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Effect of β-cyclodextrin complexation on the photochemistry of α-phenoxyacetophenone

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Abstract

The photochemistry of α-phenoxyacetophenone complexed with β-cyclodextrin was investigated in the solid state and in aqueous solution. A comparison was made with the irradiation of α-phenoxyacetophenone in different organic solvents. The main observations were as follows: (1) the photolysis of solid α-phenoxyacetophenone–β-cyclodextrin complexes preferentially yields recombination products, whereas in aqueous solution these complexes give rise to hydrogen abstraction products; (2) the photolysis of α-phenoxyacetophenone in solvents of increasing hydrogen donor ability leads to an increase in the formation of products derived from intermolecular hydrogen abstraction.

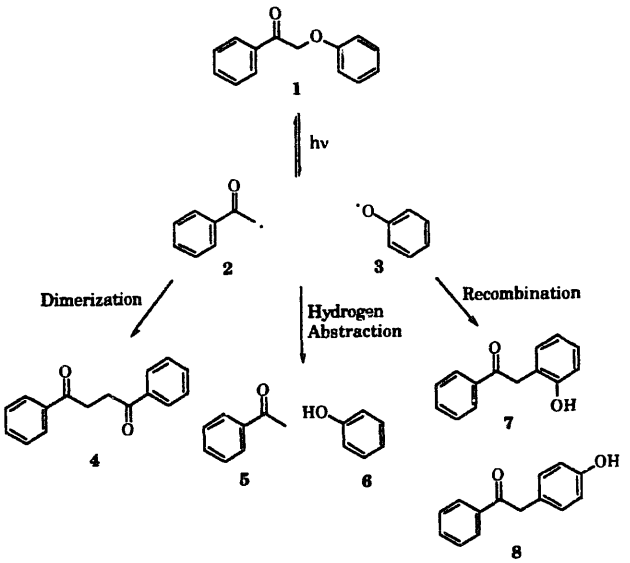
Keywords: β-Cleavage; Cyclodextrin; Hydrogen abstraction; Inclusion complex; Recombination

1. Introduction

The ability of cyclodextrin (CD) to form inclusion complexes with organic molecules has been successfully employed to modify the photochemical reactivity of guests in aqueous solution and in the solid state [1–5]. Reactivity within CD cavities is quite distinct from reaction in solution, and several examples have been reported of photoreactions in which CD influences the photochemical behaviour of the guest molecule to yield a specific reaction from the various competing pathways [2–4,6–8]. The selectivity in the photoreactions of CD complexes has been attributed to the specific tight binding of a particular conformation which may be less favoured in solution. The result is that one reaction pathway may become dominant from several competing pathways. This is a consequence of the control of the reaction by the CD via cage and conformational effects [1].

α-Phenoxyacetophenone (**1**) has a carbonyl group adjacent to the aromatic ring, and one O-aryl linkage at the α-carbon, and is used as a model in lignin studies [9]. It is believed that this compound plays an important role in the formation of phenoxyl radicals which represent one of the main intermediates responsible for the photoyellowing of paper products [9–13].

Earlier studies [14] have shown that the photolysis of **1** in benzene results in β-cleavage, generating phenacyl (**2**) and phenoxyl (**3**) radicals. These radicals react to form 1,4-diphenyl-1,4-butanedione (**4**) (by diffusion and dimerization of the phenacyl radical), acetophenone (**5**) and phenol (**6**) (by intermolecular hydrogen abstraction) and *ortho*- (**7**) and *para*-hydroxydeoxybenzoin (**8**) (by recombination with rearrangement of radicals **2** and **3**) (Scheme 1) [14]. In spite of a considerably fast rate constant for β-cleavage (approximately 3×10^7 s^{-1}) [14], a low quantum yield (approximately 0.003) was measured for this reaction. This can be



Scheme 1.

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interpreted as the consequence of the well-known competitive deactivation process involving the excited carbonyl group and the β-phenyl ring [15,16].

Irradiation of a derivative of **1** (used as a lignin model) on silica [13] gave recombination products analogous to **7** and **8**, formed as a result of ortho and para coupling of phenacyl and phenoxyl radicals. In Ref. [13], there was no evidence for the formation of the phenacyl radical dimer, suggesting that the recombination products were formed via in-cage radical processes.

In this paper, we clearly demonstrate, using steady state photolysis, that CD encapsulation influences the photobehaviour of **1**.

2. Experimental details

2.1. Chemicals

β-CD, α-bromoacetophenone, *ortho*-hydroxyacetic acid, phenylmagnesium bromide and 1,4-diphenyl-1,4-butanedione were obtained from Aldrich and were used as received. Acetophenone (Carlo Erba) and phenol (Poison) were used as received. Methanol, hexane, benzene, isopropanol, acetonitrile and tert-butanol, all of spectrophotometric grade, were obtained from Merck or Grupo Química. α-Phenoxyacetophenone (**1**) [17] and *ortho*-hydroxydeoxybenzoin (**7**) [18,19] were prepared using literature methods, and the physical constants and spectrometric data agree with the proposed structures.

2.2. Equipment

^{1}H nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AC 200 spectrometer. UV–visible absorption spectra were recorded on a Varian DMS 80. Gas chromatography (GC) analysis was performed on a Hewlett-Packard 5890 using an SE-54 capillary column. Mass spectrometry (MS) was performed using a Hewlett-Packard 5987A gas chromatograph–mass spectrometer.

2.3. Preparation of the inclusion complex

A literature method was used for the preparation of the CD complexes [6]. To a saturated solution of β-CD in water was added an equimolecular amount of **1** (in a saturated solution of methanol). Nitrogen was passed through the resulting solution for 30 min to remove the methanol and avoid its complexation with β-CD. The resulting solution was magnetically stirred for 24 h. The white precipitate formed was removed by filtration, washed with ethyl ether to remove noncomplexed **1** and finally dried under vacuum.

A complex in aqueous solution was prepared by the dissolution of 30 mg (3×10^{-5} mol) of the solid complex in 40 ml of water. The samples were sonicated at 45 °C for 30 min due to their low solubility in water.

2.4. Determination of the host to guest ratio

In order to determine the host to guest ratio for the **1**–β-CD complex in aqueous solution, ^{1}H NMR spectra were recorded for solutions of the complex with different **1** to β-CD ratios in deuterated water. The following **1** to β-CD molar ratios were analysed: 0.4, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0. These samples were sonicated for 30 min before measurement.

The NMR spectrum was also recorded of a solution of 2.0 mg of solid **1**–β-CD complex (prepared by the method described above) in 1.0 ml of deuterated water followed by Millipore filtration.

2.5. Determination of the dissociation constant for the complex 1–β-CD

The dissociation constant for the complex **1**–β-CD was determined spectrophotometrically by a modification of the Benesi–Hildebrand method (Eq. (1)) [20]

$$\frac{a\times b}{\Delta OD}=\frac{K_d}{\Delta\epsilon}+\frac{1}{\Delta\epsilon}\times(a+b) \quad (1)$$

where a is the β-CD concentration, b is the concentration of **1**, ΔOD is the change in absorbance, K_d is the dissociation constant for the **1**–β-CD complex and $\Delta\epsilon$ is the difference between the extinction coefficients of complexed and noncomplexed **1**. The change in the absorption intensity of **1** at 249 nm was measured after successive additions of CD.

Various samples containing the same concentration of **1** (1.5×10^{-5} M) and different concentrations of β-CD (0, 1.6×10^{-3}, 3.8×10^{-3}, 8.0×10^{-3} and 9.0×10^{-3} M) in water were sonicated for 30 min. The absorbance was then measured. Due to the large difference in the values of a and b, the last term in Eq. (1), i.e. $(a+b)$, simplifies to a.

2.6. Photolysis procedure

The photolysis of **1** in organic solvents (10^{-2} M) was carried out in a quartz tube in a Rayonet reactor fitted with four 300 nm lamps, after purging the solution with nitrogen for 30 min. The samples were irradiated until 10%–20% conversion to acetophenone occurred. The samples were concentrated and analysed by GC and GC–MS. GC peaks were identified by co-injection with authentic samples. An analogous photolysis procedure was used for aqueous solutions of the **1**–β-CD complex but, in this case, the samples were analysed after extraction with dichloromethane.

To perform the product distribution analysis, products derived from the phenacyl radical were used to define a hydrogen abstraction/other products ratio. This ratio was calculated by taking the peak area for the intermolecular hydrogen abstraction product (**5**) and dividing it by the sum of the peak area for products resulting from dimerization (**4**) and recombination (**7**+**8**)

Ratio = peak area for **5**/peak area for (**4**+**7**+**8**)

Solid **1**–β-CD complexes (50 mg) were placed in a Pyrex tube (some samples were saturated with O_2) and photolysed for 72 h in a dark chamber using a medium pressure mercury lamp (450 W). To obtain a uniform exposure to light, the sample tubes were fixed in a disc fitted to a low-frequency rotation motor. After irradiation, the samples were partitioned between dichloromethane (30 ml) and water (20 ml). The resulting dichloromethane solutions were combined, dried over Na_2SO_4 and then concentrated by rotary evaporation. The residue thus obtained was analysed in a similar manner to that described above.

3. Results

Our initial experiments with the **1**–β-CD complex focused on its characterization. NMR spectra for a series of samples with different molar ratios of **1** to β-CD were recorded in deuterated water. The chemical shifts for the different hydrogens of β-CD, expressed in hertz, as a function of the ratio of **1** to β-CD are shown in Fig. 1. From this plot, upfield shifts for all β-CD hydrogens are observed as the molar ratio of **1** to β-CD is changed from 0 : 1 to 1 : 1. No further significant change in the chemical shifts up to a ratio of 3 : 1 is observed. The NMR spectrum for a solution of the **1**–β-CD complex in deuterated water, prepared by the precipitation method, was also recorded. The chemical shift for the different β-CD hydrogens was similar to that obtained for the sample with a molar ratio of **1** to β-CD of 1 : 1.

After having established that β-CD readily forms a 1 : 1 complex with **1**, the stability of this complex was investigated. The dissociation constant (K_d) was determined using a method analogous to that of Benesi and Hildebrand [20], whereby changes in the UV absorption intensity of **1** at 249 nm (where **1** has an absorption maximum) were followed. The addition of β-CD to an aqueous solution of **1** revealed a hypsochromic shift as a function of β-CD concentration. A plot of $(a \times b)/\Delta OD$ vs. a is shown in Fig. 2. From the intercept and slope of this plot (see Eq. (1)), a value for K_d of $(5.6 \pm 0.5) \times 10^{-3}$ M was obtained.

The photochemistry of **1** is expected to be dependent on its environment. Scheme 1 shows the possible reaction pathways by which **1** can yield products. The relative yields of these products will depend on various factors, e.g. the ability of the medium to donate hydrogen (products **5** and **6**) and the ability of the radicals, formed through β-cleavage, to diffuse freely to yield recombination (**7** and **8**) or dimerization (**4**) products. Thus the photochemistry of **1** was investigated under different experimental conditions and the results are summarized in Table 1.

In order to determine the product distribution as a function of the hydrogen donor ability of the solvent, the photolysis of **1** was performed in the organic solvents hexane, benzene, acetonitrile, tert-butanol, isopropanol and methanol. The analysis of Table 1 shows that the ratio **5**/(**4**+**7**+**8**) increases with the capacity of the solvent to donate a hydrogen

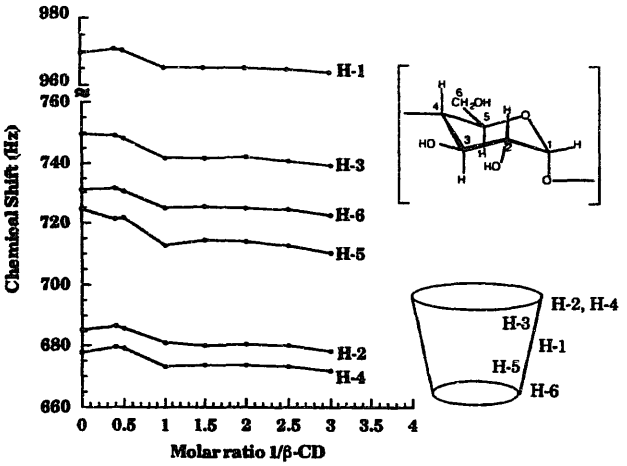


Fig. 1. Left: chemical shift of β-CD protons as a function of the molar ratio of the **1**–β-CD complex. Top right: CD unit. Bottom right: representation of the CD cavity showing the proton location.

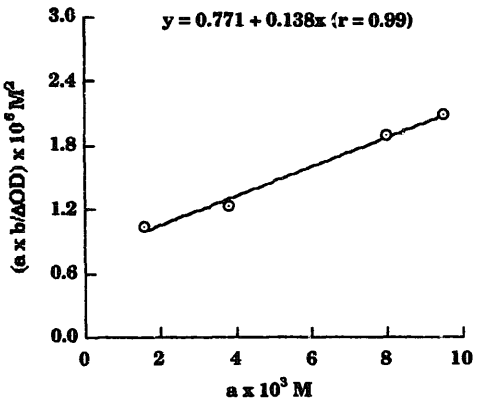


Fig. 2. Plot of $a \times b/\Delta OD$ vs. a from Eq. (1) for the **1**–β-CD complex.

Table 1
Effect of the medium on the hydrogen abstraction (**5**) to dimerization (**4**) plus recombination (**7**+**8**) ratio from phenacyl radicals

Medium	5/(4+7+8) ratio
Isopropanol	1.25 (±0.04)
Hexane	0.86 (±0.03)
Methanol	0.53 (±0.05)
Benzene	0.29 (±0.06)
Acetonitrile	0.16 (±0.04)
tert-Butanol	0.14 (±0.01)
β-CD air (solid)	0.02 (±0.01)
β-CD O_2 (solid)	0.03 (±0.01)
β-CD N_2 (aqueous)	3.18 (±0.10)

atom. Thus solvents which have a poor ability to donate hydrogen, such as benzene, acetonitrile, tert-butanol and methanol, show a smaller value of this ratio than isopropanol (a good hydrogen donor).

From the knowledge that a stable **1**–β-CD complex can be readily formed in a 1 : 1 molar ratio (see above), its photolysis was investigated under different experimental conditions (Table 1).

UV irradiation of an aqueous solution of the **1**–β-CD complex gives a value of 3.18 for the **5**/(**4**+**7**+**8**) ratio, which

is considerably higher than that obtained for the experiments conducted in organic solvents.

However, the photolysis of the **1**–β-CD complex in the solid state yields a small value, i.e. 0.02, for the **5**/(**4**+**7**+**8**) ratio (Table 1). GC and GC–MS analysis show that product formation is mainly derived from the recombination process, i.e. **7** and **8**. In this case, dimerization of the phenacyl radical is negligible in comparison with that observed during the photolysis of aqueous solutions of the **1**–β-CD complex. No oxygen effect is observed on product formation, since photolysis in air and oxygen results in a similar product distribution.

Finally, the photolysis of a mechanical mixture of β-CD and **1** results in the formation of phenol and benzoic acid as the main products.

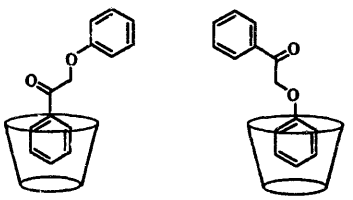
4. Discussion

The inclusion of an aromatic ring inside a CD cavity was demonstrated by Demarco and Thakkar [21]. Using ^{1}H NMR evidence, they attributed the upfield shift of hydrogens H-3 and H-5, inside the cavity, to the anisotropic magnetic effect of the aromatic ring included within the cavity.

Fig. 1 shows a plot of the frequency (Hz) of the ^{1}H resonances of CD as a function of the molar ratio of **1** to β-CD. It is readily observed that, as the molar ratio of **1** to β-CD approaches unity, there is an upfield shift of hydrogens H-3 and H-5. Furthermore, as the molar ratio is increased beyond unity, no further significant change in the chemical shift is observed. From this, it can be deduced that only one molecule of **1** complexes with one β-CD molecule. This technique has been extensively used as direct evidence for host–guest complex formation and to determine the molar ratio of complexes in aqueous solution [2,3,6,8,22,23].

The determination of the K_d value is an important part of the characterization of the complexes. The K_d value of 5.6×10^{-3} M, obtained from Fig. 2 using the Benesi–Hildebrand method [20], implies that the **1**–β-CD complex is quite stable in aqueous solution. UV spectroscopy has been used as an efficient method for the determination of the dissociation constant of CD complexes with different substrates [3,8,23]. The K_d value obtained for the **1**–β-CD complex has a similar magnitude to those reported for complexes between β-CD and various substrates, e.g. alkyldeoxybenzoin [8], alkylbenzoin ether [7], benzyl phenyl ether [2] and benzoin acetate [3].

A knowledge of the structure of the **1**–β-CD complex is essential to understand the resulting product distribution on photolysis of the complex under different conditions. Two possible modes of insertion of **1** in β-CD can be envisaged (Fig. 3). In one case, the phenacyl group is located inside the cavity (**I**) and, in the other, the phenoxyl group is inside the cavity (**II**). A previous study [24] employing *para*-methoxy-β-phenylpropiophenone, an analogous molecule to **1**, revealed that the benzoyl group was preferentially complexed inside the β-CD cavity. The study revealed a difference in the triplet lifetime between *para*-methoxy-β-phenylpropiophenone complexed with β-CD and γ-CD. The shorter triplet lifetime of the β-CD complex was interpreted to be the result of β-phenyl quenching, a common mechanism by which the triplet state of β-phenyl ketones is internally quenched [15,16]. The longer triplet lifetime of the γ-CD complex was interpreted to be the result of the incorporation of both phenyl groups within the γ-CD cavity. Ramamurthy and coworkers [6–8] have also proposed similar structures for various complexes between aromatic ketones and β-CD.



I II

Fig. 3. Proposed structures for the **1**–β-CD complex.

On photolysis of an aqueous solution of the **1**–β-CD complex, we obtained products due to ortho and para coupling of the phenacyl radical with the phenoxyl radical. The ratio of ortho to para coupling was close to two (a ratio of *ortho*-hydroxydeoxybenzoin (**7**) to *para*-hydroxydeoxybenzoin (**8**) of close to two was found during product analysis for all samples in this study, with the exception of hexane and benzene). This result is best interpreted by considering the benzoyl group to be inside the β-CD cavity. If the phenoxyl group was inside the CD cavity, the para position of the aromatic ring would be protected from attack by bulky species, such as the phenacyl radical, leaving only the ortho positions free to such attack.

In order to understand further the chemistry of **1** resulting from β-cleavage (Scheme 1), we studied the relative ratios of the products formed on photolysis of **1** in different solvents. The results of these experiments are given in Table 1 and reveal that the **5**/(**4**+**7**+**8**) ratio is dependent on the hydrogen donor ability of the solvent. The photolysis of **1** in isopropanol leads predominantly to the formation of acetophenone (**5**). As expected, experiments in solvents of poor hydrogen donor ability result in the preferential formation of products **4**, **7** and **8**. In a related study, the photolysis of **1** in thiophenol, an excellent hydrogen donor, led exclusively to the formation of phenol and acetophenone from phenoxyl and phenacyl radicals respectively [16]. This result confirms the importance of the medium in influencing the reaction course shown in Scheme 1.

Various experiments with the **1**–β-CD complex were performed in aqueous solution and in the solid state in order to investigate the photochemistry of encapsulated **1**. The photolysis of the **1**–β-CD complex in the solid state yields a small value for the **5**/(**4**+**7**+**8**) ratio (Table 1), and the preferential formation of recombination products **7** and **8** is observed in comparison with the photolysis of **1** in organic solvents. This finding reveals that the two hydrogens (H-3

and H-5) inside the β-CD cavity are not readily available to hydrogen abstraction despite their similarity to H-2 of isopropanol, and that the solid state medium inhibits the diffusion of radicals formed by β-cleavage. Similar cavity effects have been demonstrated in various studies of CD complexes, e.g. alkyldibenzyl ketone [22].

The fact that an oxygen effect is not observed after photolysis of the solid **1**–β-CD complex indicates that radicals **2** (phenacyl) and **3** (phenoxyl) probably remain as a close contact pair and therefore cannot easily react with oxygen. Similar protection by the CD cavity has been observed with other triplet probes [25].

The photolysis of a mechanical mixture of β-CD and **1** for 72 h results mainly in the formation of phenol and benzoic acid. The formation of benzoic acid can be explained by a competitive α-cleavage process, generating benzoyl radical (**9**) (Eq. (2)), which can then be oxidized to benzoic acid [6,7]. This is an intrinsic reaction of α-phenoxyacetophenone (**1**), since the photolysis of crystals of **1** leads to the same products.

$$\underset{\mathbf{1}}{\mathrm{PhCOCH_2OPh}} \xrightarrow{\alpha\text{-cleavage}} \underset{\mathbf{9}}{\mathrm{PhCO}} + \underset{\mathbf{10}}{\mathrm{PhO\dot{C}H_2}} \qquad (2)$$

The photolysis of an aqueous solution of the **1**–β-CD complex shows an increase in the amount of acetophenone **5** in comparison with that observed for the complex in the solid state. In aqueous solution, an equilibrium between complexed and uncomplexed **1** can be postulated. In this case, it is possible that the phenacyl radical may be formed either inside or outside the CD cavity. If the radical is formed outside the cavity, it is exposed to a greater number of potential hydrogen donor sites (H-1, H-2, H-4 and H-6,6′) than inside (H-3 and H-5), thus increasing the probability of formation of products arising from hydrogen abstraction. In addition, an equilibrium involving complexed and uncomplexed phenacyl radical is also expected (Eq. (3)), which allows hydrogen abstraction from outside the cavity to occur.

$$\mathrm{PhCO\dot{C}H_2/\beta-CD} \rightleftharpoons \mathrm{PhCO\dot{C}H_2} + \beta\mathrm{-CD} \qquad (3)$$

Furthermore, it is also expected that β-cleavage of **1** in the **1**–β-CD complex will result in the rapid diffusion of the phenoxyl radical, which will therefore become separated from the complexed phenacyl radical. Therefore, in aqueous solution, hydrogen abstraction products are observed in preference to recombination products. It is important to note that the low concentration (approximately 10^{-5} M) of the complex in aqueous solution also favours product formation by hydrogen abstraction rather than by radical–radical recombination. The seemingly large value of the **5**/(**4**+**7**+**8**) ratio for the complex in aqueous solution in comparison with the lower value obtained for the photolysis of **1** in isopropanol is probably due to the 1000-fold difference in concentration. The higher concentration of **1** in isopropanol solution will allow the generation of a higher concentration of radicals (in comparison with aqueous solution), increasing the possibility of radical–radical termination reactions, and resulting in a smaller value of the **5**/(**4**+**7**+**8**) ratio.

In conclusion, we have observed dramatic differences in the photochemistry of the **1**–β-CD complex in the solid and solution states; this can be attributed to the ability of radicals to diffuse in solution, whereas, in the solid state complex, molecular diffusion is more restricted and products resulting from in-cage processes are observed.

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