Mechanism of Alkaline Hydrolysis of Some HO-π-COOAr Acyl Derivatives

Giorgio Cevasco* and Sergio Thea*

C.N.R., Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici,† Dipartimento di Chimica e Chimica Industriale, Università di Genova, Via Dodecaneso 31, 16146 Genova, Italy

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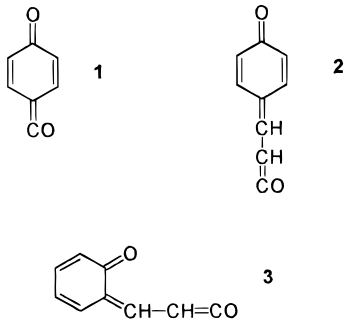
To gain knowledge on the role played by the nature of the bridge interposed between hydroxyl and carbonyl groups in esters of the title type, in principle able to hydrolyze through dissociative pathways via the conjugate base of the substrate (E1cB mechanism), we have studied the alkaline hydrolyses of 2,4-dinitrophenyl esters in which the π-system is a biphenyl, azobenzene, benzylideneaniline, or stilbene skeleton. Kinetic data, such as reactivity comparisons and Arrhenius parameters, show that these substrates react through the usual, associative, $B_{Ac}2$ mechanism. This outcome is discussed and interpreted from both structural and energetic standpoints. The data suggest that a value of 0.0 is the most appropriate assignment of the σ_p value for the benzylidenamino substituent ($C_6H_5CH{=}N-$).

We have been interested in the dissociative (E1cB) mechanism of acyl transfer reactions for over a decade. We have previously found[1] that the hydrolyses of aryl 4-hydroxybenzoates in moderately to strongly alkaline aqueous solution follow the usual associative route ($B_{Ac}2$) when the esters possess leaving groups having pK_a higher than about 6.5, whereas esters having leaving groups with lower pK_a hydrolyze through the E1cB mechanism with the participation of the unprecedented *p*-oxo ketene intermediate (**1**). We have subsequently demonstrated that the hydrolyses of aryl 4-hydroxycinnamates[2] and 2-hydroxycinnamates[3] in dioxane−water mixtures behave almost in the same way with the participation, in their dissociative paths, of the "extended" oxo ketene intermediates **2** and **3**, respectively.



Although the presence of an ionizable α-hydrogen had been previously considered a prerequisite for the occurrence of E1cB pathways in ester hydrolysis,[4] we have been able to demonstrate that the dissociative mechanism carries the reaction flux also when the hydroxyl group is π-conjugated with the reaction center in esters of the type HO-π-COOAr: the intervening backbone being a simple π-system, the aromatic ring in the case of 4-hydroxybenzoates or two π-systems linked by a single bond in the case of hydroxycinnamates.

It is generally accepted[4] that an adequate internal nucleophilicity of the substrate (which represents the ability of its ionized form to expel the leaving group), high nucleofugality of the leaving group, and relatively high stability of the putative intermediate are the driving forces for the dissociative pathway.

Our studies[1−3] indicate that interposition of an extra vinylene group between the internal nucleophile and the reaction center favors the dissociative mechanism. Comparisons between the hydrolysis rates of 2′,4′-dinitrophenyl esters of 4-hydroxybenzoic and 2- and 4-hydroxycinnamic acid indicate that, taking into account the different acidities of the esters (i.e., the acidity of the phenolic groups in the esters, which is related to nucleophilicity), the observed rate enhancement could be due to an increased stability of the "extended" intermediates that, in turn, can be ascribed to a more extended delocalization of π electrons. Analogous results come from our recent studies[5] on dissociative sulfonyl group transfer reactions where "extended" sulfoquinone intermediates are involved.

Moreover, we have recently suggested[6] the occurrence of the E1cB mechanism in the hydrolysis of an ester, 2,4-dinitrophenyl 4′-hydroxyphenylpropiolate, possessing a C−C triple bond as part of the π-conjugated system.

To improve understanding of the effects of specific structural modifications of the π-backbone on the hydrolytic pathways, we have directed our attention toward other esters possessing different molecular architecture such as two aromatic π-systems linked by a single bond or by Z=Y π-conjugated systems with Z and Y being N or CH.

In this study, we report the results of a kinetic investigation on the alkaline hydrolyses of some HO-π-COOAr esters where π is either the biphenyl moiety in compound **4a** or the isoelectronic bridge in azobenzene (**5a**), benzylideneaniline (**6a**), and stilbene (**7a**) deriva-

† Associated with the Istituto Nazionale di Coordinamento per la Chimica dei Sistemi Biologici.

(1) (a) Cevasco, G.; Guanti, G.; Hopkins A. R.; Thea, S.; Williams, A. *J. Org. Chem.* **1985**, *50*, 479. (b) Thea, S.; Cevasco, G.; Guanti, G.; Kashefi-Naini, N.; Williams, A. *Ibid.* **1985**, *50*, 1867.
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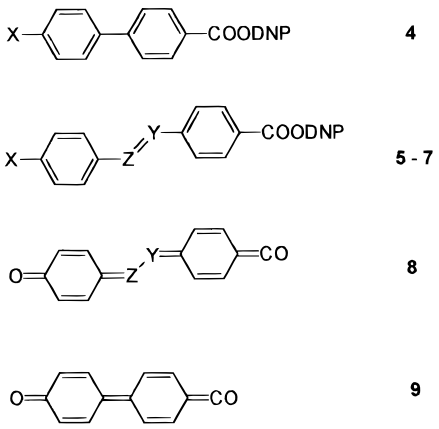
tives. Since the E1cB mechanism requires π-system



4a: X = OH; **4b**: X = H

5a: X = OH, Z = Y = N; **5b**: X = OMe, Z = Y = N

6a: X = OH, Z = CH, Y = N; **6b**: X = OMe, Z = CH, Y = N

7a: X = OH, Z = Y = CH; **7b**: X = OMe, Z = Y = CH

DNP = 2,4-dinitrophenyl

planarity to allow the conjugative interaction between the hydroxyl group and the carbonyl carbon atom and *(E)*-azobenzene and *(E)*-stilbene derivatives are thought to be essentially planar in the solid state and in solution,[7,8] it is in principle possible that the hydrolyses of *(E)*-**5a** and *(E)*-**7a** follow the dissociative pathway with the participation of unsaturated intermediates such as **8**. On the contrary, benzylideneanilines are generally not planar in those phases,[7−9] and since the aniline ring is severely twisted out of the C−N=C−C plane, **6a** should hydrolyze through the usual associative $B_{Ac}2$ mechanism. As far as **4a** is concerned, it is well-known that biphenyl itself is planar in the solid state, whereas in the gas phase and in solution the phenyl rings are twisted.[10] These observations are in agreement with the outcome of theoretical molecular mechanics calculations[11] that rotation around the bond between the phenyl rings occurs readily. In this case, it is reasonable to suppose that for the alkaline hydrolysis of **4a** a dissociative mechanism through the intermediate **9** is a possible alternative to the usual associative route.

Finally, it must be emphasized that analogues of compounds **5**−**7** are currently target molecules not only for conformational[8] and for *Z*/*E* isomerization[12] studies but also for the nonlinear optical (NLO) properties of *push*−*pull* derivatives.[7,13]

(7) For example: van Walree, C. A.; Franssen, O.; Marsman, A. W.; Flipse, M. C.; Jenneskens, L. W. *J. Chem. Soc., Perkin Trans. 2* **1997**, 799 and the following article in the issue.

(8) For example: Zamir, S.; Bernstein, J.; Ioffe, A.; Brunvoll, J.; Kolonits, M.; Hargittai, I. *J. Chem. Soc., Perkin Trans. 2* **1994**, 895 and references therein.

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(11) PCModel, Serena Software, Bloomington, IN, 1993.

(12) For example: (a) Cimiraglia, R.; Asano, T.; Hofmann, H.-G. *Gazz. Chim. Ital.* **1996**, *126*, 679. (b) Sanchez, A. M.; de Rossi, R. H. *J. Org. Chem.* **1995**, *60*, 2974.

(13) For example: Albert, I. D. L.; Marks, T. J.; Ratner, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 11174 and references therein.

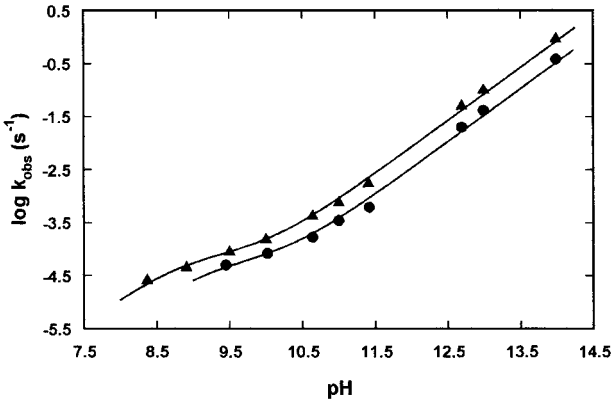

Figure 1. pH−rate profiles for the hydrolysis of 2,4-dinitrophenyl esters **5a** (triangles) and **6a** (circles) in 40% dioxane buffers at 25 °C and ionic strength 0.1 M (KCl). Lines are calculated from eq 1.

Results and Discussion

The hydrolyses of 2,4-dinitrophenyl derivatives **4a**−**7a** and, for the sake of comparison, those of the corresponding esters devoid of acidic hydrogen **4b**−**7b** were carried out under pseudo-first-order conditions in 40% dioxane/water (v/v) at 25 °C and ionic strength held constant (0.1 M) with added potassium chloride. The progress of the reactions was monitored by following the variation of absorbance due to the disappearance of the substrate or liberation of products. The products of the reactions of esters **4**−**7** in alkaline solution were identified as 2,4-dinitrophenoxide ion and the appropriate acid. This was achieved by comparison of the UV−vis spectra after completion of the reactions with authentic samples of these products under the same conditions. Esters **6a**,**b** are Schiff bases, and therefore, they may undergo hydrolysis of the azomethine group; however, control experiments clearly showed that, under the conditions employed in this work, this is a secondary reaction that takes place only after completion of the hydrolysis of carboxylic ester group. However, for this reason, the pH−rate profile (see below) for hydrolysis of ester **6a** was stopped at pH ca. 9.5.

The rates of hydrolysis of the esters **4a**−**7a** were found to obey eq 1 and are illustrated as pH−rate profiles in Figures 1 and 2.

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

In eq 1, a_H is the proton activity and K_a is the ionization constant of the hydroxyl group of the ester, which is responsible for the curvature in the pH−rate profiles. The K_a values were separately determined, and the kinetic constants can be calculated, knowing the K_a value, from primary kinetic data, by iterative nonlinear curve-fitting performed with the Fig.P program.[14] The values of the kinetic parameters k_a, the pseudo-first-order rate constant in the plateau region of the pH−rate profile (actually the plateau region is only an inflection in the case of the stilbene derivative **7a** and is very narrow in the other cases), and k_b, the second-order term related to the bimolecular attack of hydroxide ion on the ionized ester, are reported in Table 1 together with parameters and conditions relevant to the hydrolyses of these esters.

(14) Program Fig.P from Biosoft, Cambridge, U.K., 1991.

Table 1. Ionization and Rate Constants for Esters 4a−7a in 40% Dioxane at 25 °C and μ = 0.1 (pK_w = 15.00)

substrate	pK_a[a]	λ,[b] nm	k_a, s^{-1}	k_b, M^{-1} s^{-1}	k_{app}[c]	N[d]	pH[e]
4a	10.33	360	$(2.76 \pm 0.44) \times 10^{-4}$	1.90 ± 0.30	13	10	8.4−14.0
5a	8.81	480	$(8.07 \pm 0.87) \times 10^{-5}$	8.42 ± 0.62	125	10	8.3−14.0
6a	9.16	400	$(5.89 \pm 1.33) \times 10^{-5}$	3.34 ± 0.37	41	8	9.5−14.0
7a	10.46	400	$(2.05 \pm 0.12) \times 10^{-4}$	3.01 ± 0.14	7	11	8.7−14.0

[a] The error on these values is less than 0.01 pK unit. [b] Wavelength employed for pK_a determination. [c] See text. [d] Number of data points, not including duplicates. [e] pH range employed. See text for the wavelength employed for kinetics.

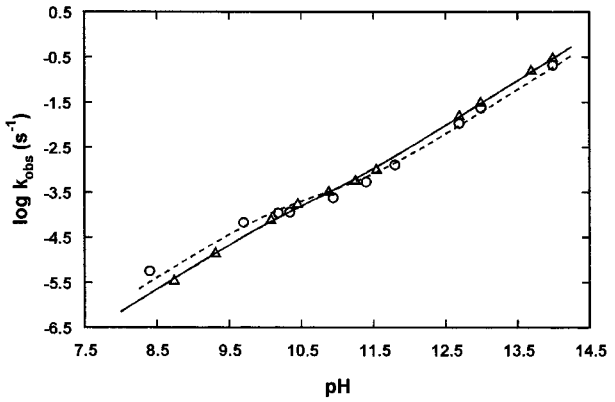

Figure 2. pH−rate profiles for the hydrolysis of 2,4-dinitrophenyl esters **7a** (triangles) and **4a** (circles) in 40% dioxane buffers at 25 °C and ionic strength 0.1 M (KCl). Lines are calculated from eq 1 (one of them is dashed for the sake of clarity).

Table 2. Second-Order Rate Constants for the Hydrolysis of Esters 4b−7b in 40% Dioxane at 25 °C and μ = 0.1

substrate	λ,[a] nm	k_{OH}, M^{-1} s^{-1}	k_{app}/k_{OH}[b]
4b	400	12.06 ± 0.04	1.1
5b	360	38.07 ± 1.80	3.3
6b	400	8.95 ± 0.03	4.6
7b	410	6.91 ± 0.25	1.0

[a] Wavelength employed for the kinetic runs. [b] Values of k_{app} are taken from Table 1.

In Table 1 the spectrophotometrically determined pK_a values are reported as well.

Since $B_{Ac}2$ and E1cB mechanisms in acyl group transfer reactions of ionizable substrates obey the same rate equation (i.e., eq 1), they cannot be differentiated kinetically, and therefore, other tools must be employed in order to elucidate the reaction mechanism. However, the limited width of plateau region in the pH−rate profiles would not suggest that the dissociative mechanism is occurring.

One of these criteria is offered by reactivity comparisons with substrate models lacking the ionizable center and that, therefore, cannot react through the E1cB mechanism. In the present case, esters **4b**−**7b** represent suitable models. Their alkaline hydrolyses obey eq 2, where K_w is the ionic product of water in the employed medium (pK_w =15.00 at 25 °C)[15] and k_{OH} is the second-order rate constant related to the $B_{Ac}2$ attack of hydroxide ion on the substrate. The relevant parameters are recorded in Table 2.

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

To carry out the aforementioned reactivity comparisons between the hydrolyses of these esters we resort, as is customary, to the *calculated* apparent second-order rate constant for the hydrolysis of esters **4a**−**7a** ($k_{app} = k_aK_a/K_w$). As shown by the data in Table 2, such values are equal or only slightly higher than the k_{OH} values determined for the esters **4b**−**7b**.

On the contrary, in the case of 2,4-dinitrophenyl 4′-hydroxybenzoate, the ratio between k_{app} and k_{OH} for the corresponding methoxy derivative is large (ca. 280),[6] thus suggesting that the two esters hydrolyze through a different mechanism. Therefore, the present results seem to indicate that all the substrates investigated in this work (**4**−**7**) hydrolyze through the same mechanism, i.e., the associative one; in particular, there is no reason to invoke the participation of the E1cB mechanism in the hydrolysis of esters **4a**, **5a**, and **7a**.

To further substantiate this conclusion, we have also calculated the activation parameters for the hydrolysis reaction of the 2,4-dinitrophenyl ester of 4-(4′-hydroxyphenyl)azobenzoic acid (**5a**). Arrhenius parameters have been used[16] to distinguish E1cB from $B_{Ac}2$ mechanisms since the bimolecular process should show a considerably more negative entropy of activation than E1cB process, in which the rate-determining step is unimolecular. The activation parameters for the hydrolysis of **5a** have been determined in the range 17−35 °C and are as follows: $\Delta S^{\ddagger} = -25.7 \pm 1.7$ eu, $\Delta H^{\ddagger} = 15.3 \pm 0.5$ kcal/mol. The largely negative value of $\Delta S^{\ddagger}$ for the hydrolysis of this ester is well within the range expected for an associative process,[17] thus excluding the incursion of a dissociative pathway in this reaction.

Therefore, although possible in principle, the E1cB mechanism does not carry the reaction flux in the hydrolyses of the esters studied in this work.

As far as compounds **4a** and **6a** are involved, this result could be ascribed to a diminished conjugative interaction between the hydroxyl and the ester groups because of deviation from planarity of the π-system (vide supra). On the other hand, comparison between the hydrolyses of ester **7a** (whose π-system is planar or nearly so) and the parent 2,4-dinitrophenyl 4′-hydroxycinnamate (which follows the E1cB hydrolytic mechanism[2]) seems to indicate that loss of aromaticity involved in reaching the rate-determining transition state of the E1cB route is large enough to make this pathway unfavorable, with respect to the associative one, when *two* (rather than *one*) *p*-phenylene units are part of the π-bridge. Of course, the same factor can be invoked for ester **5a**, and esters **4a** and **6a** as well, as their π-systems include two aromatic rings.

Since the present results give no specific indication on the effect of substitution of sp^2 nitrogen atoms for sp^2

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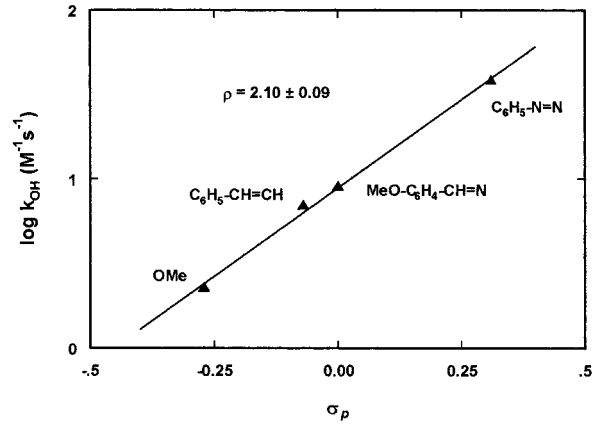

Figure 3. Hammett-σ relationship for the alkaline hydrolysis of 2,4-dinitrophenyl para-substituted benzoates. Kinetic data from Table 2 and ref 6; the σ values are taken from ref 20 (however, see text).

carbon atoms in the conjugated backbone on the dissociative mechanism, further work is required to shed light on this topic.

However, our data allow the correct assignment of the σ_p value for the benzylidenamino group ($C_6H_5CH{=}N-$) to be made; indeed, two strikingly different values have been reported in the literature for this group, namely 0.0[18] and −0.55,[19] although they were both based on ionization of substituted benzoic acids. The last value, although the authors themselves suspected it could be affected by hydrolysis of the azomethine group during p*K* determination, seems to be currently given credit (it has been recently reported in an authoritative review[20]).

Since it is reasonable to assume that in compounds such as **5**−**7** the electronic effect of the whole group $XC_6H_4Z{=}Y$ is primarily due to the nature of Z and Y (the effect of X should be quite attenuated by the two interposed groups), the polar effect of $MeOC_6H_4Z{=}Y$ should not be too much different from that of $C_6H_5Z{=}Y$ (other things being equal). Now, from the data shown in Table 2, and previous data of ours on the hydrolysis of 2,4-dinitrophenyl 4′-methoxybenzoate under the same conditions ($k_{OH} = 2.25 \pm 0.03$ M^{-1} s^{-1}),[6] it is possible to ascertain that the second-order rate constant for the hydrolysis of 2,4-dinitrophenyl *N*-(4′-methoxybenzylidene)-*p*-aminobenzoate (**6b**) fits well a Hammett relationship, as shown in Figure 3, provided that the value $\sigma_p = 0.0$ for this substrate is employed. It is worth noting that the derived Hammett sensitivity ($\rho = +2.1$) is in good agreement with the value previously determined for the alkaline hydrolysis of 2,4-dinitrophenyl benzoates in water (+1.97).[1a] Therefore, in light of the above assumption, we suggest that 0.0 is the most reliable value of σ_p for the benzylideneamino substituent. This outcome fulfills the expectation that the electron-withdrawing effect of the whole group should increase as the number of nitrogen atoms in the bridge increases.

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 Varian Gemini 200 spectrometer (200 MHz) with TMS as internal standard and acetone-d_6 or DMSO-d_6 as solvent.

Synthesis. The esters were prepared by condensation of the appropriate acid (commercial, unless otherwise stated) with 2,4-dinitrophenol by means of dicyclohexylcarbodiimide in ethyl acetate with pyridine as catalyst. After usual workup of the reaction, the resulting ester was recrystallized to constant mp. The structures of the synthesized acids and esters were confirmed by ^{1}H NMR spectroscopy. The esters were as follows; mp is given together with analytical data.

2,4-Dinitrophenyl 4-(4′-hydroxyphenyl)benzoate (**4a**)**:** mp 186−7 °C (from toluene). Anal. Calcd for $C_{19}H_{12}N_2O_7$: C, 60.0; H, 3.2; N, 7.4. Found: C, 60.4; H, 3.3; N, 7.2. **2,4-Dinitrophenyl 4-phenylbenzoate** (**4b**)**:** mp 138−9 °C (from toluene). Anal. Calcd for $C_{19}H_{12}N_2O_6$: C, 62.6; H, 3.3; N, 7.7. Found: C, 63.2; H, 3.5; N, 7.7. **2,4-Dinitrophenyl 4-(4′-hydroxyphenyl)azobenzoate** (**5a**)**:** mp 166−7 °C (from methanol). Anal. Calcd for $C_{19}H_{12}N_4O_7$: C, 55.9; H, 2.9; N, 13.7. Found: C, 55.6; H, 2.9; N, 13.5. The starting 4-(4′-hydroxyphenyl)azobenzoic acid (in the stable *E* form)[12b,21] was prepared as described in the literature.[22] **2,4-Dinitrophenyl 4-(4′-methoxyphenyl)azobenzoate** (**5b**)**:** mp 183−4 °C (from toluene). Anal. Calcd for $C_{20}H_{14}N_4O_7$: C, 56.9; H, 3.3; N, 13.3. Found: C, 57.3; H, 3.4; N, 13.0. The starting acid was obtained by methylation with dimethyl sulfate of 4-(4′-hydroxyphenyl)-azobenzoic acid (see above). **2,4-Dinitrophenyl *N*-(4′-hydroxybenzylidene)-4-aminobenzoate** (**6a**)**:** this ester, repeatedly crystallized from toluene, does not have a clear mp, most likely owing to mesomorphism. Anal. Calcd for $C_{20}H_{13}N_3O_7$: C, 59.0; H, 3.2; N, 10.3. Found: C, 58.6; H, 3.4; N, 10.0. Starting *N*-(4′-hydroxybenzylidene)-4-aminobenzoic acid was prepared, according to standard procedure, by refluxing overnight an ethanolic solution of *p*-hydroxybenzaldehyde and *p*-aminobenzoic acid. The cooled solution offered, after removal of the solvent, a crystalline, yellow solid. The ^{1}H NMR spectrum (DMSO-d_6) of this product, melting with decomposition at 247−8 °C (lit.[23] mp 229−230 °C dec), confirmed the expected structure. **2,4-Dinitrophenyl *N*-(4′-methoxybenzylidene)-4-aminobenzoate** (**6b**)**:** mp 170−1 °C (from toluene). Anal. Calcd for $C_{21}H_{15}N_3O_7$: C, 59.9; H, 3.6; N, 10.0. Found: C, 59.9; H, 3.5; N, 10.0. Starting *N*-(4′-methoxybenzylidene)-4-aminobenzoic acid was prepared by refluxing overnight an ethanolic solution of *p*-methoxybenzaldehyde and *p*-aminobenzoic acid. A pinkish crystalline solid melting at 188−9 °C was obtained upon cooling. **2,4-Dinitrophenyl 4′-hydroxy-*trans*-stilbene-4-carboxylate** (**7a**)**:** mp 185−6 °C (from toluene). Anal. Calcd for $C_{21}H_{14}N_2O_7$: C, 62.1; H, 3.5; N, 6.9. Found: C, 62.3; H, 3.6; N, 6.8. The ^{1}H NMR spectrum (acetone-d_6) of this ester showed, together with the typical, expected doublets due to the rings protons, the following signals: δ 7.46 (d, 1, J = 16.5 Hz), 7.20 (d, 1, J = 16.4 Hz). These vinylic coupling constants undoubtedly indicate a trans stereochemistry.

4′-Hydroxystilbene-4-carboxylic acid was prepared as follows. Ethyl α-bromo-*p*-toluate (obtained by esterification of the commercial acid) was treated with triphenylphosphine in anhydrous acetonitrile, under nitrogen at rt for 2 days, affording, in good yield, the corresponding benzyltriphenylphosphonium bromide. This salt was reacted with 4-acetoxybenzaldehyde following a recently reported[24] modified Wittig reaction employing 18-crown-6 and solid potassium hydroxide in dichloromethane. This reaction furnished, in good yield,

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nearly a 1:1 mixture of the *E*/*Z* isomers as judged by ^{1}H NMR spectroscopy (fortunately, in acetone-d_6 the two isomers have well-resolved and easily interpretable spectra). Our attempts to obtain complete *E* stereoselectivity by means of benzyldiphenylchlorophosphonium bromide[24] failed. The mixture of isomers was subsequently hydrolyzed in aqueous sodium hydroxide by refluxing until complete dissolution occurred. The cooled solution was acidified, affording a crystalline precipitate that was identified as 4′-hydroxystilbene-4-carboxylic acid in a ca. 1:1 mixture of the *E*/*Z* isomers as estimated by ^{1}H NMR spectroscopy (again the spectra of the two isomers are well resolved in DMSO-d_6). After condensation with 2,4-dinitrophenol in the presence of dicyclohexylcarbodiimide, the usual workup of the reaction afforded again a mixture of the *E*/*Z* isomers of the desired ester as shown by the ^{1}H NMR spectrum. Finally, the cis isomer was easily and completely converted into the trans isomer simply by treating a solution of the mixture of isomers in dichloromethane with a catalytic amount of iodine in daylight for a few hours.[25] **2,4-Dinitrophenyl 4′-methoxy-*trans*-stilbene-4-carboxylate (7b):** mp 201−2 °C (from toluene). Anal. Calcd for $C_{22}H_{16}N_2O_7$: C, 62.9; H, 3.8; N, 6.7. Found: C, 62.9; H, 4.0; N, 6.9. The ^{1}H NMR spectrum (DMSO-d_6) of this ester showed, together with the typical, expected doublets due to the rings protons, the following signals: δ 7.51 (d, 1, J = 16.6 Hz), 7.27 (d, 1, J = 16.4 Hz), 3.82 (s, 3). These vinylic coupling constants again indicate a trans stereochemistry. 4′-Methoxystilbene-4-carboxylic acid and the required *E* ester were prepared following the procedure described above for the corresponding hydroxylic acid employing 4-methoxybenzaldehyde instead of 4-acetoxybenzaldehyde.

Methods

Kinetics. The hydrolyses of the esters **4**−**7** 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 acids 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 a Kontron Uvikon 941 spectrophotometer. The reaction was initiated by adding 10 μL of a stock solution of the substrate ca. 0.01 M in dioxane to the buffer, and automated acquisition of 50−200 data points for each kinetic run was performed. Reactions were carried out with potassium hydroxide at different concentrations and with phosphate, borate, carbonate, ammonia, and Tris 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 Radiometer PHM62 meter equipped with 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 7 half-lives.

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

(25) Yang, J.-H.; Shi, L.-L.; Xiao, W.-J.; Wen, X.-Q.; Huang, Y.-Z. *Heteroatom. Chem.* **1990**, *1*, 75.

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