Articles

pH Dependent Effect of β-Cyclodextrin on the Hydrolysis Rate of Trifluoroacetate Esters

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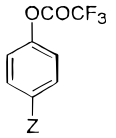
The kinetics of the hydrolysis of phenyl trifluoroacetate (**1a**) and *p*-methylphenyl trifluoroacetate (**1b**) is pH independent below pH 6 and shows first order dependence on HO^- concentration above pH 8. The reaction is weakly buffer catalyzed. In the presence of β-cyclodextrin the rate increases in a nonlinear fashion at constant pH above pH 8 but it decreases at pH 6. At pH 9.91 the ratio of rate constants for the reaction in the presence and in the absence of 0.012 M β-cyclodextrin is 11 and 2 for phenyl acetate and phenyl trifluoroacetate, respectively. The different behavior of the two substrates is attributed to different modes of inclusion. It is suggested that the reacting complex in the case of substrates **1a** and **1b** has the trifluoromethyl group inside the cavity. The inhibition of the reaction in neutral solution is attributed to a microsolvent effect and to protection of the carbonyl group toward water attack.

Cyclodextrins are cyclic oligomers of α-D-glucose which are produced by enzymatic degradation of starch. Compounds with six, seven, or eight glucose units are called α-, β-, and γ-cyclodextrin.[1] They have been shown to be a good model for hydrolytic enzymes, and many studies have been done in regard to the cyclodextrin catalyzed hydrolysis of esters,[2−6] but much less attention has been given to the effect on the reaction of amides.[7−11]

In the hydrolysis of esters important differences were found when the leaving group was changed to poorer leaving groups.[6] As 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 since the orientation of the former within the CD cavity has a geometry more suitable for acyl transfer.[3−5] It is surprising that in the case of *m*- and *p*-nitro-substituted trifluoroacetanilides the para isomer is more strongly catalyzed than the meta isomer by α-CD[7] and β-CD.[11]

In a previous work we attributed the different behavior of amides and esters to different rate-determining steps in the cyclodextrin-catalyzed reaction, and we also found different degrees of catalysis depending on the pH of the study. Since the amides were derived of perfluorinated compounds and esters were hydrocarbon derived, we considered it of interest to study the effect of cyclodextrin on the hydrolysis of perfluoroalkyl esters. We now report results regarding the hydrolysis of esters **1**, to be compared with those of amides and acetates having the same leaving group. The reactions were catalyzed at pH ≥ 9 and inhibited at pH ≤ 6. The results also indicated that replacing the methyl by a trifluoromethyl group in aryl esters leads to a less effective catalysis by β-cyclodextrin (β-CD).



1a Z=H **1b** Z=CH_3

On the other hand, in this case we only found evidences of formation of 1:1 contrary to our previous findings with amides where 1:1 as well as 1:2 inclusion complexes were formed.[10,11] The formation of 1:1 and 1:2 inclusion complexes is highly dependent on the structure of the substrates involved, and it is well known that small variations in the substrate structure can lead to considerable variation in the kinetic behavior of cyclodextrin-catalyzed reactions and in the type of complexes formed.[12−14]

Results

The hydrolysis of substrates **1** was measured as a function of pH in the range of pH 6.00 to 9.91 (Tables S1 and S2).[15] For substrate **1a** the observed rate constants were also determined at pH 1.17 (Table S1). At each pH at least two buffer concentrations were used to determine whether there was buffer catalysis. The rate barely

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(9) Komiyama, M.; Bender, M. L. *Biorg. Chem.* **1977**, *6*, 323.

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(12) Tee, O. S.; Du X.-X. *J. Am. Chem. Soc.* **1992**, *114*, 620.

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(15) Supporting Information.

S0022-3263(96)01627-1 CCC: $14.00

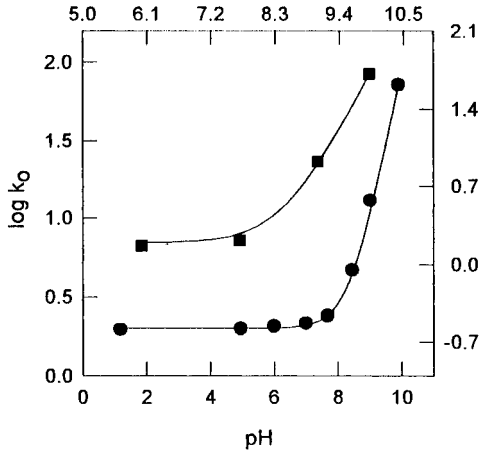


Figure 1. Observed rate constant for the hydrolysis of **1a** (● left and bottom axes) and **1b** (■ right and top axes) vs pH. Temperature 25.1 °C, solvent contains 3.8% ACN. Ionic strength 0.2 M.

Table 1. Effect of Temperature on the Observed Rate Constant (s^{-1}) for the Hydrolysis of 1a[a]

buffer, M[b]	T °C				
	5.3	15.1	25.2	34.1	44.1
0.010			2.02 ± 0.03		
0.019			2.2 ± 0.1		
0.029	0.78 ± 0.04	1.24 ± 0.07		3.14 ± 0.08	4.6 ± 0.2
0.034			2.1 ± 0.1		
0.048			2.2 ± 0.2		
0.071	0.79 ± 0.03	1.31 ± 0.06		3.4 ± 0.1	5.0 ± 0.3
0.096	0.84 ± 0.06	1.38 ± 0.06	2.30 ± 0.07	3.7 ± 0.2	5.5 ±! 0.3

[a] μ = 0.2 M. Solvent water with 3.8% v/v ACN. Each rate constant is the average of at least ten determinations. Error represents the average deviation from the mean. [b] Buffer HPO_4^{2-}/HPO_4^-; pH 6.00.

increased outside experimental error with buffer concentration. In Figure 1 the observed rate constant extrapolated at zero buffer concentration is plotted vs pH for compounds **1a** and **1b**.

The observed pseudo-first-order rate constant can be represented by an equation of the form of eq 1

$$k_o = k_w + k_{HO}[HO^-] \quad (1)$$

For **1a** the rate of the pH independent zone was determined at various temperatures (Table 1). The plot (not shown) of log k_o vs $1/T$ gives a good straight line from which the activation energy was calculated. The value of $\Delta S^‡$ (in calories per degree per mole) was calculated using eq 2.[16]

$$\frac{\Delta S^‡}{4.576} = \log_{\ o} - 10.753 - \log T + \frac{E_a}{4.576T} \quad (2)$$

The calculated values are 7.3 kcal/mol and −32.6 eu for $\Delta H^‡$ and $\Delta S^‡$, respectively. These values compare well with those determined by Moffat and Hunt[17] which are 6.26 kcal/mol and −45.9 eu in 30% aqueous acetone.

The thermodynamic parameters have also been determined in acetonitrile−water of various molar fractions, and it was shown that the $\Delta S^‡$ becomes less negative and $\Delta H^‡$ increases as the water content of the solvent increases.[18]

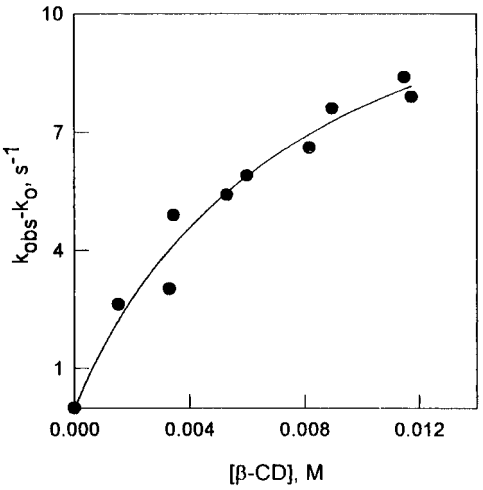


Figure 2. Effect of β-CD on the hydrolysis of **1a** at pH 9.02. Reaction conditions as in Figure 1.

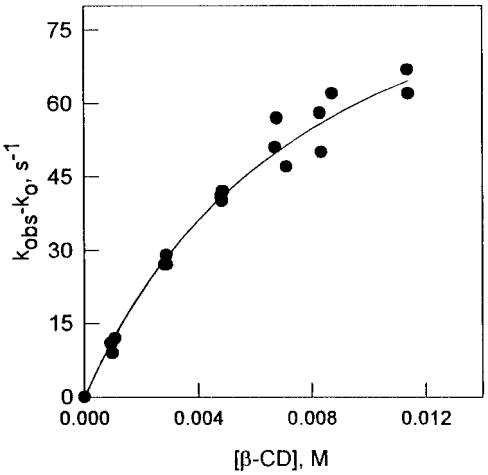


Figure 3. Effect of β-CD on the hydrolysis of **1a** at pH 9.91. Reaction conditions as in Figure 1.

Effect of β-Cyclodextrin. The hydrolysis rate of substrates **1** was measured at pH 6, 9.02, and 9.91 in the presence of several concentrations of β-cyclodextrin, and at each concentration of β-CD at least two buffer concentrations were used (Tables S3 and S4). In the case of substrate **1a** the effect of β-CD was also determined at pH 1.17 to show that the effect is similar to that at pH 6. The effect of the buffer is about the same for the two substrates in the reaction with and without cyclodextrin, and in all cases the increase in rate with buffer concentration is less than 10%. The observed rate constant at each pH and buffer concentration was subtracted from the observed rate constant at the same pH and buffer concentration, but with β-CD these values were plotted as a function of β-CD concentration (Figures 2 and 3 are representatives).[19] It can be seen that at pH 6 the rate decreases whereas at pH 9 and 9.91 it increases with cyclodextrin concentration, showing in all cases a saturation effect. The effect of β-CD on the hydrolysis

(16) March, J. *Advanced Organic Chemistry. Reactions, mechanisms and structure*, 4th ed.; John Wiley and Sons, Inc.: New York, 1992; p 225.

(17) Moffat, A.; Hunt, H. *J. Am. Chem. Soc.* **1959**, *81*, 2082.

(18) Neuvonen, H. *J. Chem. Soc., Perkin Trans 2* **1986**, 1141.

Table 2. Effect of α, β, and γ-Cyclodextrin on the Hydrolysis of 1a in Water Solution[a]

	k_{obx}, s^{-1}	
cyclodextrin[b]	pH = 6.00	pH = 9.91
none	2.30 ± 0.07	81 ± 4
α-CD	2.09 ± 0.07	101 ± 7
β-CD	1.01 ± 0.07	143 ± 14
γ-CD	1.98 ± 0.05	138 ± 14

[a] $T = 25.1 \pm 0.1$ °C. Solvent contains 3.8% v/v ACN. $\mu = 0.2$ M. [buffer] = 0.1 M [b] [CD] ~ 1.15×10^{-2} M.

Table 3. Effect of ACN on the Hydrolysis Rate of 1a[a]

	k_{obx}, s^{-1}		$k_{obs}/[H_2O]$, s^{-1} M^{-1}	
pH	4% ACN[b]	25% ACN	4% ACN	25% ACN
7.00	2.15	0.35	0.04	0.0084
9.91	71.6	17.0		

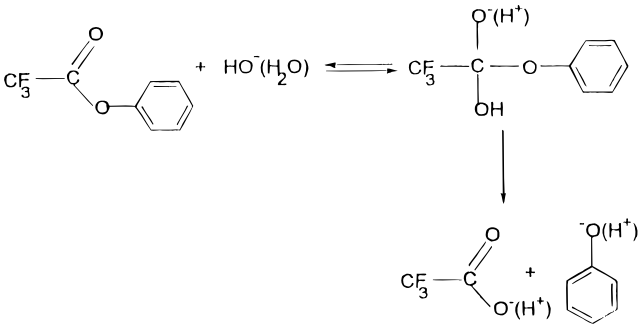
[a] $T = 25.1 \pm 0.1$ °C. $\mu = 0.2$ M. [b] Values extrapolated at zero buffer concentration.

of **1a** at pH 9.91 is significantly smaller than the catalysis observed for the reaction of phenyl acetate,[3] but different buffer and pH were used in this and in the reported study. It might be that the effect of β-CD for substrate **1** is underestimated due to competition of the buffer and substrate for the cavity; therefore, we measured the rate of hydrolysis of phenyl acetate at pH 9.91 in solutions with and without 0.012 M β-CD. The relative rate of the reaction in the presence of β-CD 0.012 M and in its absence is 11 which is in good agreement with literature values, namely, 8 at pH 10.6.[3] Under the same conditions this ratio is 2 for **1a**. The α- and γ-cyclodextrin produced effects in the same direction of β-CD but smaller in magnitude (Table 2).

The effect of decreasing the polarity of the solvent was determined for the water as well as for the HO^--catalyzed reaction in order to determine if the change in solvent polarity affected the rate in different ways. The data in Table 3 show that the decrease in polarity of the solvent due to the addition of acetonitrile produces a decrease in rate at pH 7 as well as at pH 9.91. These results are in agreement with a previous study on the effect of increasing acetonitrile in the neutral hydrolysis of phenyl trifluoroacetate.[18]

Discussion

Mechanism of Hydrolysis. The mechanism of hydrolysis of esters is usually considered to involve the formation of a tetrahedral intermediate, eq 3,[20] with the rate-determining step depending on the leaving group. However, recently William et. al.[21] have postulated a concerted mechanism for the reactions of phenyl esters with phenolate ions when the pK_a of the leaving group is within 2 and 11. Guthrie, based[22] on 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 life time due to very small barriers for the bond



formation and rupture from the intermediate. The tetrahedral intermediate from substrate **1** is expected to be more stable due to the effect of the trifluoromethyl group.[23] However, by using the data for the two compounds, a value of β_{LG} of −0.25[24] is calculated at pH > 8, and this is remarkably similar to the value of β_{LG} for phenyl acetates, namely −0.32.[25] This result may indicate that the degree of bond rupture in the transition state is similar for both reactions. Similar calculations for the water reaction give −0.61[24] for substrates **1**, indicating a more advanced transition state for the neutral than for the HO^--catalyzed reaction.

The hydrolysis of *p*-nitrophenyl trifluorocetate was shown to be general base catalyzed with imidazole and pyridine as bases in 0.56 M water in acetonitrile.[26] The reactions reported here are only very weakly catalyzed by buffers. This result may be due in part to the change in solvent and to the fact that the transition state with some degree of positive charge development due to the addition of water is relatively more stable than with a much better leaving group as the *p*-nitrophenol.[27]

Effect of Cyclodextrin. For the reactions in the presence of cyclodextrin, catalysis is observed at pH > 8 and inhibition at pH < 6.

The mechanism of catalysis of the hydrolysis of esters by cyclodextrins has been interpreted in terms of nucleophilic catalysis by the ionized OH group at the rim of the cyclodextrin which leads to the acylated cyclodextrin (Scheme 1). Also, general base catalysis of water addition has been postulated for the catalysis of some esters hydrolysis,[28] but the fact that the reactions reported here are only weakly affected by general bases suggests that the mechanism of catalysis is nucleophilic.

Under conditions where only part of the cyclodextrin is in its ionized form,[29] inclusion complex formation should take place with the ionized and the unionized cyclodextrin because it is known that ionization does not change significantly the association equilibrium constants, and, therefore, a minimum mechanism for the hydrolysis reaction in the presence of β-CD may be represented by Scheme 2.

In this scheme, S represents the substrate, CDOH and CDO^- are the neutral and ionized β-CD, and S.CDOH

(19) The small change in rate with buffer concentration might indicate general base catalysis of hydrolysis for the reaction in water. The same relative increase in rate with buffer concentration indicates that the reaction mediated by β-CD is not affected by buffer as it was found for other ester hydrolysis reactions. See Breslow, R.; Czarnniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am.Chem. Soc* **1980**, *102*, 762.

(20) Reference 16, p 378.

(21) Ba-Saif, S.; Luthra, A. K.; Williams, A. *J. Am. Chem. Soc.* **1989**, *111*, 2647.

(22) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 3941.

(23) Manion Schilling, M. L.; Roth, H. D.; Herndon, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 4272.

(24) Unpublished results from our laboratory with esters containing *p*-Cl, *m*-Cl, and *p*-F substituent groups together with the data reported here give −0.3 and −0.5 for β_{LG} for the HO^- and water reaction, respectively.

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

(26) Neuvonen, H. *J. Chem. Soc., Perkin Trans 2* **1987**, 159.

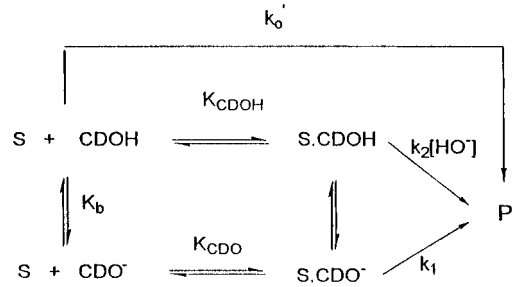
(27) Unpublished results from our laboratory indicate that for a compound with a better leaving group as *p*-chlorophenol, there is significant general base catalysis.

(28) Komiyama, M.; Inoue, S. *Bull. Chem. Soc. Jpn.*1980, *53*, 3334.

(29) The pK_a of β-CD is 12.1 (see Van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3253).

Scheme 1

Scheme 2



and $S.CDO^-$ are their respective inclusion complexes with association equilibrium constants named K_{CDOH} and K_{CDO}. The value of $K_b = K_a/K_w$ is ~100[29] and k_0' is the pseudo-first-order rate constant for the reaction in the absence of cyclodextrin. It should be noticed that the pathway involving $S.CDO^-$ is equivalent to Scheme 1. The formation of a cyclodextrin−substrate complex cannot be corroborated using other means[30] because the substrates react very fast with water.

In Scheme 2 the pathway involving the reaction of HO^- with complexed substrate ($k_2[HO^-]$) is included because there are plenty of evidence that external nucleophiles can react with complexed substrates and in some cases even at higher rate.[31,32] It should be noticed that the reaction pathways involving the complexation of the substrate with ionized cyclodextrin is kinetically equivalent and therefore undistinguishable from that involving complexation of the substrate with neutral cyclodextrin followed by ionization of the complex.

The observed rate constant for Scheme 2 is given by eq 4 where f represents the fraction of ionized β-CD as defined in eq 5.

$$k_{obs} = \frac{(fk_1K_{CDO} + (1-f)k_2K_{CDOH}[HO^-])[\beta\text{-CD}]_o + k_o[HO^-]}{1 + (fK_{CDO} + (1-f)K_{CDOH})[\beta\text{-CD}]_o} \quad (4)$$

$$f = \frac{K_b[HO^-]}{1 + K_b[HO^-]} \quad (5)$$

All our studies were done at pH < 10, then $[HO^-] < 10^{-4}$ M and $f \approx K_b[HO^-] \ll 1$. Equation 4 simplifies to eq 6 provided that K_{CDO} and K_{CDOH} are of the same order of magnitude. Ionization of one hydroxy group of cyclodextrin is not expected to change significantly the association equilibrium constant.

$$k_{obs} = \frac{(K_bK_{CDO}k_1 + K_{CDOH}k_2)[HO^-][\beta\text{-CD}]_o + [HO^-]}{1 + K_{CDOH}[\beta\text{-CD}]_o} \quad (6)$$

(30) Connors, K. A. *Binding Constants: The measurement of molecular complex stability;* John Wiley and Sons: New York, 1987.
(31) Gadosy, T. A.; Tee, O. S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 715.
(32) Barra, M.; de Rossi R. H. *Can. J. Chem.* **1991**, *69*, 1124.

Table 4. Calculated Parameters for the Hydrolysis of 1a and 1b in the Reactions with Cyclodextrin

pH	$k_o[HO^-]$,[a] s^{-1}	a[b]	b[b]
		1a	
6.00	2.06		121 ± 1[c]
9.02	13.0	$(1.7 \pm 0.3)10^3$	120 ± 40
9.91	71.6	$(1.3 \pm 0.1)10^4$	120 ± 20
		1b	
6.00	1.46	−440 ± 40	320 ± 40
9.02	8.40	$(2.5 \pm 0.2)10^3$	250 ± 40
9.91	51.20	$(1.4 \pm 0.2)10^4$	260 ± 60

[a] Value extrapolated to zero buffer concentration. [b] Parameters of eq 8 unless otherwise noted. [c] Represents the ratio of slope and intercept of a plot according to eq 10.

The rate of the reaction involving HO^- as an external nucleophile with the complexed substrate ($k_2[HO^-]$ in Scheme 2) is probably slower than the corresponding to the nucleophilic reaction of one secondary oxygen anion of the cyclodextrin (k_1 in Scheme 2) since the decrease in polarity of the solvent decreases the rate of the HO^--catalyzed reaction. It can be seen in Table 3 that when the solvent changes from 4% ACN to 25% ACN the rate constant decreases by a factor of four. Besides, the reactions at pH <7 which involve water as an external nucleophile reacting with the included substrate are slower than the corresponding one for the free substrate (see below). Then eq 6 can be simplified to eq 7.

$$k_{obs} = \frac{K_bK_{CDO}k_1[HO^-][\beta\text{-CD}]_o + k_o[HO^-]}{1 + K_{CDOH}[\beta\text{-CD}]_o} \quad (7)$$

The rate data obtained at different pH were fitted to an equation of the form of eq 8 where a and b are adjustable parameters and c is the experimentally determined value of the observed pseudo-first-order rate constant in the absence of β-CD. All the data except those of **1a** at pH 6.00 fit very well to eq 8. The values of a and b are collected in Table 4. The lines of figures 2 and 3 were drawn with the calculated parameters.

$$k_{obs} - c = \frac{a[\beta\text{-CD}]_o}{1 + b[\beta\text{-CD}]_o} \quad (8)$$

Considering the mechanism of Scheme 2 and the expression for the observed rate constant of eq 7, the values of a and b at pH > 8 are $(K_bK_{CDO}k_1 - K_{CDOH}k_o)[HO^-]$ and K_{CDOH}, respectively. Consistent with this interpretation, the value of b is pH independent. Assuming that $K_{CDOH} \approx K_{CDO}$, the value of K_bk_1 can be calculated. In all previous studies of hydrolysis of esters catalyzed by cyclodextrin, the value of K_bk_1 is usually named k_c,[33] the catalyzed rate constant. Values of ratio k_c/k_u (k_u uncatalyzed pseudo-first-order rate constant) ranging from lower than 1 to 10^5 have been obtained,[34] so it must be noted that only those values higher than 100 indicate that the intrinsic reactivity of the ionized HO at the rim of the cyclodextrin cavity is higher than that of hydroxide ion in the solution.

At pH < 8, the reactions are pH independent, indicating that water is the nucleophile. In Scheme 2, only the upper part can take place, with $k_o = k_w$ and $k_2[HO^-] = k_w^{CD}$. The observed rate constant is given by eq 9.

(33) Tee, O. S. *Adv. Phys. Org. Chem.* **1994**, *29*, 1.
(34) Breslow, R.; Czarniecki, F. M.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762.

$$k_{obs} = \frac{K_{CDOH} k_w^{CD} [\beta\text{-CD}]_o + k_w}{1 + K_{CDOH}[\beta\text{-CD}]_o} \quad (9)$$

For compound **1b** the data fit very well to an equation of the form of eq 8 with $c = k_w$ but the rate in the cavity occurs at lower rate than the rate in bulk solution (Figure 4B). The cavity of cyclodextrins are less polar than water,[35,36] and the effect of acetonitrile shows that the water as well as the hydroxide ion reaction occurs at a lower rate when the amount of acetonitrile increases in the solution so at least part of the observed inhibition may be attributed to a microsolvent effect. Another factor which may be important is the availability of the carbonyl group to react with water, since if it is immersed in the cavity it may be difficult to reach.

In the case of substrate **1a** the data could not be fitted to eq 8 but fits very well to eq 9 with the first term in the numerator equal to zero (Figure 4A). In this case, inversion of eq 9 leads to eq 10, and the reciprocal of the observed rate constant plotted vs β-CD concentration (Figure 5) gives a straight line from which K_{CDOH} can be obtained.

$$\frac{1}{k_{obs}} = \frac{1}{k_w} + \frac{K_{CDOH}[\beta\text{-CD}]_o}{k_w} \quad (10)$$

The difference in the catalytic factors for the acetate and trifluoromethyl derivatives reported here probably indicates a change in the mode of inclusion, with the trifluoromethyl inside the cavity (Figure 6A) instead of the aryl side (Figure 6B). The different mode of inclusion can be attributed to a combination of effects, such as the different hydrophobicity of methyl and trifluoromethyl groups, the shape of the group which makes the lock and key interaction more favorable, and the dipolar moment of the molecule. In fact, CPK molecular models show that the trifluoromethyl group fits very well in the β-CD cavity. The other complex (Figure 6B) should also be formed, but the kinetics should reflect the more reactive species.[37] The fact that the catalysis through the complex with the phenyl group in the cavity (Figure 6B) is less effective than the corresponding one for phenyl acetate may be a consequence of the different dipolar moments of the two compounds which determine the orientation of the substrate in the cavity.

In the reaction of **1b**, the substrate in the cavity reacts whereas **1a** does not. It may be that for the former substrate, due to the presence of the methyl group in the phenyl ring, there is more complex of type B with the aryl group inside the cavity.

Following Kurz[38] treatment which was applied to cyclodextrin-catalyzed (or inhibited) reactions by Tee,[39] the ratio $k_1K_bK_{CDO}/k_o[HO^-]$ can be regarded as the association constant of the transition state, K_{CD}^{TS}; therefore, its variation with substrate structure can give information regarding the nature of the transition state of the cyclodextrin-mediated reaction. The change in rate is determined by the strength of binding of the transition state relative to that of the substrate. When binding of the substrate is stronger than binding of the transition state, inhibition is observed.

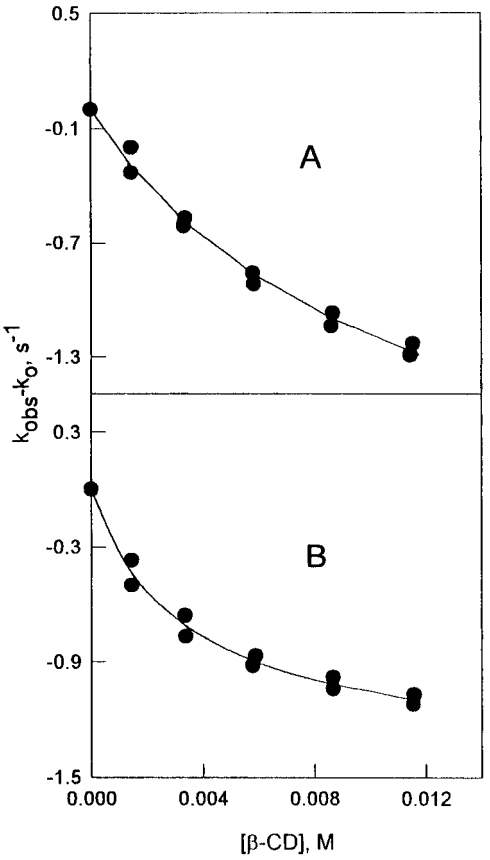


Figure 4. Effect of β-CD on the hydrolysis of **1a** (A) and **1b** (B) at pH 6. Reaction conditions as in Figures 1 and 2. The lines have been calculated with eq 9 for **1b** and the reciprocal of eq 10 for **1a** using the parameters reported in Table 4. Reaction conditions as in Figure 1.

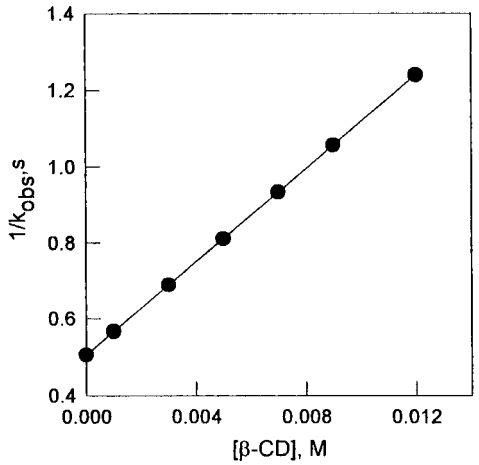


Figure 5. Plot according to eq 10 for the hydrolysis of **1a** in the presence of β-CD.

Because of the partial covalent interaction between the ester substrate and cyclodextrin, usually K_{CD}^{TS} shows strong dependence on the position and size of the substituents.[33] In Table 5 we can see the ratio of the binding constants of substrate and transition state for the reactions above pH 8 are about the same whereas the same ratios in the case of acetate esters give quite different values for the methyl-substituted and -unsubstituted ester. This result may indicate that in the case of compound **1** the reactive complex is the one with the CF_3

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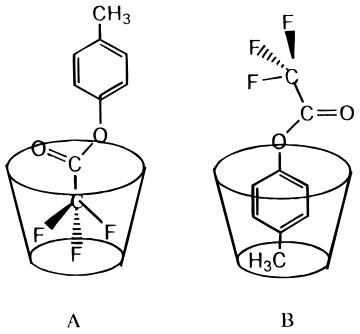

Figure 6. Schematic representation of the inclusion complexes with alkyl (A) and aryl (B) in the cavity of β-CD.

Table 5. Association Equilibrium Constant for the Substrates and Transition States for the Cyclodextrin Mediated Reactions

pH	K_{CDOH}, M^{-1}	K_{CD}^{TS}, M^{-1}	K_{CD}^{TS}/K_{CDOH}
		1a	
6.00	120[b]	$\ll$1	$\ll 10^{-2}$
>9	120[b]	246	2.2
10.60	139[a]	1886[a]	14[a]
		1b	
6.00	270[b]	16.6	0.06
>9	270[b]	571	2.1
10.60	312[a]	3030[a]	10[a]

[a] Data for the corresponding acetate taken from reference 3. [b] Average value of *b* from Table 4.

group inside (Figure 6A). The differences in K_{CD}^{TS}/K_{CDOH} in the case of the water reaction may indicate that the more reactive complex is in this case the one with aryl inclusion (Figure 6B).

Conclusions

The hydrolysis rate of compounds **1** in water are weakly base-catalyzed by buffers in basic as well as in neutral solution. Comparing the values of the observed rate constants at the same pH for **1a** and **1b**, we determined that the sensitivity of the reaction to the change in leaving group is about the same as the sensitivity for the acetates by the β_{lg}.[40] This result indicates that the mechanism are similar for both types of reactions and probably does not involve the formation of a tetrahedral intermediate with a finite lifetime.

The reactions are catalyzed by β-CD under conditions where part of the secondary OH at the rim of the cavity is ionized. The catalysis is less significant than for the reactions of the corresponding acetates, and considering the transition state binding for the catalyzed reaction and the binding of the substrate, it is concluded that the reactive complex has the trifluoromethyl group inside the cavity. The reactions in neutral solution are inhibited as a consequence of weak binding of the transition state, and this is even weaker for **1a** than for **1b** which indicates that for this reaction the reactive complex is the one with the aryl inside.

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.[41]

The β-cyclodextrin (Roquette)[42] was used as received but the purity was periodically checked by UV spectroscopy.

The substrates **1a** and **1b** were prepared by the reaction of the appropriate phenol with trifluoroacetic anhydride following literature methods.[43] The product was obtained after distillation of the remaining trifluoroacetic anhydride and acid. **1b** was distilled, and the fraction distilling at 160 °C was used (lit.[44] bp 169−170 °C). 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 comparing with the literarture.[45] Compounds **1a** and **1b** have ~5% phenol in excess. In order to determine if this affected the measured rates, reactions were carried out with the substrate and 20% of phenol added. No differences in the measured rates were found.

Kinetic Procedures. The reactions were carried out in an Applied Photophysics SF 17MV apparatus with unequal mixing. The substrate was dissolved in dry ACN and placed in the smaller syringe (0.1 mL). The larger syringe (25 mL) was filled with a 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 phenol (272 nm for **1a** and 279 nm for **1b**). The rates were measured also at other wavelengths, in order 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 could not be found, although we carefully looked for it.

The pH of the solutions containing varying concentrations of cyclodextrin was adjusted by adding a drop of dilute acid or base. The buffer was $PO_4H_2^-/PO_4H^{2-}$ at pH 6, and CO_3^{2-}/HCO_2^- at pH 9.02 and 9.91.

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Supporting Information Available: Table S1 containing the observed rate constant for the hydrolysis of **1a**, and Table S2 for **1b** as a function of pH and buffer concentration. Tables S3 and S4 containing the observed rate constant for **1a** and **1b**, respectively, at different pH, buffer, and β-CD concentrations (4 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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