The Effect of Cyclodextrins on the Hydrolysis of Carboxylic Acid Esters

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Abstract. Cyclodextrins and their derivatives act as inverse phase-transfer catalysts in the hydrolysis of carboxylic acid esters. The reaction is affected by temperature, choice of cyclodextrin and also by the stirring rate. Lipophilic esters are better hydrolyzed under inverse phase-transfer catalysis conditions than under classic phase-transfer catalysis (PTC) conditions. Some typical features of the reaction are emphasized and compared with classical PTC reactions.

1. Introduction

Carboxylic acid ester hydrolysis is one of the best known reactions in organic chemistry [1]. Traditionally it is carried out both with acid or basic catalysis (saponification). Basic conditions, for apparent thermodynamic reasons, give better reaction yield and are usually used when conditions of stability of the reaction components are fulfilled.

Frequently, however, the esters to be reacted are not sufficiently soluble in water and the two layers slow down or prevent the reaction. The application of phase-transfer catalysis (PTC) [2] to the hydrolysis of esters leads to poor results, since lipophilic carboxylate anions form stable ion pairs with onium quaternary salts and consequently poison the PTC catalyst [3]. Moreover, according to the classic PTC mechanism, the activated anion (poorly solvatated) is transferred to react in the organic phase [4].

In recent years some examples of reactions have been reported in which the organic molecule was transferred to react in the aqueous phase. Mathias [5] named this mechanism IPTC (inverse phase-transfer catalysis).

The literature has seen recent reports of phthalic acid ester hydrolysis catalyzed by cyclodextrins (cyclic oligosaccharides) [6] as IPTC catalysts [7]. Reduction [8] and oxidation [9, 10] reactions are also better performed by using cyclodextrins (CDs) under IPTC conditions.

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We report here how cyclodextrins catalyze the hydrolysis of every kind of ester overcoming typical restrictions of classic PTC. Besides, the influence of several reaction parameters are discussed.

2. Experimental

Cyclodextrins (α and γ) were purchased from Fluka (Switzerland). β-Cyclodextrin was generously provided by Roquette Italia (Cassano Spinola, Italy). Methyl-β-cyclodextrin (average degree of subsitution per glucose unit = 1.8) and hydroxy-propyl-β-cyclodextrin (average degree of substitution = 0.6 per glucose unit) were a gift of Wacker Chemie GmbH (Germany). All the esters used in the experiments were supplied by Aldrich (Germany).

Diethyl ether, hydrochloric acid and sodium hydroxide were purchased fron. Merck (Germany). All the reagents were ACS grade and used without further purification.

Gas Chromatography – Mass Spectrometry (GC-MS) analysis was performed using a HP 5970B apparatus.

In a typical experiment neat ester (27 mmol) was added to 30 mL of a solution of NaOH (10 wt.-%, 75 mmol) containing 0.4 mmol of cyclodextrin or cyclodextrin derivative. The reaction mixture was stirred for the required time at 25 °C. Once the reaction was completed, 40 mL of diethylether was added, the two layers were separated, the aqueous phase was recovered and acified with HCl 1 : 1 v : v. The carboxylic acid was recovered by filtration, dried, weighed and confirmed by melting point and/or by GC-MS analysis. Similar procedures were followed for all the esters except for ethyldecanoate and methylmyristate whose conversions were followed by GC-MS by comparison with authentic samples.

3. Results and Discussion

As far as the hydrolysis of carboxylic acid esters is concerned, the reactions are extremely slow, even with vigorous stirring of the biphasic system, in view of the extremely poor water solubility of the esters.

On the other hand, as is well known, PTC does not lead to satisfactory results in the hydrolysis of carboxylic acid esters because, as soon as the carboxylate size becomes greater than that of acetate, it tends to associate strongly to the counter ion of the onium salt (used as PTC catalyst) preventing the transfer of the activated anion into the organic layer, thus the interruption of the catalytic process readily occurs [3].

The initial reaction rate is in fact rather high with PTC catalysis, but a drastic decrease of the reaction rate quickly occurs, due to the formation of the lipophilic ion pairs.

Better results could be achieved using crown ethers as PTC catalysts since they are able to rapidly hydrolyze also very hindered esters like methylmesitoate [11].
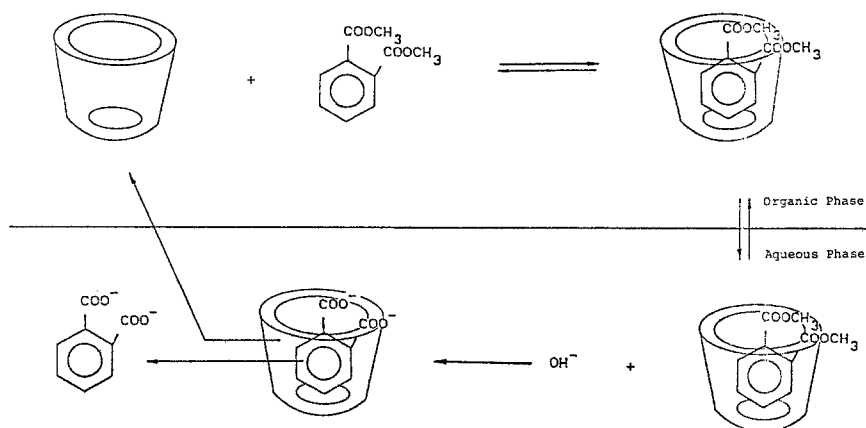
Fig. 1.   Scheme of a possible reaction mechanism for the hydrolylsis of carboxylic acid esters by using CD as catalyst.

In fact, hydrolysis of esters is one of the few reactions in which crown ethers clearly show better results than onium salts. They are, however, expensive and toxic. Moreover, CDs improve the hydrolysis reaction rate when used as catalysts under homogeneous conditions [12]. Suitable CD rim functionalization sometimes leads to derivatives acting as enzyme-mimetic compounds [13] having a very high activity and selectivity.

In the hydrolysis reaction of esters some advantages can arise from the utilization of cyclodextrins as inverse phase transfer catalysts, that form an inclusion compound with the suitable ester and solubilize the latter in the aqueous phase where the hydrolysis readily occurs. (More properly cyclodextrins act as a co-catalyst as the hydroxide anion is the true catalyst.) A possible reaction mechanism that was already proposed in the literature [9] is sketched in Figure 1.

Cyclodextrin forms an inclusion compound in the organic phase which moves to the aqueous layer where OH^- acts on the ester group. The hydrophilic nature of the carboxylate anion formed dissociates the inclusion compound and the reformed CD returns to the organic phase.

Table I reports some results obtained using several esters of various nature, both aromatic and aliphatic, with or without cyclodextrins. The last column gives the ratio, R, of catalyzed to uncatalyzed reaction yields at a given time. As in the case of uncatalyzed hydrolysis, the less hindered esters (i.e. dimethylphthalate) are hydrolyzed easier than higher homologues (i.e. diethylphthalate).

A higher enhancement in reaction rate is, however, detected with less reactive compounds. Thus, dibutylphthalate is stable to hydrolysis at 50 °C for an indefinite time without catalyst; in contrast the reaction proceeds to a certain extent in the presence of a catalytic amount of methyl-β-cyclodextrin, or simply β-CD, and consequentely a very high R value is experienced. As expected no poisoning of the

TABLE I. Hydrolysis of carboxylic acid esters under IPTC conditions. 25 °C. 20 mmol of ester, 0.4 mmol of methyl-β-CD. Constant stirring.

Ester	Time (min.)	Yield		R (Catalyzed/uncatalyzed)
		With cat.	Without cat.	
1) Dimethylphthalate	30	91.7	32.1	2.9
2) Diethylphthalate	240	85.1	24.3	3.5
3) Dibutylphthalate[a]	960	5.9	–	Very high
4) Methylphenylacetate	60	90.8	38.6	2.3
5) Ethylphenylacetate	60	29.4	7.5	3.9
6) Methylbenzoate	30	66.9	28.2	2.4
7) Ethylbenzoate	60	20.7	6.7	3.1
8) Butylbenzoate	960	16.3	3.8	4.3
9) Dimethyldipate	30	61.0	48.5	1.3
10) Diethyladipate	60	53.4	43.0	1.3
11) Ethyldecanoate[a]	960	6.0	–	Very high
12) Methylmyristate[a,b]	1440	11.9	–	Very high

[a] 50 °C.
[b] 0.2 mmol. of methyl-β-CD.

IPTC catalyst by carboxylate anions was detected. In fact, very lipophilic anions such as benzoate or decanoate and myristate also allow the hydrolysis reaction as they are unable to form ion pairs with the catalyst. Consequently high values for R were also found for these esters.

We note that this outcome can be of particular importance, if we recall that literature [15] data report how the usual PTC catalysts (such as Aliquat 336) have no effect on the hydrolysis of ethyldecanoate and a very small effect on butylbenzoate, since their carboxylate anions are strongly bound to the quaternary cation and thus the PTC catalyst loses its ability for transferal of OH⁻ into the organic phase. Therefore esters with a very high lipophilicity are more easily hydrolyzed under IPTC conditions, even when working with a relatively low sodium hydroxide concentration (10 wt.%) instead of that normally used in PTC (50 wt.%).

Table II shows some data on the influence of the cyclodextrin on the hydrolysis of some dialkylphthalates. The reaction seems to depend on the nature of the CD, the relative catalytic activities being β-CD > γ-CD > α-CD. However, we do not detect any strong evidence for selectivity towards different substrates. On the other hand the effectiveness of the catalytic action seems to be related to the solubility of the cyclodextrins. Actually, the more soluble cyclodextrin (i.e. methyl-β-CD) is also the most effective IPTC catalyst owing to its greater transfer ability among the two phases, although the increase of the solubility of the cyclodextrin does not appear to be the exclusive cause of enhancement of the catalytic action: this fact is evidenced by the moderate increase of the reaction rates using the poorly soluble β-CD and its very soluble methyl derivative. Nevertheless it is fully proved that

TABLE II. Hydrolysis of dialkylphthalates under IPTC conditions. 20 mmol of ester, 0.4 mmol of catalyst, constant stirring. 25 °C.

Ester	Time (min.)	Catalyst	R (Catalyzed/uncatalyzed)
1) Dimethylphthalate	30	Me-β-CD	2.9
2) Dimethylphthalate	30	α-CD	1.8
3) Dimethylphthalate	30	β-CD	2.2
4) Dimethylphthalate	30	γ-CD	2.1
5) Dimethylphthalate	30	HP-β-CD	1.8
6) Dimethylphthalate	30	Maltose	1.6
7) Dimethylphthalate	30	Methyl-α-glucoside	1.7
8) Diethylphthalate	240	Me-β-CD	3.5
9) Diethylphthalate	240	α-CD	2.1
10) Diethylphthalate	240	β-CD	2.7
11) Diethylphthalate	240	γ-CD	2.5
12) Diethylphthalate	240	HP-β-CD	2.2
13) Dibutylphthalate[a]	960	Me-β-CD	Very high

[a]50 °C.

water insoluble compounds are also good PTC catalysts [16] because the transfer of the anions occur on the boundary of the two phases. A similar behaviour could also occur in IPTC.

Moreover, it is reported that under homogeneous conditions the catalytic activity of the cyclodextrin largely depends on the secondary hydroxyl groups [12]. When the latter are blocked, a small inhibition of cleavage rather than an acceleration is observed. Methyl-β-CD used in this work has about half of the secondary hydroxyls blocked by methoxyl groups, but it is able to act as an inverse phase transfer catalyst. As a consequence we assume that the CD is not involved in the formation of a reactive intermediate, but only in the transferal of the organic molecule in the aqueous phase where the reaction occurs. Considering the shortness of the methyl chain bound to the CD and the low surface action of the parent CDs, micellar catalysis [17] is very unlikely here.

Nevertheless, the formation of the inclusion compound seems to be a prerequisite for the catalysis. In fact, employing linear oligosaccharides such as maltose or methyl-α-glucoside (Table II entries 6, 7), only a small enhancement in the reaction rate was detected, and always lower than by using CD catalysts.

Figure 2 reports the dependence of the yields on the amount of IPTC catalyst employed, in the hydrolysis of dimethylphthalate at 25 °C. As can be noticed an increase of the amount of the catalyst leads to a proportional growth of the conversion to phthalic acid, the other reaction conditions remaining constant. This fact has a simple explanation, since the higher the concentration of CD, the higher the number of ester molecules that are transferred to react in the aqueous phase. In the case of dimethylphthalate the reaction that occurs without CD contributes to
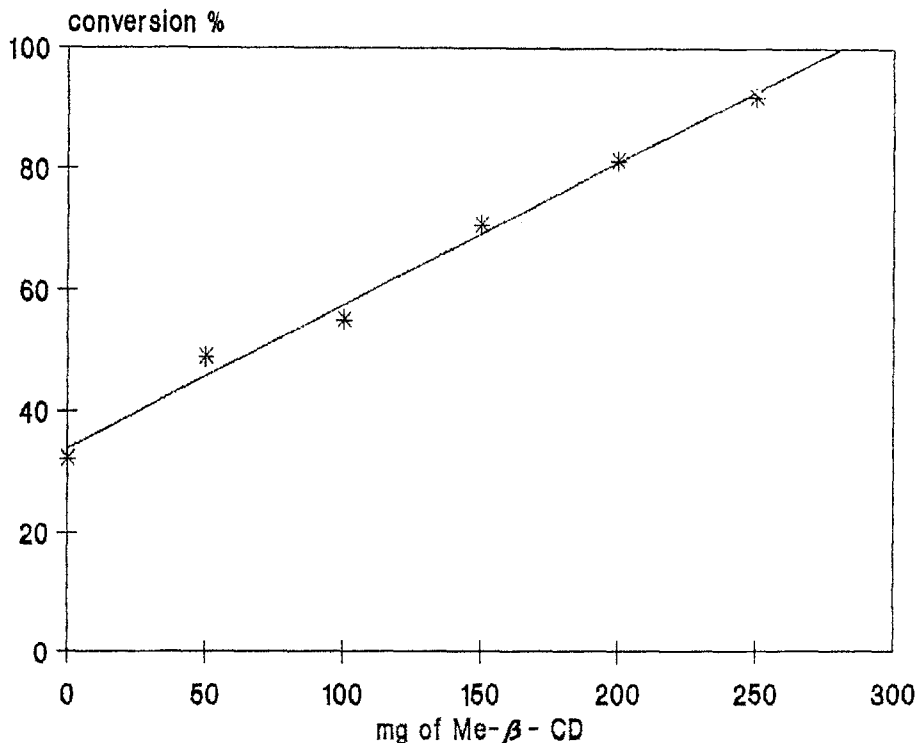
Fig. 2.   Effect on the conversion of the amount of Me-β-CD employed in the hydrolysis of dimethylphthalate. 25 °C. 30 min. Constant stirring.

the overall yield and the straight line has a defined intercept. In the case of an ester with a very high R value a zero intercept will be expected.

Figure 3 shows the influence of temperature on the R parameter for two different types of CDs, in comparison with the reaction carried out without catalyst in the hydrolysis of dimethylphthalate. As expected, the lower the temperature, the higher the difference in the reaction rates detected. Thus at 15 °C the hydrolysis catalyzed by methyl-β-CD is twice as fast as without cyclodextrin whereas very little difference was detected at 50 °C.

Figure 4 points out the influence of the stirring rate of the reaction mixture on the yield for the hydrolysis of dimethylphthalate at 25 °C for 30 minutes. It is well known, in fact, that phase transfer catalysis is not an interfacial phenomenon [18], and its reaction rate is independent of the stirring rate at least over a minimum situated between 200–300 rpm. Several other experiments confirm that the reaction rate in PTC is not controlled by diffusion [19].

In our case, the reaction rate increases with an increase of the rpm value in the absence of the IPTC catalyst. Moreover, without the IPTC catalyst, below 300 rpm no reaction was detected. In contrast with methyl-β-CD as catalyst the reaction
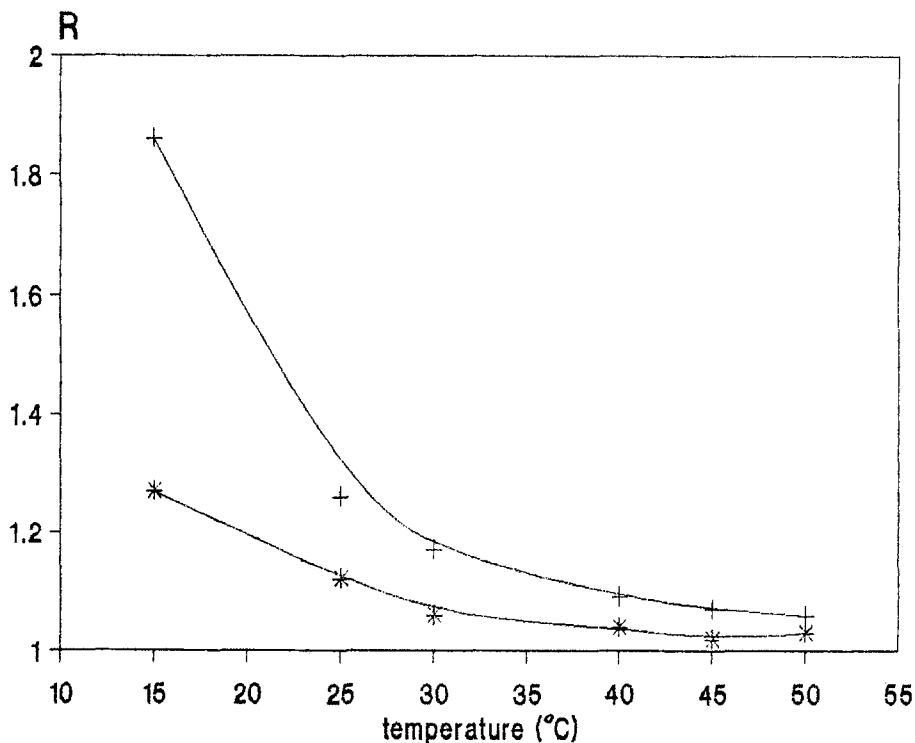
Fig. 3.   Influence of temperature on R (catalyzed/uncatalyzed ratio) parameter for the hydrolysis of dimethylphthalate. 20 mmol of ester, 0.4 mmol of catalyst. 25 °C. 30 min. Constant stirring. [∗] = β-CD, [+] = Me-β-CD.

occurs even below 200 rpm and higher reaction rates were reached, but stirring continues to have a great influence on the reaction rate.

These data require some considerations. First of all if the reaction depends on the stirring rate this could mean that the limiting step is the crossing of the molecules between the two layers. This circumstance could be at least partly ascribed to the larger size of CD molecules compared to typical onium salts and consequently to the greater difficulty of diffusion of the former. This phenomenon is not detectable in classic PTC where the limiting factor is the reaction rate of the organic reaction itself. In fact, the anion exchange between the two phases was more rapid than the reaction itself. On the other hand, under IPTC conditions the reverse seems to happen, that is the hydrolysis reaction is quite fast, while the transfer of the organic molecule is rather difficult.

This restriction could be overcome both by increasing the stirring rate and/or using a greater amount of the IPTC catalyst.
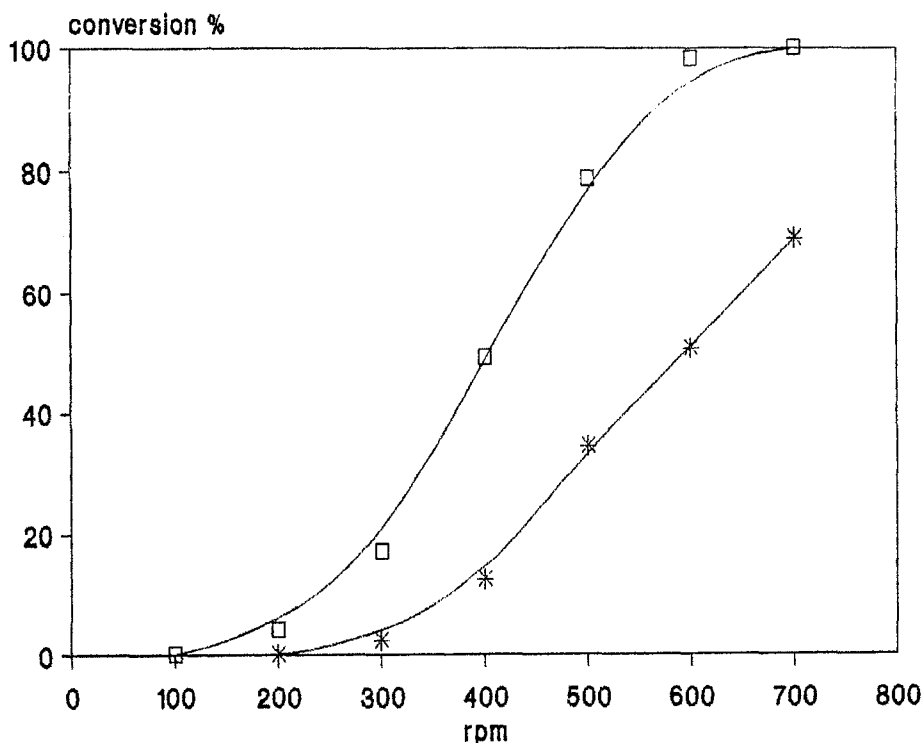
Fig. 4. Influence of the stirring rate on the conversion for the hydrolysis of dimethylphthalate. 20 mmol of ester, 0.4 mmol of catalyst. 25 °C. 30 min. [□] = Me-β-CD, [*] = without catalyst.

4. Conclusions

In this work it has been demonstrated that carboxylic acid ester hydrolysis could be better carried out by using CDs under inverse phase-transfer catalysis conditions. However, mechanistic aspects of the reaction are not well understood. In particular the interfacial transport, the solubility of the cyclodextrins in the organic phase as well as the partition coefficient between the two layers and the inhibition effect by reaction products need further investigations. This work is in progress.

Acknowledgment

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