Effect of cyclodextrin on the intramolecular catalysis of aryl hydrogen phthalate ester hydrolysis †

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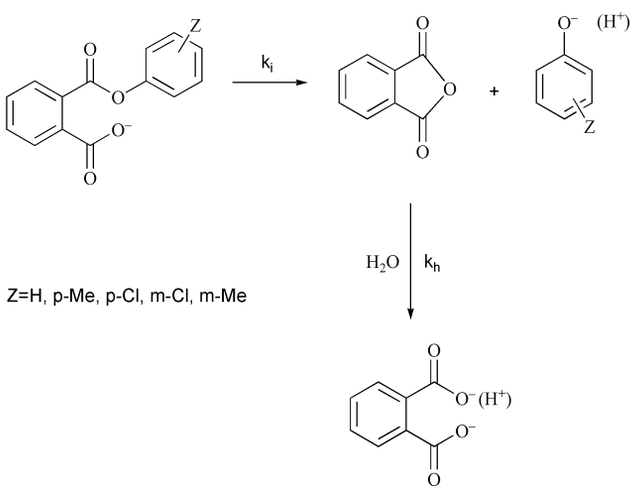
The kinetics of the hydrolysis of Z-phenyl hydrogen phthalate (Z = H, *p*-Me, *m*-Me, *m*-Cl and *p*-Cl) was studied in the presence of hydroxypropyl-β-cyclodextrin (HPCD) at pH 2.00, 3.00 and 12.00. In acid solutions these reactions involve two kinetic processes, which correspond to the formation and decomposition of phthalic anhydride. At pH 12 only the formation of phthalic anhydride could be measured because it decomposes very fast under these conditions. The rate constant for the formation of phthalic anhydride decreases as the HPCD concentration increases whereas the decomposition of phthalic anhydride is almost constant. The kinetic results are interpreted in terms of the formation of an inclusion complex of the neutral, K_{CD}^{AH}, or ionized substrate, K_{CD}^{A}, with HPCD. In all cases $K_{CD}^{AH} > K_{CD}^{A}$, so part of the observed inhibition is due to an increase in the amount of substrate in its unreactive neutral form. Comparison of the rate constants for the reaction of the complexed substrates with those in the bulk solution indicates that the transition state for the cyclodextrin-mediated reaction is less stabilised than the ionised substrate with values of $\Delta\Delta G$ ranging from 0.28 to 1.59 kcal mol^{-1} depending on the substituent on the aryl ring.

The study of intramolecular catalysis in model systems gives important information about enzyme mechanisms.[1] It has been shown that factors that favor the formation of the cyclic intermediate have enormous influence on the reaction rates.[1c,2]

Cyclodextrins, which are cyclic oligomers of α-D-glucose, have a well-defined cavity[3] and have been frequently used as microreactors that can catalyse or inhibit organic reactions by including the substrate in their cavity.[4] Intramolecular reactions are very much dependent on the relative position of the reacting groups and the time for which they are at the proper distance for reaction.[5] Inclusion in the cyclodextrin cavity may change the geometry of the substrate and so make intramolecular reactions more favourable[6] or more unfavourable than the reactions for the free substrate. Intramolecular reactions of amides have been shown to be strongly inhibited by cyclodextrins.[7] Since the mechanism of these reactions involves several steps before the rate-determining step,[8] it is difficult to interpret the inhibition since it could be due to changes in the rate-determining step, which is leaving-group expulsion, or to the previous steps, namely proton transfer and ring closure. Previously we suggested that the step which is more strongly affected is the ring-closure reaction. To demonstrate this point, we carried out a study of the hydrolysis of esters derived from phthalic acid in the presence of cyclodextrin. The hydrolysis of monoesters of phthalic acids was shown to be catalysed by the neighbouring carboxylate group when the leaving group has a pK_a lower than 13.5.[9]

In previous work we reported a kinetic study of the hydrolysis of aryl hydrogen phthalates which involves the formation of phthalic anhydride as intermediate (Scheme 1). Both rate constants were determined at a pH lower than 5.7. It was shown that the rate of formation of the anhydride (k_i) was quite sensitive to the pK_a of the leaving group.[10] In this paper we report that cyclodextrin significantly decreases the ring-closure reaction, k_i, but has almost no effect on the rate of hydrolysis of phthalic anhydride, k_h.



Scheme 1

Results and discussion

Unless otherwise noted, all the kinetic studies were carried out in water containing 3.85% v/v of acetonitrile (ACN) at 25 °C. Since phthalic anhydride is an intermediate in the hydrolysis of aryl phthalate, the kinetics of the hydrolysis of this compound was determined at pH = 2.00 and 3.00 at twelve different concentrations of hydroxypropyl-β-cyclodextrin (HPCD) in the concentration range (1.44–30) mM (Table S1). † Only one kinetic process is detected in all cases and the average rate constant up to 13 mM at pH 2.00 is (8.75 ± 0.36) × 10^{-3} s^{-1} and at pH = 3.00

† Electronic supplementary information (ESI) available: Tables S1–S6, containing the observed rate constants for the hydrolysis reactions of phthalic anhydride and Z-aryl hydrogen phthalates as a function of hydroxypropyl-β-cyclodextrin concentration and at different pH values at 25 °C; Table S7 containing data for the kinetics of *m*-methylphenyl hydrogen phthalate at different pH and buffer concentrations; Fig. S1, plot of k_i^{obs} *vs.* pH for *m*-methylphenyl hydrogen phthalate. See http://www.rsc.org/suppdata/p2/b2/b205439f/

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up to 11 mM HPCD is (8.84 ± 0.46) × 10^{-3} s^{-1}, which are the same within experimental error as the value determined in the absence of HPCD, namely (9.2 ± 0.4) × 10^{-3} s^{-1}.[10] At higher concentrations there is a small decrease in the rate: for instance, at pH = 2.00 the observed rate constants at 16, 19, 22.5 and 30 mM of HPCD are 8.0, 7.8, 7.6 and 6.9 × 10^{-3} s^{-1}, respectively.

The hydrolysis reaction of phenyl, *p*-methylphenyl, *m*-methylphenyl, *m*-chlorophenyl and *p*-chlorophenyl hydrogen phthalate was studied at pH = 2.00, 3.00 and pH = 12.00 in the presence of a variable concentration of HPCD (Tables S2–S6).† In acid solution, two kinetic processes named τ_1 and τ_2 were observed in all cases, which are associated with the build-up and decay of phthalic anhydride. In order to calculate the rate constants for the system we used a double 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 Tables S2–S6),† but we think that the second is the more accurate one, and these are the values used for all the calculations for the individual rate constants (see below). The reaction of phenyl hydrogen phthalate was also studied at pH = 2.00 but in a solvent with lower ACN content, namely 0.5%; similar results were obtained. The inhibition by HPCD is stronger under these conditions, which is consistent with the fact that ACN forms an inclusion complex with β-cyclodextrin[11] and it may compete with the substrate for the cavity. This effect is evident by comparing the relative rates at 0 and 30 mM HPCD concentration, which are 8 and 12.5 at 3.85 and 0.5% v/v ACN, respectively.

The reactivity of the phenolate anion with phthalic anhydride is quite high (the second order rate constant is 7.2 × 10^4 M^{-1} s^{-1}), so at a pH higher than 5.7 the kinetics of the system is complicated by the backward reaction of the first step in Scheme 1. However, at pH = 12.00 the rate of hydrolysis of phthalic anhydride, $k_h[HO^-]$, is 106 s^{-1} while the rate of the reaction of phenoxide anion is at most 7 s^{-1}§ so only the rate of formation of phthalic anhydride can be measured under these conditions. This is confirmed by the fact that the observed rate constant in the absence of HPCD is the value of k_i expected from the data obtained at low pH. Furthermore, this result indicates that at this pH there is no contribution from HO^- to the hydrolysis reaction. The rate constant for the reaction of HO^- with phenyl benzoate is 5.56 × 10^{-2} M^{-1} s^{-1} [12] and it is expected that the rate for the reaction of phenyl hydrogen phthalate is even lower due to steric hindrance for the *ortho* carboxylate substituent.

In all cases the reaction is inhibited by hydroxypropyl-β-cyclodextrin and the plot of k_i^{obs} *vs.* HPCD concentration is non-linear (Fig. 1 is representative). With phenyl hydrogen phthalate the reaction was also measured with β-cyclodextrin and the effect was similar to that found with HPCD. On the other hand, α- and γ-cyclodextrin do not affect the rate, which points to the importance of the size of the cavity for the inhibition (Table S2).†

On the basis of these data we suggest the mechanism shown in Scheme 2. The substrate neutral and the anion associates with cyclodextrin probably through the aryl ring of the phenol leaving group and the associated compound reacts at a slower rate than the free compound. The observed rate constant for Scheme 2 is given by eqn. (1)

$$\frac{k_i^{obs}}{f_A} = \frac{k_i + k_{CD}K_{CD}^{A}[HPCD]}{1 + K_{app}[HPCD]} \quad (1)$$

‡ In the cases where we did not have the value of the rate constant for phthalic anhydride at exactly the same concentration used for the ester, we let the program adjust this value within the limits of the observed values in the two closest concentrations of HPCD.

§ This value is calculated considering that the substrate concentration is 10^{-4} M and the second order rate constant for phenoxide anion is 7.2 × 10^4 M^{-1} s^{-1} (see ref. 10).

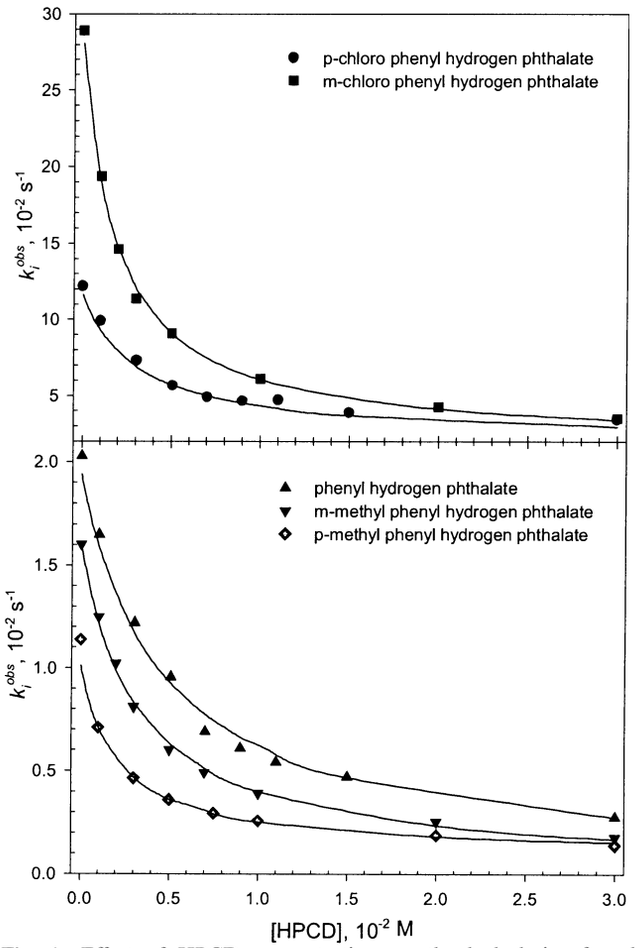
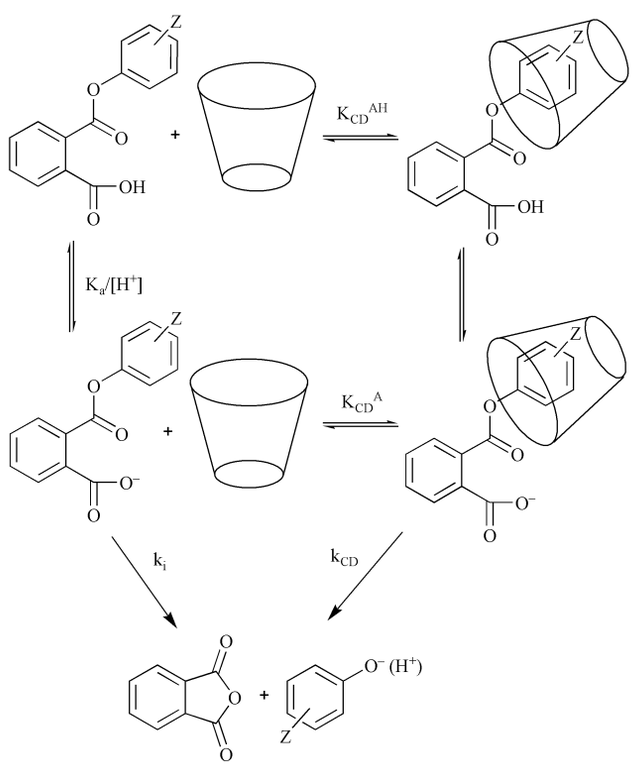


Fig. 1 Effect of HPCD concentration on the hydrolysis of aryl hydrogen phthalates at pH 3. Solvent: water and 3.85% ACN, temperature: 25 °C, ionic strength 0.5 M (NaCl as compensating electrolyte). The pH was adjusted with HCl.



Scheme 2

Table 1 Calculated rate and equilibrium constants for the hydrolysis of Z-phenyl hydrogen phthalate mediated by hydroxypropyl-β-cyclodextrin at 25 °C[a]

Z	$k_o/10^{-2}$ s^{-1} [b]	$k_{CD}/10^{-2}$ s^{-1}	K_{CD}^{A}/M^{-1}	K_{CD}^{AH}/M^{-1}	K^{TS}/M^{-1}	$\Delta\Delta G^{c}$/kcal mol^{-1}
p-Cl	21.6 ± 0.01 (22.9)	13.1 ± 0.3	98 ± 10	604 ± 32	59.4	0.28
p-Me	2.07 ± 0.03 (2.28)	0.87 ± 0.06	112 ± 17	854 ± 94	4.62	0.53
m-Cl	53.1 ± 0.5 (55)	15 ± 1	120 ± 11	981 ± 61	33.9	0.75
H	4.17 ± 0.02 (4.43)	0.4 ± 0.3	29 ± 5	393 ± 20	2.78	1.39
m-Me	3.31 ± 0.03 (3.36)[d]	0.23 ± 0.02	51 ± 6	562 ± 34	3.54	1.59

[a] Obtained from all the data for each compound and using eqn. (4) to fit the data. [b] Values within brackets are experimentally determined values taken from ref. 10 unless otherwise noted. [c] Difference in free energy for the association of the substrate and the transition state. [d] Experimentally determined value (this work).

where k_{CD} is the rate constant of the included substrate, K_{CD}^{A} is the association constant of the anion of the substrate and K_{app} is given by eqn. (2) and is the product of the association equilibrium constant of the anion of the substrate and the fraction of the anion, f_A [eqn. (3)], plus the product of the association equilibrium constant for the neutral substrate K_{CD}^{AH} and the corresponding fraction $f_{AH} = (1 - f_A)$. All the rate and equilibrium constants were calculated using eqn. (4) to fit all the data obtained at various pH values.

$$K_{app} = f_A K_{CD}^{A} + (1 - f_A) K_{CD}^{AH} \quad (2)$$

$$f_A = \frac{K_a}{K_a + H^+} \quad (3)$$

$$k_i^{obs} = \left(\frac{a + b[\text{HPCD}]}{1 + c[\text{HPCD}]} \right) f_A \quad (4)$$

In eqn. (4) $a = k_i$, $b = k_{CD}K_{CD}^{A}$ and $c = K_{app}$. The calculated parameters are given in Table 1.¶ It can be seen that in all cases K_{CD}^{A} is smaller than K_{CD}^{AH}, probably due to the more hydrophilic character of the ionic substrate. The log *P* values[13] for phenyl hydrogen phthalate and phenyl phthalate are 3.07 and 2.25, respectively.‖ On the other hand, there is a fair linear correlation (plot not shown) of the log K_{CD}^{A} values with the values for the corresponding aryl acetates,[14] which indicates that the inclusion of the substrate takes place with the aryl ring inside the cavity. It is also important to note that the difference between the association constants of the neutral and anionic substrates drives the equilibrium toward the neutral species, which do not react under our experimental conditions. Therefore the absolute inhibition of the observed rate of formation of the anhydride is stronger at low pH. For example, in the case of phenyl hydrogen phthalate, the relative rates measured at zero and 30 mM concentration are 8.9, 7.0 and 1.7 at pH 2, 3 and 12, respectively.

Included in Table 1 are the values of K^{TS}, which have been calculated following the Kurtz treatment[15,16] and represent the hypothetical association equilibrium constant for the transition state mediated by cyclodextrin defined as the ratio $k_{CD}K_{CD}^{A}/k_i$. These values are in all cases smaller than K_{CD}^{A}, indicating that the transition state is less stabilised by HPCD than the substrate itself. It can be seen in the last column of Table 1 that the differences in stabilisation between the substrate and transition states are smaller for the *p*-substituted compounds. These values probably reflect differences in the orientation of the substrates within the cavity when the substituent of the aryl ring changes. The transition state for the attack of the carboxylate neighbouring group on the carbonyl carbon of the ester group requires the carboxylate to be in the plane of the ring with the ester group approximately perpendicular. It is well known that an appropriate geometry in the initial state is a critical factor for a reaction.[5] The inclusion of the substrate in the cavity probably perturbs the energy as it reaches the most favourable geometry through interaction of the carboxylate and carboxy groups with the OH at the rim of the cyclodextrin cavity and steric compression of the transition state. It has been reported that the inclusion of 2,2-dimethylpropionic acid 2-hydroxymethyl-5-nitrophenyl ester within the cavity of β-cyclodextrin decelerates the rate of intramolecular transesterification to give 2,2-dimethylpropionic acid 2-hydroxy-4-nitrobenzyl ester by a factor of five and this was attributed to changes in the proportion of the conformers of the reactant towards the less favourable conformation for the reaction.[17] Another factor that must be considered to explain the smaller stabilization of the transition state compared with that of the reactant is the contribution to the stabilization of the complexes by hydrogen-bond formation with the OH at the rim of the cyclodextrin cavity.[18] It is likely that the carboxylate group forms such hydrogen bonds and they must be weakened in the transition state, thus decreasing the stability of the complex.

Conclusions

Since the mechanism of the intramolecular catalysis of the hydrolysis of aryl esters involves rate-limiting ring closure with the neighbouring carboxylate group, the results presented here indicate that the inhibition of the intramolecular reaction as a result of inclusion in the cavity of cyclodextrin is due to the fact that the relative positions of the reactive groups are not optimal for the reaction in the associated substrate and this decreases the efficiency of the carboxylate as an intramolecular catalyst. Moreover, the transition state is less stabilised than the substrate in the complex because there are weaker hydrogen bonds due to dispersion of the negative charge of the carboxylate group.

By comparing the relative values of k_i/k_{CD} for phenyl phthalate, phenyl phthalamic acid[7] and *N*-phenylmaleamic acid[7], which are 10, 11 and 15 respectively, we can conclude that the nature of the inhibition is similar in the reaction of amides and esters, confirming our previous proposal that the main reason for the inhibition of intramolecular catalysis in the hydrolysis of amides was due to the step involving intramolecular attack of the carboxylate group on the carbonyl carbon to form a tetrahedral intermediate.

Experimental

NMR spectra were determined on a Varian AC 200 and IR spectra on a Nicolet 5XC spectrometer. 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.[19] It is very important to use dry solvent because in the presence of traces of water the substrate hydrolyses before the solution can be used.

¶ Non-linear fitting was carried out using Sigmaplot, Handell Scientific, Version 3.02. The values of K_a used are those given in ref. 10 for all the substrates, except for the *m*-methylphenyl ester for which the value is that determined in this work (see Experimental section).

‖ The log *P* values were calculated using the software available in Chemdraw.

β-Cyclodextrin and HPCD (average degree of substitution 5.9, PM 1454) (Roquette) were a gift from Ferromet S.A. Argentina and were used without further purification. The pH measurements were done at controlled temperature and calibrated with buffers prepared according to the literature.[20]

Phthalic anhydride (Anedra) was sublimed before use. The monoaryl esters were prepared from phthalic anhydride and the appropriate phenol by adapting the method described before.[10]

The products were characterized by IR and ^{13}C NMR. The spectral data for the phenyl, *p*-chlorophenyl, *p*-methyl and *m*-chlorophenyl compounds have already been reported.[10] The data for the *m*-methylphenyl compound are as follows: ν_{max} (KBr pellets)/cm^{-1}, 1684.6 (C=O in -COOH), 1751.3 (C=O in ester). δ_C (50 MHz, $CDCl_3$) (ppm) 172.0, 166.6, 150.8, 139.7, 133.1, 132.5, 131.1, 130.0, 129.8, 129.2, 129.0, 126.9, 121.9, 118.3, 21.3.

The purity of the products was also checked by comparing the UV–vis absorption spectrum of a solution containing the fully hydrolysed ester with one at the same concentration prepared with phthalic acid and the corresponding phenol.

The values of K_a used to calculate f_A were those published,[10] except for that of *m*-methylphenyl hydrogen phthalate (3.03), which was determined in the same way from the effect of pH on the rate (Table S7 and Fig. S1). †

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 an aqueous solution containing all the other ingredients. The total acetonitrile concentration was 3.85% v/v. The solutions of the substrates for the kinetic determinations were freshly prepared in dry acetonitrile at the appropriate concentration such that the final concentration was in the order of 3×10^{-4} M (see Tables S1–S7 for the exact concentration in each experiment). †

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

The wavelengths used to monitor the reactions were within 258 and 300 nm (see the exact wavelength used in each experiment in the footnotes of Tables S1–S7). † The slowest reactions were measured in the cell (with temperature control) of a conventional spectrophotometer (Shimadzu 2101 PC) adding the substrate dissolved in acetonitrile to a solution containing all the other ingredients in the required proportions to obtain the same amount of the organic solvent as in the stopped-flow experiments.

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