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Changing Mechanisms in the β-Cyclodextrin-Mediated Hydrolysis of Phenyl Esters of Perfluoroalkanoic Acids

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The rate of hydrolysis of esters $CF_3(CF_2)_nCOOPh$ (**1** ($n = 1$), **2** ($n = 2$), and **3** ($n = 6$)) was measured at pH 6.00 and at pH higher than 9.00 in the presence of β-cyclodextrin (β-CD). For compounds **1** and **2** the reaction rate decreases as the β-CD concentration increases, and they show saturation effects at all pH. It is suggested that the substrate forms an inclusion complex with cyclodextrin. Analysis of the rate data allows calculation of the association equilibrium constant, K_{CD}, the rate constant for the reaction of the included compound, k_c, and K^{TS} which is the hypothetical association equilibrium constant for the transition state of the cyclodextrin-mediated reaction. The dependence of log K_{CD} and log K^{TS} with the number of atoms in the chain is different. We suggest that the reactions of **1** and **2** take place with the perfluorinated alkyl chain included in the cavity, whereas the transition state for the reaction of phenyl trifluoroacetate involves a complex with the aryl ring inside the cavity. At low pH the inhibition comes from the protection of the carbonyl group toward nucleophilic attack by water. In basic pH the reaction of HO^- as an external nucleophile is also inhibited. The cyclodextrin-mediated reaction involves the ionized OH group at the rim of the cyclodextrin cavity with poor efficiency due to an unfavorable orientation of the substrate in the complex. On the other hand, the reaction of compound **3** is strongly accelerated by cyclodextrin because the association of the substrate with cyclodextrin competes with the monomer−aggregate equilibrium and at high enough cyclodextrin concentration the main species present in solution is the complex between **3** and cyclodextrin.

Introduction

The effect of cyclodextrins on the basic cleavage of aryl esters of alkanoic acids of different chain length has been widely studied.[1−5] The mechanism of β-cyclodextrin (β-CD)-mediated hydrolysis of esters involves the formation of an inclusion complex between the substrate and the cyclodextrin.[6] For the reactions accelerated by cyclodextrin, one of the secondary OH groups at the rim of cyclodextrin reacts as a nucleophile with the carbonyl carbon of the ester displacing the leaving group and giving the acylated cyclodextrin. The same mechanism is responsible for the rate acceleration observed in amide hydrolysis. However, we found some important differences in the behavior of phenyl alkanoates and some amides derived from perfluorinated acids. For instance, the hydrolysis reaction of trifluoroacetanilide and *m*-nitrotrifluoroacetanilide was inhibited by β-cyclodextrin,[7] contrasting with the reactions of *p*- and *m*-nitrophenylacetate esters which are both accelerated. We attributed the different behavior of amides and esters to different rate-determining steps in the cyclodextrin-mediated reaction. Also, some of the differences in behavior may be attributed to the fact that the amides were derived of perfluorinated compounds whereas the esters were hydrocarbon derived. In fact, comparing the behavior of aryl acetates and aryl trifluoroacetates it was concluded that all the reactions of the perfluorinated esters were less accelerated than their hydrocarbon-derived analogues. The difference in behavior is mainly due to an inefficient stabilization of the transition state by β-CD for the reactions of the perfluorinated esters. Interest in the reactivity of perfluorinated compounds has grown in recent years because of the important applications of this type of compounds.[8,9] On the other hand, their interaction with β-CD has some interesting peculiarities, and several mechanism have been determined for the cyclodextrin-mediated hydrolysis reactions. In addition, the kinetics of that reactions are also dependent on the pH.[10,11] In the presence of β-CD, the rate increases in a nonlinear fashion at constant pH above pH = 8 but it decreases at

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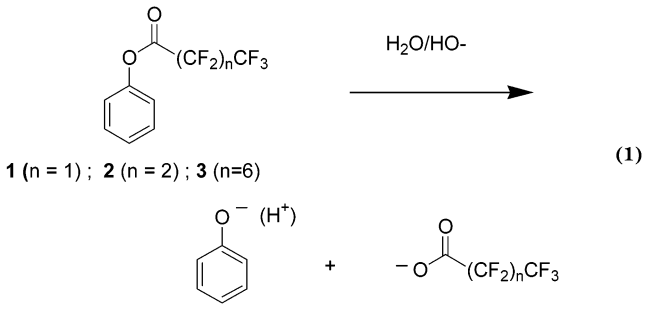
pH = 6. The behavior in alkaline pH is attributed to the nucleophilic reaction of one of the OH groups of the host, while the inhibition observed at low pH is ascribed to an unfavorable microenvironment for the reaction and protection of the carbonyl group from nucleophilic attack by water.

We report here a study of the hydrolysis reaction of phenyl pentafluoropropanoate (**1**), phenyl heptafluorobutanoate (**2**), and phenyl perfluorooctanoate (**3**). This study was carried out because the effect of the change in the length of the alkyl chain was shown to give a great deal of information regarding the nature of the complexes involved in the reactions of aryl esters of alkanoates.[12] It turns out that reactions of **1** and **2** are inhibited by the presence of cyclodextrin at low and high pH as well. This behavior contrasts with the results corresponding to the hydrocarbon-derived esters and with the behavior of aryl trifluoroacetate. For the later compound, the reactions are inhibited by β-CD at pH < 7 but accelerated at pH > 9.[10] On the other hand, reactions of compound **3** are accelerated even at very low cyclodextrin concentration. Due to the high hydrophobic character of the $-CF_2$ groups,[13] compound **3** has a high tendency to associate in water solutions and the association with cyclodextrin breaks down these aggregates, giving rise to the observed increase in rate. This result is remarkable because it points to the importance of β-CD as aggregate breaker in aqueous solution, an effect that is very important in regard to the reactivity of organic compounds in water. In recent years, there has been growing interest in the use of water as a solvent.[14]

Results

The rate constants for the hydrolysis of perfluoroalkanoates **1**−**3** were determined at pH 6.00 and at alkaline pH (eq 1).



(1)

The results obtained for substrates **1** and **2** will be described first because they are qualitatively similar, while those of **3** will be described later since they present some peculiarities.

In general, the ester reactivity diminished when the chain length increases. The hydrolysis rate constants of substrates **1** and **2** were measured as a function of pH at pH 6.00, 9.92, and 10.50. At each pH several concentrations of buffer were used. A very weak catalysis by the buffer was observed only for compound **1** at pH 6.00

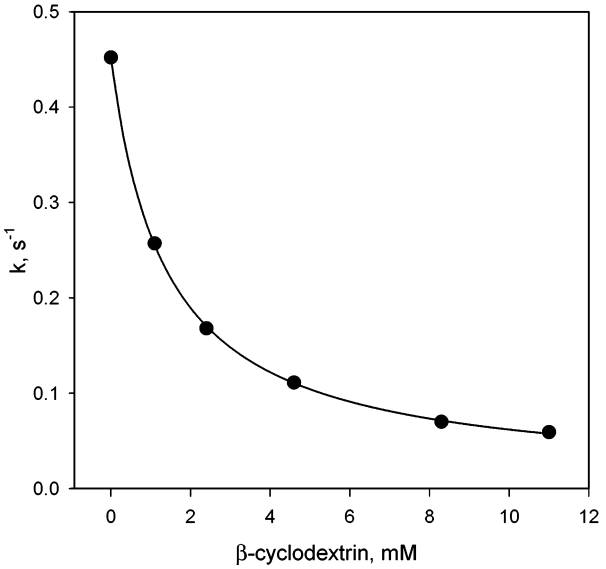


FIGURE 1. Effect of β-CD on the rate of hydrolysis of **1** at pH = 6.00 and buffer concentration 0.01 M. $[\mathbf{1}]_o = 1 \times 10^{-4}$ M; μ = 0.2 M; temp. 25.1 °C. Solvent contains 3.8% MeCN. The line was calculated using eq 2 with a = 5.68, b = 723, and c = 0.452.

(Supporting Information, Tables S1 and S2). The rate constant of the reaction was measured at 1.0×10^{-4} and 1.8×10^{-4} M substrate concentration for **1** and at 5×10^{-5} and 1×10^{-4} M for **2** at pH = 6.00. The rate constants were independent of the substrate concentration, indicating that aggregation of the substrates can be discounted under these reaction conditions.

The effect of β-CD concentration on reaction rate was determined at two buffer concentrations (Supporting Information, Tables S3 and S4). Only for substrate **1** at pH = 6.00 there were some differences in the rates measured at 0.01 and 0.1 M buffer, although in all cases the rate decreases with increasing concentration of β-CD and shows a saturation effect. (Figure 1 is representative).

For compound **1** at pH = 6.00, the observed rate constants at each buffer concentration were fitted to eq 2 where a and b are adjustable parameters, c is the observed rate constant in the absence of β-CD, which was determined independently, and [β-CD] represents the molar concentration of β-CD.

$$k_{obs} = \frac{c + a[\beta\text{-CD}]}{1 + b[\beta\text{-CD}]} \qquad (2)$$

Using parameters a and b calculated at each buffer concentration, the values of the rate constants were calculated at the same concentration of β-CD. These values were then plotted against buffer concentration, and from the intercepts of the plots the rate constants extrapolated to zero buffer concentrations were obtained. In all other reactions the complete set of data obtained at the different buffer concentrations was used and fitted to eq 2. The fact that the reactions at pH > 9.00 were inhibited by β-CD was surprising because the rate of the hydrocarbon-derived esters of the same chain length are accelerated by β-CD and the rate of the shorter members of the series, trifluoroacetate, is also accelerated at pH > 9.

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TABLE 1. Observed Rate Constants for the Hydrolysis of 3 as a Function of Substrate Concentration[a]

	λ = 242 nm		λ = 269.6 nm	
[**3**],10^{-5} M	k_1, 10^{-4} s^{-1}	k_2, 10^{-4} s^{-1}	k_1, 10^{-4} s^{-1}	k_2, 10^{-4} s^{-1}
		pH = 6.0[b]		
0.84[d]		1.2 ± 0.1		3.32 ± 0.08
0.94[d]		1.99 ± 0.05		3.22 ± 0.06
1.79[d]		0.94 ± 0.02		1.87 ± 0.07
1.81[d]		0.99 ± 0.02		1.76 ± 0.05
2.43	21 ± 2[c]	0.61 ± 0.02[c]	33 ± 6[c]	1.22 ± 0.06[c]
3.30	12.7 ± 0.7[c]	0.51 ± 0.07[c]	15 ± 1[c]	0.89 ± 0.03[c]
4.87	12.8 ± 0.5[c]	0.43 ± 0.01[c]	11.9 ± 0.4[c]	0.51 ± 0.01[c]
7.38	10.8 ± 0.4[c]	0.29 ± 0.01[c]	8.9 ± 0.4[c]	0.34 ± 0.03[c]
		pH = 9.9[e]		
1.11				900 ± 200[f]
2.20				700 ± 300[f]
8.63				160 ± 50[f]

[a] $T = (25.1 \pm 0.1)$°C; $\mu = 0.2$ M; solvent contains MeCN = 3.8%; buffer = 0.01 M. [b] Buffer Na_2HPO_4/NaH_2PO_4. [c] The values were obtained by fitting the absorbance vs time data to the following equation: $A = A_\infty + a_1e^{-k1t} + a_2e^{-k2t}$. [d] The data fit to single-exponential equation. [e] Buffer $NaHCO_3/Na_2CO_3$. [f] Each value corresponds to the average of at least 10 determinations, and the errors are standard deviation.

The results for compound **3** showed some special features not found with the substrates of shorter chain length. The hydrolysis of this compound was studied vs substrate concentration, and it was observed that the rate constant changes with the concentration of the substrate. The kinetic measurements at pH 6.00 were done following the appearance of phenol at its wavelength maximum, 269.6 nm, and others where there was a significant change with time, i.e., 242 nm. The absorbance vs time data gave a very good fit to a single-exponential equation for concentrations of **3** in the range of 8.4×10^{-6} to 1.81×10^{-5} M. However, the rate constant decreased when the concentration of the substrate increased, and analysis of the data at different wavelengths gave different values. This is a clear indication that more than one kinetic process is taking place.[15]

At concentrations higher than 2.43×10^{-5} M the reaction no longer fits to a single-exponential equation and two processes could be observed at several wavelengths. At 242 nm, for instance, an initial rise at very short times followed by a decay was observed. The first process became more visible as the substrate concentration increases (Table 1 and Figure 2).

At two key concentrations (1.0×10^{-5} and 2.5×10^{-5} M) where the observations are different (single- and double-exponential fits) we did measurements of hydrolysis rate when the buffer concentrations are modified to analyze its effect. There was no effect on the hydrolysis rate constant associated with the buffer concentration whatever substrate concentration was used.

At pH 9.9 the hydrolysis rate constants were measured for several substrate concentrations at λ = 269 nm, and the data fit well to a single exponential, but the rate constant decreased when the concentration was raised from 1.1×10^{-5} to 8.6×10^{-5} M (Table 1).

In this case it was not possible to do measurements at other wavelengths because the amplitude of the measured process was very small at the wavelength maximum of the product and at other wavelengths no measurable changes were observed.[16]

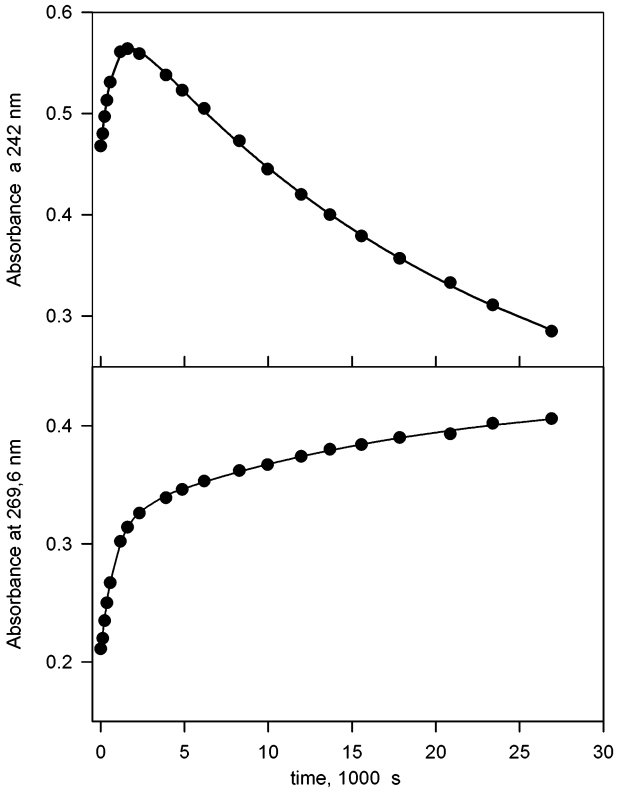

FIGURE 2. Absorbance vs time for the reaction of phenyl perfluorooctanoate (4.87×10^{-5} M) at pH = 6.00 and buffer concentration 0.01 M in water with 3.8% MeCN and ionic strength 0.2 M, (25.1 ± 0.1)° C.

In the presence of β-CD, the hydrolysis rate constant of **3** increases considerably, for instance, from 0.007 to 0.074 s^{-1} at pH 6.00 with substrate concentration of 2.4×10^{-5} M and β-CD concentration of 4.4×10^{-4} M and 5.1×10^{-3} M, respectively (Table 2). With this increment a maximum value is reached, but in the presence of further addition of β-CD, the rate constant diminishes. Similar behavior is observed at pH 6.00 and 9.90. At substrate concentrations where the kinetics fit to a double-exponential equation ($\geq 2.4 \times 10^{-5}$ M) in the absence of β-CD, addition of β-CD at concentrations $\geq 2 \times 10^{-3}$ M change the shape of the curve and it fits to a single exponential (Figure 3).

Discussion

The reactivity of perfluorinated esters diminishes when the chain becomes longer in a manner similar to that observed with hydrocarbon-derived esters. For instance, the hydrolysis rate constant of *m*-nitrophenyl esters at pH 11.7 is 0.086, 0.040, and 0.029 s^{-1} for acetate, propionate, and butanoate, respectively.[4] For perfluorinated esters, the values at pH 9.9 are 71.6, 36, and 26.5 s^{-1} for the phenyl perfluoroacetate, pentafluoropropanoate, and heptafluorobutanoate, respectively. In the

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(16) It should be noticed that at pH 6.00, the reactions were measured in a conventional spectrophotometer in 5 cm path cells, whereas at pH 9, the measurements were carried out in a stopped flow apparatus where the optical pathlength is only 1 cm.

TABLE 2. Effect of the Concentration of β-CD on the Rate Constant (s^{-1}) for the Hydrolysis of 3[a]

	[**3**], 10^{-5} M					
[β-CD], 10^{-3} M	1.085	1.790[b]	2.198	2.435	3.014	7.535
			pH = 6.00[c]			
0.44	0.017 ± 0.002			0.007 ± 0.002		
0.90	0.06 ± 0.02	0.03 ± 0.01		0.021 ± 0.002		
1.28	0.060 ± 0.009	0.043 ± 0.009		0.030 ± 0.007		
2.43	0.09 ± 0.01	0.10 ± 0.04		0.047 ± 0.008		
3.71	0.070 ± 0.006			0.063 ± 0.004		
5.07	0.060 ± 0.005	0.06 ± 0.02		0.074 ± 0.006		
7.68	0.052 ± 0.007			0.067 ± 0.004		
11.5	0.042 ± 0.004	0.04 ± 0.01		0.06 ± 0.01		
			pH = 9.90[d]			
0.17			11 ± 3[e]			
0.35	29 ± 6		19 ± 3[e]		20 ± 12[e]	17 ± 6[e]
1.30	25 ± 7		24 ± 4		17 ± 5	18 ± 7[e]
2.76	24 ± 4		25 ± 3		24 ± 4	13 ± 4[e]
5.12			20 ± 2			
10.03	20 ± 3		16 ± 2		16 ± 2	15.3±0.5

[a] T = (25.1 ± 0.1) °C; μ = 0.2 M; MeCN = 3.8%; [buffer] = 0.096 M unless otherwise noted; each value is the average of at least 10 determinations, and the error represents standard deviation of the mean. [b] [Buffer] = 0.046 M. [c] Buffer is NaH_2PO_4/Na_2HPO_4. [d] Buffer is $NaHCO_3/Na_2CO_3$. [e] Calculated neglecting the first 5−10% of the reaction.

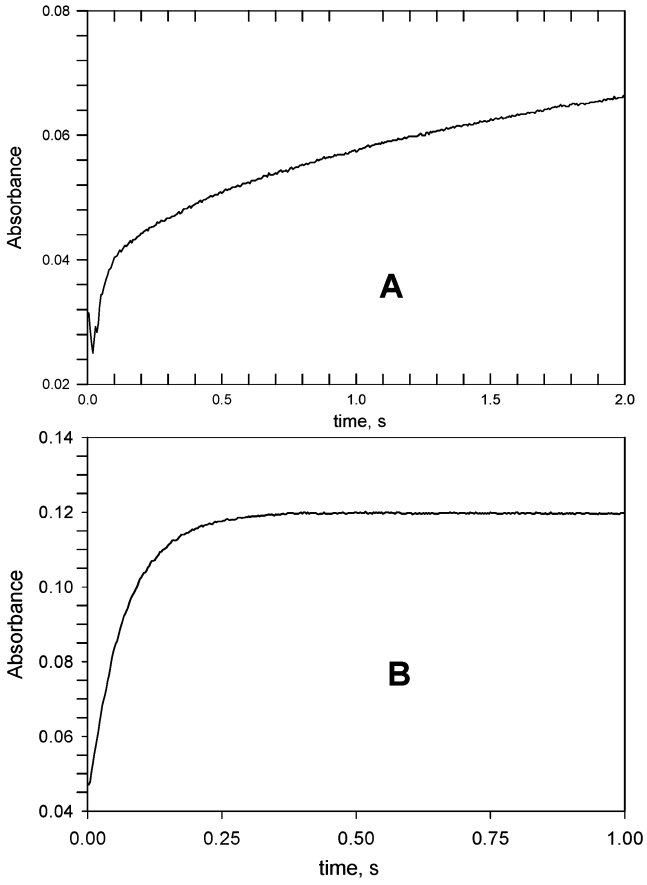

FIGURE 3. Absorbance vs time for the reaction of compound **3** (7.54×10^{-5} M) at 25.1 ± 0.1 °C, pH 9.90, buffer 0.096 M, β-CD = 3.5×10^{-4} M (A) and β-CD = 1.00×10^{-2} M (B).

hydrocarbon-derived esters, the decrease in rate is attributed to the steric effect produced by the replacement of hydrogen in the α position for a methyl group. The effect is more important for the change from acetate to propionate (rate ratio 2.1) than from propionate to butanoate (rate ratio 1.4), consistent with the smaller effect expected for the replacement of a β-hydrogen by a methyl group. It is remarkable that the rate ratios for trifluoroacetate/perfluoropropionate and perfluorpropionate/perfluorobutanoate, which are 2.00 and 1.36, respectively, are the same as those for the hydrogenated esters despite the fact that the volume of a CF_3 group is about 1.5 larger than that of a CH_3 group.[17] It appears that the increase in steric effect is compensated by the increase in electron-withdrawing effect when a CF_3 group replaces one fluorine atom in the α position.

The reactivity of perfluorooctanoate is significantly lower than that of the other two shorter esters. This low reactivity indicates that **3** is aggregated even at the lower concentration used (8.4×10^{-6} M). For hydrocarbon-derived esters it is very well established that the decrease in rate of reaction with concentration is due to self-association of the esters.[18] Besides, *p*-nitrophenyl perfluorononanamide, which was shown to be aggregated even at 2×10^{-6} M concentration, is also much less reactive than *p*-nitrophenyl acetanilide.[19]

It is known that cyclodextrins normally accelerate hydrolysis reactions of esters by the nucleophilic reaction of their ionized secondary OH groups, which leads to an acylated cyclodextrin.[20] Also, general base catalysis of water addition has been postulated for the catalysis of some ester hydrolysis.[21]However, there are several examples where β-CD inhibits reactions by a noncovalent mechanism such as a microsolvent effect. On the other hand, it can occur that the geometrical requirements for the inclusion in the cavity impose such conformation to the substrate that induces an increase or a diminution on the reaction rate.

One of the earliest examples of inhibition by cyclodextrins is the intramolecular transfer reaction of acyl group of 2-hydroxymethyl-4-nitrophenyl trimethyl acetate, which is catalyzed by α-CD but inhibited by β-CD.[22] It is

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TABLE 3. Rate and Equilibrium Constants for the Hydrolysis of Phenyl Trifluoroacetate and Substrates 1 and 2 in the Presence of β-CD[a]

substrate	pH	k_u, s^{-1} [b]	k_c, s^{-1}	k_c/k_u	k_2, $M^{-1}\ s^{-1}$ [c]	K_{CD}, $10^2\ M^{-1}$ [d]	K^{TS}, M^{-1}
phenyl trifluoroacetate[e]	6.00	2.06	0.017[f]	0.008[f]	2.2[f]	1.2	1.05[f]
	9.02	13.0	27	0.48	3.2×10^3	1.2	256
	9.91	71.6	180	2.51	2.2×10^4	1.2	246
1	6.00	0.44	0.0085	0.019	6.2 ± 0.2	7.3 ± 0.1	14
	9.92[g]	36	24	0.67	$(1.3 \pm 0.4)10^4$	5.3 ± 1.4	361
	10.49[h]	115	82	0.71	$(6 \pm 2)10^4$	7.3 ± 2.1	522
2	6.00[i]	0.29	0.015	0.051	54 ± 44	36 ± 12	186
	9.92[j]	26.5	13	0.49	$(2.8 \pm 0.9)10^4$	22 ± 6	1057
	10.50[k]	133	58.3	0.44	$(1.4 \pm 0.2)10^5$	24 ± 3	1053

[a] Solvent: water with 3.8% acetonitrile, 25 °C, ionic strength 0.2 M. [b] Values extrapolated to zero buffer concentration. [c] Corresponds to parameter *a* in eq 2, and the errors are standard deviation of the fit. [d] Corresponds to parameter *b* in eq 2 ,and the error are standard deviation of the fit. [e] Data from ref 10. [f] Data calculated by extrapolation of the data of **1** and **2** vs number of carbons. [g] Values calculated applying eq 2 to data obtained at 0.02 and 0.1 M buffer concentrations. [h] Values calculated applying eq 2 to data obtained at 0.02 and 0.08 M buffer concentrations. [i] Values calculated applying eq 2 to data obtained at 0.1 M buffer concentration. [j] Values calculated applying eq 2 to data obtained at 0.05 and 0.1 M buffer concentrations. [k] Values calculated applying eq 2 to data obtained at 0.08 M buffer concentration.

suggested that the substrate enters deeper and tighter in the bigger cavity of β-CD, so it is more difficult for it to accomplish the geometry of the transition state.

Inhibition was also observed trough a noncovalent mechanism for the hydrolysis of benzocaine[23] and of alkyl esters such as ethyl *p*-aminobenzoate and *m*- and *o*-ethyl aminobenzoate.[24] The authors suggest that the last substrates undergo total inclusion in the β-CD cavity and are shielded from nucleophilic attack by the alkoxide ion of the cyclodextrin and also by hydroxyl ion from solution.

The reaction of 4-carboxy-2-nitrophenyl acetate at pH 11.7 is accelerated by β-CD, but the reaction of the propanoate and butanoate derivatives are inhibited.[12]

The cleavage of esters that show saturation kinetics is usually explained by the reaction of the unbound substrate and that of the 1:1 substrate-β-CD complex. This is schematically shown in eqs 3 and 4, where S represents the substrate and SCD the complex of the substrate and β-CD and P the reaction products

$$S \xrightarrow{k_u} P \tag{3}$$

$$S + \beta\text{-CD} \overset{K_{CD}}{\rightleftharpoons} SCD \xrightarrow{k_c} P \tag{4}$$

The observed rate constant for this system is given by eq 5, which is of the same mathematical form of eq 2 with $a = K_{CD}k_c$, $b = K_{CD}$, and $c = k_u$

$$k_{obs} = \frac{k_u + K_{CD}k_c[\beta\text{-}CD]}{1 + K_{CD}[\beta\text{-}CD]} \tag{5}$$

From the dependence of the observed rate constant on β-CD concentration, the values of K_{CD} and k_c can be obtained, and these values are collected in Table 3.

The binding of the esters is quite dependent on the length of the perfluorinated chain (Table 3). For comparison, the results of phenyl perfluoroacetate are included in Table 3. In Figure 4 it is shown that there is a linear correlation between log K_{CD} and *N*, the number of carbons in the chain. The linear correlation obtained

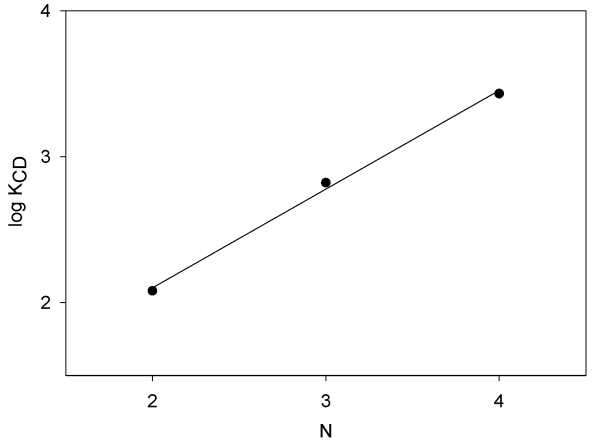

FIGURE 4. Dependence of the association equilibrium constant of perfluoroesters with β-CD with the number of carbons in the acyl chain.

indicates that the inclusion mode of the substrate is the same for the three compounds. The slope of this plot has a value of 0.67.

The association constants of sodium perfluoro alkanoates also increase with the chain length; the slope of the plot of log *K* vs *N* is 0.58 for salts with 3, 4, 5, and 7 carbon atoms in the chain.[25] Linear correlation between alkyl chain length and binding constant is usual; however, in general, the sensitivity of *K* to *N* is strongly dependent on the headgroup. The value of the slope of log *K* vs *N* for 4-nitro 2-carboxy phenyl alkanoates is 0.2,[4] whereas it is 0.1 for *p*-nitrophenyl alkanoates.[26]

In discussing the effects of β-CD on the cleavage of **1** and **2** we will make use of the kinetic parameters k_c/k_u, k_2 (=$K_{CD}k_c$) and K^{TS}.[27] The ratio k_c/k_u denotes the limiting acceleration or retardation due to β-CD, and k_2 is the second-order rate constant for S + β-CD → P. The value of k_2 measures the reactivity of β-CD toward different substrates under the reaction conditions, and so it measures the selectivity of β-CD for different substrates. The pseudoequilibrium constant K^{TS} is the apparent

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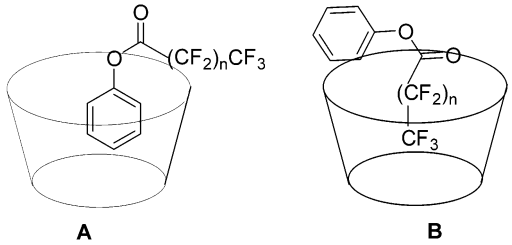
SCHEME 1. Schematic Representation of the Complexes with the Aryl Ring Inside (A) the Cavity and the Perfluorinated Chain Inside the Cavity (B)



association constant of the transition state of the β-CD-mediated reaction (symbolized as TS−CD) into the transition state of the normal reaction (TS) and β-CD, eq 6

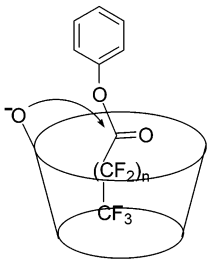
$$K^{TS} = \frac{[TS-CD]}{[TS][\beta\text{-CD}]} = \frac{k_c K_{CD}}{k_u} \qquad (6)$$

The derivation of eq 6 follows easily from the application of transition-state theory to k_u and k_c.[28]The usefulness of K^{TS} is that log K^{TS} is directly proportional to the free energy of stabilization of the transition state due to β-CD regardless of the mechanism. Thus, variation of log K^{TS} with structure may be used to probe transition-state structures and as a criterion of mechanism.

The kinetic parameters that characterize the cleavage of esters mediated by β-CD vary significantly with the alkyl chain length (Table 3). At pH 6 there is an important increase in the value of k_c/k_u from trifluoroacetate to **2** and also an important increase in the reactivity of the cyclodextrin-mediated reaction. These systematic changes are due to an increase in the stabilization of the transition state for the cyclodextrin-mediated reaction (K^{TS} from 1 to 186) as the alkyl chain is lengthened by two carbons. The slope of log K^{TS} vs number of carbons (N) is 1.1 at pH 6 and 0.46 at pH 9.9, but the data at pH 9.9 give a low correlation coefficient (0.880). On the other hand, the plot of log K_{CD} vs N has a slope of 0.67 and a good correlation coefficient (r^2 = 0.997) (Figure 4). Using the log K^{TS} at pH 9.90 for trifluoroacetate and **1** the slope is 0.17, whereas with the data for **1** and **2** the slope is 0.76. These results may indicate that the transition state for trifluoroacetate is different than that for the longer chain esters.

For the reactions at pH = 6.00, the plot of k_c/k_u vs N is linear with slope of 0.41. On the other hand, a similar plot of the data at pH 9.90 is definitively nonlinear. The data for trifluoroacetate and **1** define a line with slope of −0.57, whereas the data for **1** and **2** give a slope of −0.13. We think that all these results clearly indicate that different mechanisms operate under a different set of conditions. The perfluoroalkanoate esters may form at least two types of complexes with cyclodextrin, namely, with the aryl ring inside the cavity (Scheme 1A) and/or with the alkyl chain inside the cavity (Scheme 1B). In the case of phenyl trifluoroacetate, theoretical calculations indicate that both types of complexes are of similar energy.[29] Taking into account the high hydrophobicity of the perfluorinated alkyl chain, it is reasonable to think that the complex shown in Scheme 1B will predominate for compounds **1**−**3**.

SCHEME 2. Schematic Representation of the Transition State for the Cyclodextrin-Mediated Reaction in Basic Solutions



At low pH the nucleophile is water and it has difficulties reaching the carbonyl group of the included compound. As the chain becomes longer, the carbonyl group become more exposed to the solvent and is more easily reached by the nucleophile (k_c/k_u increases). In basic solutions, the cyclodextrin OH groups are partially ionized, and for most of the hydrolysis reactions of esters that are accelerated by cyclodextrins, the mechanism of the cyclodextrin-mediated reaction involves the reaction of one of these ionized OH groups with the substrate (Scheme 2). The rate of this reaction is strongly dependent on the orientation of the substrate in the complex.[30] Trifluoroacetate may have the right orientation in the complex, and the reaction is effectively accelerated.

For compounds **1** and **2** the predominant complex is probably that shown in Scheme 2 and the increase in the length of the chain situates the carbonyl group at a longer distance from the reactive group of the cyclodextrin. It is very well established that in intramolecular reactions the distance and orientation of the reacting groups is very important.[31] We do not think that the main nucleophile in the cyclodextrin-mediated reaction in basic pH is the hydroxide ion because in that case the kinetic parameters for phenyl trifluoroacetate, **1** and **2** should show similar trends.

The reactions of compound **3** in water occur in more than one step as is evident in Figure 2 where the absorbance at 242 nm increases and then decreases.[32] There is a good correlation between the maximum absorption reached and the concentration of the substrate. On the basis of our experience on the behavior of similar perfluorinated compounds,[33] we suggest that the faster process is associated with the aggregation process of the substrate and the slower one with the hydrolysis reaction. The aggregation phenomenon of perfluorinated compounds is much slower than that corresponding to hydrocarbon-derived compounds.[33] The rate of the first

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(29) The difference in steric energy for the complex with the aryl ring inside and that with the trifluoromethyl inside was calculated as 4.2 kcal/mol (see ref 11).

(30) The reaction of *m*-nitro phenyl acetate is more strongly accelerated than that of the para-substituted derivative due to the more favorable orientation of the substrate in the complex (see ref 20).

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process that we calculated with the two-exponential fitting of the data has a complex relationship with the aggregation phenomenon,[34] and there are not enough data to do further calculations. Besides, the nonlinear fitting is very dependent on the initial parameters used; therefore, the numbers given for the faster process in Table 1 are only indicative of the order of magnitude of the rate of the phenomenon measured.

The presence of β-CD significantly affects the rate of hydrolysis of **3**. For instance, at pH 9.9 with substrate concentration 1.1×10^{-5} M, the rate constant changes from 9×10^{-2} to 29 s^{-1} in the presence of 3.5×10^{-4} M of β-CD. At pH 6.00 the rate increases up to β-CD concentration of 5.07×10^{-3} M and then there is a slight decrease (Table 2). We suggest that β-CD forms a complex with **3** in its monomeric form; therefore, the monomer−aggregate equilibrium is disrupted due to the low concentration of the monomer in solution. The 1:1 complex of **3** with β-CD reacts at a similar rate as that expected for **3** in its monomeric form**.** The slight decrease in the rate may be attributed to the formation of a 1:2 complex as observed with hydrocarbon-derived compounds;[12] however, there is not enough data to probe this hypothesis since solubility reasons precludes the study of reactions at higher concentrations.

In conclusion, formation of inclusion complexes of esters **1**−**3** with cyclodextrin leads to different kinds of effects depending on the substrate and on the pH, and they are attributed to different mechanisms for the reactions. For substrates **1** and **2** that are monomers under the conditions of the study, the reaction is strongly inhibited in acid and basic pH as well but the mechanism of the inhibition is different under the two sets of conditions. At low pH the inhibition comes from protection of the carbonyl group toward nucleophilic attack by water. In basic pH the reaction of OH as external nucleophile is also inhibited. The cyclodextrin-mediated reaction involves the ionized OH group at the rim of the cyclodextrin cavity with poor efficiency due to an unfavorable orientation of the substrate in the complex. On the other hand, the reaction of compound **3** is strongly accelerated by inclusion in the cavity of cyclodextrin because it breaks the aggregates of the substrate.

Experimental Section

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

The pH measurements were done in a pH meter at controlled temperature and calibrated with buffers prepared in the laboratory according to the literature.[35]

The β-cyclodextrin[36] was used as received, but the purity was periodically checked by UV spectroscopy; the pure compound does not absorb above 230 nm. The substrates were prepared by the reaction of phenol with the corresponding acid chloride following literature methods.[37] The product was obtained after distillation of the remaining acid chloride and phenol. The products were characterized by IR and mass spectrometry.

Phenyl Perfluoropropanoate. IR (KBr, cm^{-1}): 3080, 1798, 1600, 1232, 1170, 833, 761, 502. MS, *m*/*z* (rel intensity): 240 (M^+, 20), 147 (1), 119 (26), 100 (36), 94 (20), 79 (46), 69 (70), 45 (100).

Phenyl Perfluorobutanoate. IR (KBr, cm^{-1}): 3074, 1799, 1602, 1223, 1194, 1143, 850, 757, 509. MS, *m*/*z* (rel intensity): 290 (M^+, 7), 169 (10), 150 (11), 119 (27), 100 (35), 94 (20), 79 (37), 69 (100), 45 (92).

Phenyl Perfluorooctanoate. IR (KBr, cm^{-1}): 3070, 1797, 1593, 1246, 1196, 1156, 847, 747, 533. MS, *m*/*z* (rel intensity): 491 ($[M + 1]^+$, 5), 490 (M^+, 3), 169 (13), 131 (30), 119 (24), 100 (15), 93 (12), 77 (100), 69 (63), 65 (59).

The purity was also controlled comparing the spectrum of a completely hydrolyzed solution with a solution of the corresponding phenol under the same conditions.

The reactions were followed by measuring the change in absorbance with time. All reactions of compounds **1** and **2** and those of compound **3** at alkaline pH were done in a stopped-flow spectrometer, with unequal mixing, as previously described.[10] The reactions of compound **3** at pH 6 were measured in a conventional UV−vis spectrophotometer. For the kinetic runs, 0.6 mL of a stock solution of **3** in acetonitrile was injected into a 5 cm optical pass length quartz cuvette containing 15 mL of a water solution containing all the other ingredients. All the reactions were carried out at (25.1 ± 0.1) °C, ionic strength (μ) 0.2 M using NaCl as compensating electrolyte, and with 3.8% acetonitrile as cosolvent.

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Supporting Information Available: Tables S1 and S2 containing the observed rate constant for hydrolysis of substrates **1** and **2** as a function of pH and buffer concentration. Tables S3 and S4 containing the observed rate constant for **1** and **2,** respectively, at different pH, buffer, and β-CD concentrations. This material is available free of charge via the Internet at http://pubs.acs.org.

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