

On the Mechanism of Ester Hydrolysis: Trifluoroacetate Derivatives

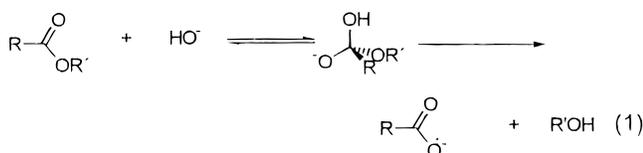
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Received March 29, 1999

The hydrolysis rate of trifluoroacetates of ArX (X = *p*-CH₃, H, *p*-F, *p*-Cl, and *m*-Cl) was measured as function of pH and buffer concentration. All the reactions were catalyzed by the buffer bases, and the Bronsted plot showed a small upward curvature. The kinetic isotope effect is ca. 2.5–2.3 for the reactions of water. The Hammett plots as well as the plots of log *k*_B vs p*K*_{lg} are linear. The slopes of these plots are remarkably similar to those corresponding to the hydrolysis of aryl acetates and aryl formates. From these results, we conclude that the reaction corresponds to general base-catalyzed addition of water and break of the leaving group with no intermediate with finite lifetime despite the fact that the trifluoromethyl group stabilized the intermediate considerably.

The mechanism of hydrolysis of esters has been considered to involve a two-step mechanism for a long time. The formation of a tetrahedral intermediate in this mechanism (eq 1) is largely rate determining.¹

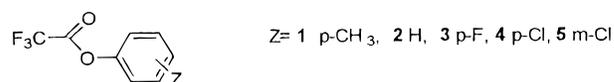


On the other hand, William et al.² have postulated a concerted mechanism for the reactions of phenyl esters with phenolate ions when the p*K*_a of the leaving group is between 2 and 11. Guthrie,³ on the basis of literature results and thermodynamic calculations of the stability of the intermediates involved, suggested that in general the aryl acetate reactions occur without intermediates of significant lifetime due to very small barriers for the bond formation and rupture from the intermediate. Further Brønsted analysis has led Jencks and co-workers to conclude that substituted phenyl formates as well as phenyl acetates react with phenolate anions through a concerted mechanism.⁴ These conclusions have not been universally accepted, and evidence from Brønsted studies favoring a stepwise reaction pathway for aryl acetates has been presented.^{5,6}

From studies of isotopic effect, Hengge⁷ concluded that the reaction of oxyanion nucleophiles with *p*-nitrophenyl acetate occurs by a concerted mechanism. These authors also suggested that the p*K*_a of the oxyanion nucleophiles

is a determining factor for the transition-state structure and that aromaticity and the accompanying delocalized nature of the attacking charge do not result in significant alteration in the transition-state structure.

Recently, we reported on the effect of cyclodextrin on the hydrolysis of trifluoroacetate esters and included some results regarding the hydrolysis of the substrates itself.⁸ Our results seemed to be more concordant with a mechanism involving a tetrahedral intermediate. Therefore, we undertook the study of other substrates in order to get insight into the mechanism for these compounds. Our aim was to determine whether the higher stability of the tetrahedral intermediate due to the trifluoromethyl group⁹ could change the transition state from concerted to stepwise. We report here the reactions of compounds **3–5** and some complementary results of those already published⁸ for substrates **1** and **2**.



Comparison of the free energy relationships of these compounds and those of related ones led us to conclude that the transition state of these reactions have the same degree of bond formation and rupture as that of acetates and formates with the same leaving group, contrary to our previous belief based on a limited number of data.¹⁰

Results

The hydrolysis of substrates **1–5** was measured as a function of pH in the range 5.00–9.91 (Tables S1–S3).^{11,8} At each pH, at least five buffer concentrations were used and the rate increased linearly with buffer concentration in all cases. The observed pseudo-

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(11) Supporting Information.

Table 1. Catalytic Rate Constants (k_B , $M^{-1} s^{-1}$) for Compounds 1–5 at 25 °C

substrate	water ^a (-0.49, ^c 1.25 ^d)	CH ₃ COO ⁻ (-0.45, ^c 1.26 ^d)	HPO ₄ ²⁻ (-0.79, ^c 1.98 ^d)	CO ₃ ²⁻ (-1.15, ^c 2.96)	HO ^{-b} (-0.30, ^c 0.69 ^d)
<i>p</i> -CH ₃	0.0273		8.85	101	6.14
H	0.0367	3.12	12.7	290	8.51
<i>p</i> -F	0.0596	4.31	27.9	891	7.26
<i>p</i> -Cl	0.0837	7.49	45.5	2158	11.8
<i>m</i> -Cl	0.111	8.51	83.7	2667	14.7

^a $k_w/53.42$. ^b $k_B \times 10^{-5}$. ^c β_{lg} value. ^d ρ value.

Table 2. Kinetic Solvent Isotope Effect for Different Bases^a

substrate	k_B^H/k_B^D			
	water	HPO ₄ ²⁻	CO ₃ ²⁻	HO ⁻
<i>p</i> -CH ₃ (1)	2.78 ± 0.13	2.1 ± 1.5	0.3 ± 0.1	0.8 ± 0.2
H (2)	2.59 ± 0.09	2.2 ± 1.1	0.2 ± 0.1	0.4 ± 0.1
<i>p</i> -Cl (4)	2.38 ± 0.16	2.2 ± 0.7	0.7 ± 0.3	0.8 ± 0.2
<i>m</i> -Cl (5)	2.49 ± 0.10	1.0 ± 0.3	0.5 ± 0.1	0.7 ± 0.3

^a The errors have been calculated using the average standard deviation of each rate constant and the following equation.

$$\Delta \frac{k^H}{k^D} = \left[\frac{\Delta k^H}{k^H} + \frac{\Delta k^D}{k^D} \right] \frac{k^H}{k^D}$$

Table 3. Dependence of the Catalytic Rate Constant k_B for the Different Bases on the pK_{BH}

X	pK_{lg}^a	β_{HO}^b	R^{2c}	β_w^d	R^{2e}	β_1^f	β_2^g
<i>p</i> -CH ₃	10.26	0.549	0.9781	0.304	0.9990	0.297	0.55
H	10.00	0.502	0.9865	0.328	0.9914	0.300	0.50
<i>p</i> -F	9.81	0.458	0.9990	0.350	0.9811	0.308	0.48
<i>p</i> -Cl	9.38	0.478	0.9991	0.368	0.9775	0.318	0.48
<i>m</i> -Cl	9.02	0.474	0.9998	0.370	0.9789	0.328	0.47

^a Values taken from Stretwieser, A.; Heathcock, C. H. *Química Orgánica*, 3rd ed.; Macmillan Publishing Co. Inc.: Madrid, Spain, 1986; p 888. ^b Calculated without the point for water. ^c Correlation coefficient for β_{HO} . ^d Calculated excluding the data for HO⁻. ^e Correlation coefficient for β_w . ^f Calculated with the data for water, acetate, and phosphate. ^g Calculated with the data for phosphate, carbonate, and hydroxide ion.

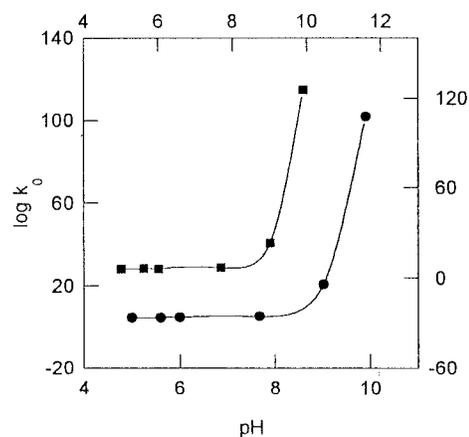
first-order rate constant can be represented by eq 2

$$k_{obs} = k_0 + k_{cat}[B_T] \quad (2)$$

where k_0 represents the buffer-independent rate constant, k_{cat} is the rate constant for catalysis by the buffer, and B represents the total buffer concentration. To determine whether the acid or base component of the buffer was the catalyst, the values of k_{cat} were plotted vs the fraction of free base. In all cases, the intercept at zero free base fraction was zero within experimental error, indicating that the base was the catalyst. In Table 1 are collected the catalytic coefficients of the various bases.

In the case of compounds 4 and 5 we attempted to determine the catalysis by chloroacetate, but the observed rate constants were the same within experimental error in the range of buffer concentration used (0.01–0.10 M, pH 2.9, 3.3, and 3.75). These results were expected since from the Brønsted β value, i.e., 0.47 (β_{HO} , Table 3), for 5, k_B is calculated as $1.16 M^{-1} s^{-1}$, and then at pH 3.75 the observed rate constant should vary within 6.06 and 6.15 s^{-1} . The measured values are 6.4 ± 0.5 and $6.7 \pm 0.6 s^{-1}$.

In Figure 1 are plotted the observed rate constants extrapolated to zero buffer concentration vs pH for

**Figure 1.** Buffer-independent observed rate constants vs pH for the hydrolysis of compounds 4 (●, left and bottom axes) and 5 (■, right and top axes).

compounds 4 and 5. A similar plot (not shown) is obtained for 3. The plots fit very well to an equation of the form of eq 3 where k_w is the water reaction and k_{HO} is the HO⁻-catalyzed reaction for the three compounds:

$$k_0 = k_w + k_{HO}[HO] \quad (3)$$

The kinetic isotope effect was determined for substrates 1, 2, 4, and 5 in neutral and in basic solution (Table S4, Supporting Information).¹¹ At each pH two or three buffer concentrations were used so the value of the isotope effect was calculated for k_w , k_B , and k_{HO} . The value of k_w^H/k_w^D was obtained from the intercept of the plot of k_{obs} vs buffer concentration in water and in deuterated water at pH 6.2 for 1 and 5 and at pH 7.07 and 7.14 for 2 and 4, respectively. The values of k_{OH} and k_{OD} are the slopes of the plots of k_0 vs OH and OD, respectively. The isotope effects (Table 2) for the buffer bases have large errors because they have been calculated from data at only two or three buffer concentrations. The errors are particularly large for HPO₄²⁻ in the reactions of 1 and 2 because the observed catalysis for this substrates is barely outside experimental errors.

Discussion

Base Catalysis. The values of the isotope effect obtained for the water reaction (Table 2) indicate that proton transfer occurs in the rate-determining step. They are similar to the values reported for the neutral hydrolysis of 4-nitrophenyl and 2,4-dinitrophenyl trifluoroacetate in acetonitrile containing 1% water, i.e., 2.3,¹² and also for the general base-catalyzed hydrolysis of aryl and alkyl formates.¹³ The kinetic isotopic effect for the buffer bases is lower than that of water and may indicate that in the mechanism of catalysis there is some contribution from nucleophilic as well as general base mechanism of catalysis. The inverse isotope effect for HO⁻ is typical for this type of reactions¹⁴ and has been interpreted as arising from desolvation of hydroxide.

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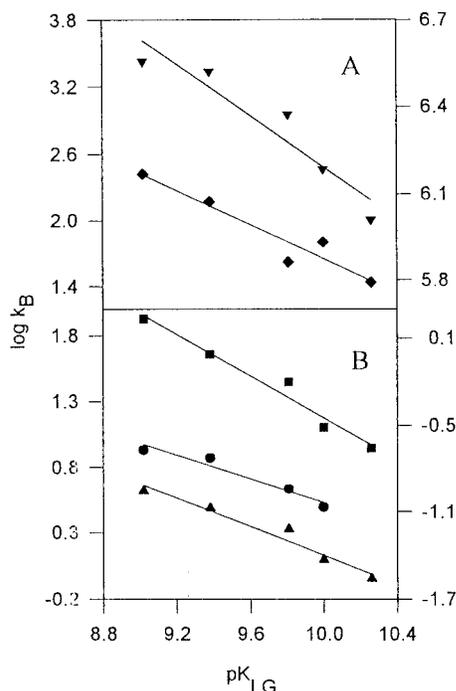


Figure 2. Dependence of the catalytic rate constant for the bases (k_B) on the pK of the leaving group (pK_{LG}): (A) CO_3^{2-} , $\beta_{LG} = -1.15$ ($r^2 = 0.897$) ∇ (right ordinate); HO^- , $\beta_{LG} = -0.30$ ($r^2 = 0.914$), \blacklozenge (left ordinate); (B) water, $\beta_{LG} = -0.49$ ($r^2 = 0.957$) \blacktriangle ; CH_3COO^- , $\beta_{LG} = -0.45$ (0.989), \bullet (left ordinate); HPO_4^{2-} , $\beta_{LG} = -0.79$ ($r^2 = 0.967$), \blacksquare (right ordinate).

We suggest that water is the nucleophile for the general-base-catalyzed pathway and the base acts as general base, removing a proton from the nucleophile in the transition state. A similar mechanism was suggested by Marlier for the alkaline hydrolysis of methyl formate based on isotope effects on oxygen¹⁵ and in several other reactions of water with different electrophiles.^{16,17}

Structure-Reactivity Correlations. There is a linear relationship between the $\log k_B$ and the pK_a of the leaving group (Figure 2). The value of β_{LG} increases in absolute number as the base becomes stronger, for acetate, phosphate, and carbonate. The slope of the line (not shown) of β_{LG} vs pK_{BH} is -0.11 , which is the same as that calculated from data reported for the general base-catalyzed hydrolysis of phenyl formates.¹³ The β_{LG} for the water reaction, i.e., -0.49 , is also remarkably similar to literature values for the formates, namely -0.46 .¹³ The value of β_{LG} for HO^- (-0.30) is lower than expected considering those of the other bases; however, it is in good agreement with the value reported for the hydrolysis of aryl acetates, i.e., -0.32 .¹⁸ The low value for this base may be explained considering that the OH reacts through its solvation shell so the negative charge is more diffuse and needs less stabilization for the electron-withdrawing groups of the phenyl substituent. An experimental consequence of this low value of β_{LG} for HO^- as compared with the other bases is that the relative contribution of the catalyzed pathway increases as the pK_a of the leaving group decreases. For instance, for $\text{CO}_3^{2-}/\text{HCO}_3^-$ buffer the ratio k_B/k_0 at pH 9.02 is, respec-

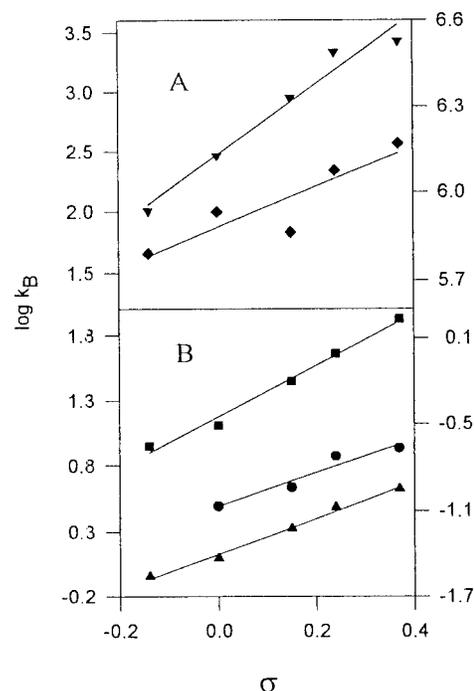


Figure 3. Hammett plots of the catalytic rate constant for the bases (k_B). The values of σ were taken from March, J. *Advanced Organic Chemistry, Reactions, Mechanism and Structure*, 4th ed.; John Wiley and Sons: New York, 1992; p 280: CO_3^{2-} , $\rho = 2.96$ ($r^2 = 0.967$), ∇ (left ordinate); HO^- , $\rho = 0.692$ ($r^2 = 0.797$), \blacklozenge (right ordinate); HPO_4^{2-} , $\rho = 1.98$ ($r^2 = 0.987$), \blacksquare (right ordinate); CH_3COO^- , $\rho = 1.26$ ($r^2 = 0.92\%$), \bullet water, $\rho = 1.25$ (0.991), (left ordinate).

tively, 11.99, 22.3, 68.1, 106, and 116 for $Z = p\text{-CH}_3$, H, $p\text{-F}$, $p\text{-Cl}$, and $m\text{-Cl}$.

The data for all the bases give linear Hammett plots (Figure 3) with a slope 1.24 and 0.69 for water and OH, respectively. This is in accordance with the lower β_{LG} for the latter base and with the Hammond postulate. The stronger base is the one less sensitive to the substituent probably because of an earlier transition state. Similarly, as observed with the change in β_{LG} with pK_{BH} also there is a linear relationship between ρ and pK_{BH} for acetate, phosphate, and carbonate with slope 0.325.

A better Hammett correlation is obtained by using the values of σ rather than those of σ^- , which is an indication that the correlation does not arise from the rate-limiting $\text{ArO}\cdots\text{C}$ bond rupture from the tetrahedral intermediate.¹⁹ In contrast, the reactions of HO^- give a better correlation with σ^- although the ρ value is lower than the corresponding to the other bases (see Table 1 and Figure 3 caption). This result is somehow inconsistent with the fact that ρ for HO^- is lower than that for the other bases as mentioned above. The fact that we are considering only four substituents and that only $p\text{-F}$ has a σ^- value significantly different from σ makes it difficult to draw a sound conclusion; for this reason, we will not discuss this point further. Experiments with substrates having groups with higher differences between σ and σ^- (for instance $p\text{-NO}_2$) are precluded because of their high reactivity under our reaction conditions.

The dependence of k_B with pK_{BH} (Figure 4) can be analyzed in different ways. One is to draw a line through

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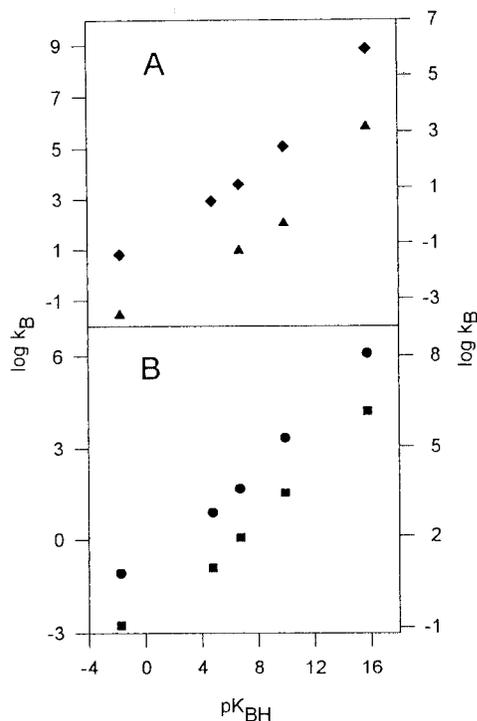


Figure 4. Brønsted plots for substrates **1**, **2**, **4**, and **5**. (A) Z = H \blacklozenge (right ordinate); Z = CH₃, \blacktriangle (left ordinate); (B) Z = *m*-Cl \blacksquare (right ordinate); Z = *p*-Cl \bullet (left ordinate).

all the anionic bases leaving the point for the water reaction out of the line. Positive deviation of the water reaction has been observed in other cases.⁴ Another possibility is to draw a line through all the points leaving the HO⁻ out of the correlation since this base seems to behave anomaly in other types of linear-free relationship correlations (see above). Finally, we can consider all the points together. In this case the Brønsted plot have a slightly upward curvature. We calculated two Brønsted values as follows. We estimated the value of β_1 drawing a line throughout the points for water, acetate and phosphate and another one using carbonate, phosphate and HO⁻. The data are listed in Table 3, and it can be seen that the value changes from approximately 0.3 to 0.5.²⁰ The reaction of trifluoroethanol with [4-(trifluoromethyl)benzyl]methyl(4-nitrophenyl)sulfonium tetrafluoroborate has a Brønsted value of 0.26 for anionic catalysts.²¹ In the hydrolysis of aryl formates a pronounced increase in β (from 0.1 to 0.3 to 1.2–1.9) was observed when the pK_a of the base increased. This increment has been attributed to a change in mechanism from general base catalyzed to nucleophilic. A similar interpretation can account for our results. However, in our case the plots are only slightly curved upward, and then it may be that there is only a small contribution from the nucleophilic mechanism. The general base-catalyzed addition of water to triaryl methyl carbocation ranges from 0.5 to 0.33.²² The β_1 value corresponds to the general base-catalyzed reaction and β_2 to reactions where there is nucleophilic as well as general base catalysis.

(20) The k_B values for **1** and **2** have large errors because the increase in rate with buffer concentration is very small.

(21) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 340.

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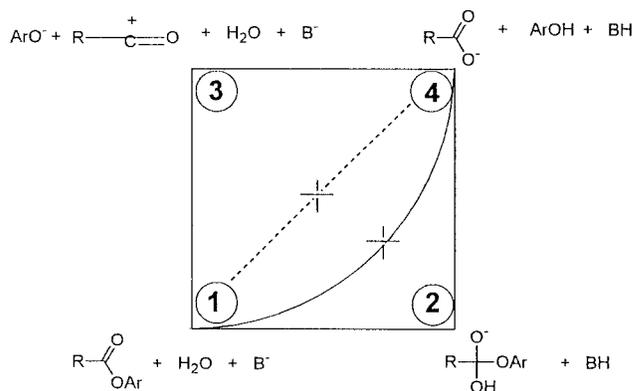
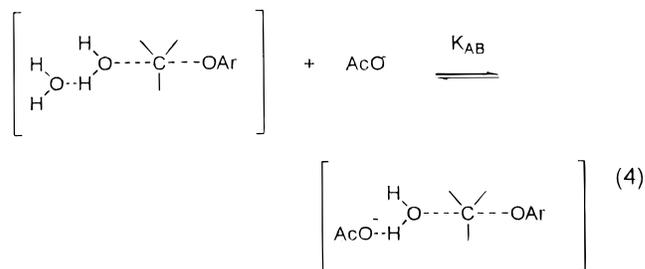


Figure 5. Schematic representation of the different reaction pathways for the hydrolysis of esters.

The possibility of catalysis by hydrogen bonding can be analyzed considering the equilibrium constant shown in eq 4 for acetate as base.



Using eq 5 as described by Hine,^{23,24} we calculate $pK_{AH} = -12.8$ for the transition state, which is far below any reasonable estimate of the acidity of the transition state; therefore, this mechanism can be disregarded.

$$\log K_{AB} = 0.013(pK_{AH} - pK_w)(pK_H - PK_{BH}) \quad (5)$$

Mechanism of the Reaction. The formation of tetrahedral intermediates in acyl transfer reactions is a matter of controversy, and concerted vs stepwise mechanisms have been discussed in terms of isotopic effects,^{7,15} linear free relationships,^{4,5} and theoretical calculations.³ To analyze the possible mechanism we can consider a Jencks–More O’Ferral diagram^{25,26} (Figure 5). In the horizontal coordinates the C–O bond formation to the nucleophile is represented, whereas in the vertical coordinates the bond rupture of the leaving group is represented.

Assuming a diagonal reaction path for R=CH₃ or H, a change of these groups by CF₃, which is strongly electron-withdrawing, should destabilize the upper left corner by at least 6 kcal/mol.²⁷ On the other hand, the substitution of the CH₃ group of acetate by CF₃ is expected to stabilize the tetrahedral intermediate. For instance, the equilibrium constant for the aldol condensation reaction shown in eq 6 is $2.66 \times 10^3 \text{ M}^{-1}$ for R=CF₃ and $1.89 \times 10^{-3} \text{ M}^{-1}$ for R=CH₃; i.e., the CF₃ leads to a stabilization of 8.4 kcal/mol.²⁸

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(25) More O’Ferral, R. A. *J. Chem. Soc. B* **1970**, 274.

(26) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705.

(27) This value is calculated considering that the pK_a of CF₃COOH is 0.23 and that of CH₃COOH is 4.75. See: Oakenfull, D. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 78.



This increase in stability is in part due to a decrease in the dissociation rate constant but mainly to a high increase in the association rate constant.

These two effects together should drive the transition state toward the tetrahedral intermediate. However, the similarities between the free energy relationship for the reactions reported here and those of formates and acetates led us to conclude that the reactions are concerted, although the position of the transition state may be closer to the tetrahedral intermediate. We conclude that the mechanisms of hydrolysis of the substrates **1–5** do not involve an intermediate and are concerted just as the hydrolysis of other aryl esters. It appears that the stabilization provided by the strongly electron-withdrawing CF_3 group is not enough to drive the reaction toward the lower right-hand corner of the diagram (Figure 4), and this is because the expulsion of the phenolate from the intermediate has no barrier.³

Experimental Section

Aqueous solutions were made up from water purified in a Millipore apparatus. Acetonitrile Merck HPLC grade was used as received.

The pH measurements were done in a pH meter Orion 720A at controlled temperature and calibrated with buffers prepared in our laboratory according to the literature.²⁹

The substrates **3–5** were prepared by the reaction of the appropriate phenol with trifluoroacetic anhydride following literature methods.³⁰ The product was obtained after distillation of the remaining trifluoroacetic anhydride, and trifluoroacetic acid was distilled in a Büchi GKR-51 Kugelrohr apparatus. The purity was controlled by comparison of the spectrum of a completely hydrolyzed solution with a mock solution of the corresponding phenol and by IR comparison with literature.³¹

Kinetic Solvent Isotopic Effect. The buffer was prepared in D_2O (95%), and the pD was measured. To this value 0.4³² was added to calculate the DO^- concentration, which is defined as $K_{\text{D}_2\text{O}}/\text{antilog pD}$ ($\text{p}K_{\text{D}_2\text{O}} = 14.914$).³³ The $\text{p}K_{\text{BD}}$ for D_2PO_4^- was calculated according to Bell.^{34,35}

$$\Delta\text{p}K = 0.017\text{p}K_{\text{BH}} + 0.44$$

For carbonate, it was determined using D_2O as solvent. The measured value is in good agreement with the one calculated as indicated above.

Kinetic Procedures. The reactions were carried out in an Applied Photophysics SF 17MV stopped-flow apparatus with unequal mixing. The substrate was dissolved in dry ACN and placed in the small syringe (0.1 mL). The large syringe (2.5 mL) was filled with water solution containing all the other ingredients. The total acetonitrile concentration was less than 4%.

All reactions were run at 25.1 ± 0.1 °C and at constant ionic strength (0.2 M) using NaCl as compensating electrolyte. The observed rate constants were determined by following the appearance of the corresponding phenols (**3**, 280 nm; **4**, 282 nm; **5**, 279 nm). The rate was measured also at other wavelengths, to see if the tetrahedral intermediate complex could be detected. Under all conditions the same value of the rate was observed and a faster process that could be attributed to the accumulation of the tetrahedral intermediate was not found, although we carefully looked for it.

Acknowledgment. This research was supported in part by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), the Consejo de Investigaciones Científicas y Tecnológicas de la Provincia de Córdoba, (CONICOR), Agencia Nacional de Ciencia y Tecnología (FONCYT), and the Universidad Nacional de Córdoba, Argentina. M.A.F. is a grateful recipient of a fellowship from CONICET

Supporting Information Available: Tables S1–S4 containing the observed rate constant for the hydrolysis of **3–5** as a function of pH and buffer concentration and the observed rate constants for the reactions in D_2O . This material is available free of charge via the Internet at <http://pubs.acs.org>.

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