
4-nitro	7.14	400	4	1.70 ± 0.04
3-nitro	8.40	408	4	1.08 ± 0.01

[a] See footnote *a* of Table 1. [b] Wavelength for kinetic runs. [c] Number of data points, not including duplicates.

Table 3. Activation Parameters for the Hydrolysis of 2,4-Dinitrophenyl Esters in KOH 5×10^{-3} M, 40% Dioxane, μ = 0.1[a]

	$\Delta H^{\neq}$, kcal/mol	$\Delta S^{\neq}$,[b] cal/mol K
4′-hydroxycinnamate	23.7 ± 0.1	13.5 ± 0.3
cinnamate	10.8 ± 0.2	-28.3 ± 0.7

[a] Temperature range: 17.4–32.5 °C. [b] Calculated at 25 °C.

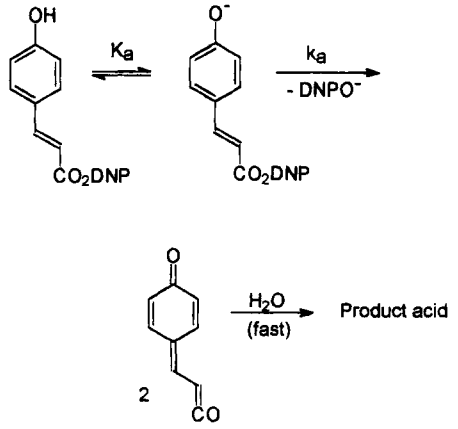
The apparent second-order rate constant (k_aK_a/K_w = 1.06×10^4 M^{-1} s^{-1}, Table 1) for the attack of hydroxide ion on neutral 2,4-dinitrophenyl 4′-hydroxycinnamate is 3 orders of magnitude larger than the second-order rate constant related to the unambiguous $B_{Ac}2$ hydrolysis of 2,4-dinitrophenyl cinnamate (10.64 M^{-1} s^{-1}, Table 2): this large difference suggests that different mechanisms operate in the two cases. Furthermore, a calculated bimolecular rate constant (k_{calc}) for $B_{Ac}2$ attack of hydroxide ion to 2,4-dinitrophenyl 4′-hydroxycinnamate can be estimated from the Hammett correlation log k/k_0 = 1.97 $\Sigma\sigma$ for the alkaline hydrolysis of substituted 2,4-dinitrophenyl benzoates.[1a] Taking into account the attenuation factor of 0.54 related to the vinylene group,[9] the relationship becomes log k/k_0 = 1.06 $\Sigma\sigma$, and it is now applicable to the $B_{Ac}2$ hydrolysis of 2,4-dinitrophenyl cinnamates. Since k_0 = 10.64 M^{-1} s^{-1}, using the σ_p substituent constant (−0.37) for the hydroxyl group we finally obtain k_{calc} = 4.36 M^{-1} s^{-1}. The apparent second-order rate costant (k_aK_a/K_w) for the 2,4-dinitrophenyl 4′-hydroxycinnamate is therefore in excess of the rate constant calculated by using the Hammett relationship by about 2500-fold, thus indicating that the actual mechanism cannot be a $B_{Ac}2$ type process.

The differences in the mechanism between the two esters are also supported by the effect of the temperature on reaction rates. The activation parameters for ester hydrolysis are reported in Table 3: the value of $\Delta S^{\neq}$ (calculated at 25 °C) for the k_a term is largely positive as expected for a dissociative, unimolecular process, whereas

(8) Fig.P from Biosoft, Cambridge, UK, 1991.

(9) Williams, A. *Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; p 127.

Scheme 2



DNP = 2,4-dinitrophenyl

the (negative) one related to the reaction of the cinnamate is well within the range characteristic of a bimolecular process.[10]

On these grounds, we propose that the hydrolysis of 2,4-dinitrophenyl 4′-hydroxycinnamate follows a dissociative pathway quite similar to that depicted in Scheme 1 . In this E1cB mechanism the unimolecular elimination of the leaving group from the conjugate base of the substrate affords the quinonoid intermediate **2** (Scheme 2), vinylogue of the *p*-oxo ketene **1**.

Further evidence for the intervention of a dissociative mechanism in the hydrolysis of 2,4-dinitrophenyl 4′-hydroxycinnamate is offered by trapping experiments carried out with added nitrogen nucleophiles (see the Experimental Section). In the presence of 0.025 M *p*-toluidine, which has no effect on reaction rate, 4′-hydroxycinnamic acid and *N*-(4-methylphenyl)-4′-hydroxycinnamamide were formed in similar amounts. Moreover, in the presence of 1.0 M ammonia a 63% yield in 4-hydroxycinnamamide was obtained, which is some 5-fold larger than the amount expected from the kinetic data (12.7%). These results are doubtless in agreement with the mechanism depicted in Scheme 2: the intermediate **2** is trapped by the added nucleophile after the rate-determining release of the leaving group.

The effect of variation of the leaving group on reactivity was also examined extending the study to other aryl 4-hydroxycinnamates. The pH dependence of the pseudo-first-order rate constants for the hydrolyses of the three dinitrophenyl esters studied obeyed eq 1, whereas those of the 2-chloro-4-nitrophenyl, 4-chloro-2-nitrophenyl, 4-nitrophenyl, and phenyl esters followed eq 3.

$$k_{obs} = k_a + k_b[OH^-]/(1 + a_H/K_a) \quad (3)$$

The second-order term k_b is related to the bimolecular attack of hydroxide ion on the ionized ester similar to that indicated as path B in Scheme 1 and causes an upward curvature, at sufficently high pH values, of the pH−rate profile. The k_b values of the dinitrophenyl esters could not be determined owing to the exceedingly high reactivity of these substrates. The k_b term gains more and more weight as the reactivity of the ester

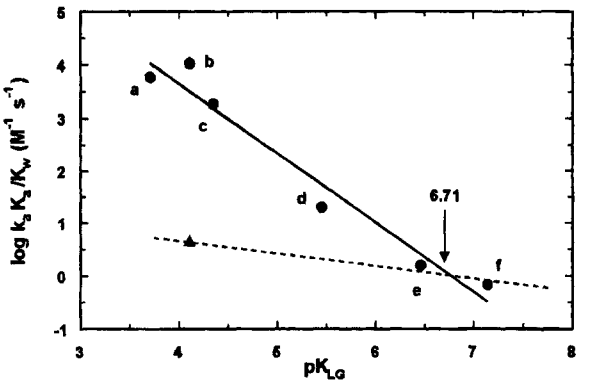


Figure 2. Brønsted plot for the hydrolysis of aryl 4-hydroxycinnamates. The line is calculated from eq 4. Identity, in increasing order of pK_a of the leaving substituted phenoxide: (a) 2,6-dinitrophenyl, (b) 2,4-dinitrophenyl, (c) 6-methyl-2,4-dinitrophenyl, (d) 2-chloro-4-nitrophenyl, (e) 4-chloro-2-nitrophenyl, (f) 4-nitrophenyl. The dashed line is calculated for the bimolecular attack of hydroxide ion on neutral aryl 4-hydroxycinnamates (see text).

decreases and the plateau region of pH is correspondingly reduced, becoming experimentally inaccessible for the unsubstituted phenyl ester. The values of k_a and k_b were calculated by iterative nonlinear curve-fitting with the Fig.P program, and those of the less reactive esters were obtained from linear plots of $k_{obs}/(1 + a_H/K_a)$ *vs* $[OH^-]$ again employing the Fig.P program. Parameters and conditions are collected in Table 1.

In the preliminary communication[4] we have proposed that a change from E1cB to $B_{Ac}2$ mechanism occurs on increasing the pK_a of the leaving substituted phenoxide as suggested by a break in linearity (and upward curvature) shown by the plot of the logarithms of the apparent second-order rate constants (k_aK_a/K_w) against pK_{LG}. This breakpoint apparently occurred at the pK_{LG} (4.8)[11] assigned to the pentachlorophenyl esters. Unfortunately, we have subsequently found that there is uncertainty about the pK_a value for pentachlorophenol since other conflicting data have been published (e.g., 5.26).[12] Moreover, further refinement of the kinetic data on the hydrolysis of the pentachlorophenyl ester revealed that they could not be very reliable, particularly at pH values where the ester is not fully ionized, most likely because of its exceedingly low solubility also in 40% dioxane. For these reasons we have now decided to discard the data concerning the pentachlorophenyl ester. Kinetic data subsequently obtained for the hydrolysis of 6-methyl-2,4-dinitrophenyl 4′-hydroxycinnamate, which has a suitable pK_{LG} value (4.35), are included in the correlation. As Figure 2 illustrates, the values of log (k_aK_a/K_w) correlate well with the pK_{LG} values (data from Table 1) giving rise to a line with a slope of −1.32 (eq 4).

$$\log (k_aK_a/K_w) = (8.92 \pm 0.72) - (1.32 \pm 0.13)pK_{LG} \quad (4)$$

This β_{LG} value is consistent with a dissociative process[13] and is in good agreement with the value (−1.33) previously found for the hydrolysis of 4-hydroxybenzoates.[1a]

Although the correlation between log k_b and pK_{LG} is

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somewhat scattered, it gives rise to a line whose slope (-0.29 ± 0.08) is normal for a regular $B_{Ac}2$ mechanism.[14]

As shown by eq 4 and Figure 2 the apparent second-order rate constants display a good Brønsted correlation, with a β_{LG} value indicative of a dissociative process, thus giving us confidence that the members of the series follow this mechanism. This conclusion is also supported by the now well-documented dissociative nature of the k_a term for the hydrolysis of 2,4-dinitrophenyl 4'-hydroxycinnamate.

Nevertheless, the possibility that a change in mechanism from E1cB to $B_{Ac}2$, similar to that observed in the hydrolysis of aryl 4-hydroxybenzoates, occurs as the leaving-group ability decreases cannot be ruled out; this point can be checked as follows. From the data of Table 2 we obtain the Brønsted relationship (eq 5) for the $B_{Ac}2$ alkaline hydrolysis of aryl cinnamates:

$$\log k_{OH} = (1.90 \pm 0.45) - (0.24 \pm 0.07)pK_{LG} \quad (5)$$

Now, if a line with a slope of -0.24 is drawn in Figure 2 (dashed line) through the point indicated as ▲ which represents the calculated value of the second-order rate constant ($k_{calc} = 4.36\ M^{-1}\ s^{-1}$, see above) for the $B_{Ac}2$-type attack of hydroxide ion on the neutral 2,4-dinitrophenyl 4'-hydroxycinnamate, it will go across the experimental line at $pK_{LG} = 6.71$.

This result indicates that the hydrolysis of 4-nitrophenyl 4'-hydroxycinnamate, whose pK_{LG} is close to the changeover point, could follow a $B_{Ac}2$ path. Indeed, the value (0.4) of the ratio between the apparent second-order rate constant for the hydrolysis of this ester (Table 1, $k_aK_a/K_w = 0.70\ M^{-1}\ s^{-1}$) and the second-order rate constant for the reaction of the corresponding cinnamate (Table 2, $k_{OH} = 1.70\ M^{-1}\ s^{-1}$) suggests that the reactions of these esters follow the same mechanism.

In this connection, we recall that in the case of 2,4-dinitrophenyl esters, which we have shown to react through different mechanisms, this ratio is about 1000. Furthermore, since it is known[14a] that changes in leaving group have only little effect on the ϱ values for the alkaline hydrolysis of substituted benzoates, we can calculate from the Hammett relationship $\log k/k_0 = 1.06\Sigma\sigma$, derived as described above for the $B_{Ac}2$ hydrolysis of 2,4-dinitrophenyl cinnamates, a value of $0.69\ M^{-1}\ s^{-1}$ for the $B_{Ac}2$-type attack of hydroxide ion on the neutral 4-nitrophenyl 4'-hydroxycinnamate, which is identical to the value of the apparent second-order rate constant of this ester ($0.70\ M^{-1}\ s^{-1}$), therefore confirming the associative nature of the hydrolysis of 4-nitrophenyl 4'-hydroxycinnamate.

The present results reinforce our proposal[4] about the participation of the E1cB mechanism in the alkaline hydrolysis of aryl 4-hydroxycinnamates having good leaving groups. The dissociative mechanism, involving an extended *p*-oxo ketene intermediate (**2** in Scheme 2), most likely gives way to the associative route as the pK_a of the leaving group increases beyond 7, this behavior being analogous to that described for the aryl 4-hydroxybenzoates (Scheme 1).

In this connection it is interesting to compare these two types of esters also in order to evaluate the effect of the interposition of a vinylene on reactivity. The first-order rate costant k_a for the hydrolysis of 2,4-dinitrophenyl 4'-hydroxycinnamate ($0.022\ s^{-1}$, Table 1) is about 65-fold larger than that of the corresponding 4-hydroxybenzoate ($k_a = 3.4 \times 10^{-4}\ s^{-1}$ at 25 °C in 40% aqueous dioxane and ionic strength 1.0 M),[15] thus indicating that the presence of a vinylene suitably placed between the internal nucleophilic center (the 4-hydroxy group) and the carbonyl carbon atom favors the hydrolytic process occurring through the dissociative path. It is now well established that the reactivity of an E1cB mechanism is dependent on the leaving group ability, the internal nucleophilicity of the substrate, which is related to the pK_a of its ionizable proton, and the stability of the putative intermediate. In the present case the leaving group is the same in the two esters under comparison; therefore, the observed difference in reactivity should be ascribed to the other two factors. In a previous work[1b] we have found that the k_a term for the dissociative hydrolysis of 2,4-dinitrophenyl esters of substituted 4-hydroxybenzoic acids in water at 25 °C obeys a Brønsted relationship against the pK_a of the 4-hydroxyl group with a selectivity of 1.15. From this β value using the data for the 2,4-dinitrophenyl 4'-hydroxybenzoate ($k_a = 3.4 \times 10^{-4}\ s^{-1}$ and $pK_a = 8.78$)[15] and the pK_a value of the 2,4-dinitrophenyl 4'-hydroxycinnamate (9.31, Table 1) we can evaluate the k_a value of a hypothetical 2,4-dinitrophenyl 4'-hydroxy-X-benzoate having exactly the same pK_a as the 2,4-dinitrophenyl 4'-hydroxycinnamate. Such value ($0.001\ 38\ s^{-1}$) accounts for only *ca.* 6% of the experimental ratio, thus suggesting that the observed increase in reactivity on going from 4-hydroxybenzoate to 4-hydroxycinnamate ester could be due mostly to an increased stability of the intermediate; indeed, the intermediate **2** should be more stable than the intermediate **1**, owing to a more extended delocalization of π electrons in the former.

The extension of π conjugation through the vinylene group is supported by the very large bathochromic effects occurring upon ionization of the hydroxy group of aryl 4-hydroxycinnamates (see Experimental Section): similar shifts are well known to occur with substituted 7-hydroxycoumarins and have been ascribed to electron delocalization.[16] Incidentally, the marked bathochromic shifts observed in this work do not agree with the hypothesis that a possible reason for the claimed preference[3] for an associative path in the hydrolysis of 2,4-dinitrophenyl 4'-hydroxycinnamate might lie in an unfavorable conformation of the cinnamate group with the aryl ring orthogonal to the ethylenic double bond.

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Supplementary Material Available: Primary kinetic data (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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