The Alkaline Hydrolysis of Aryl (2*E*)-3-(4′-Hydroxyphenylazo)propenoates. A Kinetic Study

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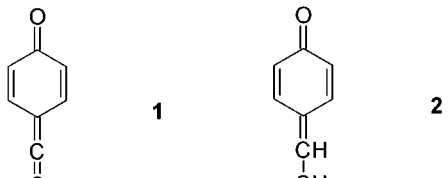
The alkaline hydrolysis of the title esters, possessing three conjugated π units between the internal nucleophile (the hydroxyl group) and the reaction center, follows an E1cB mechanism involving the participation of an "extra extended" *p*-oxo azoketene type intermediate. For the hydrolysis of the 2,4-dinitrophenyl ester kinetic data, activation parameters and trapping of the intermediate are consistent with a dissociative pathway carrying the reaction flux. The effect of the leaving group variation on reactivity agrees with the proposed mechanism, and the existence of an intermediate is also supported by diode array stopped-flow experiments. The presence of sp^2 nitrogen atoms in the conjugated backbone is beneficial to the dissociative mechanism.

Since the pioneering work of Bruice and co-workers,[1] the presence of ionizable α-protons in the substrate has been thought to be a prerequisite for the occurrence of a unimolecular elimination mechanism, by way of short-lived ketene intermediates, in the alkaline hydrolysis of esters.

We have been able to demonstrate that the E1cB mechanism carries the reaction flux even in the absence of labile proton on the atom α to the carbonyl function: we have shown that the alkaline hydrolysis of esters of the type HO-π-COOAr can occur following the dissociative mechanism provided that the hydroxyl group, acting as the internal nucleophile after ionization, is conjugated with the reaction center. In the simplest case we investigated, the hydrolysis of aryl 4-hydroxybenzoates,[2] the π-system was an aromatic ring and we showed that esters having leaving groups with pK_a values lower than about 6.5 hydrolyze through the E1cB mechanism with the participation of the unprecedented *p*-oxo ketene intermediate **1**.



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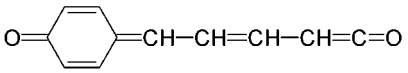

3

We have subsequently shown that the dissociative mechanism is followed also when the π-system is formed by two conjugated π units, as in aryl 4-hydroxycinnamates,[3] and we have observed that the interposition of a vinylene group appears to favor the dissociative pathway most likely owing to an increased stability of the intermediate **2**, which could be related to a larger delocalization of π electrons.

In the framework of our research on this topic, we have recently reported[4] a study on the hydrolysis of aryl (2*E*,4*E*)-5-(4′-hydroxyphenyl)pentadienoates. In these substrates, the intervening backbone between the internal nucleophile and the reaction center is constituted by three conjugated π units, i.e., one aromatic ring and two vinylenic groups. We have provided evidence that alkaline hydrolysis of esters possessing acidic leaving groups (pK_a of the leaving phenol lower than ca. 6) follows the E1cB pathway with the participation of the elongated *p*-oxo ketene intermediate **3**. Reactivity comparisons among esters sharing the same leaving group have shown that, taking into account differences in internal nucleophilicity of the substrates, the presence of additional vinylenic groups favors the hydrolytic process occurring via the dissociative pathway.

Furthermore, aiming to increase our knowledge on the factors that drive the mechanism in ester hydrolysis (*inter alia*, stability of the putative unsaturated intermediate), we have also investigated other esters possessing different molecular architecture such as two aromatic π-systems linked by Z = Y π-conjugated systems, with Z and Y being N or CH. In all cases, these substrates react through the usual associative $B_{Ac}2$ mechanism,[5] and this result could be rationalized invoking an exceedingly large loss of aromaticity on going from substrate to the transition state when two *p*-phenylene units are present in the π-conjugated bridge.

(1) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993−3003. Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956−5964.

(2) Cevasco, G.; Guanti, G.; Hopkins A. R.; Thea, S.; Williams, A. *J. Org. Chem.* **1985**, *50*, 479−484.

(3) Cevasco, G.; Thea, S. *J. Org. Chem.* **1994**, *59*, 6274−6278.

(4) Cevasco, G.; Vigo, D.; Thea, S. *J. Org. Chem.* **2000**, *65*, 7833−7838.

(5) Cevasco, G.; Thea, S. *J. Org. Chem.* **1999**, *64*, 5422−5426.

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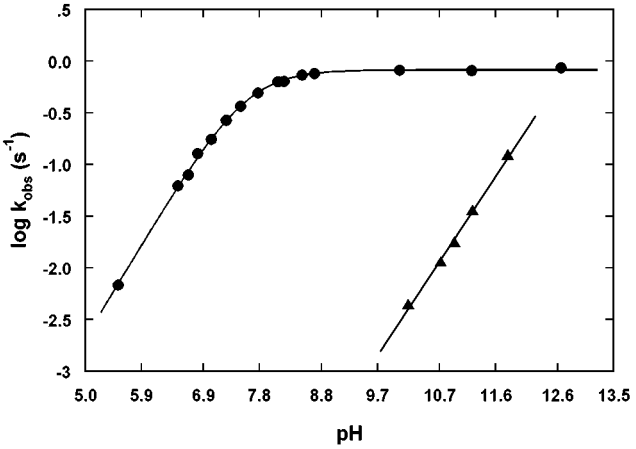
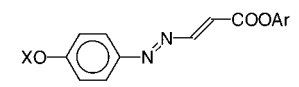
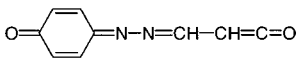


Figure 1. pH−rate profiles for the hydrolysis of 2,4-dinitrophenyl esters **4b** (solid circles) and **6** (triangles) in 40% (v/v) dioxane/water at 25 °C and 0.1 M ionic strength made up with KCl. Buffers employed to keep pH constant are listed in the Experimental Section. Lines are calculated from eqs 1 and 3, respectively.

In an attempt to improve our understanding of the effects of structural modifications on the hydrolytic pathways in the conjugated backbone, we have undertaken a kinetic study on the hydrolysis of the title esters **4**. The substitution of sp^2 nitrogen atoms for sp^2 carbon atoms in the conjugated backbone could indeed favor the dissociative pathway if, as suggested by theoretical and experimental data (see below), such substitution improves conjugation through the π bridge. We wish now to report our results on the alkaline hydrolysis of these esters that strongly support the occurrence of the E1cB mechanism with the participation of the intermediate **5**.



4a - f **6**



5

4a: X = H, Ar = 2,6-dinitrophenyl

4b: X = H, Ar = 2,4-dinitrophenyl

4c: X = H, Ar = 2-methyl-4,6-dinitrophenyl

4d: X = H, Ar = 2,5-dinitrophenyl

4e: X = H, Ar = 2-chloro-4-nitrophenyl

4f: X = H, Ar = 4-chloro-2-nitrophenyl

6: X = Me, Ar = 2,4-dinitrophenyl

Results and Discussion

The observed pseudo-first-order rate constants for the alkaline hydrolysis of 2,4-dinitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate (**4b**), at 25 °C in 40% dioxane−water (v/v) solvent and ionic strength 0.1 M (KCl), were found to follow eq 1.

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

The pH−rate profile for the hydrolysis of ester **4b** is illustrated in Figure 1 (●) and similar plots (Figure 2) were obtained for esters **4a** and **4c** (identity of substrates is shown in Table 1). In eq 1, a_H is the proton activity, k_a is the pseudo-first-order rate constant in the plateau region of pH and K_a is the ionization constant of the hydroxyl group of the ester.

The pH dependence of the pseudo-first-order rate constants for hydrolysis of esters **4d-f** obeys eq 2

$$k_{obs} = (k_a + k_b[OH^-])/(1 + a_H/K_a) \quad (2)$$

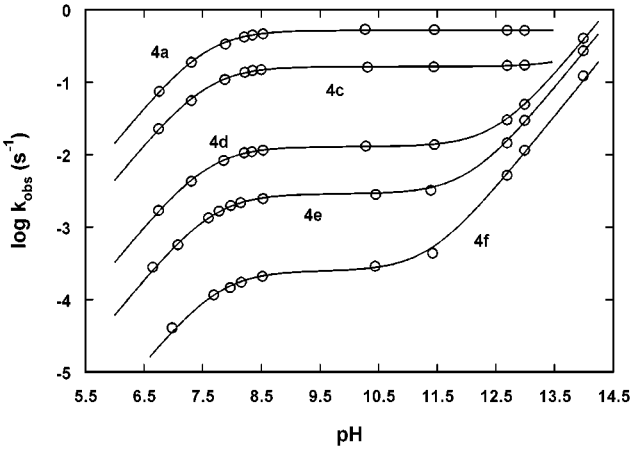


Figure 2. pH−rate profiles for the hydrolysis of aryl (2*E*)-3-(4′-hydroxyphenylazo)propenoates in 40% (v/v) dioxane/water at 25 °C and 0.1 M ionic strength made up with KCl. See the Experimental Section for buffers. Lines are calculated from eqs 1 or 2; identity is given in Table 1.

In this equation, the second-order term k_b is related to the bimolecular attack of hydroxide ion on the ionized ester and causes an upward curvature, at sufficiently high pH values, of the pH−rate profiles as depicted in Figure 2.

In Table 1 are collected experimental conditions and the values of the kinetic parameters, obtained from primary kinetic data by iterative nonlinear curve-fitting performed with the Fig.P program,[6] for the hydrolysis of the substrates **4a**−**f**. This program provides, together with the rate constants, the K_a values of the substrates. This is in particular very useful for the more reactive esters **4a**−**c** since, owing to exceedingly high reactivities, their pK_a values cannot be spectroscopically measured. Table 2 indicates that kinetic pK_a values are in good agreement with the spectroscopic ones.

The dependence on pH of the pseudo-first-order rate constants for the hydrolysis of 2,4-dinitrophenyl (2*E*)-3-(4′-methoxyphenylazo)propenoate (**6**) is also shown in Figure 1 and indicates, as expected, a simple second-order rate law in hydroxide ion and ester concentrations (eq 3).

$$k_{obs} = k_{OH} K_w/a_H \quad (3)$$

In this equation, K_w is the ionic product of water and a pK_w value of 15.00 has been reported[7] for the medium employed in this work The k_{OH} value for $B_{Ac}2$ attack of hydroxide ion on this ester, in 40% dioxane−water (v/v) solvent at 25 °C and ionic strength 0.1 M (KCl), is 183 ± 2 M^{-1} s^{-1}.

The apparent second-order rate constant ($k_{app} = k_aK_a/K_w$ = ca. 2×10^7 M^{-1} s^{-1}, Table 1) calculated for the attack of hydroxide ion on neutral **4b** is considerably larger (>10^5) than the second-order rate constant related to the $B_{Ac}2$ attack of hydroxide ion on **6** (a *smaller* value could be envisaged from σ_p values for OH and OMe, which are −0.37 and −0.27, respectively). The remarkably high ratio k_{app}/k_{OH} strongly suggests that these esters do not react through the same mechanism, i.e., the associative one. Actually, one can calculate the rate constant (k_{calc}) for the bimolecular attack of hydroxide ion

(6) Fig.P from Biosoft, Cambridge, U.K., 1991.
(7) Arned, H. S.; Fallon, L. *J. Am. Chem. Soc.* **1939**, *61*, 2374−2378.

Table 1. Hydrolysis of Aryl (2*E*)-3-(4′-Hydroxyphenylazo)propenoates (4a−f) in 40% Dioxane at 25 °C and = 0.1 M (pK_w = 15.00)

subst	leaving substituted phenoxides	pK_{LG}[a]	k_a, s^{-1}	k_b, M^{-1} s^{-1}	k_{app}, M^{-1} s^{-1}	log k_{app}[b]	N[c]	pH[d]
4a	2,6-dinitro	3.71[e]	$(5.19 \pm 0.06) \times 10^{-1}$	-	1.43×10^7	7.155	10	6.77−12.99
4b	2,4-dinitro	4.11	$(8.18 \pm 0.13) \times 10^{-1}$	-	2.11×10^7	7.324	15	5.53−12.66
4c	2-methyl-4,6-dinitro	4.35[e]	$(1.66 \pm 0.02) \times 10^{-1}$	-	4.37×10^6	6.640	10	6.75−12.99
4d	2,5-dinitro	5.22[e]	$(1.29 \pm 0.02) \times 10^{-2}$	3.75 ± 0.09	3.27×10^5	5.514	11	6.75−13.99
4e	2-chloro-4-nitro	5.45	$(2.87 \pm 0.06) \times 10^{-3}$	2.56 ± 0.10	6.00×10^4	4.778	12	6.63−13.99
4f	4-chloro-2-nitro	6.46	$(2.48 \pm 0.11) \times 10^{-4}$	1.07 ± 0.06	4.21×10^3	3.624	11	6.98−13.99

[a] Jencks, W. P.; Regestein, J. In *Handbook of Biochemistry and Molecular Biology*, 3rd ed.; Fasman, G., Ed.; Chemical Rubber Co.: Cleveland, 1976. [b] See text; K_a values are taken from Table 2. [c] Number of data points, not including duplicates. [d] pH range investigated. Buffers employed are given in the Experimental Section. [e] Kortum, G.; Vogel, W.; Andrussov, K. *Dissociation Constants of Organic Acids in Aqueous Solution*; Butterworths: London, 1961.

Table 2. Ionization Constants of Aryl (2*E*)-3-(4′-Hydroxyphenylazo)propenoates (4a−f) in Phosphate Buffers, 40% Dioxane at 25 °C and = 0.1 M

subst	10^8K_a, M	pK_a	pK_a[a]
4a			7.55 ± 0.01
4b			7.59 ± 0.01
4c			7.57 ± 0.02
4d	2.62 ± 0.21	7.58 ± 0.03	7.59 ± 0.02
4e	2.16 ± 0.13	7.67 ± 0.03	7.62 ± 0.02
4f	1.76 ± 0.12	7.76 ± 0.03	7.66 ± 0.07

[a] Measured from the kinetics.

Table 3. Activation Parameters for the Hydrolysis of 2,4-Dinitrophenyl Esters in Carbonate Buffer, 40% Dioxane, μ = 0.1 M

ester	*T* range, °C	pH	n[a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$,[b] cal/mol K
4b	9.9−29.8	11.50	5	23.2 ± 0.3	19.0 ± 1.1
6	16.5−41.4	10.95	4	16.3 ± 0.2	-12.0 ± 0.5

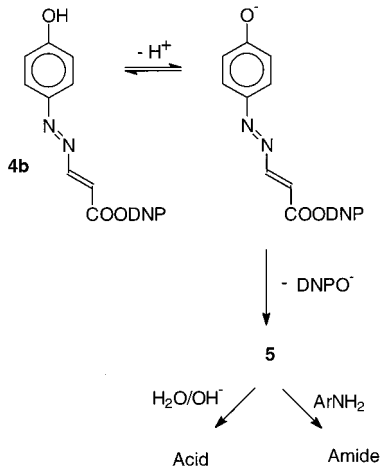
[a] Number of data points, not including duplicates. [b] Calculated at 25 °C.

on neutral **4b** from the Hammett relationship log $k/k_0 = 1.97\Sigma\sigma$ for the alkaline hydrolysis of substituted 2,4-dinitrophenyl benzoates.[1] If the attenuation factor of 0.54 related to both the vinylene[8] and azo[9] groups is taken into account (incidentally the same attenuation factor has been reported for these groups), since the overall attenuation factor is roughly given by the product of those of the intervening groups,[10] the relationship becomes log $k/k_0 = 0.57\Sigma\sigma$ and is thus valid for the $B_{Ac}2$ hydrolysis of substituted 2,4-dinitrophenyl (2*E*)-3-(X-phenylazo)propenoates. Now, employing the σ_p values for the hydroxy and methoxy groups (−0.37 and −0.27, respectively), from the k_{OH} value for **6** we finally obtain $k_{calc} = 160$ M^{-1} s^{-1}. The apparent second-order rate constant (k_aK_a/K_w, ca. 2×10^7 M^{-1} s^{-1}) for **4b** is therefore in excess of calculated k_{calc} by about 125000-fold, thus confirming the suggestion that the mechanism for the k_a term cannot be the associative one, and the simplest hypothesis is that an E1cB process involving the participation of the *p*-oxo azoketene type intermediate **5** occurs.

The determination of activation entropy of the reactions (Table 3) provides further evidence that the hydrolysis of these two esters follows different pathways. For the hydrolysis of **4b** the value of $\Delta S^{\ddagger}$ for the k_a term (measured at pH 11.50) is large and positive as expected for a unimolecular reaction, whereas the negative value of $\Delta S^{\ddagger}$ for the hydrolysis of **6** (at pH 10.95) is consistent with an associative process.[11]

The dissociative nature of the mechanism driving the hydrolysis of **4b** is fully confirmed by trapping experiments carried out with added nitrogen nucleophile. In the presence of 0.03 M *p*-toluidine, which has no effect on reaction rate, ca. 37% of *N*-(4-methylphenyl) (2*E*)-3-(4′-hydroxyphenylazo)propenamide (**7**) was found in the reaction products. This result clearly agrees with the proposed dissociative mechanism: the intermediate **5** is trapped by the added nucleophile after the rate-determining departure of the leaving group, as shown in the Scheme 1.

Scheme 1



DNP = 2,4-dinitrophenyl

$ArNH_2$ = *p*-toluidine

The effect of the leaving group variation on reactivity was also assessed. The plot of the logarithms of the apparent second-order rate constants ($k_{app} = k_aK_a/K_w$) against the pK_a of the leaving substituted phenoxide (pK_{LG}) is shown in Figure 3 (data taken from Table 1) and gives rise to a satisfactory Brønsted relationship (eq 4).

$$\log (k_aK_a/K_w) = (12.73 \pm 0.65) - (1.41 \pm 0.13)pK_{LG} \quad (4)$$

(8) Williams, A. In *Chemistry of Enzyme Action*; Page, M. I., Ed.; Elsevier: Amsterdam, 1984; p 145.
(9) Hegarty, A. F.; Tuohey, P. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1238−1243
(10) Page, M.; Williams, A. *Organic and Bioorganic Mechanisms*; Addison-Wesley Longman: Harlow, 1997; p 57.
(11) Schaleger, L. L.; Long, F. A. *Adv. Phys. Org. Chem.* **1963**, *1*, 1. Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill: New York, 1969. Douglas, K. T. *Prog. Bioorg. Chem.* **1976**, *4*, 194. Vlasak, P.; Mindl, J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1401−1403. Safraoui, A.; Calmon, M.; Calmon, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1349−1352. Broxton, T. J. *Aust. J. Chem.* **1985**, *38*, 77−83.

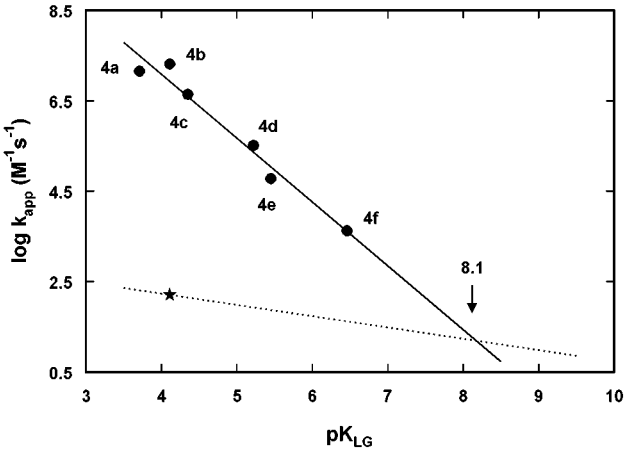


Figure 3. Brønsted plot for the hydrolysis of aryl (2*E*)-3-(4′-hydroxyphenylazo)propenoates. The line is calculated from eq 4; for the dashed line see text; the identity of the points is given in Table 1.

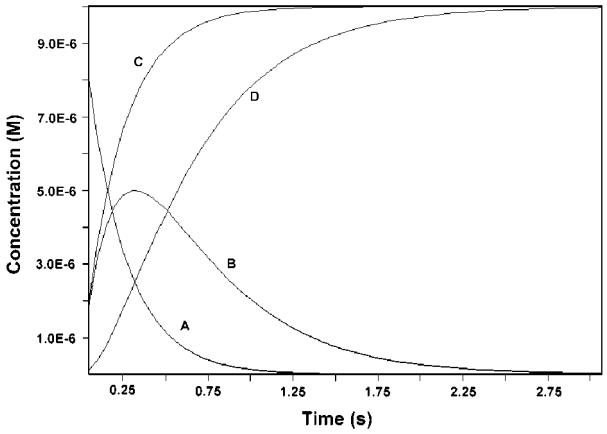


Figure 4. Best fit of concentration vs time courses from DASF experiments. Hydrolysis of 2,4-dinitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate (**4b**) in KOH 5×10^{-3} M (50% dioxane): (A) **4b**; (B) intermediate **5**; (C) 2,4-dinitrophenol; (D) acid.

The remarkably high β_{LG} value (−1.41) is consistent with the dissociative pathway,[12] thus indicating that such esters hydrolyze through intermediate **5**, and is in good agreement with those we previously found for the E1cB hydrolysis of related substrates.[2−4]

Unfortunately, we were not allowed to extend our study to esters possessing leaving phenoxides with pK_{LG} higher than 6.5 owing to the great trouble we met in their synthesis, and therefore, we cannot establish whether in the present system, as we previously observed for related substrates, a break in linearity in the Brønsted plot with upward curvature occurs as the nucleofugality of the leaving group decreases, suggesting a change in mechanism from E1cB to $B_{Ac}2$.

It is well-known that associative processes in acyl group transfer reactions involving carboxylic acid derivatives have β_{LG} values restricted in a narrow range (−0.20 to −0.25). Now, if a line with a slope of −0.25 is drawn (dashed line in Figure 4) through the point indicated as ★, which represents the calculated value of the second-order rate constant ($k_{calc} = 160$ M^{-1} s^{-1}, see above) for the $B_{Ac}2$-type attack of hydroxide ion on the neutral 2,4-dinitrophenyl ester **4b**, it will go across the experimental line at pK_{LG} ca. 8 (changeover point). It is noteworthy that this value is considerably higher than those previously found for related systems (i.e., 6.2 for 4-hydroxybenzoates,[2] 6.7 for 4-hydroxycinnamates,[3] and 6.2 for (2*E*,4*E*)-5-(4′-hydroxyphenyl)pentadienoates).[4]

Finally, the use of a diode array stopped-flow (DASF) technique has provided further evidence of the participation of an intermediate in the hydrolysis of **4b**. Repetitive scan of the UV spectrum of this ester in KOH 5×10^{-3} M (50% aqueous dioxane; the choice of this solvent composition was imposed by the use of the stopped-flow machine) was recorded in the range 390−540 nm, overall time 3 s. Experimental data were fitted using Specfit/32 global analysis system[13] with a nonlinear regression modeling by the Marquardt−Levenberg algorithm to the following equations (identity is given in the caption of Figure 4):

$$\mathbf{A} \rightarrow \mathbf{B} + \mathbf{C}$$

$$\mathbf{B} \rightarrow \mathbf{D}$$

Analysis with a fixed **C** (2,4-dinitrophenoxide ion) spectrum adequately fit all data affording, in whole agreement with the proposed mechanism, the changes of concentration with time shown for illustrative purposes in Figure 4.

Furthermore, the rate constant calculated from these data (4.3 ± 0.4 s^{-1}) shows good correspondence (taking into account the different solvent composition employed) with the value reported in Table 1 for this ester.

Comparison of the present results with those obtained in our previous studies[2−4] on the hydrolysis of related esters of the type HO-π-COOAr indicates that several pieces of evidence suggest an increasing efficiency of the dissociative mechanism on going from aryl 4-hydroxybenzoates to 4-hydroxycinnamates, 5-(4′-hydroxyphenyl)-pentadienoates, and 3-(4′-hydroxyphenylazo)propenoates. Among these, we underline that the ratio k_{app}/k_{OH} for the 2,4-dinitrophenyl derivatives is exceptionally high for ester **4** (10^5, this work) compared with those of the other substrates (ranging from 200 to 2400). Also, the yield of the amide formed follows this trend. Moreover, the breakpoint in the Brønsted plots, which indicates where the $B_{Ac}2$ mechanism gives way to the E1cB one, is evaluated to occur at an higher pK_{LG} in the present case (see above).

In conclusion, all evidence presented in this work points to the fact that the hydrolysis of title esters takes place following a E1cB mechanism, and it is further corroborated from the observation that the efficiency of such mechanism in the hydrolysis of esters of the type HO-π-COOAr is enhanced by the presence of additional π units (provided that only one *p*-phenylene unit is present in the conjugating bridge) owing to extra stabilization of the intermediate due to a more extended delocalization of π electrons. Interestingly, our findings show that esters **4** hydrolyze through the dissociative pathway more readily than 5-(4′-hydroxyphenyl)pentadienoates, although these are iso-π-electronic molecules.

(12) Williams, A.; Douglas, K. T. *Chem. Rev.* **1975**, *75*, 627−649. Gordon, I. M.; Maskill, H.; Ruasse, M. F. *Chem. Soc. Rev.* **1989**, *18*, 123−151. Thatcher, G. R. J.; Kluger, R. *Adv. Phys. Org. Chem.* **1989**, *25*, 99−265.

(13) SPECFIT 32 (version 3.0) for Window systems, 2000 Spectrum Software Associates, Marlborough, MA.

This different behavior most likely reflects a superior conjugative ability of the azo group with respect to the vinylenic group, as inferred from the reported data on the hyperpolarizability of azobenzene and stilbene derivatives.[14]

Experimental Section

General Methods. Starting reagents and solvents were purified and/or distilled before use. Buffer materials were of analytical reagent grade. Water was double distilled and preboiled to free it from dissolved carbon dioxide. Dioxane was purged of peroxides by passage of the analytical-grade product through an activated alumina column under nitrogen; the absence of peroxides was checked by the KI test. The ^{1}H NMR spectra were recorded with a 200 MHz spectrometer and TMS as internal standard.

Synthesis. Esters **4a**−**f** and **6** and the amide **7** were prepared starting from the corresponding acids. The hydroxy acid was prepared through condensation[15] of *p*-benzoyloxyphenylhydrazine (prepared by reduction[16] with $SnCl_2$ of the corresponding diazonium chloride) with methyl 2-chloro-3-oxopropionate (obtained by reaction[17] of methyl formate and methyl chloroacetate in the presence of sodium ethoxide) in ethanol with solid sodium acetate; the instantaneous dehydrohalogenation of the so obtained arylhydrazone gave methyl ester in the required 2*E* form, as confirmed by ^{1}H NMR spectroscopy. Benzoyl protecting group was removed by alkaline hydrolysis with a stoichiometric amount of KOH in cold methanol and the acid was successively liberated by treatment with bis(tributyltin)oxide (BBTO) as described.[18] The methoxy acid was analogously prepared starting from commercial *p*-methoxyphenylhydrazine. Esters and amide were finally prepared from the acids by condensation with the appropriate phenol or amine in the presence of DCC. As stated above, we were unable to prepare esters with leaving group having pK_{LG} higher than about 6.5. The DCC coupling reaction of the acid with such phenols failed as well as the alternative route through the acid chloride, that we have successfully employed in the synthesis of related esters.[4] Several attempts to transform the acid into the corresponding chloride, accomplished with different types of protection of the phenolic hydroxyl group of the acid, invariably led to decomposition of the latter with breakage of the π skeleton.

The characteristics of the new compounds, purified through column chromatography and recrystallized from toluene (unless otherwise stated), were as follows; mp is given together with analytical data. All these products were stored in a refrigerator to avoid decomposition. The stock solutions were prepared immediately prior to use and stored in the dark.

2,6-Dinitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate (4a): mp 52−3 °C; $CDCl_3$ δ 8.35 (d, 2, J = 8.60 Hz), 8.23 (d, 1, J = 13.80 Hz), 7.87 (d, 2, J = 9.60 Hz), 7.63 (t, 1, J = 8.20 Hz), 7.03 (d, 1, J = 13.4 Hz), 6.96 (d, 2, J = 9.60 Hz), 6.05 (bs, 1). Anal. Calcd for $C_{15}H_{10}N_4O_7$: C, 50.3; H, 2.8; N, 15.6. Found: C, 50.8; H, 2.7; N, 15.8. **2,4-Dinitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate (4b):** mp 135−6 °C; acetone-d_6 δ 9.01 (d, 1, J = 2.56 Hz), 8.77 (dd, 1, J = 2.56 Hz; 8.79 Hz), 8.22 (d, 1, J = 13.92 Hz), 7.98 (d, 1, J = 8.79 Hz), 7.92 (d, 2, J = 8.79 Hz), 7.08 (d, 1, J = 13.56 Hz), 7.08 (d, 2, J = 8.79 Hz). Anal. Calcd for $C_{15}H_{10}N_4O_7$: C, 50.3; H, 2.8; N, 15.6. Found: C, 51.0; H, 2.9; N, 15.3. **2-Methyl-4,6-dinitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate (4c):** mp 136−7 °C; $CDCl_3$ δ 8.83 (d, 1, J = 2.20 Hz), 8.45 (d, 1, J = 2.00 Hz), 8.25 (d, 1, J = 13.80 Hz), 7.88 (d, 2, J = 8.80 Hz), 7.04 (d, 1, J = 14.00 Hz), 6.96 (d, 2, J = 9.20 Hz), 5.64 (bs, 1), 2.47 (s, 3). Anal. Calcd for $C_{16}H_{12}N_4O_7$: C, 51.6; H, 3.3; N, 15.0. Found: C, 52.1; H, 3.5; N, 14.3. **2,5-Dinitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate (4d):** mp 132−3 °C; $CDCl_3$ δ 8.29 (s, 2), 8.25 (d, 1, J = 13.80 Hz), 7.89 (d, 2, J = 8.80 Hz), 7.00 (m, 3), 5.71 (bs, 1). Anal. Calcd for $C_{15}H_{10}N_4O_7$: C, 50.3; H, 2.8; N, 15.6. Found: C, 50.7; H, 3.0; N, 16.0. **2-Chloro-4-nitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)-propenoate (4e):** mp 126−7 °C; $CDCl_3$ δ 8.41 (d, 1, J = 2.40 Hz), 8.25 (m, 2), 7.88 (d, 2, J = 9.16 Hz), 7.49 (d, 1, 8.80 Hz), 7.00 (m, 3), 5.75 (bs, 1). Anal. Calcd for $C_{15}H_{10}N_3O_5Cl$: C, 51.8; H, 2.9; N, 12.1. Found: C, 52.3; H, 3.0; N, 12.0. **4-Chloro-2-nitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate (4f):** mp 131−2 °C; $CDCl_3$ δ 8.22 (d, 1, J = 13.92 Hz) 8.14 (d, 1, J = 2.56 Hz) 7.87 (d, 2, J = 9.16 Hz), 7.67 (dd, 1, J = 2.60 Hz; 8.80 Hz), 7.32 (d, 1, J = 8.79 Hz), 6.99 (m, 3), 5.70 (bs, 1). Anal. Calcd for $C_{15}H_{10}N_3O_5Cl$: C, 51.8; H, 2.9; N, 12.1. Found: C, 52.1; H, 3.1; N, 12.0. **2,4-Dinitrophenyl (2*E*)-3-(4′-methoxyphenylazo)propenoate (6):** mp 126−7 °C; $CDCl_3$ δ 9.01 (d, 1, J = 2.60 Hz), 8.58 (dd, 1, J = 3.00 Hz; 9.20 Hz), 8.25 (d, 1, J = 14.00 Hz), 7.93 (d, 2, J = 9.20 Hz), 7.62 (d, 1, J = 8.80 Hz), 7.01 (m, 3), 3.93 (s, 3). Anal. Calcd for $C_{16}H_{12}N_4O_7$: C, 51.6; H, 3.3; N, 15.1. Found: C, 51.8; H, 3.3; N, 15.0. ***N*-(4-Methylphenyl) (2*E*)-3-(4′-hydroxyphenylazo)propenamide (7):** mp 148−9 °C (from ethanol); Acetone-d_6 δ 9.62 (bs, 1), 9.34 (bs, 1), 8.03 (d, 1, J = 13.20 Hz), 7.80 (d, 2, 8.80 Hz), 7.68 (d, 2, J = 8.40 Hz), 7.16 (m, 3), 7.01 (d, 2, 8.60 Hz), 2.30 (s,1). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.3; H, 5.4; N, 14.9. Found: C, 68.2; H, 5.3; N, 15.0.

Methods. Product Analysis. The products of ester hydrolyses were identified as phenol and acid by comparison of the UV−vis spectra after completion of the reactions with authentic samples of these compounds under the same conditions.

Kinetics. The hydrolyses of esters **4a**−**f** and **6** in 40% v/v dioxane−water solvent were followed spectrophotometrically: the choice of the appropriate wavelength was dictated by the pH of the buffers employed in the particular kinetic run since the ionization of the hydroxyl group of both substrates and liberated acid in alkaline solutions causes large shift in the UV−vis spectra. 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 an ordinary, bouble beam spectrophotometer. The reaction was initiated by adding 10 μL of a stock solution of the substrate ca. 0.01 M in dioxane placed on the flattened tip of a narrow glass rod to the buffer. A few vertical strokes of the glass rod effected mixing and automated acquisition of 50−200 data points for each kinetic run was performed. The rate constants reported in Table 1 were obtained through the skillful use of this technique. Reactions were carried out with potassium hydroxide at different concentrations (in the pH range 12.7−14), and with succinate (pH 5.5), phthalate (pH 6.4−7.3), phosphate (pH 7.5−8.7), borate (pH 10−10.5), and carbonate (pH 11.2−11.5) buffers. In all cases, at least three different buffer concentrations, at constant pH, were employed: when buffer effects were observed 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 were measured before and after each kinetic run using a Ross combined electrode, calibrated with standard buffers. All pH values quoted for the dioxane-water solutions are relative values measured directly, no further corrections being applied. The pseudo-first-order rate constants (k_{obs}) were obtained by NLLSQ fitting of absorbance vs time data and the values reported are the averages of at least duplicate runs. Reactions were normally followed over about seven half-lives. DASF experiments were carried out with a Tri-Tech stopped-flow instrument equipped with a diode array detector.

Trapping. The hydrolysis of 2,4-dinitrophenyl (2*E*)-3-(4′-hydroxyphenylazo)propenoate in 0.05 M borate buffer (fraction of base = 0.5, 40% aqueous dioxane, ionic strength kept at 0.1 M with KCl, pH 10.10) was kinetically investigated at 400 nm in the presence of variable amounts of added *p*-toluidine: no

(14) Van Walree, C. A.; Franssen, O.; Marsman, A. W.; Flipse, M. C.; Jenneskens, L. W. *J. Chem. Soc., Perkin Trans. 2* **1997**, 799−807. Morley, J. O. *J. Chem. Soc., Perkin Trans. 2* **1995**, 731−734. Buncel, E.; Rajagopal, S. *Acc. Chem. Res.* **1990**, *23*, 226−231.

(15) Sticker, R. E. U.S. Patent 3,651,226 (Cl. 424−226; A 01*n*), 21 Mar 1972; *Chem. Abstr.* **1972,** *77*, 19397w.

(16) Lester, M. G.; Petrow, V.; Stephenson, O. *Tetrahedron* **1965**, *21*, 1761−1766.

(17) McMillan, I.; Stoodley, R. J. *J. Chem. Soc. C* **1968**, 2533−2537.

(18) Salomon, C. J.; Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1991**, *32*, 4239−4242.

effect on the rate of hydrolysis was observed varying the amine concentration in the range 0−0.03 M at constant pH. The UV−vis spectra taken at the end of the reactions carried out in the presence of the amine were significantly different from that obtained in absence of it, in particular in the range 450−550 nm. The values of the molar extinction coefficients at 500 nm of the amide, phenol, and acid were determined employing authentic samples under the same conditions, and the amide yield (ca. 37%) was calculated from the absorbances measured at this wavelength at the end of the reaction carried out in the presence of 0.03 M *p*-toluidine. The presence of the amide was also confirmed by TLC analysis.

Ionization Constants. The determinations of pK_a values were carried out by spectrophotometric titration (at 520 nm) of the ionizable substrates employing at least seven buffered solutions for each determination and extrapolating the absorption to zero time.

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