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A New, "Elongated" Oxo Ketene Intermediate in the Dissociative Hydrolysis of 2,4-Dinitrophenyl (2*E*,4*E*)-5-(4′-Hydroxyphenyl)pentadienoate

Giorgio Cevasco,* Daniele Vigo, and Sergio Thea*

CNR, Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici, Dipartimento di Chimica e Chimica Industriale, Via Dodecaneso, 31, 16146 Genova, Italy

giocev@chimica.unige.it

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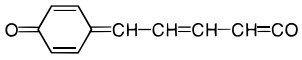
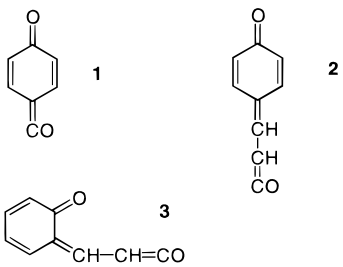
ABSTRACT



Reactivity comparison, Arrhenius parameters, and trapping of the above-depicted unsaturated intermediate strongly suggest that the alkaline hydrolysis of the title ester follows a mechanism of the E1cB type. This is the first observation of the occurrence of a dissociative route in the hydrolysis of an acyl derivative with three π-systems interposed between the hydroxyl group (the internal nucleophile upon ionization) and the reaction center. Comparison with the hydrolysis of 2,4-dinitrophenyl 4′-hydroxybenzoate shows that interposition of the vinylenic groups is beneficial to the dissociative route.

We are interested in the factors governing the competition among different mechanisms in acyl transfer processes, in particular, dissociative (E1cB) and associative ($B_{Ac}2$) pathways. We have previously found[1] that the alkaline hydrolyses of aryl 4-hydroxybenzoates having leaving groups with a pK_a lower than about 6.5 do not follow the usual associative pathway but proceed via an E1cB mechanism with the participation of an unprecedented *p*-oxo ketene intermediate (**1**).



Subsequently, we have demonstrated that the hydrolyses of aryl 4-hydroxycinnamates[2] and 2-hydroxycinnamates[3] behave almost in the same way with the participation, in their dissociative paths, of the "extended" oxo ketene intermediates **2** and **3**, respectively.

In these acyl derivatives the internal nucleophile, the ionized hydroxyl group, is conjugated with the reaction center through an interposed bridge, a single π-system, the aromatic ring in hydroxybenzoates, or two π-systems linked by a single bond in the case of hydroxycinnamates. Our studies indicate that the interposition of an extra vinylene group between the internal nucleophile and the carbonyl carbon favors the dissociative mechanism. As suggested, the kinetic advantage could be ascribed to a gain in stability of the "extended" intermediates, most likely due to increased delocalization of π electrons.

To get a better knowledge of the role played by the nature of the interposed bridge on the hydrolytic mechanism, we have recently undertaken a kinetic study[4] on the alkaline hydrolysis of the 2,4-dinitrophenyl ester **4**, and we have

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(2) Cevasco, G.; Thea, S. *J. Org. Chem.* **1994**, *59*, 6274−6278.
(3) Cevasco, G.; Thea, S. *J. Org. Chem.* **1995**, *60*, 70−73.
(4) Cevasco, G.; Thea, S. *J. Org. Chem.* **1999**, *64*, 5422−5426.

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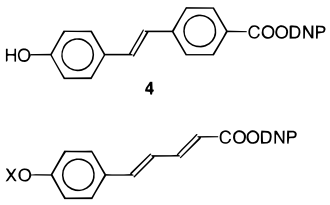
found that this species, provided with three π-conjugated systems in the bridge, hydrolyzes through the usual associative pathway. This finding has been tentatively rationalized by taking into account that two *p*-phenylene units are present in the bridge of **4** and, therefore, the loss of aromaticity involved in reaching the rate-determining transition state of the E1cB path could be large enough to make this route unfavorable.



5: X = H; **6**: X= Me

We now report the preliminary results of a study on the hydrolysis of ester **5**, which has a single *p*-phenylene unit and two vinylenic groups in its π-bridge, together with those concerning the methoxy derivative **6**. This latter, being devoid of acidic hydrogen, can react only via the associative route.

Esters **5** and **6** were prepared from the corresponding acid and 2,4-dinitrophenol.[5] The acids were obtained through a Wittig-type reaction[6] starting from ethyl 4-bromocrotonate and the appropriate aldehyde.

Molecular mechanics calculations[7] indicate that ester **5** is nearly planar only if it has (*E*,*E*) stereochemistry: π-system planarity is a prerequisite to allow the conjugative interaction between the hydroxyl group and the carbonyl carbon atom and therefore the feasibility of the dissociative path.

The hydrolyses of esters **5** and **6** 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, as previously described.[4] The progress of the reactions was followed by monitoring the change of absorbance due to disappearance of the substrate or liberation of products. The products of the reactions in alkaline solution were identified as the anions of 2,4-dinitrophenol 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.

The pH dependence of the pseudo-first-order rate constants for the hydrolyses of esters **5** and **6** obeys eqs 1 and 2, respectively, and is depicted in Figure 1.

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

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

In eq 1 (and eq 2 as well), a_H is the proton activity, K_a is the ionization constant of the hydroxyl group of the ester, k_a is the pseudo-first-order rate constant in the plateau region of the pH−rate profile, and k_b is the second-order term related to the bimolecular attack of hydroxide ion on the ionized ester. K_a was spectrophotometrically determined in separate experiment as $(1.27 \pm 0.10) \times 10^{-10}$ M, and from this value, the kinetic constants can be calculated from primary kinetic data by iterative nonlinear curve fitting performed with the Fig.P program.[8] The following values, $k_a = (1.14 \pm 0.04) \times 10^{-2}$ s^{-1} and $k_b = 0.53 \pm 0.04$ M^{-1}s^{-1}, were obtained. In eq 2 K_w is the ionic product of water in the employed medium (pK_w = 15.00 at 25 °C)[9] and a value of 3.9 ± 0.1 M^{-1} s^{-1} was obtained for k_{OH}, the second-order rate constant related to the unambiguous $B_{Ac}2$ attack of hydroxide ion on the substrate, from k_{obs} values.

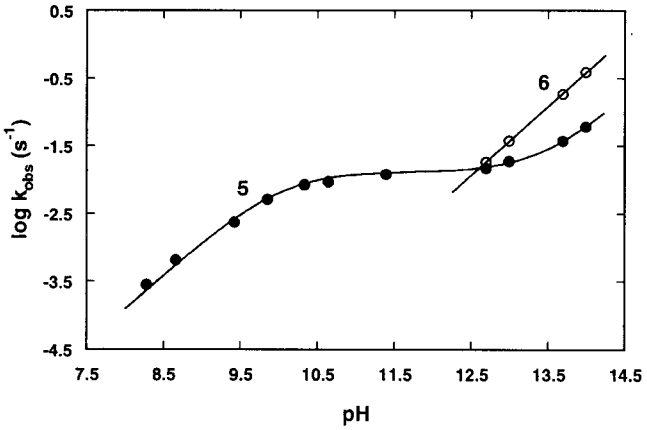


Figure 1. pH−rate profiles for the hydrolysis of 2,4-dinitrophenyl esters **5** (solid circles) and **6** (open circles) in 40% dioxane buffers at 25 °C and ionic strength 0.1 M (KCl). Lines are calculated from eqs 1 and 2.

The apparent second-order rate constant for the hydrolysis of the hydroxy ester **5** was calculated, as it is customary, by way of eq 3:

$$k_{app} = k_aK_a/K_w \quad (3)$$

The value of k_{app} (ca. 1420 M^{-1} s^{-1}) is considerably *larger* (about 350-fold) rather than *smaller*, as expected from substituent effects, than the second-order rate constant related to the $B_{Ac}2$ attack of hydroxide ion on **6**. This large kinetic advantage suggests that the mechanism carrying the reaction flux in the hydrolysis of **5** cannot be a $B_{Ac}2$-type process, and the simplest hypothesis is that an E1cB path is followed. In this process the conjugate base of **5** eliminates unimolecularly the leaving group in the rate-determining step, affording the "extra-extended" oxo ketene intermediate depicted in the abstract, which rapidly adds water to furnish the final product.

Such a proposal is corroborated by the effect of temperature on reaction rates. Activation parameters for ester

(5) Esters **5** and **6** and the amide gave satisfactory elemental and spectroscopic analyses.

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

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

(9) Arned, H. S.; Fallon, L. *J. Am Chem. Soc.* **1931**, *61*, 2374−2378.

hydrolyses are reported in Table 1; activation entropy has been frequently used to distinguish E1cB from $B_{Ac}2$ mechanisms.[10]

Table 1. Activation Parameters for the Hydrolysis of 2,4-Dinitrophenyl Esters in 5×10^{-3} M KOH, 40% Dioxane/Water, $\mu = 0.1$ M[a]

	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$,[b] cal/mol K
5	23.1 ± 0.1	10.4 ± 0.4
6	12.8 ± 0.4	-23.8 ± 1.4

[a] Temperature range: 16.5−40.6 °C. [b] Calculated at 25 °C.

As it is shown in the table, the activation entropy for the hydrolysis of the 5-(4′-hydroxyphenyl)pentadienoate **5** is large and positive as expected for a unimolecular reaction, whereas the negative value for the methoxy derivative **6** is consistent with an associative process.

Further evidence for the dissociative nature of the mechanism of hydrolysis of ester **5** is offered by trapping experiments carried out in the presence of a nitrogen nucleophile. Variable amounts of *p*-toluidine in carbonate buffer at pH ca. 11.4 have no effect on reaction rate but at 0.03 M *p*-toluidine about 30% of *N*-(*p*-tolyl)-5-(4′-hydroxyphenyl)penta-2(*E*),4(*E*)-dienamide (identified by comparison with an authentic sample)[5] was found in the hydrolysis products. This result is consistent with amine attack on the unsaturated intermediate *after* leaving group departure in the rate-determining step.

The k_a value of **5** is about 30-fold larger than that of the corresponding 4-hydroxybenzoate (3.4×10^{-4} s^{-1} in 40% dioxane at 25 °C),[11] thus indicating that the presence of additional vinylene groups favors the hydrolytic process occurring via the dissociative path. This conclusion holds also if the difference in acidity (in other words, the difference in internal nucleophilicity) between these two esters is taken into account simply by employing the same procedure previously described in the case of 2,4-dinitrophenyl 4′-hydroxycinnamate.[2]

In conclusion, we have provided, for the first time, strong evidence that the E1cB mechanism occurs in the alkaline hydrolysis of acyl derivatives having three conjugated π-systems interposed between the internal nucleophile and the reaction center. This outcome sheds more light on the role played by the stability of the reaction intermediate in our systems, giving support to rationalization previously advanced by us for compound **4**.

Supporting Information Available: Elemental analyses and some ^{1}H NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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