Effect of Cyclodextrin on the Intramolecular Catalysis of Amide Hydrolysis

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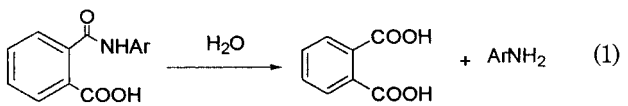
The hydrolysis reaction of phthalamic acids (HOOCArCONHR, R = p-NO_2Ph **1a,** Ph **1b**, adamantyl **1c**) and *N*-phenyl maleamic acid **2b** was studied in the presence of hydroxypropyl-β-cyclodextrin (HPCD) in acid solution. The reactions of **1**a and **1b** were studied also in the presence of β-cyclodextrin (β-CD). All the compounds formed inclusion complexes with HPCD, and the association constant was determined from the change in absorption of the substrate when the host is added in the case of **1a** (90 M^{-1}) and **2b** (49 M^{-1}). For **1c** (4×10^4 M^{-1}) a competition method was used, and for **1b** the association equilibrium constant was obtained from the kinetic data (37 M^{-1}) because it is too reactive for the spectrophotometric method. Both cyclodextrins strongly inhibited the reactions, and analysis of the kinetic data for HPCD indicated that the reactions of complexed **1a**, **1b**, and **2b** are at least 10−30 times slower than in the bulk solution whereas **1c** reacts only 4.6 times slower when it is complexed. The inhibition is attributed to changes in the geometry of the substrate due to interaction of the carboxylic group and/or the amide with the OH at the rim of the cyclodextrin. The differences in the relative effect observed for **1**c are attributed to the formation of a tighter complex with this substrate.

Intramolecular catalysis of amide hydrolysis is a reaction that has received attention as a model for enzyme catalysis.[1,2,3] The neighboring carboxylic group adds to the carbonyl carbon of the amide forming a tetrahedral intermediate which then gives the anhydride. Since the kinetic barrier to the hydrolysis of anhydrides is considerably lower than for the hydrolysis of an amide, the intramolecular addition of a carboxyl group to the amide produces a catalytic route to hydrolysis. It has been shown that factors that favor the formation of the cyclic intermediate have enormous influence on the reaction rates.[4,5] Cyclodextrins, which are cyclic oligomers of α-D-glucose have a well-defined cavity[6] and have been frequently used as microreactors which can catalyze or inhibit organic reactions by including the substrate in their cavity.[7,8] Since intramolecular reactions are very much dependent on the relative position of the reacting groups and the time that they are at the proper distance for reaction,[9] we considered it interesting to study the effect of cyclodextrin on the hydrolysis of compounds **1** and **2**, and the results are reported here. Substrate **1c** was used because it is known that adamantane derivatives form very strong complexes with β-cyclodextrines[10] so we expected a stronger effect. Quite to the contrary, the reaction of this substrate is inhibited as all the others, but the effect is less significant than for the other substrates.

Results

The reactions of **1a** and 1**b** were studied in the range of pH 1 to 4 (Table S1).[11] The rate of the reactions decreases slightly between pH 1 and 3 and more between pH 3 and 4. Increasing hydrogen ion concentration increases the reaction rate by raising the proportion of the un-ionized substrate (pK_a of **1b** = 3.62)[12] which is the active species. The spectrum of the reaction products was compared with a solution containing the corresponding aniline and phthalic acid in the expected concentration for a quantitative reaction. The spectrum as well as its first and second derivatives match that of a mock solution. These results indicate that the reaction takes place as indicated in eq 1 and that not a significant



(1)

amount of the imide is formed as was observed under other reaction conditions. Similar results were obtained with **1c** and **2b** which kinetic of hydrolysis was studied at pH 2.

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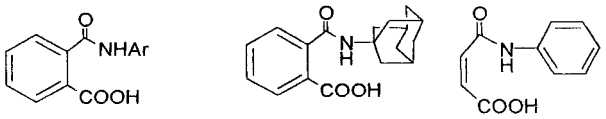


1a: Ar = p-NO_2-phenyl **1c** **2b**
1b: Ar = phenyl

Effect of Cyclodextrin. The addition of β-cyclodextrin (β-CD) or hydroxypropyl-β-cyclodextrin (HPCD) to solutions of **1a** and **2b** showed a batochromic shift of the maximum absorption, but no isosbestic point was observed. Most of the study was carried out using HPCD instead of β-CD because of the more convenient solubility of the former, which allows determinations at higher host concentrations. Using the values of the absorption measured at the wavelength of maximum change, and assuming 1:1 stoichiometry for the complexes, the equilibrium constant for the association of **1a** and **2b** with HPCD was determined by adjusting the experimental data to eq 2[13] (Table 1).

$$A = A_o + \frac{b(\epsilon_c - \epsilon_s)[S_o]K_{ass.}[\mathrm{HPCD}]_o}{1 + K_{ass.}[\mathrm{HPCD}]_o} \qquad (2)$$

In Figure 1 is shown the data for **1a**. Absorbance values measured at different wavelengths gave the same equilibrium constant, and this is a good indication that the complex has 1:1 stoichiometry. In the case of **1b** the equilibrium constant could not be determined because of the high reactivity of this compound.

On the other hand, the spectrum of **1c** does not change in the presence of β-CD or HPCD in the range of concentrations useful for the determinations ($\leq$0.03 M).[14,15] In this case we used the competition method for the determination of the association constant. The competitor used was phenolphthalein (Pht).[16] This compound has a strong absorption band at 550 nm at pH higher than 10. This band vanishes when the complex [Pht·HPCD] is formed. Adding increasing amounts of **1c** to solutions with constant concentration of Pht and HPCD, the band at 550 nm increases as Pht is displaced from the cavity for **1c**. Treating these data as indicated in the literature,[13] the value of $K_{ass.}$ was obtained (Table 1).

The hydrolysis rate decreases in all cases in the presence of HPCD in a nonlinear fashion (Figure 2 is representative). The rate of hydrolysis of **1a** and **1b** also decreases in the presence of β-CD (Table 2S).

Discussion

It was reported in the literature that compound **1a** produces the imide **3** (Ar = *p*-NO_2-Ph) when heated at 65.8 °C and at pH 4.42 in dioxane 20%−water 80%, while compound **1b** does not produce the corresponding imide under the same reaction conditions, but this compound is formed in 20% when the solvent contains 80% dioxane.[17]

Table 1. Calculated Rates and Equilibrium Constants for the Reactions of 1 and 2 in the Presence of HPCD[a]

substrate	k_o, s^{-1}	$K_{ass.}$, M^{-1}	k_{CD}, s^{-1}	k_o/k_{CD}
1a[b]	5.7×10^{-5}	(90 ± 20)[c] (84 ± 8)[d]	$<2 \times 10^{-6}$[f]	>27
1b	1.0×10^{-3}	(37 ± 3)[d]	$<9 \times 10^{-5}$[f]	>11
1c	1.2×10^{-4}	$(4.1 \pm 0.6) \times 10^4$[e] $(1.6 \pm 0.1) \times 10^3$[d]	$(2.6 \pm 0.6) \times 10^{-5}$	4.6
2b	4.0×10^{-4}	(49 ± 3)[c] (71 ± 2)[d]	$<3 \times 10^{-5}$[f]	>15

[a] Data at 40 °C, in water−ACN 4%, pH 2, ionic strenght 0.5 M unless otherwise noted. The error in k_o is less than 3% in all cases. [b] The organic cosolvent is 4% dioxane. [c] Spectrophotometric value, solvent ACN−water 4%v/v except for **1a** (dioxane 4% v/v), temperature 25 °C. [d] Kinetic value. [e] Determined by competition method in 2% ACN and pH 10.47. [f] Calculated assuming that $k_{CD}K_{ass.}[0.03]/k_o = 0.1$.

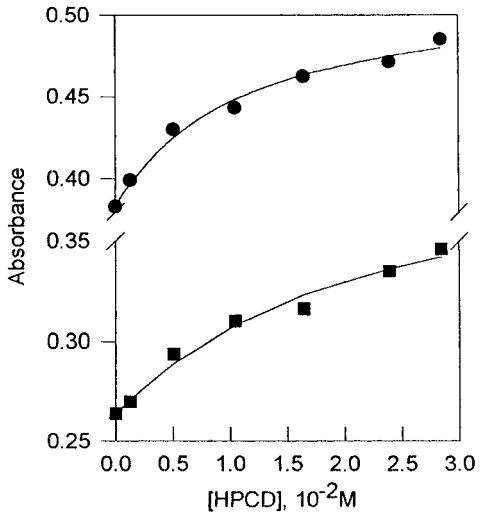
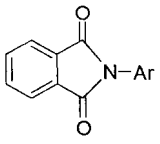


Figure 1. Absorbance of **1a** at 370 nm (■) and at 353 nm (●) vs HPCD concentration. The lines are calculated using eq 2. $[\mathbf{1a}]_o = 5 \times 10^{-5}$ M, solvent: 4% dioxane in water at pH = 2, ionic strenght 0.5 M and 25 °C.



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On the other hand, Shafer et al.[18] reported that **1b** in 0.1 M HCl and at 100 °C gave no more than 0.2% of phthalimide. These results show that pH and cosolvent concentration are important factors which determine the competition between imide and anydride formation. As stated in the results, we did not find evidence for the formation of imides, which is in agreement with the literature data mentioned above.[17,18]

The mechanism of the reaction as described in the literature[17] is shown in Scheme 1.

Under our reaction conditions, the formation of products is the rate-determining step, and the proton-catalyzed pathway (k_3) becomes significant below pH 1.[17]

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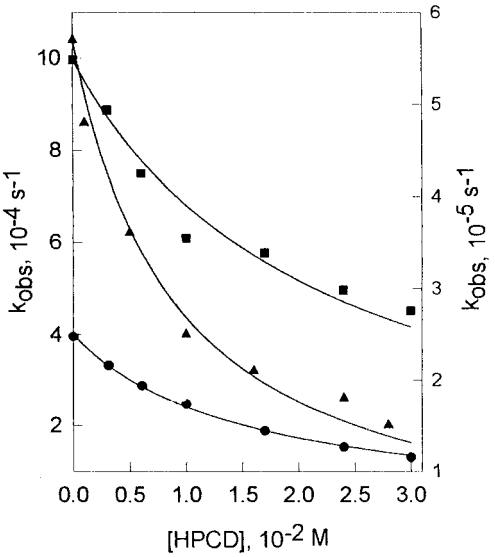


Figure 2. Dependence of the observed rate constant for the hydrolysis of **1a** (▲) (right ordinate), **1b** (■), and **2b** (●) (left ordinate) with HPCD concentration. Temperature 40 °C, pH 2 and ionic strenght 0.5 M. The lines are calculated using eq 3 with $k_{CD} = 0$.

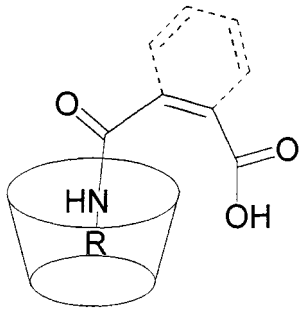
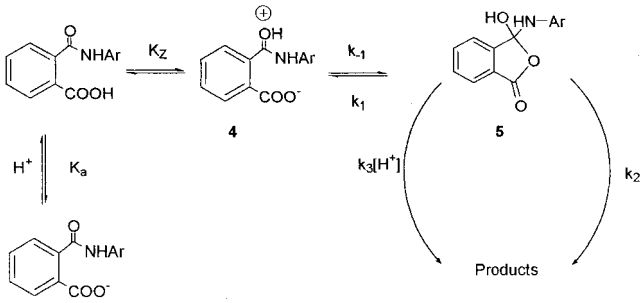


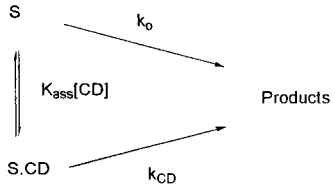
Figure 3. Schematic representation of the inclusion complexes formed between compounds **1** or **2** and cyclodextrin. R represents aryl ring (**1a**, **1b**, and **2b**) or adamantane (**1c**). The broken line for the aryl ring is to indicate that it is not present in the case of **2b**.

Scheme 1



The change in the spectrum with the addition of cyclodextrin indicates that there is some kind of interaction between them. Addition of an equivalent amount of glucose to **1a** does not produce changes in the spectrum nor in the rate of reaction. We suggest that a complex is formed with the substrate included in the cavity of cyclodextrin. The compounds have two binding sites, and the inclusion might be through any of them. We think that the complex has the structure shown in Figure 3 based on the following observations: (a) the changes in the spectrum of **1a** with cyclodextrin are similar to those found with *p*-nitroaniline;[19] (b) the association of **1c** has a much higher value than that corresponding to the other substrates, consistent with the fact that adamantane forms a very strong complex with cyclodextrin;[10] (c) Naptalam (*N*-1-naphthylphthalanilic acid) does not form a complex with β-cyclodextrin, and its rate of hydrolysis is not affected by the presence of cyclodextrins.[20] Besides the $K_{ass.}$ of substrates, **1** and **2** parallel those of the corresponding amines with β-CD, namely 40 M^{-1},[21] 260 M^{-1},[22] and 1.1×10^5 M^{-1},[23] for aniline, *p*-nitroaniline, and adamantylamine, respectively.

Scheme 2



Considering the formation of the inclusion complex of the substrate with β-cyclodextrin or HPCD, the reaction can be represented as shown in Scheme 2 where k_o represents the observed rate constant for the reaction in the bulk solution, k_{CD} is the observed rate constant for the reaction of the complexed substrate and CD represents β-CD or HPCD.

Under the conditions used in our study (pH = 2), the substrate is mainly in its neutral form since the pK_a should be in the order of that of **1b**[12] or higher. Therefore, S in Scheme 2 represents the neutral substrate.

Based on this scheme the observed rate constant is given by eq 3

$$k_{obs} = \frac{k_o + k_{CD}K_{ass.}[CD]}{1 + K_{ass.}[CD]} \qquad (3)$$

Since for **1a** and **2b** the $K_{ass.}$ was determined spectrophotometrically, we first attempted to calculate k_{CD} by nonlinear-least-squares analysis of the data[24] using eq 3 with only one adjustable parameter, but the value of k_{CD} obtained has very large error or is negative so it has no physical meaning. If $k_{CD}K_{ass.}[CD] < k_o$, eq 3 can be rearranged to eq 4

$$\frac{1}{k_{obs}} = \frac{1}{k_o} + \frac{K_{ass.}[CD]}{k_o} \qquad (4)$$

A plot according to eq 4 is linear (Figure 4) and from the ratio of slope and intercept the value of $K_{ass.}$ can be calculated and it is in reasonable good agreement with the spectrophotometric value. It should be noted that the kinetic value of $K_{ass.}$ is obtained at 40 °C whereas the spectrophotometric value was determined at 25 °C to avoid hydrolysis during the measurement. The data for **1a** with β-CD (Table 2S) plotted in the same way give a good straight line and $K_{ass.} = 46$ M^{-1} is obtained. For **1c** a similar plot is not linear, indicating that in this case

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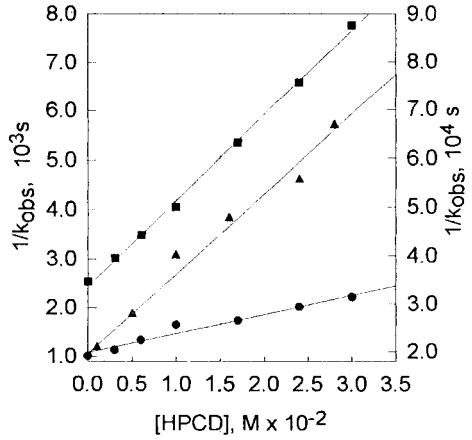

Figure 4. Plot of the reciprocal of the observed rate constant for **1a** (▲) (right ordinate), **1b** (●), and **2b** (■) (left ordinate) vs hydroxypropyl-β-cyclodextrin.

the value of $k_{CD}K_{ass.}$ is not negligible compared to the value of k_o. This may be due to the high value of K_{ass}, to a ratio k_{CD}/k_o higher than for the other substrates, or to both effects. Besides, the data for this substrate could not be adjusted to eq 3 using the value of $K_{ass.}$ determined by the competition method. Nonlinear adjustment of the data yield a value of $k_{CD} = (2.6 \pm 0.6) \times 10^{-5}$ s^{-1} and $K_{ass.} = (1.4 \pm 0.1) \times 10^3$ M^{-1} which is about 25 times smaller than the spectrophotometric value. The difference in the kinetic and spectrophotometric values can be due to the difference in reaction conditions for the two methods of determinations. The kinetic data were obtained with acetonitrile as cosolvent in 4% volume whereas the spectrophotometric data were obtained with 2% ACN.[25] It was not possible to determine the equilibrium constant in 4% ACN because under these conditions the spectrum of phenolphthalein changes only very little with the addition of the amide. Besides, in the spectrophotometric determination a buffer was used, and it is known that buffers can significantly influence the association equilibrium constants.[26] Remarkable effects of buffers were reported in the association of a β-CD derivative with *p*-nitrophenyl phosphate.[27] The values of association equilibrium constant are 6×10^4 M^{-1}, 2.1×10^5 M^{-1}, and 4.1×10^2 M^{-1} with 0.01 M Tris, imidazole, and phosphate, respectively. Considering the good correlation of the data through eq 4, we conclude that k_o/k_{CD} must be 10−30 or higher for substrates **1a**, **1b**, and **2b**, indicating a very strong inhibition. On the other hand, for **1c** this ratio is only 4.6.

The addition of dioxane to water produces a decrease in the observed rate of hydrolysis of phthalanilic acids,[17] and also the rate of hydrolysis of carboxylic esters decrease and then increase when organic solvents are added. The complex behavior was attributed to several factors such as changes in the dielectric constants of the reaction medium[28] and the change from an ionic to polar transition state.[29] The inhibition of the intramolecularly catalyzed hydrolysis rate by inclusion in the cyclodextrin cavity could be explained by a microsolvent effect; however, in this case we would expect about the same inhibition for all the substrates, and this is not the case.

The mechanism of the reaction involves several reaction steps (Scheme 1). It is known that in maleamic acid changing the substituents on the double bond has a significant effect on the rate, and this was attributed to modification of the equilibrium constant for the formation of the tetrahedral intermediate.[30] The largest acceleration for intramolecular catalysis is observed when the groups are held in close proximity in comformationally rigid molecules as in the maleate system.[1,3]

To interpret the effect of cyclodextrin on the observed rate, we have to consider that under the conditions used in our study, the rate-determining step for the reactions in water solution is the amine expulsion from the tetrahedral intermediate.[17] We think that it is not likely that this rate is so much decreased for complexation by cyclodextrin as to explain the inhibition observed. We believe that the main effect must be due to a decrease in the equilibrium constants for the intramolecular proton transfer to form **4** and/or for the formation of the tetrahedral intermediate **5** (Scheme 1). The formation of the zwitterionic intermediate **4** is very important for the catalysis because it is known that the carboxylate groups do not catalyze the reaction,[1,17] and it could be that the hydrophobic cavity of cyclodextrin significantly decreases this equilibrium constant due to changes in the dipolar moment of the molecule. It is known that the contribution of dipolar interactions to the formation of inclusion complexes is minor,[31] then we do not expect a great difference in K_Z for free and bound substrates. We suggest that the inhibition is mainly due to a decrease in the equilibrium constant for the formation of the tetrahedral intermediate **5** due to a decrease in the rate of intramolecular ring closure. We also suggest that the inclusion complex of the substrate with the cyclodextrin perturbs the distribution of conformers in the ground-state, forcing it to adopt an unfavorable orientation for the intramolecular catalysis. The effectiveness of the inclusion to modify the conformers distribution should depend on the geometry of the fit. Compound **1c**, having the adamantane with a great affinity for the cavity and very tight fit, leaves the rest of the molecule free to adopt the adequate conformation for the reaction and exposed to the solution. In the case of the other substrates the complexes are looser so the structure of the complex may adopt a geometry that maximizes the hydrogen bond interaction with OH at the rim of the cavity at the expenses of the conformation more appropriate for the reaction. It is interesting to note that these reactions can be considered as a simple model for noncompetitive inhibition of enzymatic catalysis.

Experimental Section

Aqueous solutions were made up from water purified in a Millipore apparatus. Acetonitrile Merck HPLC grade was used as received, and dioxane was purified as in previous work.[32] β-Cyclodextrin and HPCD (average degree of substitution 5.9,

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MW 1476) (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 in our laboratory according to the literature.[33]

Compounds **1a** and **1b** were prepared by adding the corresponding aniline (0.01mol) to a chloroform solution of phthalic anhydride[17] (yield 62 and 75%, respectively). The product was recrystallized from chloroform. For compound **1c** the solvent was boiling pyridine, and the product was isolated after evaporation of the solvent and recrystallized from chloroform (yield 48%).[34] Compound **2b** was prepared by adding a solution of maleic anhydride in acetonitrile to a solution of aniline in the same solvent (yield 87%). The compounds were characterized by GC-MS, and the purity was checked by comparison of the hydrolyzed solution with a mock solution containing phthalic acid and the amine.

Kinetic Determinations. They were done as reported[35] at 40 °C, ionic strength 0.5M (NaCl), and 4% of organic solvent that is dioxane for **1a** and acetonitrile for **1b**, **1c**, and **2b.** HCl or acetic/acetate buffer were used to regulate the pH. The observation wavelengths were 380 nm for **1a**, 275 for **1b**, and **2b** and 225 nm for **1c**.

Equilibrium Determinations. For **1a** and **2b** the method used was as described previously.[36] The absorbance of the solution was measured at 370 and 353 nm for **1a** and 312, 320, and 330 nm for **2b**, and the values obtained give very good fit to eq 2.

The same method was used for phenolphthalein (2.6×10^{-6} M) at pH 10.47 (buffer CO_3^{2-}/CO_3H^- 0.1M) in water containing 2% ACN and ionic strength 0.5 M and HPCD within 1.49×10^5 M and 1.02×10^{-3} M. The absorbance was measured at 550 nm. The value obtained was $(1.50 \pm 0.04) \times 10^4$ M^{-1} in good agreement with literature values,[16] namely $(2.0 \pm 0.4) \times 10^4$ M^{-1} for β-CD and $(1.2 \pm 0.1) \times 10^4$ M^{-1} for HPCD. For the determination of the equilibrium constant for **1c** a solution containing phenolphthalein 6×10^{-6} M and HPCD 6×10^{-5} M at pH 10.47 was added to a solution of **1c** in ACN so that the final concentration of the organic solvent was 2% v/v, and that of **1c** varies within 9.22×10^{-6} M and 1.54×10^{-4} M.

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Supporting Information Available: Table S1 and S2, containing the observed rate constant for substrates **1** and **2** as function of pH and cyclodextrin concentration. This material is available free of charge via the Internet at http://pubs.acs.org.

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