β-Cyclodextrin Effects on the Photo-Fries Rearrangement of Aromatic Alkyl Esters

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The photolysis of phenyl propionate (**1a**) and phenyl valerate (**1b**) in water and in solutions containing β-cyclodextrin (CD) leads to the corresponding *p*-hydroxyphenyl alkyl ketone **2**, *o*-hydroxyphenyl alkyl ketone **3**, and phenol **4**. When the reactions are carried out in the presence of oxygen there is a decrease in the total amount of rearrangement products, but the inhibition is less marked in the presence of CD. The [3]/[2] ratio for **1b** increases when CD concentration changes from 0 to 10 mM. These changes are due to the increase in the quantum yield for the formation of **3** and a decrease in the quantum yield for **2** in solutions containing CD. The [3]/[2] ratio for **1a** decreases in the presence of CD although both quantum yields increase with CD concentration. Under the conditions used in this study, the substrate reacted in the bulk solution and in the cavity of CD. The quantum yields for the formation of **3** and **4**, Φ_{CD}^3 and Φ_{CD}^4, are higher for the included substrate than the corresponding values for the free substrate while Φ_{CD}^2 is higher than Φ_w^2 for **1a** but lower for **1b**. This effect is attributed to the different orientation of the substrates in the cavity of CD. Besides, Φ_{CD}^4 also increases due to the availability of hydrogens bonded to secondary carbons in the cavity of the cyclodextrin.

Introduction

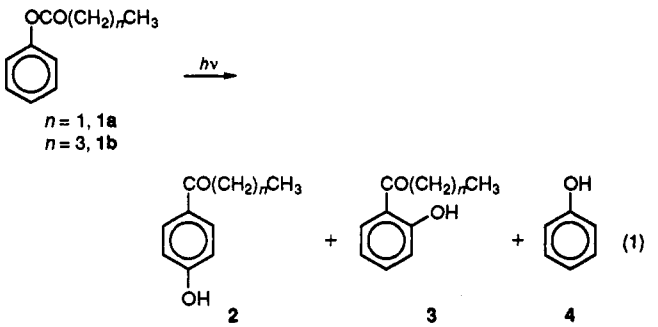
During the last years, we have been concerned with the study of several aspects of the chemistry of cyclodextrins, which are doughnut-shaped molecules formed by six, seven, or eight glucose units (α, β, or γ) and are able to form inclusion complexes with a great variety of compounds.[1] This property of cyclodextrins is responsible for the changes in the reactivity and selectivity of organic reactions. In this respect, we have reported some examples.[2,3]

It has been reported that cyclodextrin induces ortho selectivity in the photorearrangement of phenyl esters and anilides in solution and in the solid state.[4] Some previous findings for phenyl acetate (**1**) in the presence of β-cyclodextrin (CD)[5] in aqueous media show that the para-substituted product is formed predominantly. Results from our laboratory for the photo-Fries rearrangement of acetanilide[6] and phenyl acetate[7] are consistent with the increase in the ortho product.

We have undertaken the study of the photolysis of phenyl propionate and phenyl valerate in water solutions in the presence of CD as well as in the solid state in order to determine the effect of the alkyl chain length on the nature of the inclusion complex formed and on the quantum yield for the ortho- and para-rearrangement products.

Results

Photolysis. The photolysis of **1** (phenyl propionate, $n = 1$, **1a**, phenyl valerate, $n = 3$, **1b**) in water solution and in solutions containing CD leads to *p*-hydroxyphenyl alkyl ketone **2**, *o*-hydroxyphenyl alkyl ketone **3**, and phenol **4** (eq 1).



We determined the product distribution spectrophotometrically (see Experimental Section). The results of these experiments are summarized in Table I where it can be seen that the yield of rearrangement products decreases when oxygen is present in the solution. The oxygen inhibition in aqueous solution contrasts with the results reported in other solvents[8,9] but it is in agreement with the results for phenyl acetate under the same conditions.[7] On the other hand, the addition of CD increases the [3]/[2] ratio from 2 to 4 in deoxygenated solutions and from 2 to 3 in oxygenated solutions of **1b** but there is very little change for the reactions of **1a**. It should be noted that the O_2 inhibition is less marked in the presence of CD.

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Table I. Effects of Oxygen and β-Cyclodextrin on the Photolysis of Phenyl Alkanoates (1) in Aqueous Solutions[a]

condn	$[CD]_o$,[c] mM	yields,[b] % 3	2	[3]/[2][d]
	1a = Phenyl propionate[e]			
N_2		10.25	5.98	1.72 ± 0.02
O_2		1.37	1.06	1.29 ± 0.01
N_2	15	16.49	9.16	1.9 ± 0.1
O_2	15	11.07	9.13	1.24 ± 0.02
O_2	1a–CD[f]	0.64	0.62	1.03 ± 0.02
	1b = Phenyl Valerate[g]			
N_2		6.0	3.0	2.0
O_2		1.0	0.5	2.0
N_2	10	9.0	2.3	4.0
O_2	10	1.5	0.48	3.1
O_2[h]		10.0	5.0	2.0
O_2[h]	10	20.0	6.4	3.1
O_2[h]	1b–CD	5.4	1.6	3.4

[a] T = 25 °C. [b] Absolute yields based on the initial substrate concentration. [c] Initial concentration. [d] Average ratio from at least four determinations carried out at regular intervals during the irradiation time. [e] [1a] = 2 mM. Irradiation time = 120 min. [f] Irradiation time = 40 min. [g] [1b] = 0.4 mM. Irradiation time = 30 min. [h] Irradiation time = 60 min.

Inclusion Complex Formation. The addition of CD to a water solution of the substrate (2 mM for **1a** and 0.45 mM for **1b**) produced a small bathochromic shift (1 nm) in the absorption band of 1 centered at 257.2 nm and also an increase in absorbance, indicating that an inclusion complex is being formed. It was not possible to determine an equilibrium constant because the changes in optical density are very small and no isosbestic point is obtained, indicating that there is more than one type of complex. Similar results were obtained with other substrates.[3]

Quantum Yield Determinations. The addition of increasing amounts of CD results in an increase in the quantum yield (Φ) of **3a** (≈ 50%) and **3b** (≈ 30%). On the other hand, the Φ for **2a** increases by a factor of 2 but for **2b** it decreases (≈ 40%). In all experiments we observed an important increase in the quantum yield of 4. These results are summarized in Table II where it is seen that the [3]/[2] ratio increases steadily with the CD concentration for valerate but it decreases for propionate.[10]

Cyclodextrin Complex Photolysis. The solid 1–CD complex, prepared as described in the literature,[11] was irradiated during 40 or 60 min (see Table I). There was about 6% reaction for **1b** and 2% for **1a**, and the [3]/[2] ratio had a value similar to that obtained with each substrate under the photolysis conditions at 15 mM CD concentration (see Table I).

Cross Experiments. It is known that photo-Fries rearrangements are intramolecular reactions, but the experiments that prove this were done in nonprotic solvents.[12] We considered it of interest to determine if in protic solvents the reactions were intramolecular, so a mixture of compounds **5** and **6** was irradiated in 50:50 methanol/water. Only the products of the intramolecular rearrangement, **7** and **8**, were obtained.

(10) A reviewer has suggested that the differences in concentration of products as the concentration of CD increases might be due to differences of oxygen concentration in the solutions, but this is very unlikely because all the solutions were prepared from the same stock solution and the determinations were done simultaneously. Besides, when the runs of similar concentration were repeated, the same trends in the concentration of products were observed.

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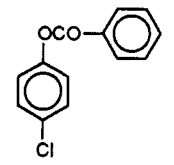
Table II. Effects of β-Cyclodextrin on the Quantum Yields (Φ) of the Products Formed in the Photolysis of Phenyl Alkanoates in Aqueous Solutions[a]

$[CD]_o$,[c] mM	Φ_{exp}[b] 3	2	4	[3]/[2]
	1a = Phenyl propionate[d]			
	0.10	0.06	0.05	1.7
1	0.12	0.07	0.12	1.6
2	0.13	0.08	0.10	1.6
4	0.13	0.09	0.12	1.5
6	0.14	0.10	0.12	1.4
10	0.15	0.13	0.11	1.1
	1b = Phenyl Valerate[e]			
	0.104	0.050		2.0
1	0.110	0.039	0.06	2.8
2	0.113	0.036	0.07	3.1
4	0.120	0.034	0.07	3.5
6	0.121	0.031	0.08	3.9
8	0.125	0.032	0.10	3.9
10	0.130	0.030	0.12	4.3

[a] T = 25 °C. [b] Observed quantum yield for the formation of the product below. [c] Initial concentration of CD. [d] [1a] = 2 mM. Maximum irradiation time = 30 min. [e] [1b] = 0.4 mM. Maximum irradiation time = 30 min.



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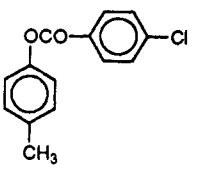

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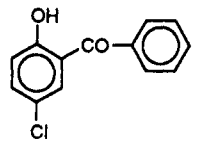

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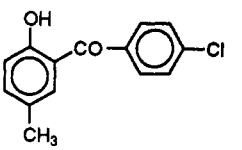

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Discussion

The photo-Fries rearrangement of 1 (phenyl acetate) has been extensively studied in protic[13] as well as in nonprotic solvents[8] and in the vapor phase,[14] but there have not been detailed studies in aqueous solutions.[5] The general mechanism accepted for the reaction[9,15] is shown in Scheme I.

The primary photochemical process produces a pair of radicals which upon recombination lead to the rearranged products **2** and **3**. The formation of the phenol is strongly dependent on the viscosity of the reaction medium, and arises from the escape of the phenoxyl radical from the solvent cage.[9,15]

The quantum yield ratio for the ortho to para product changes from 1.4 in ethanol to 9 in hexane for phenyl acetate. This change is mainly due to a decrease in the quantum yield for the para product while the ortho product does not change. This effect is attributed to the "solvent caging" effect where ethanol would produce the strongest solvent cage because of the relatively high degree of molecular association.[9]

In the presence of cyclodextrin at the maximum concentration used, only a fraction of the substrates **1a** and **1b** are complexed; therefore, the photochemical

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(14) Meyer, J. W.; Hammond, G. S. *J. Am. Chem. Soc.* **1970**, *92*, 2187.
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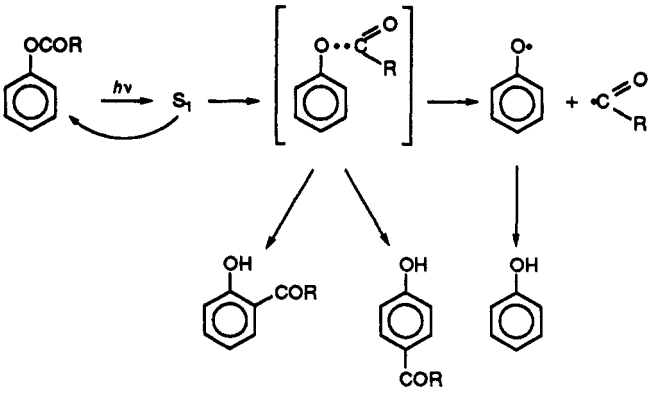
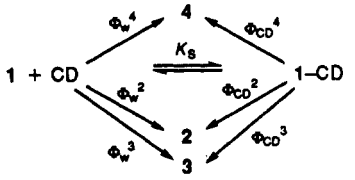
Scheme I



Scheme II



reaction must be taking place in both environments.[16] The kinetic scheme must be represented as in Scheme II where Φ_w^i and Φ_{CD}^i are the quantum yields for each product (i = 2–4) in water and in CD, respectively.

The quantum yield observed for each product, Φ_{exp}^i, may be described by eq 2. where f ($f = K_S[CD]/1 + K_S[CD]$)

$$\Phi_{expl} = \Phi_{wl}(1 - f) + \Phi_{CDi}(\epsilon_0/\epsilon_w)f \qquad (2)$$

is the fraction of complexed substrate (1–CD) and ϵ_c/ϵ_w is a correction factor for the differences in light absorption by 1–CD and 1. This value is ≈ 1 for these reactions.

After f is replaced in eq 2, the equation can be rearranged to eq 3.

$$\frac{1}{\Phi_{wi} - \Phi_{exp}^i} = \frac{1}{\Phi_{wi} - \Phi_{CDi}} + \frac{1}{(\Phi_{wi} - \Phi_{CDi})K_S[CD]} \qquad (3)$$

Table II shows that Φ_{exp}^3 and Φ_{exp}^4 increase when the CD concentration increases, while Φ_{exp}^2 increases for **1a** but decreases for **1b**. From the intercept of a plot (not shown) of the left-hand side of eq 3 vs $[CD]^{-1}$, the values of Φ^{CD} for **2–4** were calculated, and these values are collected in Table III. The ratio of intercept over the slope yields the value of the association constant $K_S \approx 500$ and $\approx 1000\ M^{-1}$ for **1a** and **1b**, respectively. These values are only approximate because there is some scatter in the plots,[17] but they are within the range expected.[18] The value Φ_{CD}^4 of **1b** was determined using one pair of values of Φ_{exp}^4 since the values could not be adjusted to eq 3 due to difficulties with the procedures used in the quantification of phenol.

Table III. Quantum Yields of the Products Formed in the Photolysis of Phenyl Alkanoates (PhOCOR) for the Free (Φ_w) and the Complexed Substrate (Φ_{CD}) in Aqueous Solutions[a]

	Φ_w[c]			
PhOCO–R[b]	3	2	4	3/2[d]
–CH_3[e]	0.16	0.067	0.048	2.3
–CH_2CH_3	0.10	0.060	0.050	1.7
–$(CH_2)_3CH_3$	0.104	0.050		2.0
	Φ_{CD}			
PhOCO–R[b]	3	2	4	3/2[d]
–CH_3[e]	0.22	0.053	0.25	4.2
–CH_2CH_3	0.14	0.12	0.15	1.2
–$(CH_2)_3CH_3$	0.136	0.029	0.18	4.7

[a] T = 25 °C. [b] Substrate concentrations and irradiation times for **1a** and **1b** as indicated in Table II. [c] Observed quantum yield for the formation of the product above. The estimated error in each calculated value is about 10%. [d] Ratio of yield of *o*-hydroxyphenyl alkyl ketone and *p*-hydroxyphenyl alkyl ketone. [e] See ref 7 for experimental conditions.

In Table III, results of the quantum yields of phenyl acetate, propionate, and valerate are compared. It can be seen that Φ_{CD}^3 and Φ_{CD}^4 are in all cases higher in the reactions of the included substrates than in water whereas Φ_{CD}^2 shows the same trend for acetate and valerate but behaves differently for propionate.

Studies regarding the penetration of substituted benzene rings in the cavity of cyclodextrin indicate that the ortho position is not sterically hindered.[19] The substrate included is in a less polar microenvironment than that in the bulk solution as indicated by the observed bathochromic shift in the absorption band; therefore, the increase in Φ_{CD}^3 can be attributed to a microsolvent effect, since it is known that Φ^3 increases in nonpolar solvents.[9] The change in polarity may also be responsible in part for the increase observed in Φ_{CD}^4, since it was reported that the quantum yield for the formation of **4** is higher in hexane (h) than in ethanol (e) ($\Phi_h^4/\Phi_e^4 = 2.6$).[9] As the formation of phenol is attributed to the escape of radicals from the solvent cage, we suggest that an important part of the products is formed from the recombination of radicals which are not in the solvent cage but are trapped in the cavity of the cyclodextrin. Under this condition, the competition with hydrogen abstraction becomes more important than in water solution because there are 14 available hydrogen atoms bonded to secondary carbons and close to the radical center inside the cavity of cyclodextrin.

The reactivity of complexed substrates is very much determined by the structure of the complexes where the orientation within the cavity is of great importance. There are examples in the literature that show that small changes in structure lead to very different behaviors. For instance,

(16) We assume that the photophysical and photochemical primary processes are the same as those for phenyl acetate, and they are not appreciably altered by association with CD. The possibility of diffusion out of cyclodextrin during the singlet-state lifetime of the complexed molecule of phenyl acetate appears as an attractive explanation for the small changes in the experimental quantum yields. We think that this is unlikely because singlet-state lifetimes are in the range of 10^{-9} s, whereas the rate of diffusion of organic species outside the cavity of CD is in the order of 10^4–$10^6\ s^{-1}$ (see, for instance: Schiller R. L., Lincoln S. F., Coates J. H. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 2123.

(17) The slopes of plots for **2a** and **3a** are (4.3 ● 0.2) × 10^{-2} and (1.4 ± 0.3) × 10^{-2}, the intercepts 12 ± 2 and 22 ± 3. The correlation coefficients are 0.98 and 0.99, respectively. The corresponding values for **2b** and **3b** are (2.1 ± 0.2) × 10^{-2} and (6.7 ± 0.5) × 10^{-2} for the slopes and 50 ± 2 and 38 ± 4 for the intercepts with a correlation coeffient of 0.99 for both plots. As mentioned above, spectrophotometric data indicate that there is more than one type of complex. Therefore, the values of K_S estimated from plots according to eq 3 should be a function of the equilibrium constant of all the complexes involved as long as all of them have 1:1 substrate/cyclodextrin stoichiometry. The solid complex has this composition, but the possibility of formation of complexes of 1:2 stoichiometry in solution cannot be disregarded (see: Tee, O. S.; Du, X.-x. *J. Am. Chem. Soc.* **1992**, *114*, 620. Granados, A.; de Rossi R. H. *J. Org. Chem.* **1993**, *58*, 1771). The data reported here do not allow the determination of complexes of higher stoichiometry.

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(19) Wang, Y.; Eaton, D. F. *Chem. Phys. Lett.* **1985**, *120*, 441.

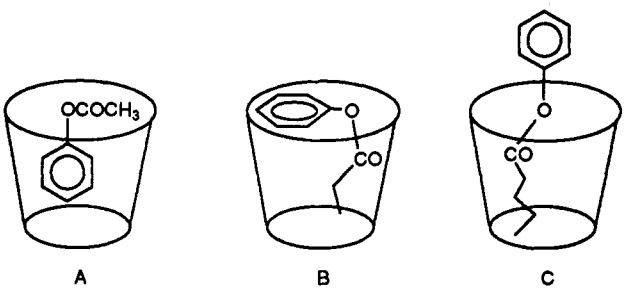

Figure 1.

the hydrolysis of *p*-nitrophenyl propionate is catalyzed by α-CD[18] whereas that of *o*-methylphenyl propionate is inhibited.[20] It is also possible that more than one type of complex are formed and one of them is the most reactive.[21] The changes in the quantum yield with the change in the length of the alkyl chain can be rationalized in terms of the formation of different types of complexes which we can represent as in Figure 1.

The mode of inclusion of phenyl acetate is well established,[1] and the ortho selectivity was attributed to steric hindrance for the migration of the acyl group to the para position of the phenyl group.[7] We suggest that phenyl propionate binds to CD with partial inclusion of both the aryl ring and the alkyl chain (Figure 1, B); CPK molecular models show that this is possible. The alkyl chain acts as a spacer that induces a tight fit between the host and the guest. A tight fit between the host and the guest is of great relevance to reactivity.[23]

In the suggested complex, one of the ortho positions of phenyl propionate is sterically hindered, contrary to what happens for phenyl acetate where the two ortho positions are equivalent; therefore, if we consider a statistical factor of two for the latter substrate, the reactivities of ortho and para positions are significantly higher in the phenyl propionate complex than in the bulk solution which can be attributed to a favorable orientation in the tight complex.

On the other hand, CPK molecular models show that the size of the alkyl chain of phenyl valerate is too big to fit into the cavity of CD together with the aryl ring; therefore, the complexes should have either the alkyl or the aryl ring in the cavity. Considering that the hydrophobicity is one of the major driving forces for complexation,[1,24] as well as literature data already mentioned,[4a,18,25,26] we suggest that the reacting complex is the one shown in Figure 1C.

The reactivity of the ortho and para positions should be similar to those of the complex of phenyl acetate as is observed.

Experimental Section

Reagents. The water used was obtained from a Millipore apparatus. Compounds **1–3**, prepared as reported in the literature[27,28] or used as the commercial reagents (Aldrich), as received, were used; **4** (Merck, analytical grade) was used without further purification. Compounds **1a** and **1b** were purified by HPLC, since the main impurity was phenol which is one of the reaction products and it has strong absorption at the wavelength of irradiation. The samples were repeatedly chromatographed until the phenol content was less than 0.1%. The purity of compounds **1–4** was checked by high-performance liquid chromatography (HPLC). β-cyclodextrin (Roquete) was used as received. Its purity was determined by ultraviolet–visible spectrophotometry (UV). Methanol was HPLC grade (Sintorgan).

Apparatus. The spectrophotometric determinations were carried out in a Shimadzu UV 260. A Varian Vista 5500 liquid chromatograph equipped with a Varian 2550 UV–vis detector and a Varian 4290 integrator was used for the HPLC analysis. The analytical column was a MicroPack 15 cm × 4 mm MCH-5-n-cap, and the preparative one was a MicroPack 50 cm × 8 mm MCH-10.

Photolysis Method. The reactions were carried out in a quartz reactor up to 10% conversion. Solutions of **1** (2 mM) with or without CD were irradiated at 254 nm with an immersion-type low-pressure mercury lamp of 6 W with either bubbling nitrogen or nothing. The solid complex **1**–CD was irradiated in the same reactor but in a horizontal position at the same height of the filament lamp. In all cases the reactor was covered with aluminum foil. To check the photostability of the products, solutions containing **2a**, **3a** (0.7 mM), **2b**, **3b** (0.03 mM), and **4** (0.7 mM and 0.03 mM) in pure water and in water with 15 mM CD were irradiated.

No change in the UV spectrum was observed during the irradiation time chosen for each substrate **1**, indicating that the products are stable under these conditions.

Quantum Yield Determinations. Aqueous solutions of the substrates (**1a** = 2 mM and **1b** = 0.4 mM) and the required amount of CD contained in square quartz cuvettes were placed in a merry-go-round apparatus. They were irradiated with a low-pressure mercury lamp (254 nm, 6 W) which was covered to stop irradiation at regular time intervals. The spectra of the solutions were taken to determine the yield of the photoproducts as indicated in the next section. The irradiation was stopped when about 5% conversion was obtained, and the solutions were analyzed by HPLC to check the concentration of the product calculated by the spectrophotometric method. The results of both analytical methods agree within experimental error. The concentrations of **2–4** are plotted vs time, the slopes were used to calculate the quantum yield, and these values and those of the **3**/**2** ratios are reported in Table II. The quantum yields were determined using a solution of acetanilide in water as actinometer for **1a** and phenyl acetate in water for **1b**. The quantum yield for acetanilide[6] and phenyl acetate[7] were reported previously.

We found no differences between the quantum yield of solutions bubbled with nitrogen for 15 min before irradiation and those used without this treatment, which might be indicating that oxygen was not efficiently eliminated by our procedure.

Analytical Methods. UV–Visible Spectrophotometry. The analysis of the products by spectrophotometry was carried out by the multicomponents–multilambda method as described previously.[7]

High-Performance Liquid Chromatography. In order to check the concentration of products obtained from the spectrophotometric analysis, the samples of each reaction were analyzed by HPLC. The results obtained by both methods show good agreement.

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