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Kinetic Study of the Hydrolysis of Phthalic Anhydride and Aryl Hydrogen Phthalates

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The kinetics of the hydrolysis of phthalic anhydride and X-phenyl hydrogen phthalate (X = H, *p*-Me, *m*-Cl, and *p*-Cl) were studied. Several bases accelerate the reaction of phthalic anhydride: acetate, phosphate, *N*-methyl imidazole, 1,4-diazabicyclo[2,2,2]octane (DABCO), and carbonate. Phosphate, DABCO, and *N*-methyl imidazole react as nucleophiles, whereas the data do not allow the determination of whether the other bases react in the same way or as general bases catalyzing the water reaction. The rate constants for all of them including water and HO^- define a Brönsted plot with $\beta = 0.46$. The kinetics of the hydrolysis of the esters were studied below pH 6.20, and the mechanism involves the formation of phthalic anhydride, which then is hydrolyzed to the phthalic acid. Phenoxide ion has a very high rate constant for the reaction with phthalic anhydride, so above pH 6.20 it competes significantly with the hydrolysis of the anhydride. The reactions of the esters as a function of pH allow the determination of the kinetic pK_a which are 3.06, 3.02, 2.95, and 2.93 for X = H, *p*-Me, *m*-Cl, and *p*-Cl, respectively. The data also show that the catalysis by the neighboring carboxy group takes place only when it is ionized (i.e., as carboxylate).

The study of intramolecular catalysis in model systems gives important information about enzyme mechanisms.[1−3] In connection with our studies of the effect of cyclodextrin in intramolecularly catalyzed reactions,[4] we became interested in the study of the effect of a neighboring carboxylic group on the hydrolysis of esters.

The hydrolysis of monoesters of phthalic acids was shown to be catalyzed by the neighboring carboxy group when the pK_a of the alcohol leaving group is higher than 13.5 and by the carboxylate when the leaving group has a lower pK_a.[5] In this paper, we report the effect of substituents on the aryl ring of the phenol leaving group. It was found that the reaction is quite sensitive to the pK_a of the leaving group ($\beta_{lg} = -1.15$), indicating a significant bond breaking in the transition state. Since phthalic anhydride is a known intermediate in this type of reaction,[5] we also include here a study of the kinetics of the hydrolysis of this compound under the same conditions used for the esters.

Results and Discussion

Phthalic Anhydride. The rate of hydrolysis of this compound was determined at different pHs in the range 0.63−10.50 at 25 °C and in water containing a small amount of acetonitrile. In the pH range 0.63−3, HCl was used to regulate the pH, and above pH 3, several buffers were used (see Table S1 in the Supporting Information). At pH 5.0 and 5.7 there was a small catalysis using acetic/acetate as buffer (Table S1), but the observed change in absorbance adjusted very well to a single-exponential curve. At pH 6.20 and 7.24, $H_2PO_4^-/HPO_4^{2-}$ was used as buffer, and two kinetic processes, well separated in time, can be detected. The rate constant for the slower process cannot be measured because it is too slow for the stopped-flow technique. In one experiment carried out in a conventional spectrophotometer at pH 6.20 with total buffer concentration 0.08 M, a k_{obs} value of 1.26×10^{-3} s^{-1} was determined.

The reaction of phthalic anhydride with HPO_4^{2-} is known to form phthaloyl monophosphate with rate constant 1.23 M^{-1} s^{-1}, and then the mixed anhydride is hydrolyzed with a slower rate.[6] From the slopes of the linear plots of k_{obs} for the fast process versus total buffer concentration (not shown) at pH 6.2 and 7.24 and the pK_a of the phosphate monoanion (6.28 at ionic strength 0.5 M),[7] the second-order rate constant for the reaction of HPO_4^{2-} with phthalic anhydride is calculated as 1.02 and 1.21 M^{-1} s^{-1} in good agreement with the literature value mentioned above. The intercepts of the plots are the same within experimental error at pH 6.20 and 7.24.

At pH 6.20, 6.80, and 7.80, *N*-methyl imidazole was used as buffer. Only one kinetic process was detected in this case, and the observed rate constants are collected in Table S2. It can be seen in Figure 1 that at pH 7.80 there is a nonlinear dependence between the observed rate constant and the total buffer concentration. These results can be interpreted as shown in Scheme 1, where B represents the buffer base, in this case *N*-methyl imidazole.

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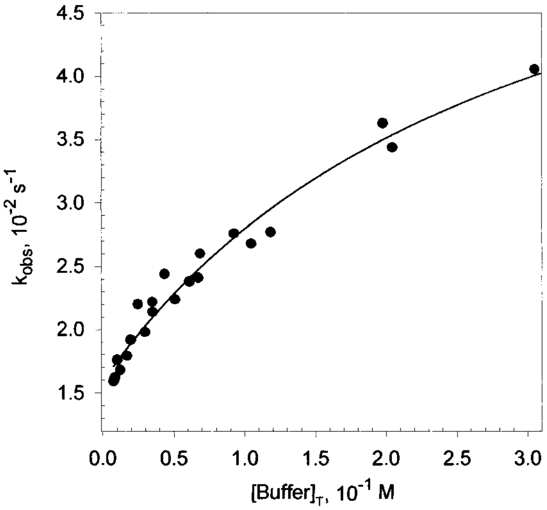
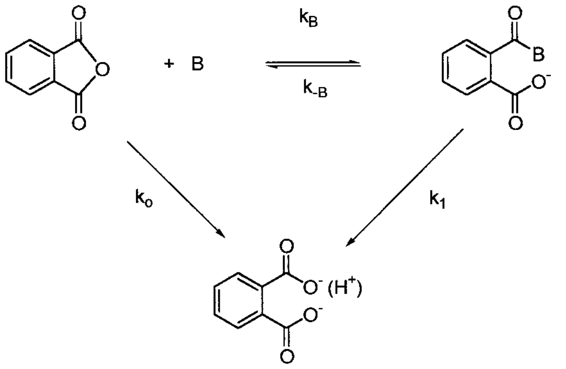


Figure 1. Observed rate constant for the hydrolysis of phthalic anhydride as a function of total *N*-methyl imidazole concentration at 25 °C, pH 7.8, and ionic strength 0.5 M. The line was calculated using eq 1 with $k_o = 1.59 \times 10^{-2}$ s^{-1}, $K_B = 3.75$ M^{-1}, $k_1 = 0.074$ s^{-1}, and the fraction of *N*-methyl imidazole as base = 0.799.

Scheme 1



By considering Scheme 1 and assuming that the formation of the intermediate **1** is in fast equilibrium with the reactants, the observed rate constant in the presence of *N*-methyl imidazole is given by eq 1 where $K_B = k_B/k_{-B}$

$$k_{obs} = \frac{k_o + K_B k_1[B]}{1 + K_B[B]} \qquad (1)$$

The reaction of phthalic anhydride with nucleophiles is well documented in the literature.[6,8]

Using eq 1 to fit the data for *N*-methyl imidazole at pH 7.80, we can calculate $k_o = 0.0159$ s^{-1}, $K_B = 3.75$ M^{-1}, and $k_1 = 0.074$ s^{-1}. The initial slope of the plot of k_{obs} versus *N*-methyl imidazole concentration gave $K_B k_1 = 0.287$ M^{-1} s^{-1} in good agreement with the value obtained by nonlinear fitting. At pH 6.80 and by using the same value of K_B, $k_1 = (6.3 \pm 0.7) \times 10^{-2}$ s^{-1} is calculated. This is a reasonable value compared with that obtained at pH 7.80. The value of k_1 is about 8 times higher than the rate constant for the hydrolysis of phthalic anhydride, while the relative rate of reaction of acetyl *N*-methylimidazole and acetic anhydride is 16.[9-11]

Table 1. Rate Constants for the Hydrolysis of Phthalic Anhydride in the Presence of Bases

base	pK_a	k, M^{-1} s^{-1}
H_2O	−1.74	1.67×10^{-4} [a]
AcO^-	4.75	1.61×10^{-2} [b]
$HPO_4{}^{2-}$	6.28	1.1[c]
N-methyl imidazole	7.20	0.277[d]
DABCO	9.22	11.5[d]
$CO_3{}^{2-}$	9.78	106[e]
HO^-	15.7	10636[f]

[a] Calculated from the average of the rate constants extrapolated at zero buffer concentration obtained at pHs between 0.63 and 5.7 divided by 55. [b] Calculated from data at pH 5.00 and 5.7. [c] This is k_B in Scheme 1, data obtained at pH 6.2 and 7.8. [d] This represents $K_B k_1$, Scheme 1, data obtained at pH 7.8. [e] Calculated from the data at 8.9, 9.5, and 10.5. [f] Taken from the slope of a plot of k_{obs} at zero buffer concentration vs $10^{-(14-pH)}$ in the pH range 8−10.5.

Using 1,4-diazabicyclo[2,2,2]octane (DABCO) as buffer at pH 7.8, the observed rate constant has a linear dependence with the buffer concentration in the range 0.0087−0.08 M concentration. The intercept 1.44×10^{-2} s^{-1} represents k_o, and this value is in reasonably good agreement with the value measured at the same pH with *N*-methyl imidazole (see above). The slope of this plot is 11.5 M^{-1} s^{-1}, and it should be $k_1 K_B$. This value cannot correspond to k_B in Scheme 1 because it is expected to be much higher. The rate constant for the aminolysis of phthalic anhydride is independent of the pK_a of the amine for nucleophiles of pK_a > 8.[8] The value k_B for morpholine (pK_a = 8.7) is 2.1×10^5 M^{-1} s^{-1} [8], so k_B in Scheme 1 for DABCO (pK_a = 9.2)[12] should be of this order of magnitude.

At pH between 8.90 and 10.50, $CO_3{}^{2-}/HCO_3{}^-$ was used as buffer (Table S3). In this case, only one kinetic process is observed. The slope of the plot of k_{obs} versus $CO_3{}^{2-}$ concentration is 106 M^{-1} s^{-1}. We did not detect, as in the case of the phosphate reaction, any slow process, so we cannot say whether the catalysis by carbonate represents basic catalysis or the nucleophilic reaction with the anhydride.

The second-order rate constants for reactions of all the bases are collected in Table 1. A Brönsted plot (Figure 2) using all the data has a reasonable correlation coefficient and gives $\beta = 0.46$ despite the fact that the rate constants do not have the same mechanistic meaning in all cases. The reaction of water represents the addition of water catalyzed by a water molecule,[13] the reaction of $HPO_4{}^{2-}$ represents the nucleophilic addition of this species on the carbonyl group, and the reactions of *N*-methyl imidazole and DABCO are the products of the equilibrium constant for the addition of the nucleophile times the rate constant for the hydrolysis of the intermediate ($k_1 k_B/k_{-B}$ in Scheme 1). These results should be a warning for the interpretation of the effect of bases in the hydrolysis reactions, since one usually assumes that a good Brönsted plot implies the same mechanism, and a β value around 0.5 is attributed to general base-

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(8) Hall, W. E.; Higuchi, T.; Pitman, H. I.; Uekama, K. *J. Am. Chem. Soc.* **1972**, *94*, 8153.

(9) The rate constant of the water reaction for acetic anhydride is 0.17 min^{-1} (ref 10) and that of *N*-methylacetyl imidazole is 2.8 min^{-1} (ref 11).

(10) Kirsch, J. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1964**, *86*, 837.

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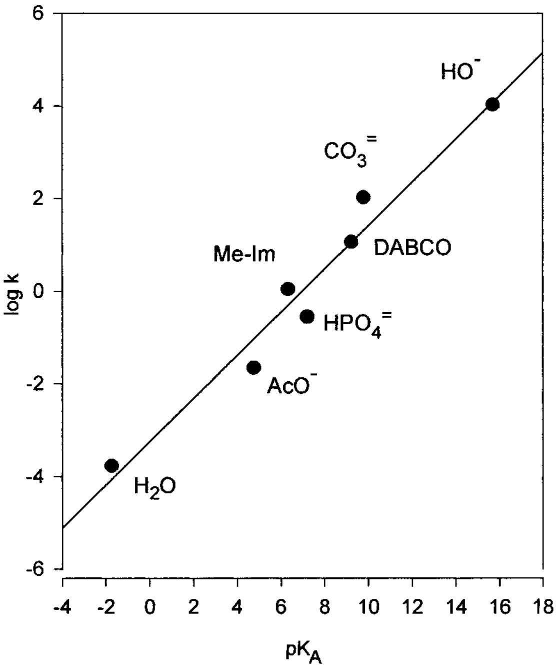

Figure 2. Brönsted plot for the hydrolysis of phthalic anhydride catalyzed by bases (data from Table 1).

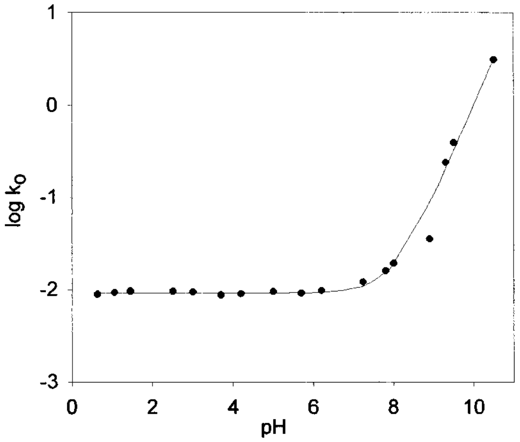

Figure 3. pH rate profile for the hydrolysis of phthalic anhydride at 25 °C and ionic strength 0.5 M. The line was calculated using $\log(0.0092 + 10\,640 \times 10^{-(14-\mathrm{pH})})$.

catalyzed reactions rather than to nucleophilic reactions.[14−16]

Using the data of the observed rate constants extrapolated to zero buffer concentration, the pH profile shown in Figure 3 is obtained. The average value of the flat region of the pH profile is 9.2×10^{-3} s^{-1}, and it is in good agreement with the value reported for slightly different reaction conditions, namely 12.3×10^{-3} s^{-1} [5] and 10.5×10^{-3} s^{-1}.[13] The rate of hydrolysis of phthalic anhydride is 23 times that of benzoic anhydride,[17] and this difference in reactivity may be attributed to ring strain in the former.

The reaction of phthalic anhydride was also studied in the presence of phenol at pH 7.24 at two buffer concentrations (Table 2). In this case, there are two kinetic processes (τ_1 and τ_2) well separated in time. Each of them was independently adjusted to a monoexponential function, and the observed rate constant was calculated.

Table 2. Rate Constants for the Fast Process (τ_1) in the Reaction of Phenol with Phthalic Anhydride[a]

$H_2PO_4^-/HPO_4^{2-}$ 0.01 M[b]		$H_2PO_4^-/HPO_4^{2-}$ 0.05 M[b]	
[phenol], 10^{-3} M	τ_1^{-1}, s^{-1}	[phenol], 10^{-3} M	τ_1^{-1}, s^{-1}
0	0.0227	0	0.067
1.15	0.201	1.0	0.229
1.22	0.231	1.2	0.268
1.42	0.244	1.4	0.299
1.62	0.280	1.6	0.340

[a] pH 7.24, ionic strength 0.5 M, temperature 25 °C. The values of τ are the average of 4−10 determinations, and the standard deviation is less than 2%. [b] Total buffer concentration.

The faster relaxation time (τ_1) is attributed to the reaction of the anhydride with buffer, with the solvent, and with phenol. Using phosphate as buffer, the intercept of the plots of τ_1^{-1} versus phenol concentration is in good agreement with the expected value as measured independently at the same pH and buffer concentration but without phenol. Besides, the slopes of the plots at the two phosphate concentrations are the same within experimental error, and from these slopes, a value of $(7.2 \pm 0.2) \times 10^4$ M^{-1} s^{-1} is calculated for the second-order reaction of PhO$^-$ with phthalic anhydride.[18] The reactivity of the phenoxide anion is far above the value expected from the Brönsted line drawn with all the other bases. Comparing the rate of hydrolysis of acetic and phthalic anhydrides, we found that the former is 3.3 times more reactive than the latter when water is the nucleophile, but the relative reactivity of the two anhydrides is in the opposite direction with stronger nucleophiles such as phenoxide and hydroxide ions.[19,20] It is interesting to note that when comparing a series of carbonyl derivatives of increasing reactivity such as *p*-nitrophenyl and 2,4-dinitrophenyl acetate 1-acetoxy-4-methoxy-pyridinium perchlorate[16] and phthalic anhydride, the relative reactivity between PhO$^-$ and HO$^-$ increases, and this is mainly because the reactivity of PhO$^-$ increases more than that of HO$^-$ as the reactivity of the substrate increases. This result may indicate that desolvation of the nucleophile becomes important when the substrate is very reactive. The importance of desolvation in the reactions of nucleophiles is well documented.[21]

The second kinetic process (τ_2) is related to the hydrolysis of phenyl hydrogen phthalate formed during the first kinetic process, but at the pH of this study (7.24), it does not shows a pure first-order behavior, and it will not be discussed further.

Aryl Hydrogen Phthalate. The hydrolysis reaction of phenyl, *p*-methylphenyl, *m*-chlorophenyl, and *p*-chlorophenyl hydrogen phthalate was studied at pH above 0.60 and below 5.70. With the exceptions mentioned below, it shows two kinetic processes which are identified with the

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(14) Bruice, P. Y.; Bruice, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 5523.
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(18) To calculate this value, the slopes of the lines drawn using the data reported in Table 2 were divided by the fraction of PhO$^-$ 2.29×10^{-3} calculated with the pK_a of phenol determined at ionic strength 0.5 M which is 9.88.

(19) The second-order rate constant for the reaction of acetic anhydride with HO$^-$ is 10^3 M^{-1} s^{-1} (ref 10) and that of the phenoxide ion is also 10^3 M^{-1} s^{-1} (ref 20).

(20) Basaif, S. A.; Maude, A. B.; Williams, A. *J. Chem. Soc.*, *Perkin Trans. 2* **1994**, 2395.

(21) Terrier, F.; Moutiers, G.; Xiao, L.; Le Guével, E.; Guir, F. *J. Org. Chem.* **1995**, *60*, 1748−54.

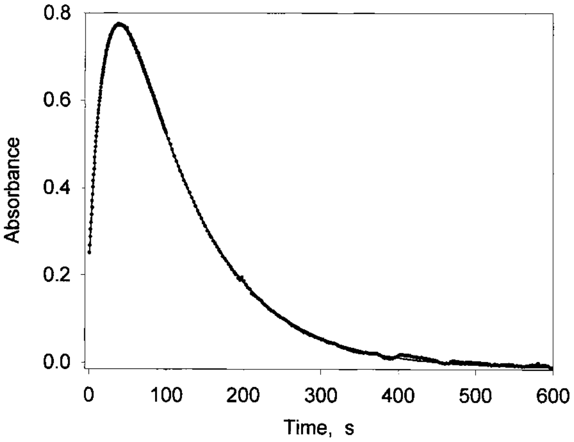
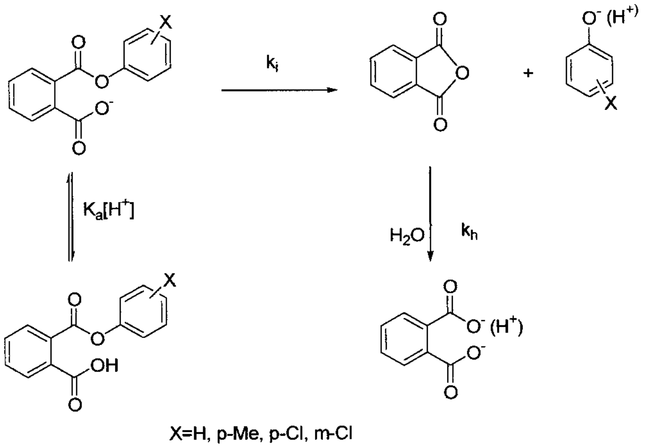


Figure 4. Absorbance at 300 nm vs time for the reaction of phenyl hydrogen phthalate at pH = 5.7 with buffer AcOH/AcO$^-$ (0.08 M) and 25 °C. The line is calculated by fitting the experimental data to Abs = $a_1e^{-t/\tau_1} + a_2e^{-t/\tau_2} + B$ with $\tau_2^{-1} = 1.04 \times 10^{-2}$ s^{-1}.

Scheme 2



buildup and decay of phthalic anhydride, Scheme 2. Figure 4 is a representative plot of the absorbance versus time under these conditions.

The hydrolysis rate constant for the phenyl ester was also measured at pH higher than 5.7, but in this case, the backward reaction of the phenol with the anhydride complicated the kinetics of the system, so it will not be discussed here.

For phenyl and *p*-methylphenyl esters at pH lower than 2, the decomposition of the intermediate is too fast, and only one kinetic process is observed which corresponds to the formation of phthalic anhydride (Table S4). Above pH 2, the rate constant for the formation of the anhydride increases linearly with 1/H$^+$ while that of the hydrolysis of phthalic anhydride remains constant, so both processes can be measured.

The ring closure reaction (k_i) is slightly dependent on buffer concentration (Table S5). Using phosphate as buffer, the changes in absorbance fit to a three-exponential equation, while at the same pH using *N*-methyl imidazole as buffer, the data are well represented by a two-exponential equation. This is consistent with the results obtained for the hydrolysis of phthalic anhydride (see above). To calculate the rate constants for the system, we used a double (or triple)-exponential equation to fit the data, or we set the value corresponding to the hydrolysis of the anhydride as the measured value. Both methods gave comparable results (see Table S5), but we think that the second is the more accurate one, and these are the values reported in Table 3.

Table 3. Rate Constants and Kinetic pK_a for the Hydrolysis of X-Aryl Hydrogen Phthalates[a]

X	k_i, 10^{-2} s^{-1} [b]	pK_a[c]
H	4.43 ± 0.07	3.06 ± 0.04
p-Me	2.28 ± 0.02	3.02 ± 0.02
m-Cl	55 ± 1	2.95 ± 0.06
p-Cl	22.9 ± 0.2	2.93 ± 0.02

[a] Ionic strength 0.5 M, temperature 25 °C, acetonitrile 3.85%. [b] Rate constant for the ring closure reaction (see Scheme 2). [c] Calculated from the observed rate constant for the ring closure reaction at different pH.

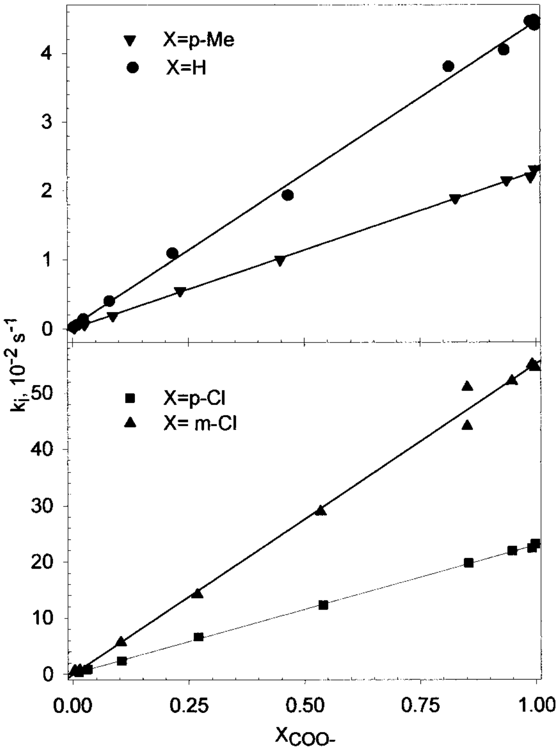


Figure 5. Rate constant vs fraction of carboxylate anion for the four esters studied: phenyl hydrogen phthalate, *p*-methylphenyl hydrogen phthalate, *m*-chlorophenyl hydrogen phthalate, and *p*-chlorophenyl hydrogen phthalate.

The observed rate constant for the ring closure reaction plotted versus pH gives a sigmoid curve (not shown) similar to that reported in the literature for phenyl hydrogen phthalate.[5] From the inflection point of those curves, the kinetic pK_a was calculated (Table 3). In the case of the phenyl ester, the value obtained of 3.06 is in good agreement with the literature value, that is, 3.36 at 1 M ionic strength and 30 °C.[5]

The observed rate constant can be plotted as a function of the fraction of substrate in the carboxylate form, x_A (Figure 5). The intercept at $x_A = 0$ is zero within experimental error, indicating that the neutral substrate is very unreactive. The intercept at $x_A = 1$ is k_i (Scheme 2) and is shown in Table 3.

The β_{lg} for the ring closure reaction is −1.15 that implies a considerable C−O bond breaking in the rate-limiting transition state. A value of $\beta_{lg} = -1$ was found for the intramolecular aminolysis of 2-substituted benzoate esters,[22] and a value of $\beta_{lg} = -1.15$ was found in the carbonate catalyzed reaction in the hydrolysis of aryl trifluoroacetates.[23] The high value of the β_{lg} probably indicates that the ring closure takes place without the formation of a tetrahedral intermediate with finite lifetime. The results are also consistent with the rapid formation of a tetrahedral intermediate that undergoes rate-limiting elimination of phenoxide.[24]

The second-order rate constant for the reaction of phenyl benzoate with HO^- is 5.56×10^{-2} M^{-1} s^{-1}.[25] Assuming a β value of 0.5, we can calculate the rate constant for the nucleophilic reaction of a carboxylate of pK_a 3.06 as 8.5×10^{-6} M^{-1} s^{-1}. Since the rate constant for the intramolecular reaction of the carboxylate in phenyl hydrogen phthalate is 4.43×10^{-2} s^{-1}, the effective molarity is 5×10^3 M, a typical value for intramolecular reactions.[26]

In conclusion, we have determined that the hydrolysis of phthalic anhydride is catalyzed by buffer bases such as phosphate, acetate, *N*-methyl imidazole, DABCO, and carbonate, and in the case of the amines and phosphate, the nucleophilic mechanism can be inferred from the data. Phenol is very reactive toward this electrophile, and this fact complicates the kinetics of the hydrolysis of phenyl hydrogen phthalate at pH higher than 5.70. The hydrolysis of aryl hydrogen phthalate occurs with the formation of phthalic anhydride as the intermediate, and only the deprotonated carboxylate group is effective for intramolecular catalysis. Besides, the reactions have a high β_{lg}, indicating that there is significant C−O bond breaking in the transition state.

Experimental Section

Aqueous solutions were made up from water purified in a Millipore apparatus. Acetonitrile Merck HPLC was dried on silica gel 10% p/v as described in the literature.[27] It is very important to have the solvent dried because with traces of water the substrates hydrolyzes before the solution can be used.

The pH measurements were done at controlled temperature and calibrated with buffers prepared according to the literature.[28]

Phthalic anhydride (Anedra) was sublimated before use. The monoaryl esters were prepared from phthalic anhydride and the appropriate phenol by adapting the method described in the literature.[29] The products were characterized by IR and ^{13}C NMR. The spectroscopic data are collected in Table 4. The IR of phenyl hydrogen phthalate agrees with the reported spectrum.[29] The purity of the products was also checked by comparing the UV−vis absorption spectrum of a solution containing the fully hydrolyzed ester with one at the same concentration prepared with phthalic acid and the corresponding phenol.

The pK_a of phenol at ionic strength 0.5 M was determined by measuring the pH of solutions 0.0462, 0.0305, and 0.150 M of phenol half-neutralized with NaOH. The pH values of these solutions were 9.876, 9.888, and 9.882.

Table 4. IR and ^{13}C NMR for the X-phenyl Hydrogen Phthalates

X	IR, cm^{-1} [a]	^{13}C NMR, ppm[b]		
H	1695.5 (C═O in −COOH)	172.4	166.5	150.8
	1770.5 (C═O in ester)	133.0	132.5	131.1
		130.0	129.7	129.5
		129.0	126.0	121.3
p-CH_3	1677.5 (C═O in −COOH)	172.3	166.8	148.6
	1758.1 (C═O in ester)	136.0	133.2	132.4
		131.1	130.1	130.0
		129.8	129.0	121.0
		20.8		
p-Cl	1713.7 (C═O in −COOH)	171.8	166.3	149.3
	1759.5 (C═O in ester)	132.8	132.6	131.6
		131.4	130.2	129.6 sh
		129.1	122.7	
m-Cl	1709.7 (C═O in −COOH)	171.8	166.2	151.2
	1742.6 (C═O in ester)	134.8	132.6 sh	131.4
		130.3	130.2	129.6
		129.0	122.1	119.8
		126.4		

[a] KBr pellets. [b] In *d*-chloroform.

Kinetic Procedures. Most reactions were carried out in an Applied Photophysics SF 17MV apparatus with unequal mixing. The substrate dissolved in dry acetonitrile was placed in the smaller syringe (0.1 mL). The larger syringe (2.5 mL) was filled with a water solution containing all the other ingredients. The total acetonitrile concentration was 3.85%. The solutions of the substrates for the kinetic determinations were freshly prepared in dry acetonitrile in the appropriate concentration to get a final concentration of 5×10^{-4} M.

All reactions were run at 25.0 ± 0.1 °C and at constant ionic strength (0.5 M) using NaCl as the compensating electrolyte. The observed rate constants were determined by measuring the change in absorbance at 300 nm. In some of the experiments, the pH of the solution was checked after the reaction by measuring it in the discarded solution, and the changes observed were always less than 0.03 pH units. The kinetic traces were fitted with one-, two-, or three-exponential equations using the software of the SF apparatus.

The wavelengths used to monitor the reactions were 255 nm for phenyl hydrogen phthalate at pH 0.63, 1.06, and 1.45, 260 nm for *p*-methylphenyl hydrogen phthalate at pH 0.68, 1.45, and 2.00, and 300 nm for phenyl hydrogen phthalate at pH 2.00 and for phthalic anhydride at pH 0.63, 1.06, 1.45, and 2.00. These reactions were measured in a cell, with temperature control, of a conventional spectrophotometer adding the substrate dissolved in acetonitrile to a solution containing all the other ingredients in the required proportion to have the same amount of the organic solvent as in the stopped-flow experiments.

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Supporting Information Available: Tables S1−S5, containing the observed rate constant for phthalic anhydride and aryl hydrogen phthalates as a function of pH and buffer concentration. This material is available free of charge via the Internet at http://pubs.acs.org.

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