Kinetics and Mechanism of the Alkaline Hydrolysis of 2,4-Dinitrophenyl 4′-Hydroxyphenylpropiolate

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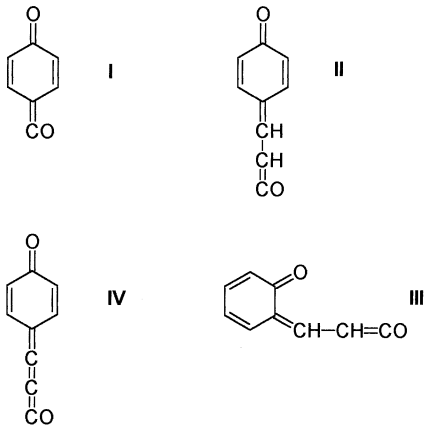
The alkaline hydrolysis of the title ester was studied in 40% dioxane/water (v/v) solutions. Kinetic data, reactivity comparisons with model substrates and activation parameters appear to suggest the occurrence of a dissociative E1cB pathway although participation of the associative mechanism cannot be definitely ruled out.

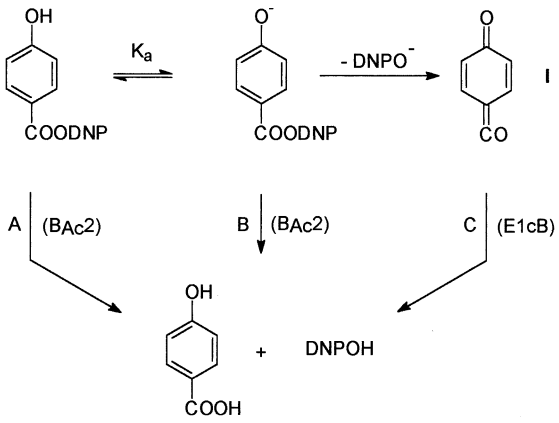
We are interested in the factors that govern the competition among different acyl transfer reaction mechanisms (in particular dissociative versus associative pathways, i. e. E1cB and $B_{Ac}2$) and have discussed this subject in a number of papers. We have at first found[1] that the hydrolyses of aryl 4-hydroxybenzoates in moderately to strongly alkaline aqueous solution follow the usual associative route (paths A and B in Scheme 2) when the esters possess leaving groups with a pK_a higher than about 6.5; whereas esters having leaving groups with lower pK_a hydrolyse by the E1cB mechanism with the participation of the unprecedented *p*-oxo ketene intermediate (**I**, Scheme 1 and path C in Scheme 2). Subsequently, we have 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 **II** and **III** (Scheme 1), respectively.

Scheme 1



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

Scheme 2. DNPOH = 2,4-dinitrophenol



Our previous studies[1][2][3] show that the interposition of a vinylene group between the internal nucleophile and the reaction centre favours the elimination-addition process. Indeed, comparisons between the hydrolysis rates of 2′,4′-dinitrophenyl esters of 4-hydroxybenzoic, 2- and 4-hydroxycinnamic acid indicate that, taking into account the different acidity of the esters (and therefore the difference in their internal nucleophilicity), the observed rate enhancement could be due to an increased stability of the "extended" intermediates which, 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.

In order to extend our knowledge on the occurrence of dissociative carbonyl group transfer and hoping to shed more light on the role played by the stability of the intermediate in such processes we have undertaken a kinetic

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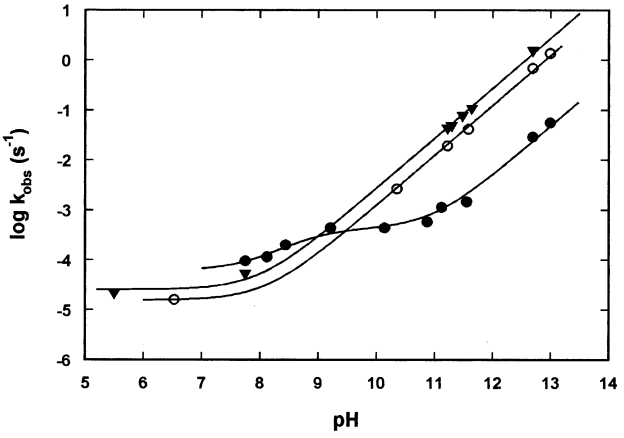
study on the alkaline hydrolysis of the title ester **1**. In this case a C−C triple bond is interposed between the aromatic carbon atom *para* to the hydroxy group and the reaction centre, thus the dissociative route should lead to the putative intermediate **IV**, characterized by a conjugated and cumulated double-bond system which, therefore, could greatly influence the mechanistic pathway.

The observed pseudo-first-order rate constants for the hydrolysis in 40% dioxane/water (v/v) solvent at 25°C and an ionic strength of 0.1 M (KCl) of 2,4-dinitrophenyl 4′-hydroxyphenylpropiolate (**1**) were found to obey Eq. 1.

$$k_{obs} = k_0 + \{(k_a + k_b\,[OH^-])/(1 + a_H/K_a)\} \quad (1)$$

In this equation a_H is the proton activity whereas K_a is the ionization constant of the hydroxy group of the ester, which was determined spectrophotometrically at 360 nm employing Tris buffer (pK_a = 8.76 ± 0.02). The values of the kinetic parameters in Eq. 1 can be calculated, knowing the K_a value, from primary kinetic data, reported in the pH/rate profile in Figure 1 (•), by iterative nonlinear curve fitting performed with the FigP program[6]. Owing to trouble due to a side reaction (see Experimental Section) we report only a rough valuation of the constant related to the spontaneous, uncatalysed hydrolysis of the substrate ($k_0 \approx 6 \times 10^{-5}$ s^{-1}). The values of the other two kinetic parameters, k_a (the pseudo-first-order rate constant in the narrow plateau region of the profile depicted in Figure 1) and k_b (the second-order term related to the bimolecular attack of hydroxide ion on the ionized ester, similar to that indicated as B in Scheme 2) are reported in Table 1 together with parameters and conditions relevant to the hydrolyses of the other esters.

Figure 1. pH/rate profiles for the hydrolysis of 2,4-dinitrophenyl 4′-hydroxyphenylpropiolate (filled circles), 4′-methoxyphenylpropiolate (open circles) and phenylpropiolate (filled triangles) in dioxane/water 40% (v/v) at 25°C and an ionic strength of 0.1 M (KCl); lines are calculated from Eqs. 1 and 2



Since $B_{Ac}2$ and E1cB mechanisms (path A and C in Scheme 2, respectively) in acyl group transfer reactions of ionizable substrates obey similar rate equations, they cannot be differentiated kinetically and therefore other mechanistic tools must be employed in order to elucidate the reaction mechanism.

One of these criteria is offered by reactivity comparisons with substrate models lacking the ionizable centre, that therefore cannot react by the E1cB mechanism. In this case, esters **2** and **3** represent suitable models. The dependence on pH of the pseudo-first-order rate constants for the hydrolyses of these esters in the same conditions above indicated for the hydrolysis of **1** are reported in Figure 1 (open circle for **2** and triangle for **3**) and were found to follow Eq. 2.

$$k_{obs} = k_0 + (k_{OH}\,K_w/a_H) \quad (2)$$

where K_w is the ionic product of water in the medium employed (pK_w = 15.00)[7], k_0 is the constant related to the spontaneous, uncatalysed hydrolysis of the substrate and k_{OH} is the second-order rate constant related to the unambiguous $B_{Ac}2$ attack of hydroxide ion on the ester. The parameters are reported in Table 1.

In order to carry out the reactivity comparison between the hydrolyses of these esters it is necessary to calculate, as it is customary, the apparent second-order rate constant for the hydrolysis of **1** ($k_{app} = k_aK_a/K_w$ = 643 M^{-1} s^{-1}). As shown by the data in Table 1 such value is only slightly higher (2 to 4 times) than the k_{OH} values determined for the esters **2** and **3**.

As stated above, the hydrolysis of 2,4-dinitrophenyl 4′-hydroxybenzoate (**4**) takes place in aqueous solution by way of an E1cB mechanism and the apparent second-order rate constant for the hydrolysis of **4** in water at 25°C is ca. 250 times higher than the second-order rate constant for the hydrolysis of the corresponding 4-methoxybenzoate (**5**)[1]. However these results come from experimental data obtained in a medium different from the present one and therefore, to eliminate any doubt, we have studied the hydrolyses of the esters **4** and **5** in the same conditions as those employed in this work.

The pH dependence of the pseudo-first-order rate constants for the hydrolysis in 40% dioxane/water (v/v) solvent at 25°C and an ionic strength of 0.1 M (KCl) of 2,4-dinitrophenyl 4′-hydroxybenzoate (**4**) and 4′-methoxybenzoate (**5**) obey Eqs. 3 and 4, respectively, and are depicted in Figure 2.

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

$$k_{obs} = k_{OH}\,K_w/a_H \quad (4)$$

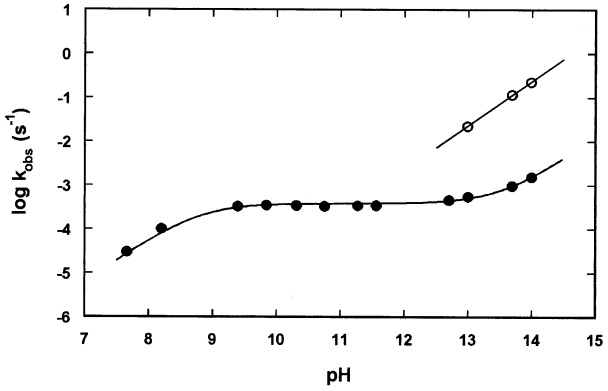
Equations 3 and 4 differ from equations 1 and 2 only because these latter contain a term related to the spontaneous hydrolysis of the substrates. The ionization constant of **4** in this medium was spectrophotometrically determined at 310 nm in Tris buffers (pK_a = 8.78 ± 0.01) allowing the determination of the kinetic parameters that are reported in Table 1. The ratio between the apparent second-order rate constant for the hydrolysis of **4** (k_{app} = 639 M^{-1} s^{-1}) and the second-order rate constant for the hydrolysis of **5** is about 280. This large kinetic advantage confirms that also in this mixed solvent the mechanism carrying the reaction flux in the hydrolysis of **4** cannot be a $B_{Ac}2$-type process, therefore pointing toward a dissociative pathway.

Table 1. Kinetic data for the hydrolysis of 2,4-dinitrophenyl esters **1**−**5** in dioxane/water 40% (v/v) at 25°C

	2,4-Dinitrophenyl	$10^5\ k_0/s^{-1}$	k_a/s^{-1}	k_b or $k_{OH}/M^{-1}\ s^{-1}$	N[a]	pH[b]
1	4′-Hydroxyphenylpropiolate	ca. 6	$(3.7 \pm 0.8) \times 10^{-4}$	4.8 ± 0.7	10	7.7−13.0
2	4′-Methoxyphenylpropiolate	1.6 ± 0.2	−	140.9 ± 0.7	6	6.5−13.0
3	Phenylpropiolate	2.5 ± 0.3	−	321.8 ± 1.9	7	5.5−12.7
4	4′-Hydroxybenzoate	−	$(3.8 \pm 0.2) \times 10^{-4}$	$(1.18 \pm 0.14) \times 10^{-2}$	12	7.7−14.0
5	4′-Methoxybenzoate	−	−	2.2 ± 0.1	3	13.0−14.0

[a] Number of data points, not including duplicates. − [b] pH range employed (see also Figures).

Figure 2. pH/rate profiles for the hydrolysis of 2,4-dinitrophenyl 4′-hydroxybenzoate (filled circles) and 4′-methoxybenzoate (open circles) in dioxane/water 40% (v/v) at 25°C and an ionic strength of 0.1 M (KCl); lines are calculated from Eqs. 3 and 4



On the contrary, the ratio between the values of k_{app} for **1** and k_{OH} for **2** is not so large ($k_{app}/k_{OH} = 4.5$).

A rough estimate of the second-order rate constant for the associative attack of hydroxide ion onto the neutral form of **1** can be calculated from a *two-point* Hammett relationship based on the k_{OH} values for the reactions of esters **2** and **3** and the ordinary σ substituents constants. This value (ca. 105 $M^{-1}\ s^{-1}$) is about six times *lower* than k_{app}, thus indicating that the hydrolysis of **1** shows an enhanced reactivity with respect to that expected on the basis of a regular $B_{Ac}2$ process.

In this connection, it is noteworthy to stress that, as shown in Table 1, the second-order rate constant for the hydrolysis of **2** is more than 60 times larger than that of compound **5**. Since these esters share the same leaving group, the higher reactivity of **2** is most likely due to the strong electron-withdrawing effect of the triple bond α to the carbonyl group, which strongly favours the associative attack of hydroxide ion on the carbonyl carbon atom. Therefore, it is reasonable to suppose that the ratio between the values of k_{app} for **1** and k_{OH} for **2** is not so high as it could be otherwise expected simply because k_{OH} is high. In other words, it is possible that the hydrolysis of **1** follows a dissociative mechanism and that the kinetic advantage of the E1cB mechanism over the $B_{Ac}2$ one is not so large as previously observed since the associative path is largely facilitated by the electronic effect of the triple bond.

Arrhenius parameters have been used[1][2][3][8] to distinguish E1cB from $B_{Ac}2$ mechanism since the bimolecular process should show a considerably more negative entropy of activation than the E1cB process, in which the rate-determining step is unimolecular. The activation parameters for the hydrolysis of esters **1** and **2** are reported in Table 2. The large, negative value of $\Delta S^{\neq}$ for the hydrolysis of **2** is well within the range expected for an associative process[9] whereas the small value of the entropy of activation for the k_a term, related to the hydrolysis of **1**, seems to suggest the incursion of a dissociative pathway.

We have previously found that in the hydrolyses of similar systems[1][2][3] a change in mechanism from associative to dissociative, revealed by an upward break in Brønsted-type plots, occurs when the nucleofugality of the leaving group increases, and therefore associative and dissociative reaction paths may well coexist in the hydrolysis of an ester having a leaving group of appropriate pK_a. Now, if one admits that in the alkaline hydrolysis of aryl 4-hydroxyphenylpropiolates the mechanistic changeover point could fall close to the pK_a of the 2,4-dinitrophenol (4.11), the present kinetic results could be rationalized in terms of coexistence of mechanisms. In the hydrolyses of related systems[1][2][3] the break in mechanism occurs at about $pK_a = 6.0-6.5$; in the present case the shift of the (hypothetical) break-point towards lower pK_a values could be due to the fact that the triple bond greatly favours the associative pathway.

The occurrence of a change in mechanism could be verified by a kinetic study on the effect of leaving-group variation on reactivity for a series of aryl esters of 4-hydroxyphenylpropiolic acid. However, the difficulty of the synthesis of these esters and the interference of the side reaction described in the Experimental Section are not encouraging. Furthermore, substituted phenols having pK_a

Table 2. Activation parameters for the hydrolysis of 2,4-dinitrophenyl esters in dioxane/water 40% (v/v), $\mu = 0.1$

	2,4-Dinitrophenyl	Temp. range/°C	pH	$\Delta H^{\neq}$/kcal mol^{-1}	$\Delta S^{\neq}$/cal $mol^{-1}\ K^{-1}$[a]
1	4′-Hydroxyphenylpropiolate	25−44.5	10.25	20.6 ± 0.4	-4.3 ± 1.4
2	4′-Methoxyphenylpropiolate	17−34.5	12.69	9.7 ± 0.2	-26.5 ± 0.7

[a] Calculated at 25°C.

values lower than that of 2,4-dinitrophenol, whose esters should hydrolyse by the E1cB mechanism, are few and hardly available.

Resort to stronger leaving groups such as chloride was tried but several attempts to prepare 4-hydroxyphenylpropynoyl chloride following the procedure reported in ref.[10] for other arylpropiolic acid chlorides failed.

In conclusion, the results of this study do not allow us to assess unequivocally whether the reaction proceeds by an $B_{Ac}2$ or an E1cB mechanism but they strongly suggest the participation of a dissociative pathway.

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Experimental Section

General: Commercial 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 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. − UV/Vis: Kontron Uvikon 941. − ^{1}H NMR: Varian Gemini 200 (200 MHz); $CDCl_3$ and [D_6]acetone as solvents, TMS as internal standard.

Synthesis of the Substrates: Several methods are available for the preparation of substituted phenylpropiolic acids and esters, but our efforts to obtain 4-hydroxyphenylpropiolic acid by the classical[11] dehydrobromination of dibromocinnamic acids or by a more recent one-step procedure[12] employing 4-hydroxybenzaldehyde as starting material failed. On the contrary, this latter method was successfully employed to obtain 4-methoxyphenylpropiolic acid (starting from 4-methoxybenzaldehyde), which was subsequently condensed with 2,4-dinitrophenol by means of dicyclohexylcarbodiimide to furnish the model ester 2′,4′-dinitrophenyl 4-methoxyphenylpropiolate (**2**). This condensation was also employed to prepare another substrate model, 2,4-dinitrophenyl phenylpropiolate (**3**), starting from phenylpropiolic acid.

The synthesis of ester **1** was accomplished through the following procedure. In the first step, a palladium-catalysed ethynylation[13], 4-iodophenol was treated with trimethylsilylacetylene in the presence of catalytic amounts of bis(triphenylphosphane)palladium dichloride and copper(I) iodide in triethylamine to give, after alkaline removal of the terminal silyl group[13], 4-hydroxyphenylacetylene. This ethynylarene, obtained in almost quantitative yield, although extremely unstable even if stored in a refrigerator, was converted into 4-hydroxyphenylpropiolic acid (yield ca. 60%) by reaction with *n*-butyllithium and carbon dioxide[14]. The acid was condensed with 2,4-dinitrophenol employing dicyclohexylcarbodiimide. In this case, however, owing to the formation of several by-products, the yield was very low and the purification of the ester required column chromatography on silica gel and repeated recrystallizations.

The esters were stored in a refrigerator and protected from moisture to avoid decomposition.

4-Hydroxyphenylpropiolic Acid: M.p. 115−116°C (from toluene). − ^{1}H NMR ([D_6]acetone): δ_H = 7.50 (d, 2 H, J = 8.0 Hz), 6.92 (d, 2 H, J = 8.0 Hz). − $C_9H_6O_3$: calcd. C 66.7, H 3.7; found C 65.7, H 3.7.

2,4-Dinitrophenyl 4′-Hydroxyphenylpropiolate (**1**): M.p. 109−110°C (from toluene). − ^{1}H NMR ([D_6]acetone): δ_H = 8.99 (d, 1 H, J = 2.7 Hz), 8.75 (m, 1 H), 7.95 (dd, 1 H), 7.65 (d, 2 H, J = 8.8 Hz), 6.98 (d, 2 H, J = 8.8 Hz). − $C_{15}H_8N_2O_7$: calcd. C 54.9, H 2.5, N 8.5; found C 55.4, H 2.5, N 8.2.

2,4-Dinitrophenyl 4′-Methoxyphenylpropiolate (**2**): M.p. 124−125°C (dec., from toluene). − ^{1}H NMR ($CDCl_3$): δ_H = 8.99 (d, 1 H, J = 1.5 Hz), 8.55 (m, 1 H), 7.62 (m, 3 H), 6.95 (d, 2 H, J = 9.0 Hz), 3.89 (s, 3 H, CH_3). − $C_{16}H_{10}N_2O_7$: calcd. C 56.1, H 2.9, N 8.2; found C 56.2, H 3.0, N 8.3.

2,4-Dinitrophenyl Phenylpropiolate (**3**): M.p. 93−94°C (from ethanol). − ^{1}H NMR ($CDCl_3$): δ_H = 9.00 (d, 1 H, J = 2.5 Hz), 8.58 (m, 1 H), 7.55 (m, 6 H). − $C_{15}H_8N_2O_6$: calcd. C 57.7, H 2.6, N 8.9; found C 58.4, H 2.6, N 8.5.

The characteristics of 2,4-dinitrophenyl 4′-hydroxybenzoate (**4**) and 4′-methoxybenzoate (**5**) have been previously reported[1].

Rate Measurements: The hydrolyses of the esters **1**−**5** in 40% (v/v) dioxane/water solvent were followed spectrophotometrically by monitoring at 400 nm the release of 2,4-dinitrophenol (in the case of ester **1**, since its conjugate form strongly absorbs at 400 nm, the kinetic runs at pH higher than ca. 10 were followed by monitoring the disappearance of the substrate itself at 360 nm). 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 the spectrophotometer. The reaction was initiated by adding 10 µl of a stock solution of the substrate ca. 0.01 M in dioxane, (prepared immediately prior to use for ester **1**, see below) 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 citrate, malonate, 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 versus time data and the values reported are the averages of at least duplicate runs. Reactions were normally followed over about seven half-lives. Unfortunately, the kinetics of the hydrolysis of compound **1** at pH values lower than ca. 10.5 were complicated by a side reaction, which was apparent only near the end of the hydrolysis reaction, i.e. after three to four half-lives, and resulted in small deviation from the exponential course in the final zone of the absorbance-versus-time plots. Such (slight) deviations seemed to increase as the pH of the solution decreased. At pH values higher than 10.5 and employing stock solutions prepared immediately prior to use no deviations were detected when the reactions were followed up to ca. 98% of the total and excellent kinetic plots were obtained in all cases. Interestingly, it was noted that also kinetic runs carried out at high pH employing stock solutions, prepared one or two days before, exhibited the aforesaid anomalous course. However, the rate constants so obtained did not differ from those determined from runs performed at the same pH values but employing freshly prepared stock solution of compound **1**. This observation gave us confidence in the kinetic data obtained in the entire pH range spanned. Such behaviour was observed also when the stock solu-

tions were prepared in other organic solvents like acetonitrile, acetone, chloroform.

Product Analysis: TLC analysis, UV/Vis and ^{1}H-NMR spectroscopy were employed to ascertain that 2,4-dinitrophenol and the arylpropiolic acid were the sole products of hydrolysis of the esters. Repetitive scans of the UV/Vis spectra during hydrolyses of ester **1** at high pH values showed three good isosbestic points and the final spectra exactly matched the mock infinity one. At pH lower than about 10.5 only one isosbestic point was maintained (at 340 nm) and the others (at lower wavelengths) showed small variations. Moreover, the final spectra were a little different (a few percent) from the mock spectrum in the 250−300-nm region where 4-hydroxyphenylpropiolic acid shows its maximum absorbance. Taking into account that the acid (alone or in the presence of 2,4-dinitrophenol) is quite stable under the reaction conditions these observations confirm the occurrence of a side reaction as revealed by the kinetics. We have not further investigated this side reaction but, as it appears that it can be ascribed to the contemporary presence of the hydroxy group and of the triple bond, and since ^{1}H-NMR spectra of old stock solutions of **1** showed large degradation (not only hydrolysis) of the ester, we could suppose that a nucleophilic attack of the hydroxy group to the C-β atom of the triple bond takes place leading to a vinyl ether which subsequently hydrolyses giving rise to total liberation of 2,4-dinitrophenol. Similar nucleophilic additions to activated acetylenic compounds have been reported in the literature[15]. Such a reaction does not occur on 4-hydroxyphenylpropiolic acid since in the pH range explored it is fully ionized and the negative charge diminishes the electrophilicity of the triple bond[16].

Ionization Constants: The determination of the pK_a of the substrates was previously described[2].

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