Hydrolysis of aryl hydrogen maleate esters mediated by cyclodextrins — Effect on the intramolecular catalysis[1]

Gabriel O. Andrés, O. Fernando Silva, and Rita H. de Rossi

Abstract: Kinetic studies of the hydrolysis of Z-aryl hydrogen maleates (Z = H, *p*-CH_3, *m*-CH_3, *p*-Cl, *m*-Cl) were carried out in the presence and absence of hydroxypropyl-β-cyclodextrin (HPCD) at variable pH from 1.00 to 3.00. The reaction involves the formation of maleic anhydride as an intermediate and the rate of its formation is strongly dependent on the pH. This is because the neighboring carboxylate group is a better catalyst than the carboxylic group. The rate constant for the formation of maleic anhydride decreases as the HPCD concentration increases in a nonlinear fashion. The results were interpreted in terms of the formation of a 1:1 inclusion complex of the esters with HPCD. The neutral (HA) and anionic (A) species of the substrate have different association constants (K_{CD}^{HA} and K_{CD}^{A}). In all cases studied, K_{CD}^{HA} is higher than K_{CD}^{A} for the same substrate. This difference is responsible for a decrease in the amount of the anionic substrate (reactive species) in the presence of HPCD, which results in a diminution of the observed rate constant. Besides, the rate constant for the reaction of the complexed substrate is smaller than that in the bulk solution indicating that the transition state of the cyclodextrin mediated reaction is less stabilized than the anionic substrate. The values of $\Delta\Delta G^{\ddagger}$ are almost independent of the substituent on the aryl ring and range within 0.48 and 1.05 kcal mol^{-1} (1 cal = 4.184 J). There is no correlation between K_{TS} and the association constant of the substrate indicating that the factors stabilizing the transition state are different from those that stabilize the substrate.

Key words: cyclodextrins, intramolecular catalysis, hydrolysis, inhibition.

Résumé : Opérant à des pH divers allant de 1,00 à 3,00, en présence et en absence de la hydroxypropyl-β-cyclodextrine (HPCD), on a réalisé une étude cinétique de l'hydrolyse de maléates acides de Z-aryle (Z = H, *p*-CH_3, *m*-CH_3, *p*-Cl et *m*-Cl). La réaction implique la formation d'anhydride comme intermédiaire et sa vitesse de formation dépend fortement du pH parce que le groupe carboxylate voisin est un meilleur catalyseur que le groupe carboxylique. La constante de vitesse pour la formation de l'anhydride maléique diminue d'une façon non-linéaire avec une augmentation de la concentration de HPCD. On interprète les résultats en fonction de la formation d'un complexe d'inclusion 1:1 des esters avec le HPCD. Les espèces neutre (HA) et anionique (A) du substrat ont des constantes d'association différentes, K_{CD}^{HA} et K_{CD}^{A}. Dans les cas étudiés, pour un même substrat, les valeurs de K_{CD}^{HA} sont supérieures à K_{CD}^{A}. En présence de HPCD, cette différence est responsable d'une diminution dans la quantité de substrat anionique (espèce réactive), ce qui conduit à la diminution observée de la constante de vitesse. De plus, la constante de vitesse pour la réaction du substrat complexé est plus faible que celle du substrat en solution ce qui indique que l'état de transition de la réaction catalysée par la cyclodextrine est moins stabilisé que celui du substrat anionique. Les valeurs de $\Delta\Delta G^{\ddagger}$ sont pratiquement indépendantes de la nature du substituant sur le noyau aromatique et elles se situent entre 0,48 et 1,05 kcal mol^{-1} (1 cal = 4,184 J). Il n'existe pas de corrélation entre K_{TS} et la constante d'association du substrat ce qui indique que les facteurs stabilisants l'état de transition sont différents de ceux qui stabilisent le substrat.

Mots clés : cyclodextrines, catalyse intramoléculaire, hydrolyse, inhibition.

[Traduit par la Rédaction]

Introduction

Intramolecular catalysis has been used as a model system because it gives important information about enzyme mechanisms (1–3). These reactions are very much dependent on the relative position of the reacting groups and the time that they remain at the proper distance for reaction (4).

Cyclodextrins (CD), which are cyclic oligomers of α-D-glucopyranose, have a well-defined cavity (5). They form inclusion complexes with a wide variety of species in aqueous

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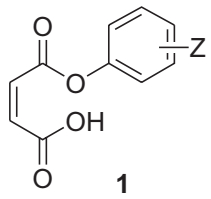
solution (6, 7), and this effect has resulted in multiple industrial applications (8, 9). As a result of the host–guest interaction between the organic substrate and the cyclodextrin, the rate of the reactions usually change and it can also be responsible for interesting changes in reaction mechanisms that are well-documented in the literature (10–12). CDs have been frequently used as microreactors that can catalyze or inhibit organic reactions by including the substrate in their cavity (13, 14).

CDs have also been derivatized to improve some desired property (7, 15), such as hydrophilicity or hydrophobicity (16, 17).

We are interested in the cyclodextrin effect on the intramolecular catalysis because inclusion in the cyclodextrin cavity may change the geometry of the substrate and therefore make intramolecular reaction more favorable (18) or more unfavorable (19) than the reaction of the free substrate.

In previous work, we studied the effect of CD on the hydrolysis of aryl hydrogen phthalate esters (20, 21). We suggested that the Z-aryl ring is included in the CD cavity, and the structure of the substrate is distorted making the intramolecular attack of the carboxylate on the carbonyl of the ester more difficult, and consequently, the rate of the intramolecular reaction decreases. In this paper we report the effect of cyclodextrins on the hydrolysis reaction of Z-aryl hydrogen maleate (**1**) where hydroxypropyl-β-cyclodextrin (HPCD) produces an important decrease in the rate of the anhydride formation, but the behavior is somewhat different from that found for aryl hydrogen phthalate esters indicating differences in the mechanism of the cyclodextrin mediated reaction.



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Z = H, *p*-CH_3, *m*-CH_3, *p*-Cl, *m*-Cl

Results and discussion

Rate constants for the hydrolysis of Z-aryl hydrogen maleates (Z = *p*-CH_3, *m*-CH_3, H, *p*-Cl, *m*-Cl) and maleic anhydride were obtained by measuring the change in the absorbance at an appropriate wavelength with time. All the kinetics studies were carried out in water containing 3.85% *v*/*v* of acetonitrile (ACN) as the co-solvent and at 25 °C.

Maleic anhydride is an intermediate in the hydrolysis of monoaryl maleate esters (22, 23), therefore it is important to determine the effect of CD on its rate of hydrolysis to understand the effect of cyclodextrin on the hydrolysis of the esters. The reactions of maleic anhydride were studied at pH 2.00 and 3.00 at seven different concentrations of hydroxypropyl-β-cyclodextrin (HPCD) between 2.5 and 30 mmol/L. Only one kinetic process was observed in all cases and the rate constants were the same, within the experimental error, at both pH. The ratio between the rate constant at the highest HPCD concentration (30 mmol/L) and the rate constants without HPCD were 0.93 and 1.01 at pH 2.00 and 3.00, respectively (Supplementary material, Table D1).[3] We also studied the hydrolysis of maleic anhydride at the highest HPCD concentration with different concentrations of a potential competitor for the cyclodextrin cavity (11). The rate constants were not affected by compounds that are known to form inclusion complexes and the observed rate constants were always the same within experimental error (Table D2).[3]

Table 1. Rate constants for the formation of maleic anhydride in the hydrolysis of Z-aryl hydrogen maleates in the presence of different competitors and at constant HPCD concentration.

	p-CH_3[a]	H[b]
Competitor concentration	k_i^{obs} ($\times 10^{-3}$ s^{-1})	k_i^{obs} ($\times 10^{-3}$ s^{-1})
Cyclohexanol ($\times 10^{-3}$ mol/L)		
0	1.37±0.04	4.12±0.03
25	2.21±0.02	5.93±0.4
50	4.24±0.01	10.1±0.1
100	5.3±0.3	11.7±0.6
***tert*-Butyl alcohol ($\times 10^{-3}$ mol/L)**		
100	2.06±0.02	5.6±0.1

Note: Rate constants were obtained in a conventional spectrophotometer at pH 2.00, HPCD concentration 0.03 mol/L, ionic strength 0.5 mol/L, temperature 25 °C, acetonitrile 3.85%. The standard errors were obtained from at least two determinations.

[a]λ = 281 nm.

[b]λ = 271 nm.

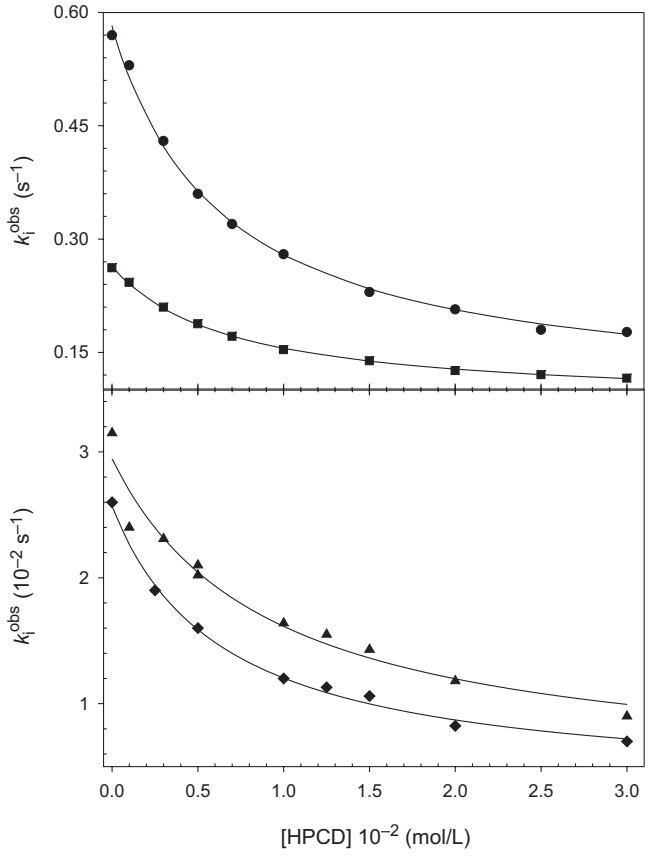
The hydrolysis reaction of phenyl-, *p*-methylphenyl-, *m*-methylphenyl-, *p*-chlorophenyl-, and *m*-chlorophenyl hydrogen maleate was studied at pH 1.00, 2.00, 2.50, and 3.00 in the presence of a variable concentration of HPCD (Tables D3–D7).[3] Two kinetic processes were observed at some wavelengths, and they are associated with the formation and hydrolysis of maleic anhydride. To calculate the rate constants for the system we choose a wavelength where the anhydride did not absorb and the formation of Z-phenol is the only process measured. Under these conditions the data can be fitted by a single exponential equation and the rate constants calculated correspond to the formation of the maleic anhydride.

The addition of HPCD decreases the rate of formation of the anhydride, whereas γ-cyclodextrin did not show any effect and α-cyclodextrin showed a minor decrease in rate (Table D8),[3] therefore, the size of the cavity plays an important role on the inhibition observed.

We studied the effect of guests that may be included in the cyclodextrin cavity on the cyclodextrin retarded hydrolysis. At constant HPCD concentration (30 mmol/L) in the presence of cyclohexanol (25–100 mmol/L) and *tert*-butyl alcohol (100 mmol/L), the observed rate constants are higher than in the absence of the competitor (Table 1). The ratios between the rate constants for the hydrolysis in the presence of cyclohexanol at the higher concentration used

[3] Supplementary data for this article are available on the Web site or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada. DUD 4026. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Fig. 1. Effect of HPCD concentration on the hydrolysis of aryl hydrogen maleates at pH 3. Solvent: water and 3.85% acetonitrile, temperature: 25.0 °C, ionic strength: 0.5 mol/L (NaCl as compensating electrolyte). The symbols for different plots of k_i^{obs} vs. HPCD concentration are: *m*-chlorophenyl hydrogen maleate (●), *p*-chlorophenyl hydrogen maleate (■), *m*-methylphenyl hydrogen maleate (▲), *p*-methylphenyl hydrogen maleate (◆).



(100 mmol/L) and the rate constant for the hydrolysis without the competitor are 3.86 and 2.84 by *p*-methyl- and phenyl hydrogen maleate, respectively. The ratios for the same substrates were 1.50 and 1.36 when the competitor was *tert*-butyl alcohol. The addition of a competitor that binds to the HPCD lowers the free host concentration, resulting in an increase in k_i^{obs} as result of a higher free substrate concentration. Cyclohexanol shows a greater effect than *tert*-butyl alcohol, consistent with the values of the corresponding association constants with β-cyclodextrin, which are 676 and 46 $(mol/L)^{-1}$, respectively (11). These results confirm that there is an effective inclusion complex between the substrate and HPCD because the size of the competitor should not affect any other kind of interaction responsible for the inhibition observed. On the other hand, the smaller effect observed for the phenyl hydrogen maleate is attributed to the smaller association constant in relation to *p*-methyl hydrogen maleate (see the following).

The plot of k_i^{obs} vs. HPCD concentration is nonlinear in all cases (Fig. 1 is representative), and the data were very well fitted by eq. [1]. All the parameters are pH dependent and the value of *c* decreases as the pH increases.

$$[1] \qquad k_i^{obs} = \frac{a + b[\text{HPCD}]}{1 + c[\text{HPCD}]}$$

Based of the results described in the previous section, we suggest the mechanism shown in Scheme 1. The neutral substrate and its anion associates with cyclodextrin with a different association constant. The observed rate constant for Scheme 1 is given by eq. [2].

$$[2] \qquad k_i^{obs} = \frac{k_i + k_{CD}K_{CD}^{A}[\text{HPCD}]}{1 + K_{app}[\text{HPCD}]} f_A$$

where k_i and k_{CD} are the rate constants of the free and complexed anionic substrate, respectively, K_{CD}^{A} is the association constant of the anion of the substrate with HPCD, and K_{app} is given by eq. [3]. It is the product of the association equilibrium constant of the anionic substrate and the fraction of the anion (f_A, eq. [4]) plus the product of the association equilibrium constant of the neutral substrate and the corresponding fraction ($f_{HA} = (1 - f_A)$).

$$[3] \qquad K_{app} = f_A K_{CD}^{A} + (1 - f_A)K_{CD}^{HA}$$

$$[4] \qquad f_A = \frac{K_a}{K_a + H^+}$$

Equation [2] is mathematically equivalent to eq. [1] with $a = k_i f_A$, $b = k_{CD}K_{CD}^{A}f_A$, and $c = K_{app}$. The rate and equilibrium constants obtained are shown in Table 2, which were calculated using eq. [2] to fit all the data obtained at various pH values. In Scheme 1, only the intramolecular reaction of the carboxylate group is considered because it is known that the reaction of the carboxylic acid does not compete with this (22, 23).

We had previously reported for monoaryl esters of phthalic acid that the ratio of association constants for the neutral (K_{CD}^{HA}) and anionic (K_{CD}^{A}) species (20) for the different substrates give values in a range of 6–10. In the case of the monoaryl hydrogen maleates, the difference between the two equilibrium constants is smaller; it amounts only to a factor of two to four (Table 2). Besides there is very small variation of K_{CD}^{HA} and K_{CD}^{A} among the various substrates, which contrasts with the results for monoaryl phthalate esters where there is a significant change in equilibrium constants with the substituents in the aryl ring (20).

The difference in equilibrium constant for the neutral and anionic substrates is important for the observed effect of HPCD because this difference drives the equilibrium toward the neutral species, which is much less reactive than the anionic species (23). Therefore, the absolute inhibition of the observed rate constant is stronger at low pH. For example, in the case of phenyl hydrogen maleate, the relative rates measured at 0 and 30 mmol/L concentrations were 5.1 and 2.7 at pH 1.00 and 3.00, respectively.

Included in Table 2 are the values of K_{TS}. These values have been calculated following the Kurz treatment (24), which was first applied for cyclodextrin mediated reactions by Tee and co-workers (25–27). It represents the hypothetical association equilibrium constant for the transition state for the reaction mediated by cyclodextrin and is defined as the ratio $k_{CD}K_{CD}^{A}/k_i$. The values of K_{TS} are in all cases smaller than the K_{CD}^{A} for the substrates, indicating that inclusion in the cyclodextrin cavity stabilizes the substrate more

Scheme 1.

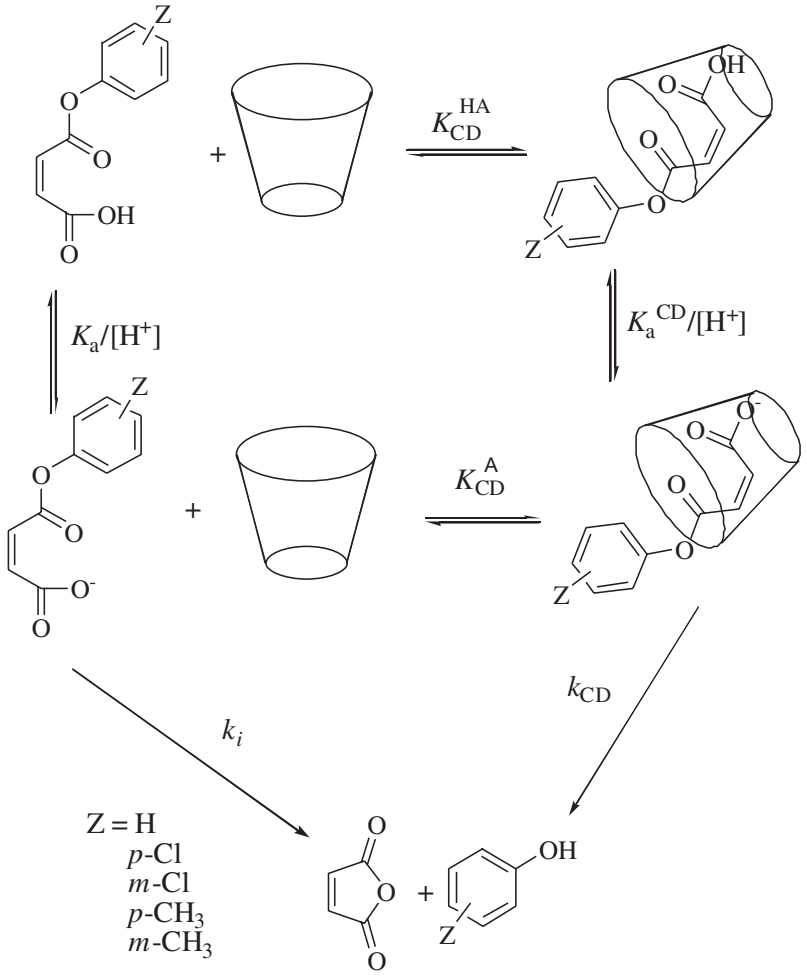


Table 2. Rate and equilibrium constants for the anhydride formation in the hydrolysis of Z-aryl hydrogen maleates mediated by HPCD.

Z	pK_a	k_i ($\times 10^{-2}$ s^{-1})	k_{CD} ($\times 10^{-2}$ s^{-1})	K_{CD}^{A} (mol/L)$^{-1}$	K_{CD}^{HA} (mol/L)$^{-1}$	K_{TS} (mol/L)$^{-1}$[a]	$\Delta\Delta G$ (kcal mol^{-1})[b]
p-Cl	2.64	37.9±0.6	17.0±0.9	101±8	255±18	45	0.48
H	2.43	5.0±0.3	1.5±0.3	104±30	208±57	31	0.72
p-CH_3	2.66	3.7±0.1	0.9±0.1	82±14	313±26	20	0.84
m-CH_3	2.36	3.6±0.1	0.8±0.3	66±22	303±75	15	0.88
m-Cl	2.56	79±2	14±2	141±16	211±31	24	1.05

Note: Obtained from all of the data for each compound and using eq. [2] to fit the data.
[a]The values were determined according to ref. 25.
[b]The difference in free energy for the association of the transition state and the substrate.

than the transition state. In the last column of Table 2, the values of $\Delta\Delta G^{\ddagger}$ that are a measure of the differences in stabilization between substrate and transition state are collected. It is remarkable that the values are about the same for all the substrates, which again contrasts with the results of the aryl phthalate esters where there is a significant variation among the different esters; for instance, $\Delta\Delta G^{\ddagger}$ is 0.20 and 1.59 kcal/mol for the *p*-chloro and *m*-methyl derivative, respectively (20).

We conclude that in this case the orientation of the main complexes is as shown in Scheme 1, namely, with the maleic moiety pointing towards the primary hydroxyl side of the cavity. There are several examples in the literature where anionic compounds are oriented in that way. For instance, benzoate anion and 4-biphenyl carboxylate anion are axially included in the cavity of β-cyclodextrin with an orientation that locates the carboxylate group at the primary hydroxyl side (28) and the same type of orientation was demonstrated for the complex between β-cyclodextrin and β-naphthyloxyacetatate in the solid as well as in solution (29).

The transition state for the attack of the neighboring carboxylate group on the carbonyl carbon of the ester re-

Table 3. IR, ^{13}C NMR, ^{1}H NMR, and melting points for the Z-aryl hydrogen maleates.

Z	IR (cm^{-1})[a]	^{13}C NMR (ppm)[b]		^{1}H NMR (ppm)[b]	mp (°C)
		174.8	129.6	7.21 (m, 5H)	
H	1748.7 (COOH)	167.3	126.6	6.52 (m, J = 12 Hz, 2H)	89.5–92.7
	1708.0 (COOR)	150.5	122.7		
		130.7	121.2		
		175.1	129.6		
		167.7	127.9		
p-Cl	1748.9 (COOH)	148.8	122.7	7.34 (m, 4H)	100.9–102.5
	1705.4 (COOR)	134.7	121.4	6.54 (m, J = 12 Hz, 2H)	
		131.8			
		174.0	129.9		
		167.3	127.0		
m-Cl	1748.8 (COOH)	146.1	122.7	7.27 (m, 4H)	123.6–124.7
	1708.5 (COOR)	133.3	121.9	6.54 (m, J = 12 Hz, 2H)	
		130.4	119.6		
		166.9	132.2		
		165.2	130.1	7.07 (m, 4H)	
p-CH_3	1748.7 (COOH)	147.7	121.0	6.53 (m, J = 12 Hz, 2H)	97.8–100.1
	1708.0 (COOR)	136.4	20.9	2.34 (s, 3H)	
		133.0			
		167.0	129.3		
		165.0	127.4	7.12 (m, 4H)	
m-CH_3	1763.1 (COOH)	149.8	121.6	6.52 (m, J = 12 Hz, 2H)	76.4–79.2
	1702.6 (COOR)	140.0	118.0	2.33 (s, 3H)	
		132.8	21.2		
		130.5			

[a]KBr pellets.
[b]In *d*-chloroform as the solvent.

quires 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 (30, 31). The inclusion of the substrate with the geometry shown in Scheme 1 probably decreases the degree of freedom of the carboxylate group to reach the appropriate geometry for reaction, and therefore, the transition state is destabilized compared to the reaction of the free substrate. It is also possible that the cyclodextrin makes some changes in the most stable conformation of the substrate, making it more difficult to reach the adequate position for intramolecular attack (32).

Conclusions

The intramolecular catalysis of hydrolysis of Z-aryl hydrogen maleate is affected by the presence of HPCD, where the size of the cavity plays an important role. The results presented here indicate that the inhibition of the intramolecular reaction as a result of inclusion in the cavity of the cyclodextrin is due to two main factors. One is the difference between the association constants for the neutral and anionic substrate that drive the equilibrium toward neutral species that is much less reactive than the anion. The second fact is steric restriction imposed for the inclusion in the substrate to reach the transition state, which is evident from a decrease in the stabilization of the transition state compared to the substrate.

From the similarities of the equilibrium constants for the substrates and also the similarities in the destabilization energy of the corresponding transition state we infer that the reactive complexes have the maleic moiety inside the cavity contrary to what was observed for aryl phthalate where inclusion of the aryl ring in the cavity was suggested.

Experimental

Materials

Maleic anhydride (Aldrich) and substituted phenols (Aldrich) were sublimed before use (33). HPCD (average degree of substitution 5.9, PM 1454) (Roquette) was a gift from Ferromet S.A. Argentina and was used without further purification.

The monoaryl esters were prepared from the maleic anhydride and the appropriate phenol by adapting the method described in the literature (34). The esters were characterized by ^{13}C and ^{1}H NMR and IR spectra; all this information along with melting points are summarized in Table 3. IR and NMR spectra were done on Nicolet 5SXC FT-IR (KBr pellets) and Bruker AC 200 (200 MHz) spectrometers, respectively. The purity of the products was also checked by comparing the UV–vis absorption spectrum of a solution containing the fully hydrolyzed esters with one at the same concentration prepared with maleic acid and the corresponding alcohol.

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 (33).

Kinetic procedures

The reactions were carried out in a stopped-flow Applied Photophysics SF 17MV apparatus (SF) with unequal mixing. The correspondent Z-aryl hydrogen maleate or the anhydride dissolved in dry acetonitrile was placed in the smaller syringe (0.1 mL). The large syringe (2.5 mL) was filled with a water solution containing all the other ingredients; the cyclodextrin concentration was varied between 0 and 30 mmol/L. The solutions of the substrate for the kinetic determinations were freshly prepared in dry acetonitrile in the appropriate concentration to get a final concentration of 2×10^{-4} mol/L. The total acetonitrile concentration was 3.85% *v*/*v*. When the rate was too slow for the stopped-flow apparatus the kinetic determinations were carried out in a thermostatted cell of a conventional spectrophotometer (Shimadzu UV2101) as described in previous work (21).

All reactions were run at 25.0 ± 0.1 °C and at constant ionic strength (0.5 mol/L) using NaCl as the compensating electrolyte. The pH measurements were carried out using a pH meter at controlled temperature and calibrated with buffers prepared according to the literature (35).

The observed rate constants were determined by measuring the change in absorbance at 250, 268, 271, 273.5, or 281 nm, depending on the substrate. In some of the experiments, the pH of the solution was checked after the reaction by measuring it in the discarded solution, and the change observed were always less than 0.03 pH units. The kinetic traces were fitted with one exponential equation using the software of the SF apparatus.

Acknowledgements

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