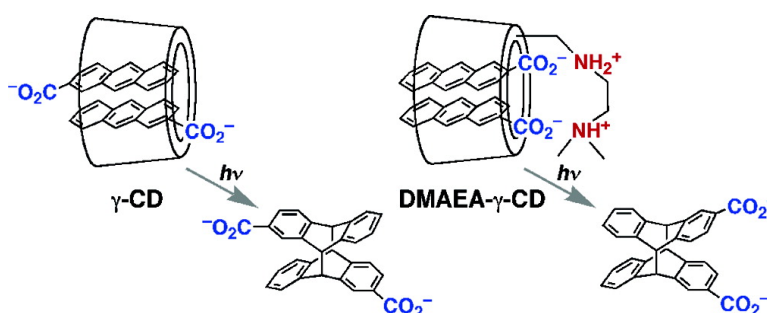## Communication

Electrostatic Manipulation of Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylate within □-Cyclodextrin Cavity through Chemical Modification. Inverted Product Distribution and Enhanced Enantioselectivity

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Electrostatic Manipulation of Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylate within γ-Cyclodextrin Cavity through Chemical Modification. Inverted Product Distribution and Enhanced Enantioselectivity

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Stereochemical control of photocycloaddition is one of the most intriguing topics in current photochemistry.[1,2] Substrate preorientation prior to photoirradiation, achieved through supramolecular interactions, has recently been exploited to realize high regio-[3] and enantioselectivities.[4] Among the hosts, or template molecules, used for organizing substrates, cyclodextrin (CD) is particularly attractive because of its inherently chiral cavity that efficiently binds a variety of organic guests in aqueous solutions.[5] Such a chiral environment has been utilized in several thermal and photochemical enantiodifferentiating reactions.[6–9]

Tamaki et al. showed that γ-CD accelerates the [4 + 4] photocyclodimerizations of 1- and 2-anthracenesulfonates and 2-anthracenecarboxylate (AC) upon inclusion in its cavity.[10,11] They also reported that one of the chiral products is nonracemic, although its enantiomeric excess (ee) was not determined. Recently, we examined the complexation and enantiodifferentiating photocyclodimerization behavior of AC mediated by native γ-CD and demonstrated that γ-CD preferentially includes two AC molecules in its cavity to form diastereomeric 1:2 complexes, which upon irradiation photodimerize resulting in a mixture of syn and anti head-to-tail (HT) and head-to-head (HH) cyclodimers 1−4 (Scheme 1).[12] The product distribution and ee are determined exclusively upon complexation in the ground state to preferentially afford the HT dimers 1 and 2 as major products in 85−90% combined relative yields. The ee of 2 was 32% in aqueous solution at 25 °C but was enhanced to 41% at 0 °C. As a consequence of the electrostatic repulsion, the combined yield of HH dimers 3 and 4 was low and the ee of 3 never exceeded 5%. Very recently, Ikeda et al. examined the same photodimerization in the presence of 6-mono- and $6^A,6^X$-dipyridinio-γ-CDs to give 1−4 in similar HH/HT ratios but with a lower ee for 2 (10−30%) and an appreciably improved ee for 3 (1−13%).[13]

In this communication, we demonstrate that a dramatic switching of the product selectivity and a significant ee enhancement can be simultaneously achieved in the photocyclodimerization of AC by tethering a dicationic flexible sidearm to γ-CD. This was made possible through a crucial manipulation of the electrostatic interactions between the guest's carboxylate anion and the host's ammonium cations (introduced to the single sidearm) and also by lowering the temperature and solvent polarity.

6^A-(2-(Dimethylamino)ethylamino)-6^A-deoxy-γ-CD (DMAEA-γ-CD) was used as a templating chiral host for photochirogenesis. As shown in Table 1, the use of DMAEA-γ-CD at pH 7 only slightly increased the combined yield of HH dimers 3 and 4 from the original 12% obtained with native γ-CD to 16%, and the ee of 3 from 3 to 5%. The formation of HH dimers 3 and 4 inevitably

Scheme 1. [4 + 4] Photocyclodimerization of 2-Anthracenecarboxylate
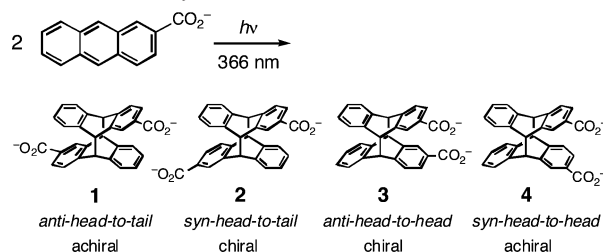
requires the electrostatically unfavorable approach of two negatively charged AC monomers, and thus it is the minor path under conventional conditions. However, the two positively charged ammonio groups introduced in DMAEA-γ-CD can facilitate the formation of head-to-head oriented 1:2 complexes by canceling the electrostatic repulsion between the two AC molecules accommodated in the same cavity.[14]

As judged from the pK_a values reported for analogous compounds,[15] DMAEA-γ-CD is likely to be monocationic at neutral pH but becomes dicationic at pH ∼5. By lowering the solution pH to 5, we increased the yield of HH dimers significantly to 31% and the ee of 3 rose to 7% (Table 1).[16] This unambiguously indicates that only the doubly charged DMAEA-γ-CD can effectively switch the isomer distribution to head-to-head, with the enhancement of the ee of 3.

The electrostatic interaction can be augmented by reducing the solvent polarity; thus, when ethylene glycol was added to the aqueous buffer solution, the yield of HH dimers 3 and 4 increased at the expense of HT dimers 1 and 2 (Table 1). As the ethylene glycol content was raised from 0 to 50%, the combined yield of 3 and 4 increased from 31 to 35%, with an accompanying enhancement of the ee from 7 to 12%.[17] The observed effect of solvent polarity is in sharp contrast to that observed for native γ-CD (Supporting Information).

Temperature also greatly affected the product distribution and ee. The effects of temperature were investigated in 1:1 mixture of aqueous buffer and ethylene glycol or methanol. As shown in Table 1, lowering the temperature led to a significant enhancement of the combined yield of 3 and 4 from 35% at 25 °C to 72% at −45 °C in aqueous ethylene glycol and to 74% at −59 °C in aqueous methanol. At the same time, the ee of 3 was enhanced dramatically from 12% at 25 °C to 40% at −45 °C in aqueous ethylene glycol. Eventually, the highest yield and enantioselectivity were achieved in 50% aqueous methanol at −59 °C, affording 3 in 42% yield and 41% ee.

As demonstrated in the previous native γ-CD case,[12] the ee of the chiral product is a direct function of the relative stability of the

Table 1. [4 + 4] Photocyclodimerization of AC in the Presence and Absence of γ-CD or DMAEA-γ-CD Hosts[a]

host	solvent/mol %		pH	temp °C	irradiation time/min	conversion %	relative yield (%)[b,c]						% ee[b,d]	
	water	EG					1	2	3	4	1 + 2	3 + 4	2	3
none	100	0	7	25	40	75.2	41.8	37.0	12.6	8.6	78.8	21.2	0.2	−0.5
γ-CD	100	0	7	25	4	93.8	43.4	44.4	7.0	5.2	87.8	12.2	32.0	−2.6
DMAEA-γ-CD	100	0	7	25	4	94.9	43.5	40.4	8.9	7.2	83.9	16.1	26.0	−5.1
	100	0	5	25	4	86.1	36.9	32.1	11.9	19.1	69.0	31.0	16.9	−7.3
	50	50	5	25	5	53.6	34.8	30.2	14.6	20.4	65.0	35.0	7.4	−12.2
	50	50	5	−10	5	70.2	25.5	14.4	19.9	41.2	39.9	61.1	2.1	−23.5
	50	50	5	−45	5	80.6	23.9	7.9	31.5	40.8	31.8	72.3	−1.0	−39.6
	50	50[e]	5	−59	5	82.9	20.1	5.5	41.7	32.7	25.6	74.4	3.2	−41.2

[a] Aqueous buffer solutions (25 mM phosphate buffer for pH 6 and 7, acetate buffer for pH 5) containing 0.5 mM AC and 1 mM cyclodextrin were photoirradiated under argon at 366 nm using a medium-pressure mercury lamp equipped with optical filters (Toshiba UV-35 and UV-D36C). [b] The product analysis was performed using chiral HPLC with tandem columns of Intersil ODS-2 (GL Science) and Chiralcel OJ-R (Daicel). The relative yield and % ee were determined by the peak area on the HPLC chromatogram detected by the absorbance at 254 nm. The product distribution and ee were practically independent of the conversion (irradiation time). [c] Errors in relative yields are ±0.5%. [d] Absolute configurations of **2** or **3** were not determined. Hence the first eluted enantiomer from the column combination used is tentatively given a positive sign to its ee value, while the second one a negative sign. Errors in % ee are from ±0.5% for the major products to ±3% for the minor products. [e] Methanol was used in place of ethylene glycol.

Scheme 2. Diastereomeric 2:1 Complex of AC with DMAEA-γ-CD and the Subsequent Photocyclodimerization to the Corresponding Enantiomeric Cyclodimers **3**
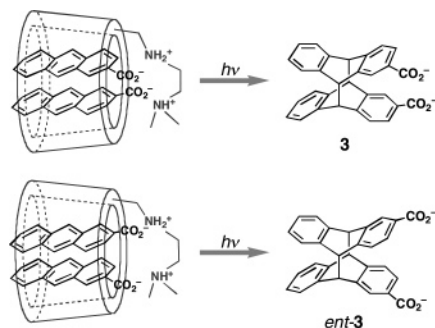
diastereomeric precursor complexes of AC with DMAEA-γ-CD in the ground state (Scheme 2).

A global examination of the data in Table 1 reveals that reducing solvent polarity and/or temperature synchronously increases the yield and ee of **3**. This is a promising practical guideline for supramolecular photochirogenesis, indicating that stabilization of the precursor complex enhances the diastereodifferentiation.[18]

In this preorganization−preorientation approach to supramolecular photochirogenesis using a rigid cavity and a flexible sidearm, we have shown that the dicationic group attached to CD can switch the major products from HT dimers to the originally disfavored HH dimers, with an unprecedented enhancement of the ee of **3** from 3 to 41% by maximizing the complex stability. The present strategy may have some analogy with the ionic chiral auxiliary approach employed by Scheffer to achieve enantioselective control in the solid state,[19] although our approach is more flexible and hence controllable by various environmental factors. We may further emphasize that this kind of electrostatic manipulation of product and enantioselectivity by host modification is not restricted to cyclodextrin hosts but can also be expanded to a variety of supramolecular systems as a versatile methodology.

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