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An Unprecedented Concerted Pathway in the Alkaline Hydrolysis of S-Aryl Thioesters

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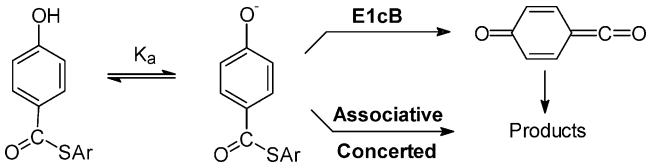


Kinetic data indicate that the hydrolysis of *S*-2,4-dinitrophenyl 4′-hydroxythiobenzoate in mild alkaline solutions (pH 8−11) most likely follows a dissociative, E1cB pathway, through a *p*-oxoketene intermediate, whereas at higher pH values an associative mechanism carries the reaction flux. Free linear energy relationships obtained from a kinetic study on the alkaline hydrolyses of substituted S-aryl 4′-hydroxythiobenzoates seem to suggest that the associative pathway is a concerted, one-step process, rather than the classical mechanism via a tetrahedral intermediate.

The reactions of thiocarbonyl derivatives with nucleophiles are of enormous interest not only in chemistry but also in biochemistry, since they take place in several biological processes.

Although the kinetics and mechanism of the reactions of nucleophiles with esters and other carbonyl derivatives are well documented,[1] the same reactions with thiocarbonyl derivatives have not received similar attention, and only recently Castro[2] covered this topic in an excellent review.

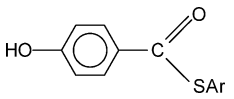
Most of the research on thiol esters has followed the discovery that acylated coenzyme A is a thiol ester,[3] and the hydrolysis of alkyl and aryl thioacetates (and thioalkanoates) in aqueous solution has been the subject of kinetic studies.[4] However, to the best of our knowledge, only two papers (one in Cyrillic characters) report scanty data on the alkaline hydrolysis of aryl thiobenzoates.[5]

We have long been interested in the alkaline hydrolysis of active aryl esters of 4-hydroxybenzoic acid, and we have provided convincing evidence that the reaction occurs via a dissociative pathway, the E1cB mechanism, through a *p*-oxoketene intermediate.[6] This finding prompted us to investigate the hydrolysis of S-aryl 4-hydroxythiobenzoates, aiming at verifying if also these thioesters can hydrolyze through dissociative pathways. Thioesters, indeed, are commonly believed to possess good leaving groups (arenethiols are more acidic than the corresponding phenols), and thus, this mechanistic hypothesis appears reasonable.

Moreover, the incursion of dissociative mechanisms in acyl group transfer processes was shown by Douglas[4c] in the basic hydrolysis of *S*-acetoacetyl-coenzyme A.

Added interest for such an investigation came from the fact that the reaction under scrutiny represents a simple model of the last step of microbial degradation of chlorinated aromatic compounds, a group of the most serious environmental pollutants, carried out by some soil-dwelling microorganisms. In particular, *Pseudomonas* sp. strain CBS-3 is able to convert 4-chlorobenzoate (well-known as a byproduct in the microbial breakdown of aromatic pollutants) into 4-hydroxybenzoyl-CoA thioester,[7] and the final step of this biochemical pathway is indeed the hydrolysis of such a thioester catalyzed by 4-hydroxybenzoyl-CoA thioesterase. It is interesting to note that the determination of the three-dimensional structure of this enzyme rules out the possibility of a chemical pathway involving the formation of a hydroxybenzoyl−enzyme intermediate, and a mechanism in which a carboxylate residue activates a water molecule for subsequent nucleophilic attack at the thioester carbonyl carbon has been proposed.[7a]

In this paper we report the results of a kinetic study on the alkaline hydrolyses of some S-aryl 4-hydroxythiobenzoates (**I**−**VI**; identities are given in the caption of Figure 2).



The pH dependences of the pseudo-first-order rate constants for the hydrolyses, in 40% dioxane/water (v/v) at 25 °C and ionic strength held constant (0.1 M) with added KCl, of *S*-2,4-dinitrophenyl 4′-hydroxythiobenzoate (**I**) and 4′-methoxythiobenzoate (**VII**) obey eqs 1 and 2, respectively, and are depicted in Figure 1 , where a_H is

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

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

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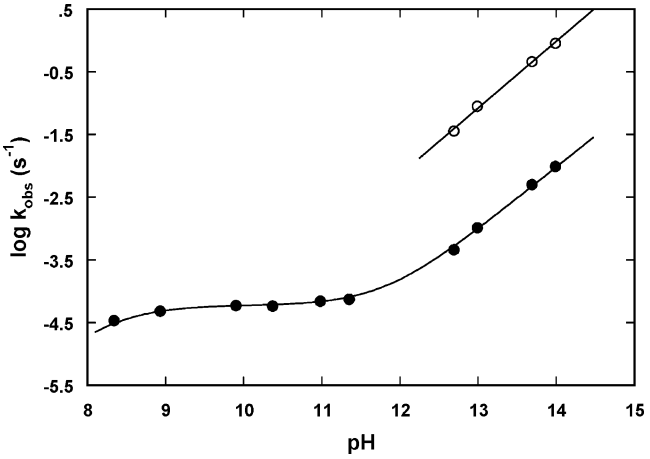


FIGURE 1. pH−rate profiles for the hydrolysis of 2,4-dinitrophenyl esters **I** (solid circles) and **VII** (open circles) in 40% dioxane buffers at 25 °C and ionic strength 0.1 M (KCl). Lines are calculated from eqs 1 and 2.

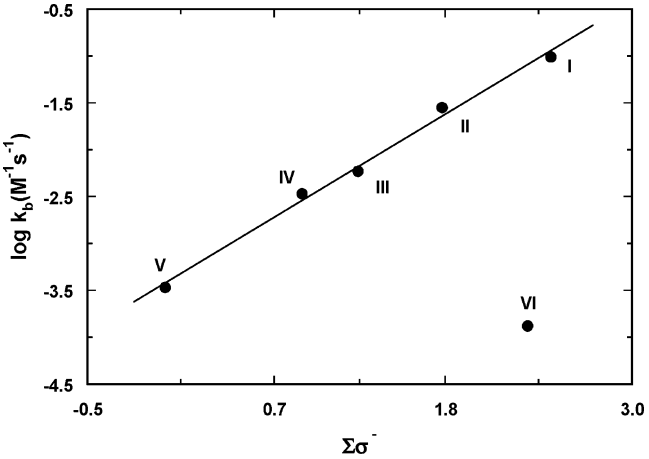


FIGURE 2. Hammett plot for the alkaline hydrolysis of S-aryl 4′-hydroxybenzoates. The line is calculated from eq 3. Legend: **I**, 2,4-dinitrophenyl; **II**, 2-nitro-4-(trifluoromethyl)phenyl; **III**, 4-nitrophenyl; **IV**, 4-cyanophenyl; **V**, phenyl; **VI**, pentachlorophenyl.

the proton activity, K_a is the ionization constant of the hydroxyl group of the ester **I**, 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 **I**. K_a was determined spectrophotometrically in a separate experiment as $(4.7 \pm 0.2) \times 10^{-9}$ M, and from this value, the kinetic constants can be calculated from primary kinetic data by iterative nonlinear curve fitting. The values $k_a = (5.9 \pm 0.2) \times 10^{-5}$ s^{-1} and $k_b = (9.3 \pm 0.4) \times 10^{-2}$ M^{-1} s^{-1} were obtained for hydrolysis of **I**. In eq 2 K_w is the ionic product of water in the employed medium (a value of 15.5 was assessed for the pK_w value at 25 °C of this dioxane/water mixture),[8] and a value of 10.2 ± 0.3 M^{-1} s^{-1} was obtained for k_{OH}, the second-order rate constant related to the unambiguous $B_{Ac}2$-type attack of hydroxide ion on substrate **VII**, from k_{obs} values.

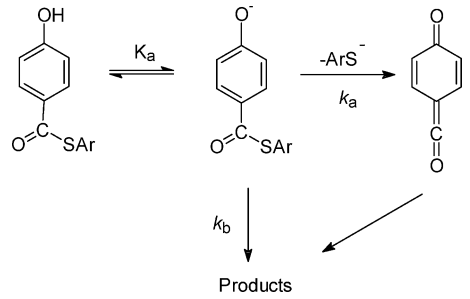
As it is customary, the apparent second-order rate constant for the hydrolysis of the hydroxy ester **I** was calculated by means of eq 3.

$$k_{app} = k_a K_a / K_w \qquad (3)$$

The value of k_{app} (ca. 877 M^{-1} s^{-1}) is considerably *larger* (about 90-fold) rather than *smaller*, as expected from substituent effects (σ_p values for OH and OMe are −0.37 and −0.27, respectively), than the second-order rate constant related to the $B_{Ac}2$ attack of hydroxide ion on **VII**. This large kinetic advantage suggests that the mechanism carrying the reaction flux in the hydrolysis of **I** cannot be a $B_{Ac}2$-type process, and the simplest hypothesis is that an E1cB path is followed, with the participation of the *p*-oxoketene intermediate, shown in Scheme 1, which we have already observed in the case of aryl 4-hydroxybenzoates.[6]

Such a mechanistic proposal is supported by the effect of temperature on reaction rates. Activation parameters for ester hydrolyses were determined in the temperature range 18−48 °C: activation entropy (calculated at 25 °C) for ester **I** was $+18.62 \pm 1.68$ eu (in the plateau region), whereas for **VII** it was -27.35 ± 0.19 eu (1 eu = 4.184 J $K^{-1}mol^{-1}$). Such a negative value is consistent with an associative process, and the large positive value found for the hydroxy ester suggests that a unimolecular reaction occurs. Indeed, activation entropy has been frequently used to distinguish E1cB from $B_{Ac}2$ mechanisms.[9]

SCHEME 1



The effect of the leaving group variation was also examined: for this purpose more S-aryl 4-hydroxythiobenzoates (**II**−**VI**) were prepared and their hydrolyses were investigated. Unfortunately, the reactivities of these esters are very low; therefore, the kinetics were carried out only in the pH range 11−14. In this region k_b, the bimolecular attack of hydroxide ion on the ionized ester, predominates and therefore the k_a value, and thus k_{app}, is not experimentally accessible.

Figure 2 shows the Hammett plot of log k_b against σ^- values. From this figure, it appears that the point corresponding to the pentachlorophenyl ester **VI** largely deviates from the linear relationship:

$$\log k_b = (-3.42 \pm 0.07) + (1.00 \pm 0.05)\sigma^- \qquad (4)$$

This is rather surprising, since in our previous studies on the hydrolysis of oxygenated esters we often employed

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TABLE 1. Rate Constants for the Alkaline Hydrolyses of S-Aryl 4-Hydroxythiobenzoates[a]

substrate[b]	k_b, M^{-1} s^{-1}	pK_{LG} [g]	pH[c]	n[d]
I	$(9.82 \pm 0.05) \times 10^{-2}$	3.40	9.90−13.99	4
II	$(2.84 \pm 0.02) \times 10^{-2}$	4.32[e]	10.76−13.99	5
III	$(5.90 \pm 0.10) \times 10^{-3}$	4.61	12.69−13.99	3
IV	$(3.36 \pm 0.02) \times 10^{-3}$	4.96[e]	12.69−13.99	4
V	$(3.39 \pm 0.05) \times 10^{-4}$	6.52	12.69−13.99	3
VI	$(1.20 \pm 0.01) \times 10^{-4}$	2.27[f]	13.87−14.39	3

[a] Conditions: 40% dioxane/60% water, $\mu = 0.1$ M, $T = 25$ °C. [b] See caption to Figure 2 for identification of substrates. [c] pH range experimentally spanned. [d] Number of data points, not including duplicates. [e] This work. [f] Estimated from the relationship between known pK values of 18 phenols and thiophenols in water at 25 °C: $pK_{ArOH} = (2.11 \pm 0.17) + (1.18 \pm 0.03)pK_{ArSH}$, employing the value of 4.79 for pentachlorophenol (Cevasco, G.; Thea, S. *J. Org. Chem*. **1998**, *63*, 2125). [g] Literature values (**I**: Castro, E. A.; Ureta, C. *J. Chem. Soc. Perkin Trans. 2* **1991**, 63; **III**, **V**: Castro, E. A.; Ureta, C. *J. Org. Chem.* **1989**, *54*, 2153), unless otherwise stated.

pentachlorophenol as the leaving group and no anomalous behavior was observed in any instance.

Equation 4 relates kinetic data with σ^- rather than σ values, and this suggests that in the transition state of the rate-determining step the negative charge on sulfur atom is largely developed and, thus, the bond between the carbon and sulfur atoms should be considerably loosened.[10]

Also in the Brønsted plot (not shown here, data being reported in Table 1) the point related to ester **VI** largely deviates from the linear correlation, whereas the other thioesters obey the relationship

$$\log k_b = (1.69 \pm 0.46) - (0.81 \pm 0.09)pK_{LG} \quad (5)$$

This β_{LG} value (−0.81) is surprisingly large for an associative, $B_{Ac}2$, process: for this pathway values ranging from −0.1 to −0.3 are indeed usually found.[4d,11]

We have previously reported[12] a β_{LG} value of −0.20 for the corresponding reaction of hydrolysis of aryl 4-hydroxybenzoates. In terms of effective charge, since the overall change in the acyl transfer process is −1.7 (β_{EQ}),[13] it is possible to show that when the leaving oxygen goes from the reagent to transition state, the effective charge changes from 0.7 to 0.5 (0.7−0.2). This small change suggests that in the transition state the fission of the bond between the carbonyl carbon atom and the leaving oxygen is not advanced, as expected for an associative pathway. The small value (0.12) of the Leffler index[13] supports the $B_{Ac}2$ process with rate-determining formation of the tetrahedral intermediate as well.

In the present case, if the value of −1.4 reported[14] for β_{EQ} (for the overall change) is employed, the effective charge on the leaving sulfur on going from reagent to transition state changes from 0.4 to −0.4 (0.4−0.8), thus indicating a large increase of the negative charge on the sulfur. The value of the Leffler index is now ca. 0.6. These results strongly indicate that in the transition state the bond breaking is well advanced, as should occur in a $B_{Ac}2$-type process with rate-determining breakdown of the tetrahedral intermediate or in a one-step, concerted mechanism.

However, the very large difference in leaving group ability between OH^- and ArS^- nucleofuges does not support a preferential expulsion of arenethiolate ion from the tetrahedral intermediate, thus making the occurrence of a stepwise, associative process unreliable.

It is therefore reasonable to propose that the alkaline hydrolysis (at high pH values) of these S-aryl 4-hydroxythiobenzoates follows a concerted pathway rather than the classical associative pathway, with the participation of the tetrahedral intermediate.

Present results add support to recent work, both theoretical and experimental, indicating that the incursion of concerted mechanisms in acyl group transfer processes is larger than is usually believed.[15]

Experimental Section

Starting reagents and solvents were purified and/or distilled before use. Buffer materials were of analytical regent 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.

4-Cyanothiophenol was prepared from 4-aminobenzonitrile through the ethyl xanthate, affording a product with mp 51−52 °C (lit[16] mp 50−51 °C).

Esters **I**−**VI** were prepared, following a procedure already employed,[17] from the protected (silylated) acid chloride and the appropriate thiophenol. *S*-2,4-Dinitrophenyl 4′-methoxythiobenzoate (**VII**) was obtained from 4-methoxybenzoic acid and 2,4-dinitrothiophenol in the presence of DCC. The reaction products of the hydrolyses were checked by UV−vis spectra by comparison with authentic samples. Hydrolyses of esters were carried out in 40% dioxane/60% water (v/v) at 25 °C and the ionic strength held constant (0.1 M) with added KCl. Kinetic runs and the determinations of ionization constants of ester **I**, 4-cyanothiophenol, and 2-nitro-4-(trifluoromethyl)thiophenol were carried out as previously described.[6,17] The exceedingly low solubility in water of pentachlorothiophenol prevents the determination of a reliable pK_a value.

Spectra were recorded at 200 MHz in acetone-d_6 (unless otherwise stated) with TMS as internal standard; compounds were recrystallized from toluene (unless otherwise stated).

***S*-2,4-Dinitrophenyl 4′-Hydroxythiobenzoate (I):** mp 167−169 °C; ^{1}H NMR δ 9.67 (bs, 1), 8.91 (d, 1, $J = 2.2$ Hz), 8.63 (dd, 1, $J = 8.6$; 2.2 Hz), 8.18 (d, 1, $J = 8.8$ Hz), 7.97 (d, 2, $J = 8.8$ Hz), 7.05 (d, 2, $J = 8.8$ Hz). Anal. Calcd for $C_{13}H_8N_2O_6S$: C, 48.8; H, 2.5; N, 8.7. Found: C, 49.2; H, 2.6; N, 8.6.

***S*-2-Nitro-4-(trifluoromethyl)phenyl 4′-Hydroxythiobenzoate (II):** mp 155−157 °C; ^{1}H NMR δ ($CDCl_3$) 8.29 (s, 1), 7.96 (d, 2, $J = 9.2$ Hz), 7.92 (m, 2), 6.92 (d, 2, $J = 9.2$ Hz), 5.65 (bs, 1). Anal. Calcd for $C_{14}H_8F_3NO_4S$: C, 49.0; H, 2.4; N, 4.1. Found: C, 49.2; H, 2.5; N, 4.0.

***S*-4-Nitrophenyl 4′-Hydroxythiobenzoate (III):** mp 160−161 °C; ^{1}H NMR δ 9.55 (bs, 1), 8.35 (d, 2, $J = 9.2$ Hz), 7.97 (d,

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2, J = 8.8 Hz), 7.84 (d, 2, J = 9.2 Hz), 7.03 (d, 2, J = 9.0 Hz). Anal. Calcd for $C_{13}H_9NO_4S$: C, 56.7; H, 3.3; N, 5.1. Found: C, 56.8; H, 3.3; N, 5.0.

***S*-4-Cyanophenyl 4′-Hydroxythiobenzoate (IV):** mp 179−180 °C; ^{1}H NMR δ 9.55 (bs, 1), 7.96 (d, 2, J = 8.8 Hz), 7.91 (d, 2, J = 8.8 Hz), 7.76 (d, 2, J = 8.8 Hz), 7.03 (d, 2, J = 9.2 Hz). Anal. Calcd for $C_{14}H_9NO_2S$: C, 65.9; H, 3.6; N, 5.5. Found: C, 65.8; H, 3.5; N, 5.6.

***S*-Phenyl 4′-Hydroxythiobenzoate (V):** mp 172−173 °C (lit[18] mp 170−171 °C); ^{1}H NMR δ 9.45 (bs, 1), 7.95 (d, 2, J = 8.8 Hz), 7.51 (m, 5), 7.02 (d, 2, J = 8.8 Hz).

***S*-Pentachlorophenyl 4′-Hydroxythiobenzoate (VI):** mp 225−227 °C; ^{1}H NMR δ 9.65 (bs, 1), 7.99 (d, 2, J = 8.6 Hz), 7.06 (d, 2, J = 8.6 Hz). Anal. Calcd for $C_{13}H_5Cl_5O_2S$: C, 38.8; H, 1.2. Found: C, 38.9; H, 1.1.

***S*-2,4-Dinitrophenyl 4′-Methoxythiobenzoate (VII):** mp 121−123 °C (from ligroin); ^{1}H NMR δ 8.91 (d, 1, J = 2.6 Hz), 8.64 (dd, 1, J = 8.6; 2.4 Hz), 8.19 (d, 1, J = 8.4 Hz), 8.04 (d, 2, J = 9.0 Hz), 7.16 (d, 2, J = 8.8 Hz), 3.96 (s, 3). Anal. Calcd for $C_{14}H_{10}N_2O_6S$: C, 50.3; H, 3.0; N, 8.4. Found: C, 49.9; H, 3.0; N, 8.5.

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