Effect of β-Cyclodextrin on the Hydrolysis of Trifluoroacetate Esters

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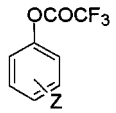
The hydrolysis of p-F, p-Cl, and m-Cl phenyl trifluoracetates was studied in the presence of β-cyclodextrin (β-CD). The reactions are inhibited by β-CD at pH 6 while they are catalyzed in alkaline solution. MM3 calculations reproduce some of the experimental results. The substrates form inclusion complexes with β-CD which are of similar stability as those of the corresponding acetates; however, the association of the transition state is less favorable in these reactions than in those of the acetates, and consequently less stronger catalysis is observed.

Cyclodextrins (CD) are cyclic oligomers of α-D-glucose, which are produced by enzymatic degradation of starch. Compounds with six, seven, or eight glucose units, respectively, are called α-, β-, and γ-CD.[1] They are good models for hydrolytic enzymes, and many studies have been done on CD-catalyzed hydrolysis of esters.[2,3,4,5,6] Important differences were found when the leaving group was changed to poorer leaving groups.[6] When the reaction takes place within an inclusion complex in which the phenyl group of the ester resides in the hydrophobic cavity of CD, the efficiency of the ester cleavage relative to that by hydroxide ion is generally greater for meta than for para substituents because the orientation of the former within the CD cavity has geometry more suitable for acyl transfer.[3,4,5]

The hydrolysis of phenyl acetate in the absence and in the presence of β-CD has been studied computationally[7] by means of semiempirical MO calculations (AM1)[8] and considering the effect of solvent by the Langevin dipole solvent model.[9] This work provides an important insight into the role of the macrocycle cavity in catalysis and to the necessity of including thermal conformational sampling in modeling structural reorganization of cyclodextrin along the hydrolysis reaction path.

In previous work we reported important differences in the behavior of phenyl and *p*-methyl phenyl trifluoroacetate esters when compared with the corresponding acetate esters[10] which we attributed to a different mode of inclusion. In this paper, we report a kinetic study of the hydrolysis of trifluoroacetate esters **1**−**3** that bear better leaving groups than those previously studied,[10] and also one of them, **3**, has a meta substituent. It is known that substituents in meta position favor the orientation of the substrate in a position appropriate for the reaction, which results in stronger catalysis. For instance, the ratios of the catalyzed (k_c) and uncatalyzed (k_u) rate constants for *p*- and *m*-chlorophenyl acetate are 13 and 35, respectively.[11] In contrast, no significant differences of the ratio are observed for substrates **2** and **3**. We also report here some molecular mechanics calculations which were done to aid in the interpretation of the results.



1 (Z=p-F) **2** (Z = p-Cl) **3** (Z = m-Cl)

Results

The hydrolysis rates of substrates **1**−**3** were measured at pH 6.00 and 9.02 in the presence of several concentrations of β-cyclodextrin (β-CD). At each concentration of the macrocycle at least four concentrations of buffer were used (Table S1−S3).[12] The observed rate constant at each

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(12) Supporting Information.

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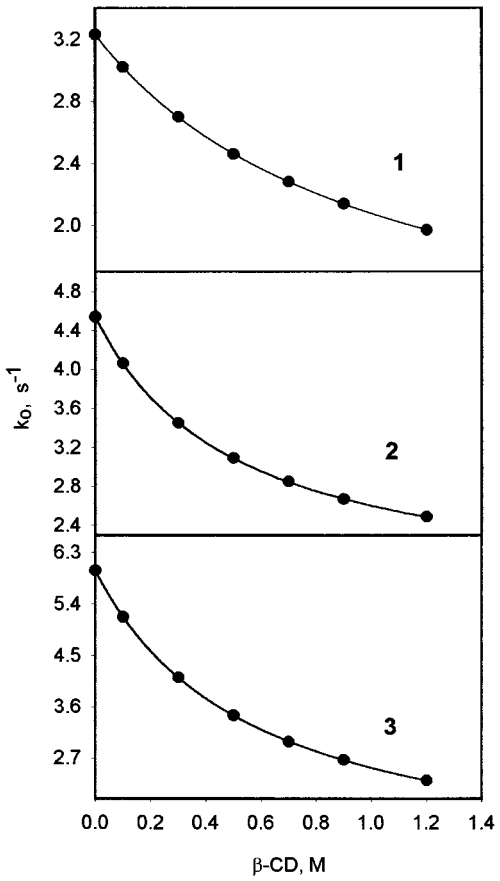


Figure 1. Effect of β-CD on the rate of hydrolysis of **1**−**3** at pH 6. Rate constants were extrapolated to zero buffer concentration. Temperature: 25 °C. Solvent 3.8% ACN. The lines were calculated using eq 9 and the parameters shown in Table 3.

pH and each buffer concentration was plotted against β-CD concentration, and the plots were fitted by using eq 1

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

where a and b are adjustable parameters, c is the observed rate constant in the absence of β-CD, and [β-CD] represents the molar concentration of β-CD.

Using the parameters a and b calculated at each buffer concentration, the values of the rate constants were calculated for the same concentration of β-CD. These values were then plotted against buffer, and from the intercept of the plots, the rate constants extrapolated to zero buffer concentration were obtained. At pH 6 the rate decreases whereas at pH 9 it increases with β-CD concentration, showing in all cases a saturation effect (Figures 1 and 2).

The hydrolysis of phenyl acetates with different substituents on the aromatic ring has been studied at alkaline pH, but there are very few studies about their hydrolysis at neutral pH because of their low reactivity. To compare our results at pH 6 with that of an acetate derivative, we studied the reaction of *p*-nitrophenyl acetate in the same environment. The effect of β-CD on the hydrolysis of this substrate at pH 6 is significantly smaller than that observed at pH 10.6 by Bender et al.[3] These authors found that the relative rate of the reaction

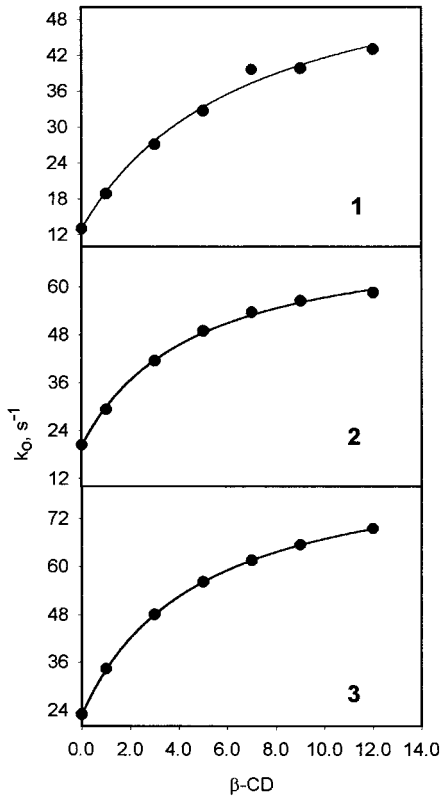
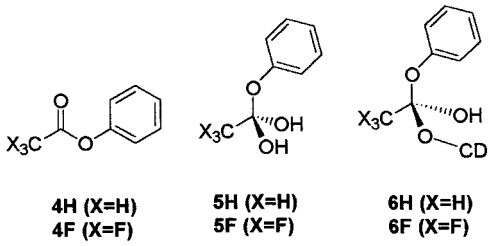


Figure 2. Effect of β-CD on the rate of hydrolysis of **1**−**3** at pH 9.02. Rate constants were extrapolated to zero buffer concentration. Temperature 25 °C. Solvent 3.8% ACN. The lines were calculated using eq 8 and the parameters shown in Table 3.

in the presence of β-CD 0.012 M and in its absence is 6.7, while in this case it is 1.4. We note that the catalysis observed for the acetate contrasts with the inhibition found for the perfluorinated esters.



Theoretical Calculations. The inclusion of phenyl acetate, **4H**, and phenyl trifluoroacetate, **4F**, into the β-CD cavity was emulated following previously described methodology[13] using Allinger's MM3 force field.[14,15] The optimization was done using the full matrix Newton−Raphson method. The four orientations shown in Figure 3, **A**−**D**, were used for the inclusion emulation (at 1 Å intervals). The calculated (MM3) relative steric energies[16] for the various orientations are collected in Table 1. Orientation **A** (Figure 1S), where the phenyl ring is inside the cavity and the CF_3CO or CH_3CO portion of the molecule is protruding through the smaller rim of the cyclodextrin cavity, is always computed to be by far the most stable. On the other hand the energy minimum for inclusion in orientation **D** (Figure 3), where the trifluoromethyl group is deeply included into the CD cavity, is about 5 kcal/mol more stable for the trifluoroacetate than for the acetate (note in Table 1 that the SE is 9.2 and

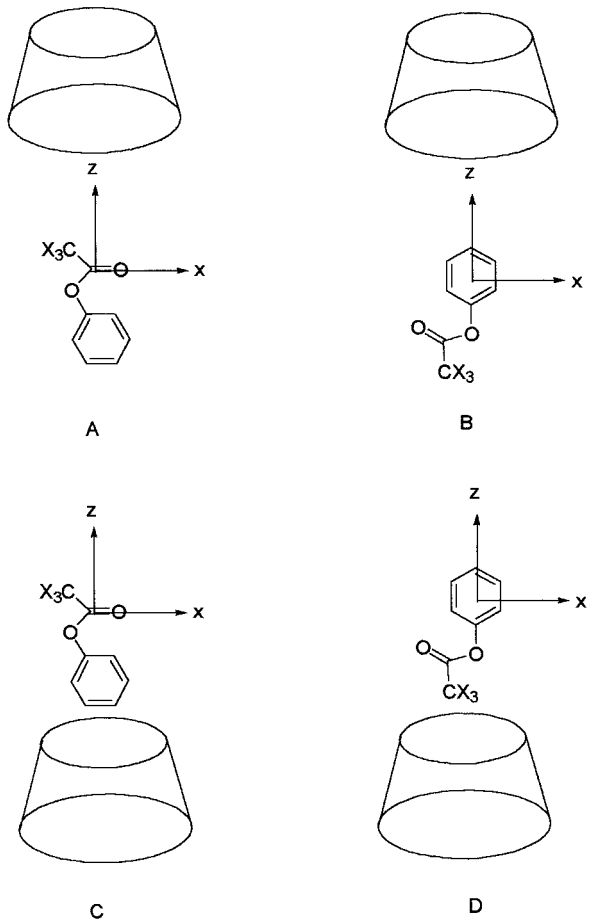


Figure 3. The four substrate orientations considered for the emulation of the complexation of **4H** and **4F** by molecular mechanics (MM3) calculations.

Table 1. Calculated (MM3) Relative Steric Energy (rel SE, in kcal/mol) for the Minimized Structures of the Complexes of 4H and 4F with β-Cyclodextrin in the Four Orientations Considered (see Figure 3)

	rel SE (kcal/mol)	
orientation	**4H**	**4F**
A	0.0	0.0
B	7.5	6.9
C	6.2	6.3
D	9.2	4.1

4.1 for **4H** and **4F**, respectively), in agreement with the higher hydrophobicity of the CF_3 group.

Table 2. Steric Energy (SE, kcal/mol), Heat of Formation (ΔH_f, kcal/mol), Free Energy of Formation (ΔG_f, kcal/mol), as Obtained by the MM3 Calculations on Species Involved in Mechanisms a and b (see text)

		SE	ΔH_f	ΔG_f
	water[a]	0.00	−57.85	−54.69
	β-CD	62.70	−1463.54	750.24
with H	4H	9.40	51.61	74.69
	4H/β-CD[b]	55.49	−1430.89	823.54
	5H	5.47	16.33	84.79
	5H/β-CD[b]	45.53	−1472.33	830.67
	6H	61.48	−1402.46	832.31
with F	4F	24.96	−64.67	73.14
	4F/β-CD[b]	67.99	−1550.24	817.61
	5F	13.54	−108.59	76.5
	5F/β-CD[b]	49.94	−1599.95	816.14
	6F	69.27	−1526.69	823.40

[a] Experimental thermodynamic values obtained from *General Chemistry*; Atkins, P. W., Ed.; Scientific Am. Books: New York, 1989. [b] Represents the complex of the corresponding compound with β-CD.

Tetrahedral compounds **5H**, **5F**, **6H**, and **6F** were calculated as models for the transition states for the hydrolysis reactions. Compounds **6** represent the tetrahedral intermediates formed by the attack of one of the secondary OH groups of β-CD on the carbonyl carbons of the esters, and they are models for the transition states in the CD-catalyzed pathways.

The hydrolysis pathways considered were the following:

(a) The normal acyl cleavage mechanism of ester hydrolysis in basic media. MM calculations cannot be undertaken on the hydroxyl anion because of the absence of parameters, and we used the protonated species as suitable reaction models (eq 2).

$$\text{4H (4F)} + H_2O \longrightarrow \textbf{5H, 5F} \longrightarrow \text{Products} \qquad (2)$$

(b) Complexation of **4H** or **4F**, followed by the formation of **6H** or **6F**, respectively, which are finally transformed into the products, eqs 3 and 4.

$$\text{4H,4F} + \beta\text{–CD} \longrightarrow \text{4H,4F / }\beta\text{–CD} \qquad (3)$$

$$\text{4H,4F / }\beta\text{–CD} \longrightarrow \textbf{6H,6F} \qquad (4)$$

The computed energies for reactants, complexes and intermediates involved in each mechanism are shown in Table 2.

Considering mechanism a (eq 2), it is worth noting here that reactions involving fluorinated compounds are computed to be faster than the corresponding nonfluorinated compounds in agreement with what has also been experimentally observed. The $\Delta\Delta G$ value calculated using the data shown in Table 2 for **4H** and **4F** reacting according to eq 2 is 6.8.[17] These data indicate that **4F** should be about 900 times more reactive than **4H**. The observed differences in reactivity, i.e., 7.34×10^{-4} s^{-1} at pH 10.6 for phenyl acetate[11] and 71.6 s^{-1} at pH 9.91 for

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(16) Allinger, N. L. *Molecular Mechanics*; ACS Monograph 177; American Chemical Society: Washington, DC, 1982; p 4.

(17) These numbers were obtained as follows $\Delta\Delta G_f = [\Delta G_f (\textbf{5H}) - \Delta G_f (\textbf{4H})] - [\Delta G_f (\textbf{5F}) - \Delta G_f (\textbf{4F})]$.

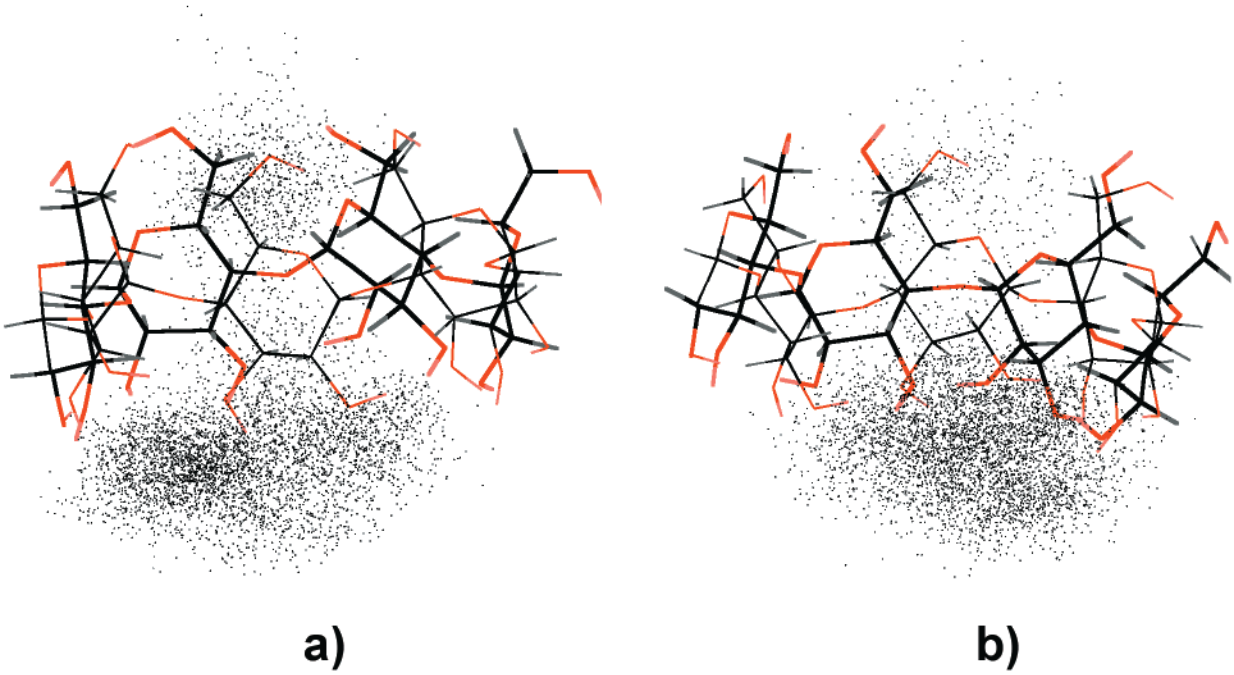


Figure 4. Schematic representation of the position for the carbonyl carbon (represented by dots) during the MD simulation of the β-CD inclusion complex. (a) Corresponding to the **4H** complexation; (b) Corresponding to the **4F** complexation.

trifluorophenyl acetate,[10] indicate even higher energy differences.

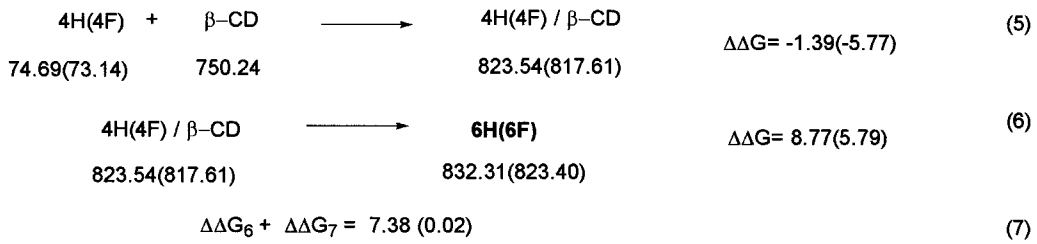
Concerning the complexation process, inclusion of fluorinated compounds is favored against inclusion of nonfluorinated compounds according to the calculated complexation energies that differ by 3 kcal/mol in ΔH and by more than 4 kcal/mol in ΔG (Table 2). This difference is mainly due to the torsional term, dipole−dipole interactions, and the long-range van der Waals interactions. The experimental values of the complexation constants for compounds **4H** and **4F** are about the same, namely 139 M^{-1} [11] and 120 M^{-1},[10] respectively. The absence of solvent in our calculations, the use of nonrepresentative structures or the use of nonproper parameters for the fluorine atom may be responsible for this discrepancy. Molecular dynamics (MD) simulations (1000 ps, 300 K) in water were carried out to solve the first two points. Computations were performed using the most stable structures for orientations **A** and **B** obtained in the MM3 calculations. The AMBER*[18] force field and the GB/SA solvation model[19] were used in the MacroModel package.[20] The obtained results show the same tendency as the previous ones and indicate higher stability of **4F**/β-CD than **4H**/β-CD. Thus an inadequate set of parameters for the fluorine atom is probably the reason for this disagreement.

The MD simulations for the inclusion complexes between β-CD and **4H** and **4F** can also be used to estimate the geometry for the inclusion complexes. Orientation B is now favored, and a schematic representation of the position for the carbonyl carbon along the simulation time is shown in Figure 4. Interestingly, this force field calculation shows that the carbonyl group prefers to be near the secondary OH groups, which are the reactive ones in cyclodextrin-catalyzed reactions.

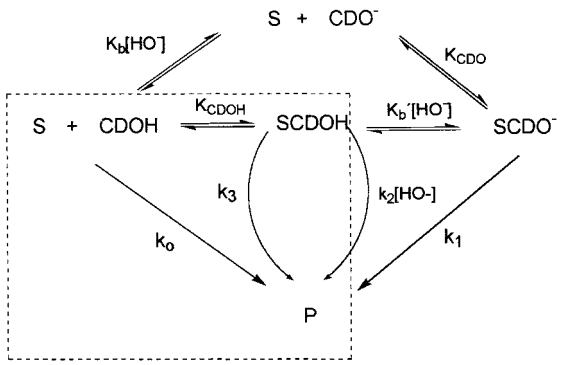
The accelerating effect of β-CD on the acyl cleavage reaction is reproduced by calculations because the activation energies in the absence of β-CD are always greater than the values obtained in the presence of β-CD. Using the data shown in Table 2, we calculated the $\Delta\Delta G$ values for the reactions catalyzed by β-CD as shown in eqs 5−7. It can be seen in eq 7 that the $\Delta\Delta G$ values for the overall reaction of **4H** and **4F** in the presence of β-CD are significantly lower than the corresponding values for eq 2. In this case, the differences in free energy of formation between tetrahedral intermediates **5H** (**5F**) and the substrates **4H**(**4F**) are 10.1(3.36) kcal/mol. These results are consistent with the observation of catalysis by cyclodextrin.

Discussion

The hydrolysis reactions of the esters **1**−**3** show catalysis by CD at pH > 9. They are also buffer catalyzed, and this effect takes place in the presence and absence of β-CD (Table S1).[12] The buffer-catalyzed reactions have



Scheme 1



been discussed in a previous work.[21] For reactions mediated by CD, the buffer effects are difficult to interpret because buffers significantly affect the association equilibrium constants with different guests[22] and should also affect the interaction of the transition state with CD. Besides, it has been shown that the nucleophilic reaction of CD with esters is general base catalyzed by imidazole,[23] so it may be possible that the buffers used in this study could act as general base catalysts of the cyclodextrin-mediated reaction. Therefore, we have extrapolated the rate constants to zero buffer concentration in all cases. At pH 6 the reactions are inhibited by CD and catalyzed by buffers, thus for the reasons indicated above, all the data used was extrapolated to zero buffer concentration. Figures 1 and 2 show the dependence of the extrapolated values of the observed rate constant with β-CD concentration.

The mechanism of catalysis of the hydrolysis of esters by CDs has been explained in terms of nucleophilic catalysis by the ionized secondary OH group at the CD rim, which leads to the acylated CD. Also, general base catalysis of water addition has been postulated for the catalysis of some esters hydrolysis.[24]

Under conditions where only part of the β-CD is in its ionized form,[25] inclusion complex formation should take place with the ionized and the un-ionized β-CD. Therefore, a minimum mechanism for the hydrolysis reaction in the presence of β-CD may be represented by Scheme 1.

In Scheme 1, S represents the substrate, CDOH and CDO^- are the neutral and ionized β-CD, and S·CDOH and $S{\cdot}CDO^-$ are their respective inclusion complexes with association equilibrium constants named K_{CDOH} and K_{CDO}. The rate constants k_3 and k_2 involve, respectively, the reaction of water and HO^- with the complexed substrate, and k_1 represents the rate constant for the nucleophilic reaction of β-CD with the included substrate.

Table 3. Experimentally Determined Parameters for the Hydrolysis of Aryl Trifluoroacetates 1−3 and Aryl Acetates[a]

substrate	pH	k_o, s^{-1} [a]	k_c[b]	K_{CDOH}, M^{-1}	K_{CD}^{TS}, M^{-1}
p-F (**1**)	6.00	3.23	0.915	99 ± 1	28
	9.02	13.1	61.2	145 ± 29	677
	10.6[a]	1.2×10^{-3}	2.0×10^{-2}	128	2174
p-Cl(**2**)	6.00	4.45	1.65	198 ± 13	73
	9.02	20.4	73.9	219 ± 17	793
	10.6[a]	1.6×10^{-3}	2.2×10^{-2}	312	4166
m-Cl(**3**)	6.00	5.99	0.579	176 ± 1	17
	9.00	22.9	88.1	210 ± 1	808
	10.6[a]	2.0×10^{-4}	7.0×10^{-3}	370	12820

[a] Data for the corresponding aryl acetate taken from ref 11. [b] k_c is $K_b'k_1$ for the reactions at pH 9.02 and k_3 for those at pH 6.00.

The value of $K_b = K_a/K_w$ is ∼100,[25] and k_0 is the pseudo-first-order rate constant for the reaction in the absence of β-CD. The formation of a β-CD-substrate complex cannot be corroborated using other means such as NMR spectroscopy[26] because the substrates react very fast with water.

The observed rate constant for the reactions at pH 9 after some simplifications is given by eq 8,[27]

$$k_{obsd} = \frac{k_o + K_b K_{CDO} K_1 [\beta\text{-CD}]_o [HO^-]}{1 + K_{CDOH}[\beta\text{-CD}]_o} = \frac{k_o + K_b' K_{CDOH} k_1 [\beta\text{-CD}]_o [HO^-]}{1 + K_{CDOH}[\beta\text{-CD}]_o} \quad (8)$$

where K_b' is the ionization constant of β-CD in the complex divided by K_w. On the other hand, at pH 6 the observed rate constant is given by eq 9. Under these conditions only the part of the scheme that is inside the dotted line square is considered.

$$k_{obsd} = \frac{k_o + k_3 K_{CDOH}[\beta\text{-CD}]_o}{1 + K_{CDOH}[\beta\text{-CD}]_o} \quad (9)$$

Both equations have the mathematical form of eq 1. The value of $K_b'k_1$ can be calculated from the parameter a obtained for the reactions in basic solutions. In all previous studies of hydrolysis of esters catalyzed by cyclodextrins, the value of $K_b'\,k_1$ is usually given as k_c,[11] the catalyzed rate constant. In Table 3 the values of k_o determined in the absence of CD and those of k_3, $K_b'k_1 = k_c$ and K_{CDOH} obtained by fitting the experimental data to eqs 8 and 9 are collected. The values of K_{CDOH} obtained in basic and acid solutions are in fair agreement which gives support to the proposed mechanism.

Following Kurz[28] treatment which was applied to CD-catalyzed (or inhibited) reactions by Tee,[29] the ratio $k_1K_b'K_{CDOH}/k_o$ and k_3K_{CDOH}/k_o can be regarded as the association constant of the transition state, K_{CD}^{TS}. Therefore its variation with structure gives information regarding the nature of the transition state of the CD-mediated reaction. The changes in rate are determined by the strength of binding of the transition state relative

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(27) Equation 9 is obtained considering that k_3 and $k_2[HO^-]$ are negligible compared with k_1 (see ref 10) and also assuming that $Kb'[HO^{-}] \ll 1$ which is true if $K_{b'} \approx K_b$.
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to that of the substrate. When binding of the substrate is stronger than binding of the transition state, inhibition is observed. In the reactions of aryl acetates due to the partial covalent interaction between the ester substrate and CD in the transition state, K_{CD}^{TS} usually shows strong dependence on the position and size of the substituents.[11] In Table 3 we can see that for the reactions in basic solutions, there are no significant differences between the values of the association constant for the substrates when the acetates are compared with trifluoroacetate derivatives; however, the values of K_{CD}^{TS} are significantly different. Similar results were obtained with phenyl trifluoroacetate and *p*-methylphenyl trifluoroacetate.[10] It is evident that the reason for the small catalysis for the perfluorinated compounds is due to less efficient stabilization of the transition state relative to the ground state for the reactions of these derivatives.

Comparison of the calculated free energy for the rate-limiting step in mechanism b (eq 6) with that for the reaction in the absence of cyclodextrin (eq 2), shows that the difference in free energy for the reaction in water and that mediated by CD for **4H** compared with **4F** is 3.8 kcal/mol.[30] This result is in agreement with the fact that the catalysis observed is less significant for the perfluorinated compounds.

In conclusion, the results presented here indicate that the less efficient catalysis by β-CD for the reactions of trifluoroacetate esters compared with acetate esters is not due to different mode of inclusion of the substrates as we previously[10] suggested but to smaller stabilization of the transition state for the perfluorinated esters (Table 3). This effect can be attributed to steric factors because the CF_3 group has a considerably higher van der Waals volume than the CH_3,[31] and so the transition state for the reaction with cyclodextrin is more sterically hindered than that of the corresponding acetate.

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 the laboratory according to the literature.[32] The β-cyclodextrin (Roquette)[33] was used as received but the purity was periodically checked by UV spectroscopy, the pure compound do not absorb above 230 nm. The substrates were prepared by the reaction of the appropriate phenol with trifluoroacetic anhydride following literature methods.[34] The product was obtained after distillation of the remaining trifluoroacetic anhydride and trifluoroacetic acid. The purity was controlled by comparison of the spectrum of a completely hydrolyzed solution with a solution of the corresponding phenol and by IR in comparison with literature data.[35] The kinetic procedures were described in previous work.[10]

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Supporting Information Available: Table S1−S3, containing the observed rate constant for substrates **1**−**3** as function of pH, buffer, and cyclodextrin concentration, and Figure S1, showing the calculated structure of complex with orientation A. This material is available free of charge via the Internet at http://pubs.acs.org.

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(30) With the data reported in Table 2, $\Delta\Delta G$ values for eq 2 are 64.8 and 58 for **4H** and **4F**. The rate-determining step and the corresponding energy values for the β-CD-catalyzed reaction is shown in eq 6, namely 8.77 and 5.79. Then the relative value for **4H** and **4F** is calculated as $(64.8 - 8.77) - (58 - 5.79) = 3.8$.

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