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A remarkable stereoselectivity switching upon solid-state versus solution-phase enantiodifferentiating photocyclodimerization of 2-anthracenecarboxylic acid mediated by native and 3,6-anhydro-γ-cyclodextrins

Cheng Yang,[a] Masaki Nishijima,[b] Asao Nakamura,[a] Tadashi Mori,[b] Takehiko Wada[b] and Yoshihisa Inoue[a,b,*]

[a]*ICORP Entropy Control Project, JST, Japan*
[b]*Department of Applied Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan*

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Abstract—The enantiodifferentiating [4+4] photocyclodimerization of anthracenecarboxylic acid (AC) mediated by native, mono- and di-3,6-anhydro-γ-cyclodextrins was investigated in both aqueous solution and solid-state. The solid-state photolyses gave inherently disfavored *head-to-head* photodimers in much higher chemical and optical yields than in the aqueous solution.

Stereocontrol is a critical issue in chiral photochemistry from the mechanistic and synthetic points of view.[1] Photolysis of ordered substrates in the solid-state is a unique and efficient approach to the stereocontrolled photoproducts,[2] enabling the absolute asymmetric synthesis without using any external chemical or physical chiral source.[2a,b] A variety of photoreactions, which are inert or unselective in solution-phase, proceed in good stereoselectivity within the clathrates of chiral compounds formed by cocrystallization.[3] Similarly, amorphous supramolecular complex of substrate with chiral host, such as cyclodextrins (CDs),[4] modified zeolites,[5] and chiral nanopore,[6] can be subjected to asymmetric photoreactions. Of chiral supramolecular hosts, CDs, truncated cone-shaped macrocyclic oligosaccharides, are of our particular interest, possessing an inherently chiral hydrophobic cavity which accommodates a wide range of organic guests.[7] We have recently reported the enantiodifferentiating [4+4] photocyclodimerization of anthracenecarboxylic acid (AC) mediated by natural and synthetic hosts, which affords four photodimers, that is, achiral *anti-head-to-tail* (HT) photodimer **1** and *syn-head-to-head* (HH) photodimer **4**, and chiral *syn*-HT photodimer **2** and *anti*-HH photodimer **3** (Scheme 1).[8] Native γ-CD can significantly accelerate the photocyclodimerization of AC by forming stable 1:2 host–guest complex in aqueous solution, and afford HT photodimers in good yield and enantiomeric excess (ee).[8a] It has been shown that the relatively low stereoselectivity for HH photoproducts can be improved by using modified γ-CDs and also by manipulating the external effectors, such as temperature, solvent, and pressure.[8b–d] In this work, we demonstrate that the stereoselectivity can be manipulated or even switched by changing the reaction media from solution to solid-state in the photocyclodimerization of AC mediated by mono- and di-3,6-anhydro-γ-CDs **5**–**9** (Scheme 2).

Photoirradiation of AC with native γ-CD in pH 9.0 aqueous buffer solution gives the HT photodimers (**1** and **2**) in ca. 90% combined yield and ee of 41% for **2**.[8a] It is obvious that the electrostatic repulsion between the two anionic AC molecules accommodated in the same cavity discourages the formation of HH photodimers in aqueous solution. To avoid this repulsive interaction, we attempted to carry out the photoreaction under acidic condition. However, this is unsuccessful due to the very poor solubility of AC at pH lower than

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* Corresponding author. E-mail addresses: c.yang@inoue.jst.go.jp; inoue@chem.eng.osaka-u.ac.jp

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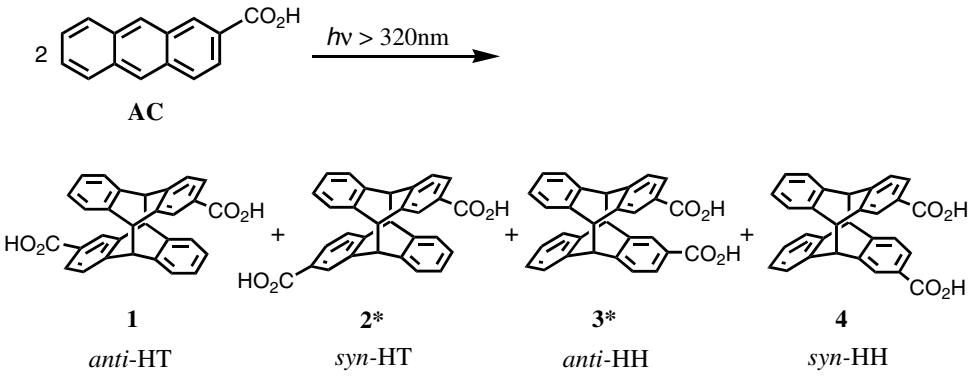
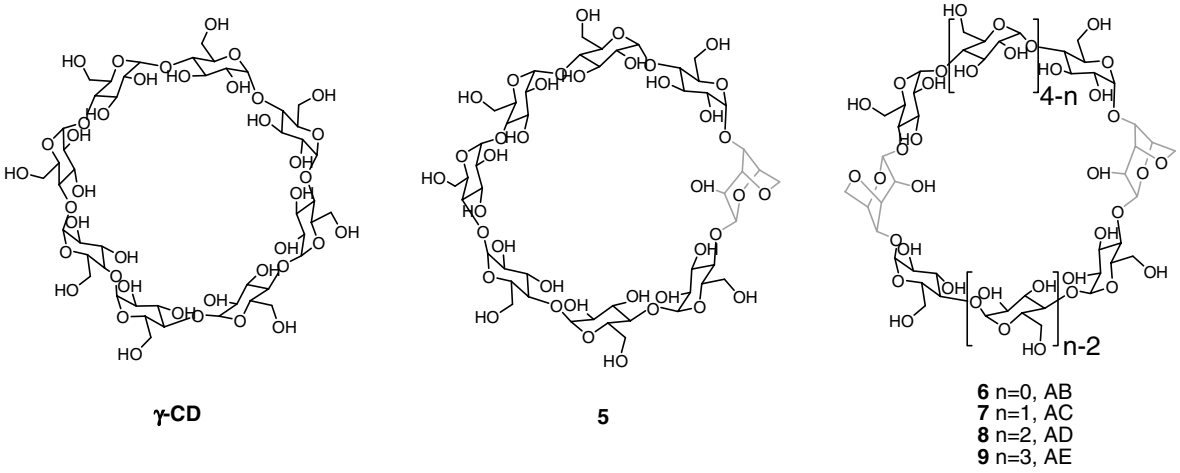


Scheme 1. Photocyclodimers formed upon irradiation of AC.



Scheme 2. Chiral hosts employed for the enantiodifferentiating photocyclodimerization of AC.

5.0 (pK_a of AC at 25 °C is 4.18).[9] We then examined the CD-mediated photodimerization in the solid-state, where two AC molecules in the cavity are electrically neutral and hence no longer repulsive to each other, giving more chance to the HH photodimers.

The solid-state complex was prepared by mechanically grinding an equimolar mixture of AC and γ-CD with a mortar and pestle, and a KBr pellet containing the resultant complex was examined by IR, UV, and circular dichroism spectroscopy. As shown in Figure 1, the carbonyl's stretching vibration shifted from 1685.5 to 1687.4 cm^{-1} in the IR spectra, presumedly due to a partial loss of hydrogen-bonded AC dimers as a result of the inclusion into the CD cavity. The solid-state circular dichroism spectrum, obtained by averaging the spectra measured at two rotation angles perpendicular to each other, showed strong induced circular dichroism signals at the AC's ^1B_b and ^1L_a bands (Fig. 2), unambiguously demonstrating inclusion of AC into the CD cavity.

Photolysis of the solid-state complex sandwiched by two Pyrex glass plates was performed at room temperature by using a high pressure mercury lamp fitted with a Toshiba UV-35 glass filter, and the reaction mixture was subjected to the HPLC analysis on tandem columns of

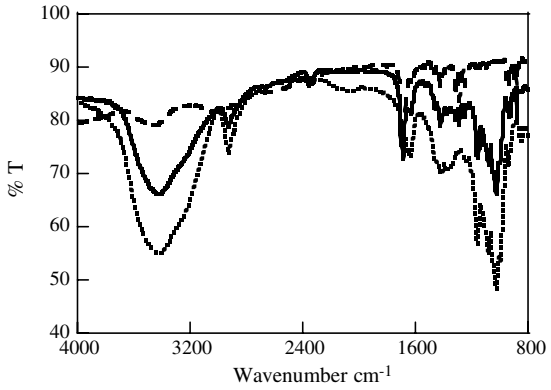


Figure 1. IR spectra of AC (dashed line), γ-CD (dotted line), and a 1:1 mixture of AC and γ-CD (solid line).

Inertsil ODS-2 and Chiralcel OJ-R. In marked contrast to the strong preference for HT photodimers (89% relative yield) upon solution-phase photodimerization mediated by native γ-CD, the inherently disfavored HH photodimers became the major products (63% yield) upon solid-state photolysis (Table 1). This suggests that the HH arrangement of AC pairs is much favored in the solid-state complex, which is rationalized by the absence of the electrostatic repulsion between the two anionic

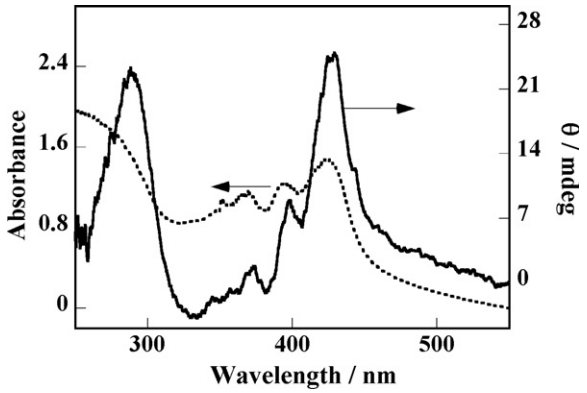


Figure 2. UV (dotted line) and circular dichroism (solid line) spectra of 1:1 mixture of AC and γ-CD.

AC-carboxylates and the elimination of the steric repulsion between the solvation shells around the carboxylate. The yield of the chiral photodimer **2**, which is the most abundant product (46% yield) in the solution-phase reaction, was greatly suppressed to 11% with accompanying decrease in ee from 41% to 6.1%. On the other hand, photolysis in the solid-state greatly improved the yield of the HH photodimer **3** to 27.7% and slightly increased its ee from −1.2% to −5.1%.

The dramatic switching of stereoselectivity observed upon solution versus solid-state irradiation encouraged us to further examine the supramolecular photochirogenesis using modified γ-CDs **5**–**9**,[10a] which bear one or two 3,6-anhydroglucose residues at the A, B to A, E positions of the CD ring. The 3,6-anhydroglucoside unit takes a $^1C_4$ chair conformation with its 2-OH directed toward the cavity interior.[10] Thus, the incorporation of 3,6-anhydroglucose residue(s) into γ-CD distorts the cavity shape from C_8 symmetry to C_1 or C_2 symmetry, and therefore the photocyclodimerization with these modified γ-CDs is expected in general to afford distinctly different isomer- and enantioselectivities from those obtained with native γ-CD.

However, most of the modified γ-CDs gave product distributions very similar to that obtained with native γ-CD at least upon irradiation in aqueous solutions, excepting the C_2-symmetric host **9** which preferred *anti*-HT photodimer **1** (52% yield) at the expense of *syn*-HT photodimer **2**. All of the modified γ-CDs gave lower ee's for **2** and only slightly improved the ee of **3** up to −3.9% (by using **8**) or gave the antipodal **3** in 2.7% ee (by using **7**). These results may be attributed to the increased flexibility of the γ-CD ring caused by the introduction of 3,6-anhydroglucoside unit(s), which disrupts the hydrogen bonding network on the secondary rim of γ-CD, making the ring structure too flexible to strictly confine the included AC pairs in solution.

Photolyses of AC complexes with **5**–**9** were then performed in the solid-state to give the results shown in Table 1. Contrary to the solution-phase irradiation, the solid-state photolyses afforded HH photodimers **3** and **4** in greatly improved combined yields of 43–63%. In particular, the yield of chiral HH photodimer **3** was increased from 6–9% to 31–35% by using di-3,6-anhydro-γ-CDs **6**–**9**. While the ee of **2** was reduced irrespective of the hosts examined, the ee of **3** was significantly increased up to −37% upon irradiation with **6**. Consequently, the isomer- and enantioselectivities obtained in the solid-state are nicely complementary to those in aqueous solution, where both yield and ee of **3** are poor. It is also noted that mono- and in particular di-3,6-anhydro-γ-CDs afford much higher ee's (−16% to −37%) for **3** than native γ-CD (−5.1% ee) in the solid-state. The wide variation of ee, reflecting the relative position of the anhydroglucoside units in **6**–**9**, reveals the crucial role of host structure on the product's ee.

Table 1. Photocyclodimerization of AC mediated by native and 3,6-anhydro-γ-CDs in solution and solid-state[a]

Medium	Host	Relative yield[c] (%)				% ee[c,d]		Product ratio		
		1	**2**	**3**	**4**	**2**	**3**	HH/HT[e]	*anti*/*syn*	
									1/2	**3/4**
Aqueous solution	γ-CD[b]	42.9	46.3	6.1	4.7	41.2	−1.2	0.12	0.93	1.47
	5	42.0	45.3	7.1	5.6	36.7	−2.7	0.15	0.93	1.26
	6	42.7	44.5	7.7	5.1	33.1	−1.7	0.15	0.96	1.51
	7	43.3	43.1	8.6	5.0	12.8	2.7	0.16	1.00	1.72
	8	44.2	41.4	7.8	6.7	15.6	−3.9	0.17	1.07	1.16
	9	52.4	35.0	7.1	5.5	38.3	−0.6	0.14	1.50	1.29
Solid-state	γ-CD	26.3	11.2	27.7	34.8	6.1	−5.1	1.67	2.35	0.80
	5	35.9	21.2	22.1	20.8	5.1	−28.6	0.75	1.69	1.06
	6	27.1	19.7	30.8	22.4	8.7	−36.6	1.14	1.38	1.38
	7	26.1	17.3	33.4	23.2	2.7	−32.5	1.30	1.51	1.44
	8	25.7	18.2	34.5	21.6	6.3	−15.8	1.28	1.41	1.60
	9	32.6	17.4	31.9	18.1	5.3	−34.8	1.00	1.28	1.89

[a] A 1:1 mixture of AC and native or modified γ-CD was irradiated at 366 nm by using a high-pressure Hg lamp fitted with a Toshiba UV-35 glass filter at 0 °C for photoreactions in aqueous buffer solution (pH 9.0) and at room temperature for solid-state photoreactions.

[b] Ref. 8a.

[c] The conversions after 2 h irradiation were >95% and 11.5–18.7% for solution-phase and solid-state photoreactions, respectively. Relative yield and ee were determined by using a tandem column of Intersil ODS-2 (GL Science) and Chiralcel OJ-R (Daicel); error in ee: ±0.7%.

[d] Positive/negative ee sign corresponds to the excess of the first/second-eluted enantiomer, respectively.

[e] [**3**+**4**]/[**1**+**2**].

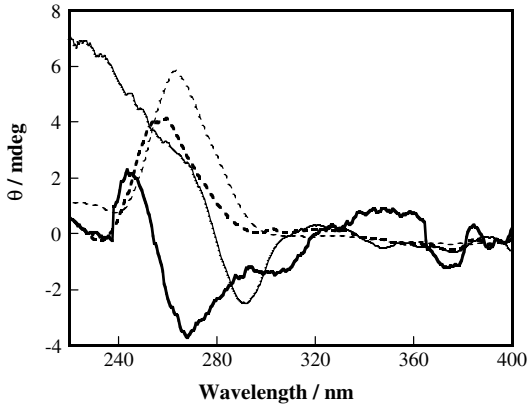


Figure 3. Circular dichroism spectra of 1:1 mixture of AC with **6** in aqueous solution (thin dotted line) and solid-state (thin solid line), and with **8** in aqueous solution (thick dotted line) and solid-state (thick solid line).

It should be pointed out that the enantiodifferentiation in this CD-mediated photocyclodimerization may involve two distinct mechanisms, that is, the population of diastereomeric 1:2 host–guest complexes in the ground state and their relative reactivity in the excited state. However, the high photodimerization quantum yield[11] and the extremely efficient fluorescence quenching upon inclusion of two ACs in a γ-CD cavity[8a] both observed in aqueous solutions indicate that the diastereodifferentiating 1:2 complexation is the major source of enantioselectivity of the photoproducts. To explore the difference in complex structure, the circular dichroism spectra of AC complex with γ-CDs (**6** and **8**) were examined in solution and solid-state. As illustrated in Figure 3, completely different circular dichroism spectra were obtained in aqueous solution and in the solid-state, supporting that the switching of the stereoselectivity is primarily attributable to the varied arrangement of AC pairs in the ground state.

In summary, we demonstrated for the first time that the isomer- and enantioselectivity of photocyclodimerization of AC mediated by native and 3,6-anhydro-γ-CDs are switched in the solid-state versus aqueous solution. Further studies on the structure of these supramolecular complexes and mechanistic details of the switching of the stereochemistry are currently in progress.

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