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EFFECT OF CYCLODEXTRIN ON INTERMOLECULAR PHOTOALKOXYCARBONYLMETHYLATION OF ANISOLE

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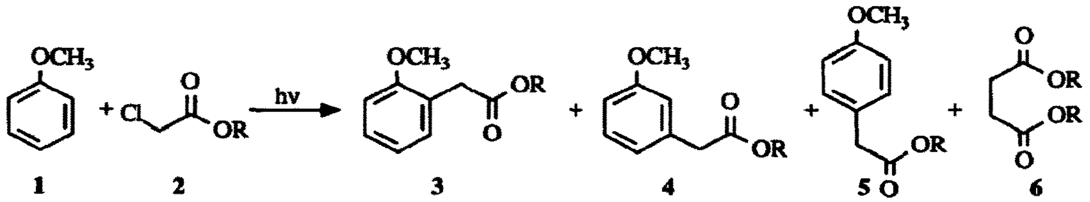
Summary: The photolyses of anisole (**1**) and pentyl chloroacetate (**2b**) in isotropic media produce both alkylation products **3b-5b** and dipentyl succinate (**6b**). In α- and β-CD complexes in aqueous solutions, **6b** was absent and the *o*-alkylation product **3b** was predominant. A cage effect and geometric control are attributed to the observed selective product distribution in α- and β-CD complexes in aqueous solutions.

Cyclodextrins (CDs) are known as host molecules to induce selectivity in photochemical reactions of encapsulated guest molecules.[1] In most of the photoreactions studied, however, CDs were used to demonstrate restriction in molecular motions of the generated fragments of a *single* reactant molecule. The produced fragments, then, chose selectively one of several possible reaction pathways.[2] In contrast, only a few *bimolecular* photochemical reactions in CDs have been reported.[3,4] Here we wish to present preliminary results on the first intermolecular photoalkoxycarbonylmethylation of anisole **1** in CDs.



a $R{=}CH_2CH_3$
b $R{=}(CH_2)_4CH_3$

Scheme 1

Earlier, in organic solvents, the intermolecular photochemical alkylation of **1** by ethyl chloroacetate (**2a**) in the presence and absence of Lewis acids was reported.[5] Direct irradiation (36 h) of an ethyl acetate (EtOAc) solution containing **1** (1 M) and **2a** (0.1 M), but no Lewis acid, produced the alkylation products **3a**, **4a** and **5a** in a ratio of ca. 5:2:1, respectively (14% yield). Only trace amounts of diethyl succinate (**6a**) were found. Higher yields (38%) were observed from the photolysis of anisole:ethyl acetate (9:1) solutions containing 0.1 M of **2a**. It was also noted that chloroacetate quenches the fluorescence of **1**.[5,6] In the absence of Lewis acids, the authors[5] suggested a mechanism involving energy transfer from the excited singlet state of **1** to chloroacetate followed by C-Cl bond homolysis. Our interest was focused on bringing together both **1** and pentyl chloroacetate (**2b**) into the CD cavity and studying their photoreactivity in the CD microenvironment.

In the present study, the results of the solvent photolyses[7] of **1** and pentyl chloroacetate (**2b**) are presented and compared with those obtained from CD complexes in aqueous solution (CD_{aq}). When an EtOAc solution containing equal concentrations of **1** (0.1 M) and **2b** (0.1 M) was photolyzed for 24 h, both alkylation (*o*-, *m*- and *p*-) products **3b**-**5b** and dipentyl succinate (**6b**) were observed in a ratio of ca. 4:1 (Table 1).[8] The ratio of *o*:*m*:*p* was ca. 1.5:1:1, respectively (Table 1). However, at a higher concentration of **1** ([**1**] = 1 M; [**2b**] = 0.1 M) in an EtOAc solution, the alkylation/succinate product ratio decreased to 3:1 while the alkylation product ratio changed slightly (*o*:*m*:*p* = ca. 3:1:1). In a protic solvent, such as methanol, the yield of *o*-alkylation product **3b** was increased, while the formation of **6b** was lowered (Table 1).

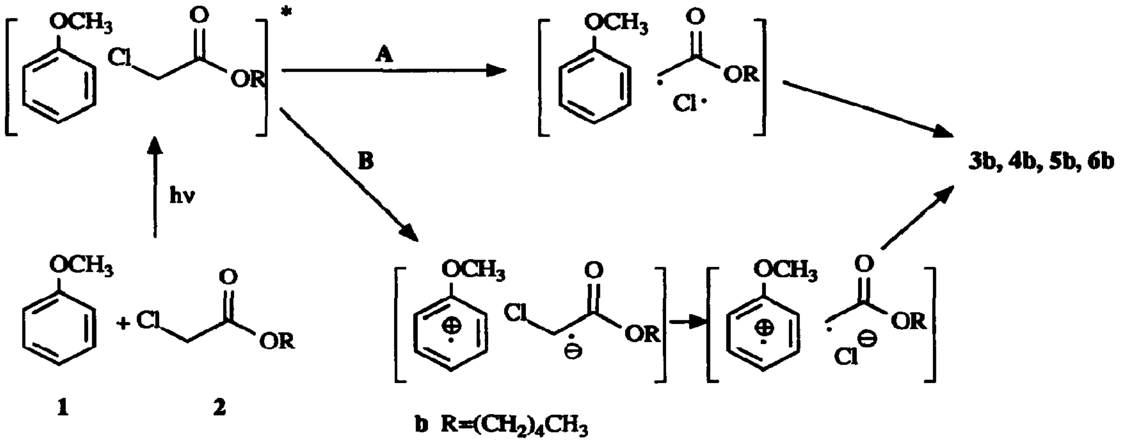
Table 1. Product distribution from the photolysis of **1** and **2b** under various conditions[7,8]

Medium (1:2b)	Photolysis Time (h)	Photoproducts (%) 3b	4b	5b	6b
EtOAc (0.1M:0.1M)	24	34	20	25	21
EtOAc (1M:0.1M)	24	44	15	16	25
MeOH (0.1M:0.1M)	24	65	17	8	10
MeOH (1M:0.1M)	24	69	7	13	11
α-CD ($3x10^{-3}$M:$3x10^{-3}$M)	5	80	5	15	0
β-CD ($3x10^{-3}$M:$3x10^{-3}$M)	5	67	8	25	0
γ-CD ($3x10^{-3}$M:$3x10^{-3}$M)	5	53	10	28	9

Addition of **1** (3×10^{-3} M) and **2b** (3×10^{-3} M) to an aqueous solution saturated in CD produced a white precipitate which was filtered off, washed first with distilled water, then diethylether and finally air-dried. The obtained solid was redissolved in water to get a transparent solution for the photolysis.[7] The photolysis of α- and β-CD_{aq} gave a product mixture in which **6b** was non-existent (Table 1) and a dramatically altered alkylation product ratio of *o*:*m*:*p* [ca. 13:1:2 (α-CD_{aq}) and 8:1:3 (β-CD_{aq})] was obtained. However, in γ-CD_{aq}, the photoproduct distribution was similar to that found in organic solvents: **6b** was observed along with the alkylation products (ratio *o*:*m*:*p* = ca. 2.3:1:1.6). It is noteworthy that as the CD cavity size increases, the yield of the *o*-alkylation product **3b** decreases while a systematic increase in yields of *m*- and *p*-alkylation product formation **4b** and **5b**, respectively, takes place.

Evidence for the formation of a ternary complex **1** + **2** + **β-CD** was obtained from spectrophotometric as well as ^{1}H NMR studies.[9] As reported,[10] while the presence of β-CD in aqueous solution did not change the absorption maximum, it increased the optical density (at 274 nm) of **1**. The higher the β-CD concentration, the greater the absorption (OD_{274}) of **1**. This result indicates the presence of **1** encapsulated in the CD cavity. In a set of separate experiments, however, five different aqueous solutions of β-CD (10^{-4} M to 9×10^{-4} M) were made and constant concentrations of **1** (5.07×10^{-4} M) and **2** (6.06×10^{-4} M) were added to each of the solutions. In this case, a gradual increase in [β-CD] caused a pronounced decrease in the absorption of **1**.[11] The combination of the above results indicates that **2b** interacts with **1** inside the CD cavity. Furthermore, the presence of **2b** in β-CD_{aq} renders the microenvironment of **1** more polar than in β-CD_{aq} solution alone. Further evidence for the ternary complex was obtained from the ^{1}H NMR spectral data. **1** + **2** + **β-CD** solid complex was dissolved in DMSO-d_6 solution and its ^{1}H NMR spectrum clearly showed the signals of individual protons corresponding to β-CD, **1** and **2**. The upfield shifts[12] observed for protons H-3 and H-5 of β-CD in D_2O can be attributed to the diamagnetic anisotropic shielding effect of the aromatic ring of **1**. In the case of α- and γ-CD, the ternary complex formation was believed to be similar to that of β-CD.

Based on limited studies on quenching and photoalkylation, Yonemitsu *et al.* suggested that chloroacetate esters would probably behave similarly to chloroacetamides.[13] As shown in Scheme 2, after energy transfer, the mechanism for the formation of alkylation products **3b**-**5b** might involve either (A) C-Cl bond homolysis or (B) electron transfer to give an ion radical pair followed by C-Cl bond heterolysis. The structure of the resulting α-chloroacetate ester anion radical intermediate permits the heterolysis of the C-Cl bond to produce a neutral radical which is stabilized by the carbonyl group. Prior to photoalkylation, the diffusion of $\cdot CH_2COOR$ radicals into the solvent followed by recombination affords **6b**.



Scheme 2

The observed results can be rationalized as follows: The absence of **6b** in α- and β-CD_{aq} is attributed to the prevented diffusion of a $\cdot CH_2COOR$ radical by CD. Such a cage effect by CD on free radicals was reported earlier.[2] The presence of **6b** in γ-CD_{aq} suggests that due to the large size of the cavity, photogenerated free radicals escape freely like in solvents. In an organic solvent such as EtOAc, *o*-alkylation is preferred over *p*-alkylation. In α- and β-CD complexes, *o*-selectivity is seen at the expense of *m*-alkylation. The preference for *o*-alkylation does not seem to correspond with the electron spin density values of the aromatic ring of **1**.[14]

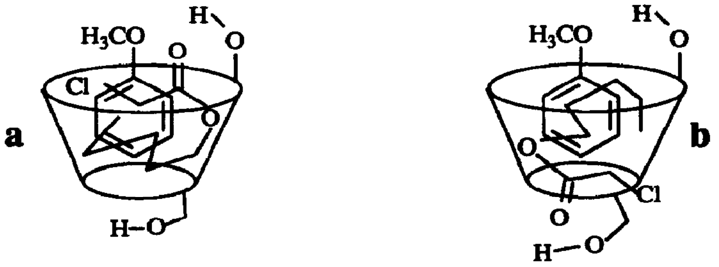


Figure 1

In solvents, the observed product ratio seems to be correlated to a preferred geometric relation between the aromatic ring and the chloroacetate ester group of **2b**. The polar C=O bond of the ester **2b** in solvents may have some interaction with the methoxy group in **1**. In α- and β-CD complexes, however, such interaction may be enhanced due to selective binding of **1** and **2b** (Figure 1a) such that the CD rim blocks the *m*-position of the aromatic ring from attack by a $\cdot CH_2COOR$ radical. The possible structure as shown in Figure 1b might account for the formation of *p*-alkylation product **5b**. The presence of photoproduct **4b** in α- and β-CD_{aq} may be due to the fact that the reaction also occurs in the bulk aqueous phase. Our explanation for the observed *o*-selectivity in α- and β-CD complexes is speculative at this stage and further studies are necessary to establish a detailed mechanism.

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7. Photolysis conditions: 400 W Medium pressure mercury lamp (Hanovia) using quartz vessels; no nitrogen bubbling; conversion limited to about 30%.
8. The photoproducts were identified by comparing the GC retention times with those of authentic samples [Sichromat 1-4, 25 m x 0.272 mm (i.d.) OV 101 glass capillary column]. Error limit ±5%. Authentic samples were synthesized by H_2SO_4-catalyzed esterification of the corresponding methoxyphenylacetic acids. All the esters (**2b-6b**) were characterized by ^1H NMR.
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11. At β-CD concentrations of 10^{-4} M, 3 x 10^{-4} M, 5 x 10^{-4} M, 7 x 10^{-4} M and 9 x 10^{-4} M the observed OD_{274} values were 0.553, 0.549, 0.548, 0.539 and 0.529, respectively.
12. 360 MHz ^1H NMR chemical shifts [D_2O;δ(Hz)] for protons of β-CD[9] and its complexes with **1** and **1** + **2b** are provided; H_2O as internal standard at δ=4.63 ppm.

	H-1	H-2	H-3	H-4	H-5	H-6
β-CD	1760.5	1248.8	1362.9	1225.6	1323.3	1331.6
β-CD+**1**	1760.7	1250.8	1351.8	1225.1	1313.0	1326.1
β-CD+**1**+**2b**	1758.6	1247.4	1352.8	1224.2	1308.5	1328.5

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