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Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylic Acid Mediated by γ-Cyclodextrins with a Flexible or Rigid Cap

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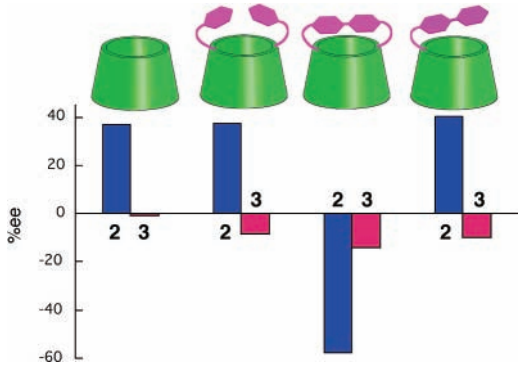
ABSTRACT



A series of modified γ-cyclodextrins (CDs) with a flexible or rigid cap, synthesized and used as chiral supramolecular hosts for mediating the enantiodifferentiating photocyclodimerization of 2-anthracenecarboxylic acid, significantly improved the chemical and optical yields of chiral head-to-head cyclodimer 3, while the γ-CD with a rigid cap dramatically inverted the stereochemical outcomes and further improved the enantioselectivities of both head-to-tail and head-to-head dimers 2 and 3.

Supramolecular photochirogenesis offers an intriguing access to chiral photochemical transformation[1] and has been successfully realized by using natural and synthetic hosts such as cyclodextrins (CDs),[2] zeolites,[3] biomolecules,[4] chiral templates,[5] and chiral nanoporous materials.[6] CDs are the most frequently investigated chiral hosts for enantio- and diastereoselective photoreactions since they are inherently chiral, readily available, UV transparent, and able to bind a wide range of organic substrates in their hydrophobic cavities.[7] Consequently, a considerable amount of CD-mediated chiral photoreactions, including photoisomerization of cyclooctenes[8a−c] and diphenylcyclopropanes,[8d] photocy-

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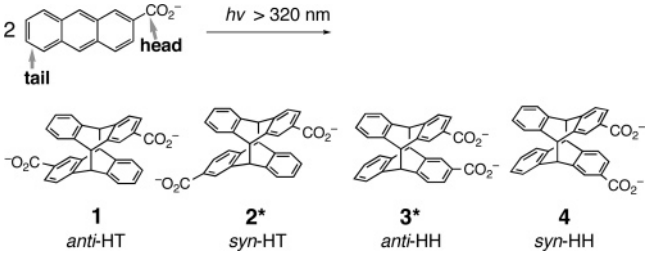
clization of *N*-alkylpyridones,[8e] tropolone alkyl ethers,[8f] and phenoxyalkenes,[8g] photodecarboxylation of aryl esters,[8h] photoinduced radical cleavage/recombination of benzoin,[8i] and photocyclodimerization of anthracenecarboxylic acid (AC),[8j−n] have been investigated in solid and/or solution phase. However, despite their unique advantages, difficulty still remains in modifying the chiral environment of CD cavity as a tool for manipulating the stereochemistry of photoreactions. In particular, to obtain the opposite enantiomers by using antipodal chiral sources, a strategy commonly employed in conventional asymmetric syntheses, is unfeasible for CD-mediated reactions. In this regard, the use of external entropy factors has recently been shown to be promising.[8c]

We recently reported the enantiodifferentiating photocyclodimerization of AC using native and modified γ-CDs as chiral hosts.[8k−n] Native γ-CD gives head-to-tail (HT) cyclodimers **2** (Scheme 1) in good yields with enantiomeric excess (ee) of up to 41% but head-to-head (HH) cyclodimer **3** in low yield and ee.[8k] The sophisticated modification of γ-CD and the control by temperature, solvent, and pressure were found to be effective for manipulating the stereochemistry of the photocyclodimerization of AC.[8l−n]

In the present study, we intended to reveal the effects of capped γ-CDs on the photocyclodimerization of AC, since the capping is known to significantly modify the binding and reaction behavior of native CD.[9] It is of particular interest

Scheme 1



to control the stereochemical outcomes of the photocyclodimerization through the capping modification.

Modified γ-CDs with a flexible (**5** and **7**) or rigid cap (**6**) (Figure 1) were prepared by reaction of γ-CD with the

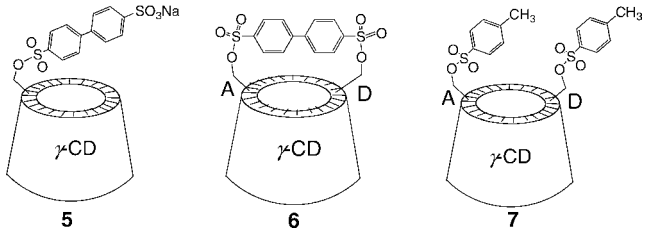


Figure 1. Capped γ-CDs.

corresponding arenesulfonyl chlorides in pyridine.[10,11] These capped γ-CDs **5**, **6**, and **7** displayed negative CD peaks at 262, 276, and 210 nm, respectively, in the ^1L_a transition region of the capping chromophores.[11] The sector rule,[12] applied to this system, indicates that the arenesulfonyl moiety is shallowly perching on the rim of CD, rather than deeply penetrating into the cavity, thus endowing expanded hydrophobic cavities compared with that of native γ-CD.

The complexation behavior of **5**−**7** with AC was studied by UV−vis, NMR, and CD spectroscopy,[11] and the association constants for the stepwise formation of 1:1 (K_1) and 1:2 complex (K_2), were assessed by using the least-squares-fit analysis (Table 1). All of the capped γ-CDs gave K_1 values

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Table 1. Association Constants for the 1:1 and 1:2 Complexation of Native and Modified γ-CDs with AC

host	association constant[a]		
	K_1[b]/M^{-1}	K_2[c]/M^{-1}	K_1K_2/10^6 M^{-2}
γ-CD[d]	182	56700	10.3
5	6870	3130	21.5
6	1280	12500	16.0
7	320	7620	2.4

[a] Association constant obtained at 20 °C. [b] For 1:1 complexation of AC and γ-CD. [c] For the 1:1 complex and AC making 1:2 complex. [d] Reference 8k.

that were significantly larger than that for native γ-CD; in particular, **5** showed a marked enhanced K_1 by a factor of 38. On the other hand, the K_2 values obtained with **5**−**7** are 5−18 times smaller than that for native γ-CD. This result implies that the capping moiety facilitates the first inclusion of AC molecule, serving as a spacer to occupy the remaining cavity, but the co-included cap prevents the access of the second AC. The enhancement of the overall association constant (K_1K_2) is greater for **5** (2.1-fold) than for **6** (1.6-fold), probably due to the reduced cavity size of the latter. In contrast, host **7** shows a much reduced K_1K_2 value than native γ-CD, for which the competition of AC with the self-included tosylate caps is likely to be responsible. The weaker induced CD signals observed for **7** (than for **5** and **6)** may support this rationalization.[11]

Photoirradiations (366 nm) of aqueous solutions of AC (0.8 mM) and capped γ-CD (2 mM) were carried out by using a high-pressure Hg lamp equipped with an optical glass filter (UV-35). The use of capped γ-CDs considerably improved the yields of HH cyclodimers **3** and **4**, as compared with the results obtained with native γ-CD (Table 2). This seems reasonable, since the HH-oriented AC pair, with their hydrophobic "tails" being directed to the "cap," will be more stabilized in the cavity than the HT-oriented AC pair, as a result of the existence of the hydrophobic cap which repels the hydrophilic carboxylate.

Despite the appreciable difference in product distribution, hosts **5** and **7** afforded cyclodimer **2** in 34−40% ee in water at 0 °C and 20−24% ee in 1:1 methanol−water at −45 °C, both of which are comparable to those obtained with native γ-CD. This indicates that the chiral environment for the formation of **2** is not greatly alternated by the flexible caps. However, to our surprise, the product's chirality was *inverted* to afford the antipodal **2** in an enhanced ee of −57.6% upon photodimerization with **6**, which is functionally and structurally similar to **5** and **7**, except for the rigidity of the capping moiety.

CPK model examinations revealed that the aromatic capping groups of **5** and **7** can freely rotate around the C6−O6 and O6−S bonds, and hence, the included AC pairs are not strictly confined, eventually providing the chiral environment similar to that of native CD. However, in the case of **6**, one of the HT-oriented AC molecules included in the cavity inevitably expose its carboxylate group to the aqueous solution through the narrow window surrounded by the biphenyl moiety and the γ-CD's E, F, G, and H glucose units. The positional and rotational freedoms of such an AC are much reduced. This model was experimentally supported by the NMR spectral studies. As shown in Figure 2c, the CD proton signals of [**6**·AC] complex are scattered over a wide range of 1.86−5.21 ppm. Such a strong anisotropic effect proves that the included AC molecules are restricted in motion (rotation) in the cavity of **6** so as to magnetically differentiate each glucose unit. In addition, the well-resolved eight-proton signals of the biphenylene group indicate that its rotation around the longitudinal axis is prohibited. Hence, we attribute the origin of the dramatic inversion of product chirality to the confinement effect of the rigidly capped γ-CD. In contrast to the numerous precursor complexes formed from native and flexibly capped γ-CDs, the complex obtained from **6** is rather limited in number. As for the precursor to **2**, only two conformers are allowed to exist and dictate the stereochemical course of photocyclodimeriazation to **2**. As illustrated in Figure 3, an antiparallel AC pair, whose carboxylate near the primary rim is oriented to the H glucose

Table 2. Photocyclodimerization of AC in the Presence of Native or Capped γ-CDs[a]

host	T/°C	solvent/wt %		conversion[b]/%	relative yield[c]/%				% ee[c,d]		ratio		
		water	MeOH		**1**	**2**	**3**	**4**	**2**	**3**	HH/HT[e]	anti/syn **1/2**	anti/syn **3/4**
γ-CD	0	100	0	88.2	42.9	45.5	6.9	4.7	37.1	−0.8	0.13	0.94	1.47
5	0	100	0	79.3	40.3	40.7	10.1	8.9	40.3	−9.8	0.23	0.99	1.13
6	0	100	0	82.5	39.2	28.0	20.1	12.7	−57.6	−14.1	0.49	1.40	1.58
7	0	100	0	71.8	39.6	38.6	11.7	10.1	37.4	−8.2	0.28	1.03	1.16
γ-CD	−45	50	50	57.5	46.4	33.2	13.3	7.1	28.8	−8.7	0.26	1.40	1.87
5	−45	50	50	61.2	51.3	26.8	14.3	7.6	20.4	−35.1	0.28	1.92	1.89
6	−45	50	50	65.8	37.3	23.0	28.5	11.1	−40.4	−35.9	0.66	1.63	2.56
7	−45	50	50	56.0	41.1	24.7	23.7	10.5	24.3	−35.0	0.52	1.66	2.25

[a] Aqueous buffer solutions (pH 9) containing 0.8 mM AC and 2 mM γ-CD were irradiated under Ar at 366 nm by using a high-pressure mercury lamp through a glass filter (Toshiba UV-35). [b] Estimated from the UV−vis spectral changes after 5 min irradiation. [c] Relative yield and ee determined by chiral HPLC using a tandem column of Intersil ODS-2 (GL Science) and Chiralcel OJ-R (Daicel). [d] Positive/negative ee sign corresponds to the excess of the first/second-eluted enantiomers, respectively. [e] [**3** + **4**]/[**1** + **2**].

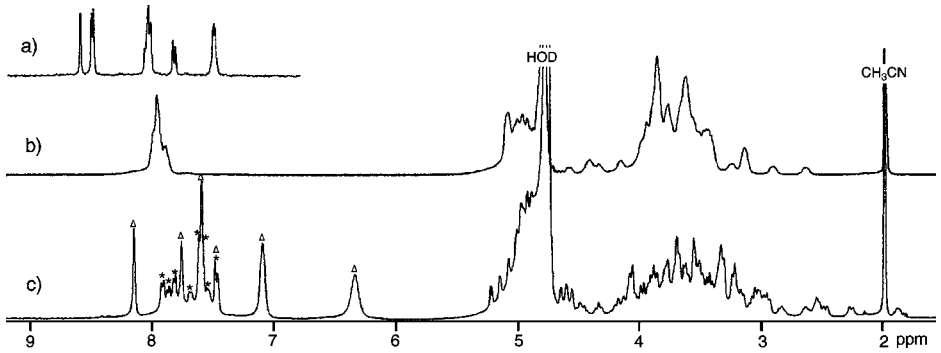

Figure 2. ^{1}H NMR spectra of (a) AC, (b) **6**, and (c) AC (4 mM) + **6** (3 mM) in D_2O at pD 9. Asterisks and triangles indicate the biphenyl and AC signals, respectively.

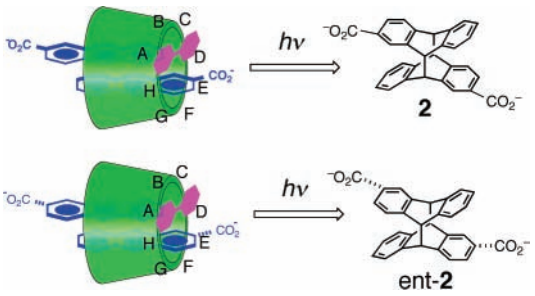

Figure 3. Enantioselective production of **2** with **6**.

unit, yields an enantiomer of **2** upon iradiation, while that oriented to the E glucose affords the antipode.

When the photoreaction with **6** was carried out in 50% aqueous methanol at −45 °C, the yield of **3** was further improved to 28.5% (Table 2). Interestingly, although the ee's of **2** obtained in 50% methanol are smaller than that obtained in water, much enhanced ee's of −35% were consistently obtained for **3** by using any of the capped γ-CDs. Thus, for **3**, rigidly capped γ-CD **6** shares similar enantioselectivity with its flexible counterparts. This is not surprising since the hydrophobic tail component of parallel-oriented AC pairs should be accommodated inside the cavity rather than leaning out the narrow window.

We may conclude that the rigid capping of CD can more critically manipulate the photochemical and stereochemical outcomes of photocyclodimerization of AC and even induce a dramatic inversion of the product's chirality through the strict confinement in the chiral CD cavity. This finding is highly instructive for the rational design of chiral hosts for controlling supramolecular chirogenic processes.

Supporting Information Available: Preparation and characterization of **5**−**7**. UV−vis and CD spectral studies and CPK models for the complexation behavior of these capped γ-CDs with AC. This material is available free of charge via the Internet at http://pubs.acs.org.

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