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Enantiodifferentiating [4 + 4] photocyclodimerization of 2-anthracenecarboxylate catalyzed by $6^A,6^X$-diamino-$6^A,6^X$-dideoxy-γ-cyclodextrins: Manipulation of product chirality by electrostatic interaction, temperature and solvent in supramolecular photochirogenesis

Cheng Yang [a], Gaku Fukuhara [b], Asao Nakamura [a], Yumi Origane [a], Kahee Fujita [c], De-Qi Yuan [c], Tadashi Mori [b], Takehiko Wada [b], Yoshihisa Inoue [a,b,*]

[a] *The ICORP Entropy Control Project, JST, 4-6-3 Kamishinden, Toyonaka 560-0085, Japan*
[b] *Department of Molecular Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan*
[c] *Graduate School of Biomedical Sciences, Nagasaki University, 1-14 Bunkyo-machi, Nagasaki 852-8521, Japan*

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Abstract

$6^A,6^X$-Dideoxy-$6^A,6^X$-diamino-γ-cyclodextrins (X = B, C, D and E) **5a–d** were synthesized as chiral hosts for catalyzing the enantiodifferentiating [4 + 4] photocyclodimerization of 2-anthracenecarboxylic acid (ACA). The electrostatic interaction between **5a–d** and ACA efficiently affected the preorganization of two ACA molecules within the γ-CD cavity, and improved the yields of *head-to-head* cyclodimers. By lowering the reaction temperature or solvent polarity, the electrostatic interaction was further enhanced. The *anti-to-syn* ratio of the *head-to-head* isomers gradually increased by changing the host from **5a** to **5d** (with increasing distance between the two amino groups on the CD rim), demonstrating a good structure–function relationship in this supramolecular photoreaction system. The chiral sense and enantiomeric excess of the photoproducts obtained are significantly affected, and even inverted, by solvent composition and reaction temperature. This temperature- and solvent-controlled chirality switching behavior is proven to originate from the contribution of non-zero differential entropy ($\Delta\Delta S^{\ddagger}$) in the enantiodifferentiating process. This finding is the first example of a chirality inversion driven by entropy-related factors, such as solvent and temperature, in a non-sensitized asymmetric photoreaction. The sign of $\Delta\Delta S^{\ddagger}$ was switched by the composition of solvent and exhibited an excellent compensatory relationship against the differential enthalpy ($\Delta\Delta H^{\ddagger}$), revealing that the photoenantiodifferentiation is governed not only by enthalpy but also by entropy, and also that the enantiodifferentiation mechanism does not vary throughout the whole system, irrespective of the condition changes.

Keywords: Enantiodifferentiation; Photocyclodimerization; Anthracenecarboxylic acid; Diamino-γ-cyclodextrin; Chirality inversion; Enthalpy–entropy compensation

1. Introduction

Supramolecular photochirogenesis is one of the most intriguing areas of current photochemistry, being interdisciplinary and lying amongst asymmetric synthesis, photochemistry and supramolecular chemistry [1]. In contrast to the extensive investigation of diastereodifferentiating photoreactions employing the chiral auxiliary approach, enantiodifferentiating photoreactions, in which chiral information is delivered through non-covalent interactions from a chiral entity to a prochiral substrate, had not been explored until very recently. One of the major obstacles is the lack of suitable chiral hosts or complexing agents, which can efficiently interact and transfer their chiral information to prochiral substrates in the ground and excited states. Only a few suc-

* Corresponding author. Tel.: +81 6 6879 7920; fax: +81 6 6879 7923.
E-mail address: inoue@chem.eng.osaka-u.ac.jp (Y. Inoue).

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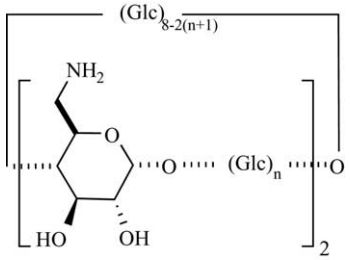
cessful examples are known, such as, chirally modified zeolites [2], synthetic templates [3], cyclodextrins (CDs) [4], proteins [5] and DNA [6] as chiral sources affording enantiomeric products with good-to-excellent orientational and stereochemical selectivity. Amongst the hosts investigated, CD has attracted considerable attention because of its ready availability and inherently chiral cavity [7]. Rao and Turro studied the CD-mediated asymmetric photoreaction of benzaldehyde and obtained optically active benzoin [4a]; Ramamurthy and co-workers reported the enantiodifferentiating photocyclization of tropolones and pyridones as well as the photoisomerization of diphenylcyclopropanes performed in the presence of CD in solution and in the solid state [4b–d]. Inoue et al. investigated the enantiodifferentiating geometrical photoisomerization of cyclooctene and enantiodifferentiating photocyclodimerization of anthracenecarboxylate using native and/or modified CDs as chiral hosts [4e–f,8].

The cavity of γ-CD is large enough to encapsulate two small organic molecules, and was thus employed to improve the efficiency as well as the orientational and stereochemical selectivities of photocyclodimerizations [8–12]. Photocyclodimerizations of anthracene derivatives [8–10], stilbene derivatives [11], coumarin derivatives [12] and tranilast [13] in solution or in the solid state have been studied by using γ-CD as a molecular reaction vessel. Recently, enantiodifferentiating photocyclodimerization of 2-anthracenecarboxylic acid (ACA) has attracted much interest [8–10]. Photocyclodimerization of ACA yields *head-to-tail* (HT) *anti*- and *syn*-cyclodimers **1** and **2** and *head-to-head* (HH) *anti*- and *syn*-cyclodimers **3** and **4** (Scheme 1), of which cyclodimers **2** and **3** are chiral. The photocyclodimerization mediated by native γ-CD gave HT cyclodimers as major products and afforded cyclodimer **2** in up to 41% enantiomeric excess (ee) and cyclodimer **3** in <5% ee [8a]. However, native CDs binds guest molecules of suitable size and shape, mainly *via* nondirectional hydrophobic interactions [14], which are often insufficient for precisely regulating the orientation of guests within the CD cavity. In order to manipulate the preorganization of two ACA molecules in a γ-CD complex, and thus achieve a highly sophisticated level of control of the photocyclodimerization of ACA, we prepared $6^A,6^X$-dideoxy-$6^A,6^X$-diamino-γ-cyclodextrins **5a–d** (X = B, C, D and E) (Scheme 2), envisaging that the combined effects of the hydrophobic and electrostatic interactions working between the anionic guest ACA and the cationic hosts **5a–d** would effectively modify the orientational and enantiomeric selectivity of the photocyclodimerization of ACA. Very recently, a similar idea, employing dipyridinio-γ-CDs, was reported by Ikeda et al. revealing improvements in both the yield and ee of the HH cyclodimers [10].



5a: n=0, AB

5b: n=1, AC

5c: n=2, AD

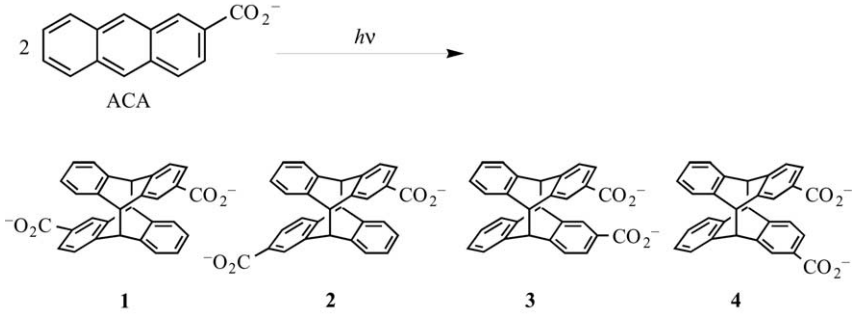
5d: n=3, AE

Scheme 2. $6^A,6^X$-Dideoxy-$6^A,6^X$-diamino-γ-cyclodextrins **5a–d**.

2. Experimental

2.1. General methods

All NMR spectra were measured with a JEOL JNM-EX 400 spectrometer in D_2O or in a mixture of D_2O and methanol-d_4 using acetonitrile as an internal standard. Mass spectra were recorded on a JEOL JMS-DX303 mass spectrometer, using FAB ionization. HPLC analyses were performed employing tandem columns of Inertsil ODS-2 (GL Science) and Chiralcel OJ-R (Daicel) and a mixture of 0.2 M phosphate buffer (pH 2.5) and acetonitrile (63:37, v/v) as an eluent. Reagent grade γ-CD and 2-anthracenecarboxylic acid



Scheme 1. [4 + 4] Photocyclodimerization of 2-anthracenecarboxylate.

were purchased from Tokyo Chemical Industry Inc. and were used without further purification.

2.2. Synthesis

2.2.1. Synthesis of 6^A,6^X-dideoxy-6^A,6^X-diazido-γ-CDs

A mixture of 6^A,6^X-di-*O*-(*p*-tosyl)-γ-CD [15] and sodium azide was stirred for 24 h in dry DMF at 90 °C. After the DMF was removed in vacuo, the residue was dissolved in water and subjected to reversed-phase column chromatography. The fractions were collected and freeze-dried to give isomeric 6^A,6^X-dideoxy-6^A,6^X-diazido-γ-CDs (X = B, C, D and E).

6^A,6^B-Dideoxy-6^A,6^B-diazido-γ-CD. Yield: 72%, FAB-MS *m/z*: 1347($M+H^+$). ^{1}H NMR (D_2O) δ: 5.03(m, 8H), 3.09–3.71 (m, 28H), 3.63–3.56 (m, 11H), 3.51–3.46 (m, 9H); ^{13}C NMR (D_2O) δ: 102.83, 102.74, 102.69, 102.48, 82.69, 82.61, 81.71, 81.60, 81.53, 73.96, 73.96, 73.69, 73.66, 73.29, 73.23, 73.17, 72.94, 72.78, 71.66, 71.33, 61.35, 61.24, 52.09, 52.00.

6^A,6^C-Dideoxy-6^A,6^C-diazido-γ-CD. Yield: 78%, FAB-MS *m/z*: 1347($M+H^+$). ^{1}H NMR (D_2O) δ: 5.03(m, 8H), 3.91–3.75 (m, 28H), 3.61–3.56 (m, 11H), 3.52–3.48 (m, 9H); ^{13}C NMR (D_2O) δ: 102.46, 102.38, 102.15, 102.11, 82.19, 82.13, 81.46, 81.35, 81.30, 81.21, 73.66, 73.57, 73.45, 73.00, 72.90, 72.61, 72.55, 72.49, 72.43, 71.23, 61.04, 60.98, 51.72.

6^A,6^D-Dideoxy-6^A,6^D-diazido-γ-CD. Yield: 82%, FAB-MS *m/z*: 1347($M+H^+$). ^{1}H NMR (D_2O) δ: 5.02(m, 8H), 3.91–3.68 (m, 28H), 3.61–3.56 (m, 11H), 3.52–3.48 (m, 9H); ^{13}C NMR (D_2O) δ: 102.42, 102.35, 102.31, 102.09, 82.12, 81.33, 81.23, 81.18, 73.64, 73.55, 73.42, 72.98, 72.89, 72.89, 72.46, 72.42, 71.21, 61.03, 60.97, 51.69.

6^A,6^E-Dideoxy-6^A,6^E-diazido-γ-CD. Yield: 76%, FAB-MS *m/z*: 1347($M+H^+$). ^{1}H NMR (D_2O) δ: 5.00(m, 8H), 3.88–3.67 (m, 28H), 3.57–3.54 (m, 10H), 3.50–3.45 (m, 10H); ^{13}C NMR (D_2O) δ: 102.40, 102.34, 102.05, 82.08, 81.34, 81.23, 73.65, 73.55, 73.45, 73.01, 72.97, 72.91, 72.60, 72.48, 72.42, 71.24, 61.00, 51.71.

2.2.2. Synthesis of 6^A,6^X-dideoxy-6^A,6^X-diamino-γ-CDs (**5a–5d**)

A solution of 6^A,6^X-dideoxy-6^A,6^X-diazido-γ-CDs 269 mg (0.2 mmol) and triphenylphosphine 157 mg (0.6 mmol) in dry DMF (8 mL) was stirred at ambient temperature for 48 h, to which was added a 28% aqueous ammonium solution (2 mL) with stirring over 10 min. The resulting solution was stirred for an additional 5 h, and poured into cool acetone (100 mL). The precipitate thus formed was collected by filtration, and was purified by recrystallization from a mixture of water and acetone to give pure **5a**–**d**.

6^A,6^B-Dideoxy-6^A,6^B-diamino-γ-CD (**5a**). Yield: 87%; FAB-MS: *m/z* 1295.5 ($M+H^+$); ^{1}H NMR (D_2O): δ 5.02 (m, 8H), 3.87–3.75 (m, 28H), 3.58–3.48 (m, 14H), 3.39 (m, 2H), 2.99 (m, 2H), 2.77 (m, 2H); ^{13}C NMR (D_2O): δ 102.39, 102.27, 102.1, 82.84, 82.75, 81.21, 81.03, 80.92, 73.64, 73.08, 73.03, 72.98, 72.73, 72.64, 72.5,60.97, 60.88, 42.07, 41.98.

6^A,6^C-Dideoxy-6^A,6^C-diamino-γ-CD (**5b**). Yield: 91%, FAB-MS: *m/z* 1295.5 ($M+H^+$); ^{1}H NMR (CD_3OD-D_2O, 1:1): δ 5.03 (m, 8H), 3.86–3.78 (m, 28H), 3.58–3.50 (m, 14H), 3.40 (m, 2H), 3.07 (m, 2H), 2.84 (m, 2H); ^{13}C NMR (CD_3OD-D_2O, 1:1): δ 102.47, 102.39, 102.30, 102.11, 102.01, 82.95, 82.90, 81.23, 81.12, 80.90, 80.77, 73.66, 73.59, 73.53, 73.01, 72.94, 72.51, 72.41, 60.96, 60.88, 41.94.

6^A,6^D-Dideoxy-6^A,6^D-diamino-γ-CD (**5c**). Yield: 90%; FAB-MS: *m/z* 1295.5 ($M+H^+$); ^{1}H NMR (CD_3OD-D_2O, 1:1): δ 5.02 (m, 8H), 3.85–3.75 (m, 28H), 3.58–3.48 (m, 14H), 3.39 (m, 2H), 2.97 (m, 2H), 2.76 (m, 2H); ^{13}C NMR (CD_3OD-D_2O): δ 102.48, 102.34, 102.25, 102.18, 102.10, 82.91, 81.20, 81.15, 81.07, 80.99, 80.91, 73.72, 73.64, 73.59, 73.03, 72.89, 72.65, 72.62, 72.50, 60.96, 60.87, 42.02.

6^A,6^E-Dideoxy-6^A,6^E-diamino-γ-CD (**5d**). Yield: 89%; FAB-MS: *m/z* 1295.5 ($M+H^+$); ^{1}H NMR (D_2O): δ 5.02 (m, 8H), 3.86–3.75 (m, 28H), 3.65–3.48 (m, 14H), 3.39 (dd, 2H, *J* = 9.2 Hz, *J* = 9.6 Hz), 3.00 (dd, 2H, *J* = 13.6 Hz, *J* = 13.6 Hz), 2.78 (dd, 2H, *J* = 13.6 Hz, *J* = 14 Hz); ^{13}C NMR (D_2O) δ: 102.5, 102.29, 102.10, 82.92, 81.15, 81.13, 80.88, 73.69, 73.62, 73.58, 73.08, 72.86, 72.52, 72.32,60.96, 60.90, 41.94.

2.2.3. Photoreaction

All irradiations were performed in a temperature-controlled water/ethylene glycol bath. The light source employed was a 300 W high-pressure mercury lamp equipped with a uranium filter. A 3-mL aqueous methanol solution (0–100% methanol content), containing 6^A,6^X-dideoxy-6^A,6^X-diamino-γ-CD **5a**–**d** (0.4 mM) and ACA (0.4 mM), was irradiated under an argon atmosphere at wavelengths longer than 320 nm.

3. Results and discussion

3.1. Synthesis of 6^A,6^X-dideoxy-6^A,6^X –diamino-γ-CDs (**5a–d**)

Four regioisomers of 6^A,6^X-di-*O*-(*p*-tosyl)-γ-CDs were obtained in 2.7–4.4% yield by the disulfonylation of the primary hydroxyls of γ-CD with tosyl chloride in pyridine according to the reported procedure [15]. 6^A,6^X-Dideoxy-6^A,6^X–diazido-γ-CDs were prepared in 72–82% yield by the nucleophilic substitution reaction of the corresponding 6^A,6^X-di-*O*-(*p*-tosyl)-γ-CDs with sodium azide, respectively. By reduction with triphenylphosphine, 6^A,6^X-dideoxy-6^A,6^X-diazido-γ-CDs were converted to 6^A,6^X-dideoxy-6^A,6^X –diamino-γ-CDs (**5a**–**d**) in 87–91% yield.

3.2. Enantiodifferentiating [4 + 4] photocyclodimerization of 2-anthracenecarboxylate catalyzed by **5a–d**

3.2.1. Orientational selectivity of the photocyclodimerization of ACA: effects of distance between the two amino groups in **5a–d**

The cavity of native γ-CD can accommodate two ACA molecules in the longitudinal direction to form very stable 1:2 inclusion complexes, and consequently effectively accelerates the [4 + 4] photocyclodimerization of ACA [8,9a]. There are several orientationally and diastereomerically isomeric 1:2 complexes, which transform into the corresponding product isomers upon irradiation. The product distribution of the photocyclodimerization of ACA mediated by γ-CD primarily depends on the population of those 1:2 diastereomeric precursor complexes in the ground state [8a]. To elucidate how the two amino groups of the regioisomers **5a–d** affect the host–guest complex, as well as the photocyclodimerization of ACA, we made a comparison of the product distribution of the photoreaction mediated by **5a–d** against that of native γ-CD.

In the presence of native γ-CD, the irradiation of ACA at 0 °C in a buffer solution produced HT cyclodimers **1** and **2** as major products with a HH/HT ratio of 0.13 (Table 1). The low yield of the HH cyclodimers is most likely due to the electrostatic repulsion between the carboxylate anions of the two ACAs in the cavity, which destabilizes the parallel, or *head-to-head*, 1:2 complexes. By using the dicationic **5a–d** as hosts, the formation of the HH cyclodimers was greatly enhanced at the expense of HT cyclodimers. The HH/HT ratios were improved to 0.34–0.39 under comparable conditions. This result clearly indicates that the electrostatic interaction between positively charged ammonium of the CD and the negatively charged carboxylate of ACA stabilizes the 1:2 inclusion complexes having a *head-to-head* orientation. The ion pair interaction can be enhanced by lowering reaction temperature and also by reducing solvent polarity. As shown in Table 1, the combined yield of HH cyclodimers **3** and **4** was further increased in 50% methanol solution at −45 °C, with a considerable accompanying decrease in the yield of cyclodimer **2**. Thus, the HH/HT ratio was improved up to 0.87 upon complexation with **5c**, which is much higher than that (0.23) obtained with native γ-CD.

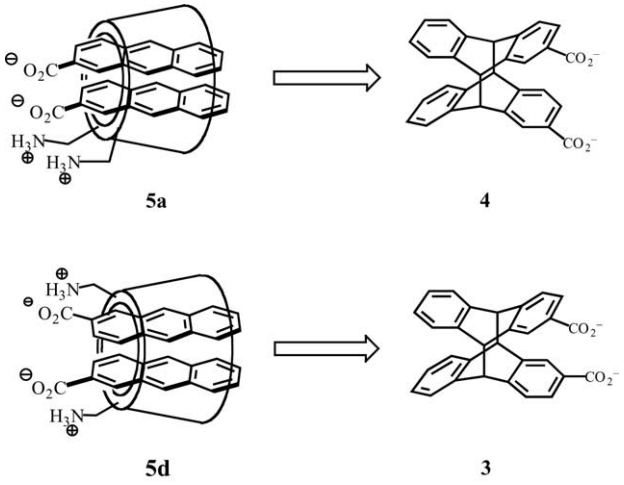
The yields of *syn*- and *anti*-HH cyclodimers obtained upon irradiation with **5a–d** are extremely sensitive to the relative position of the two amino groups introduced to the CD rim. Under comparable reaction conditions, the yield of the *anti*-HH cyclodimer **3** gradually increases at the expense of the *syn*-HH cyclodimer **4**, with increasing distance between the two amino groups in **5a–d**. As a result, the **3**/**4** ratio shows a progressive increase (by 2.4 times) from 0.74 for **5a** to 1.81 for **5d** in aqueous buffer solution at 0 °C, and a sharper increase (by 3.3 times) from 0.87 for **5a** to 2.90 for **5d** in 50% methanol solution at −45 °C. This result differs significantly from that reported by Ikeda et al. [10], where cyclodimer **3**, rather than **4**, is preferred by all of the regioisomeric dipyridinio-γ-CDs.

This switching behavior of the product ratio is an excellent example of a structure–function relationship, which can be rationalized as follows: the two amino groups in **5a**, located next to each other on the rim, electrostatically attract and align two ACA molecules in a parallel syn orientation, which is then ready to photocyclize to *syn*-HH cyclodimer **4** upon irradiation (Scheme 3). As the inter-amino distance increases on going from **5a** to **5d**, the anti orientation becomes more favorable and the syn/anti ratio is switched when the second amino group is located on the *C* glucose moiety, i.e. **5b**, and ultimately the *anti*-HH cyclodimer **3** dominates upon irradiation with **5d**.

Table 1
Photodimerization of ACA in the presence of γ-CD or **5a–d**[a]

Host	Temperature (°C)	Solvent (vol%)		Relative yield (%)[b]				%ee[b,c]		Ratio		
		Water	MeOH	**1**	**2**	**3**	**4**	**2**	**3**	HH/HT[d]	*anti/syn*	
											1/2	**3/4**
γ-CD	0	100	0	42.9	45.5	6.9	4.7	37.1	−0.8	0.13	0.94	1.47
5a	0	100	0	39.0	35.3	10.9	14.8	−4.0	4.2	0.35	1.10	0.74
5b	0	100	0	38.9	33.2	13.4	14.5	−1.5	−5.8	0.39	1.17	0.92
5c	0	100	0	37.4	36.2	14.9	11.5	15.4	−0.2	0.36	1.03	1.30
5d	0	100	0	37.3	37.1	16.5	9.1	20.3	−4.2	0.34	1.00	1.81
γ-CD	−45	50	50	48.4	32.8	12.6	6.3	32.8	−11.9	0.23	1.48	2.00
5a	−45	50	50	39.6	22.0	17.9	20.5	−9.9	−12.4	0.62	1.80	0.87
5b	−45	50	50	38.7	19.3	21.6	20.4	−15.9	−26.9	0.72	2.01	1.06
5c	−45	50	50	36.3	17.1	30.2	15.4	−0.7	−23.0	0.87	2.13	1.83
5d	−45	50	50	35.2	21.8	31.9	11.0	9.2	−19.8	0.75	1.61	2.90

[a] A 25 mM aqueous phosphate buffer solution (pH 7), containing cyclodextrin (0.4 mM) and ACA (0.4 mM), was irradiated under an argon atmosphere at wavelengths longer than 320 nm using a high pressure mercury lamp (300 W) fitted with a uranium filter.
[b] Relative yield and ee were determined using tandem columns of Intersil ODS-2 (GL Science) and Chiralcel OJ-R (Daicel).
[c] Positive/negative ee sign corresponds to the excess of the first/second-eluted enantiomer, respectively.
[d] [**3** + **4**]/[**1** + **2**].



Scheme 3.

3.2.2. Solvent effects upon enantiodifferentiating photocyclodimerization of ACA in the presence of 5a–d

One of the important factors to be considered when performing chemically and optically efficient photoenantiodifferentiations is the effect of the solvent. The crucial role of the solvent in governing product chirality of the photoreaction was first demonstrated in the asymmetric photoisomerization of cyclooctene sensitized by optically active polyalkyl benzenepolycarboxylates [16]. It was revealed that the product's ee obtained in the photosensitization of cyclooctene are highly dependent on the solvent employed, with the chiral sense of photoproduct being invertable simply by altering the solvent polarity. More recently, a dramatic switching of product chirality in the supramolecular enantiodifferentiating photoisomerization of cyclooctene sensitized by benzoate-appended β-CD at ambient temperature was observed [17].

In general, the use of a low polarity solvent enhances the electrostatic interaction but reduces the hydrophobic affinity of a guest for the CD cavity [4e]. To clarify the effects of solvent on the photocyclodimerization of ACA mediated by diamino-γ-CD **5a–d** we performed the photoreaction in a methanol–water mixed solvent system of various compositions. The product distributions obtained at 0 °C for the photocyclodimerization in solutions of varying methanol contents are shown in Table 2. The combined yields of HH cyclodimers **3** and **4** was steadily increased by raising the methanol content, with lowering yields of HT cyclodimers **1** and **2**. The HH/HT ratios obtained upon catalysis with **5a**, **5b**, **5c** and **5d** were appreciably improved from 0.35, 0.39, 0.36 and 0.34 in aqueous solution to 0.44, 0.59, 0.51 and 0.51 in methanol solution, respectively. These changes are attributable to the enhanced electrostatic interactions arising from the decreasing dielectric constant of the solvent. Likewise, the selectivity for HH cyclodimers **3** and **4** was also improved by adding methanol to the aqueous buffer solution. In the case of the photoreaction catalyzed by **5a**, increasing methanol content led to the formation of HH isomers in favor of **4**, with the **3**/**4** ratio decreasing from 0.74 in aqueous buffer to 0.65 in methanol. In sharp contrast, lowering the solvent polarity re-

Table 2
Effect of solvent on the photocyclodimerization of ACA catalyzed by **5a–d** [a]

Host	Solvent (vol%)		Relative yield (%)				%ee		Ratio		
	Water	MeOH	**1**	**2**	**3**	**4**	**2**	**3**	HH/HT	*anti/syn*	
										1/2	**3/4**
5a	100	0	39.0	35.3	10.9	14.8	−4.0	4.2	0.35	1.10	0.74
	75	25	38.5	34.5	11.3	15.7	−5.4	2.8	0.37	1.12	0.72
	50	50	37.8	33.9	11.9	16.4	−7.3	−1.7	0.39	1.12	0.73
	25	75	38.3	31.0	12.3	18.4	−6.9	−1.6	0.44	1.24	0.67
	0	100	36.8	32.6	12.1	18.5	1.8	2.8	0.44	1.13	0.65
5b	100	0	38.9	33.2	13.4	14.5	−1.5	−5.8	0.39	1.17	0.92
	70	30	36.8	29.3	16.5	17.5	−12.7	−9.9	0.52	1.26	0.95
	50	50	35.2	32.1	16.1	16.6	−11.8	6.5	0.49	1.09	0.98
	20	80	36.0	29.4	17.6	17.0	−0.3	31.8	0.53	1.22	1.04
	0	100	34.3	31.8	17.1	16.8	−0.3	6.5	0.51	1.08	1.02
5c	100	0	37.4	36.2	14.9	11.5	15.4	−0.2	0.36	1.03	1.30
	75	25	36.6	33.7	18.2	11.5	2.1	−7.3	0.42	1.09	1.58
	50	50	37.8	32.1	19.2	10.9	−0.8	−1.7	0.43	1.18	1.76
	25	75	38.2	31.6	19.4	10.8	−1.5	12.6	0.43	1.21	1.80
	0	100	36.8	29.5	21.5	12.2	−1.2	5.1	0.51	1.25	1.76
5d	100	0	37.3	37.1	16.5	9.1	20.3	−4.2	0.34	1.00	1.81
	75	25	37.6	33.4	20.0	9.0	7.7	−9.5	0.41	1.13	2.22
	50	50	36.4	33.5	21.2	8.9	4.1	−4.0	0.43	1.09	2.38
	25	75	33.9	31.4	25.5	9.2	−0.7	20.3	0.53	1.08	2.77
	0	100	33.4	32.8	25.9	7.9	−1.2	7.1	0.51	1.02	3.28

[a] Photoirradiation was performed at 0 °C. For other conditions, see Table 1.

markably improved the **3**/**4** ratios upon catalysis with **5c**–**d** to afford a maximal **3**/**4** ratio of 3.28 for **5d** in pure methanol. As already mentioned above, if the distance between two amino groups is small, the *syn*-HH isomer **4** is preferred, but, if the distance is large, the *anti*-HH isomer **3** is preferred. Such preferences should be exaggerated by decreasing solvent polarity.

Very interestingly, the product chirality critically depended on the methanol content in aqueous solution. Increasing methanol content in aqueous solution caused significant changes in the ee of cyclodimer **3**, and even inverted the enantiomer selectivity. For example, the photocyclodimerization of ACA catalyzed by **5b** in 0% and 30% methanol solution afforded cyclodimers **3** in −5.4% and −9.9% ee, respectively, but the antipodal product was produced in +6.5% ee in 50% methanol solution, with the product's ee dramatically enhanced to +31.8% in 80% methanol solution. The inversion of product chirality by changing the methanol content was also observed in the photocyclodimerization mediated by **5a**, **5c** and **5d**, indicating that the solvent actually plays a crucial role in controlling the stereochemical outcome of the supramolecular photocyclodimerization system. This finding means that we can obtain both antipodal products simply by changing the solvent, which is difficult to achieve in conventional thermally driven or enzymatic asymmetric syntheses.

*3.2.3. Temperature effect upon the product distribution and ee of the photocyclodimerization in the presence of **5a–d***

The advantage that the mechanism and the rate of photoreaction are both inherently less sensitive to temperature changes allows us to study the photocyclodimerization over a wide temperature range. We investigated the effects of temperature on the product distribution and ee in the photocyclodimerizations of ACA mediated by **5a**–**d** in methanol–water mixtures. Table 3 illustrates the results of the photocyclodimerizations performed in 50% methanol solution at temperatures ranging from −45 to 55 °C. Lowering the temperature also enhances the electrostatic interaction, and therefore the combined yield of HH-dimers **3** and **4** was greatly increased. By lowering the irradiation temperature, the **3**/**4** ratio decreased when **5a** was used, but considerably increased in the case of **5c** and **5d**.

Interestingly, significantly temperature-dependent chirality switching behavior was observed for cyclodimer **3** in this supramolecular photocyclodimerization system. For instance, in the photocyclodimerization mediated by **5b**, the ee of **3** produced at 55 °C was +30.7%, but was gradually decreased by lowering the irradiation temperature and even inverted to −4.0% at −10 °C, and eventually reached −26.9% at −45 °C. Similar chirality inversion be-

Table 3
Effect of temperature on the photocyclodemerization of ACA catalyzed by **5a**–**d**[a]

Host	Temperature (°C)	Relative yield (%)				%ee		Ratio		
		1	**2**	**3**	**4**	**2**	**3**	HH/HT	*anti/syn*	
									1/2	**3/4**
5a	55	39.6	32.7	11.4	16.3	−1.2	5.5	0.38	1.21	0.70
	40	39.1	34.6	11.6	14.7	−3.8	3.2	0.37	1.13	0.79
	20	37.4	34.5	12.1	16.0	−5.5	1.4	0.39	1.08	0.76
	10	37.8	33.9	11.9	16.4	−7.3	−1.7	0.39	1.12	0.73
	0	34.7	29.5	16.3	19.4	−8.9	−2.9	0.56	1.18	0.84
	−10	34.3	26.8	16.2	22.7	−14.9	−4.1	0.64	1.28	0.71
	−45	39.6	22.0	17.9	20.5	−9.9	−12.4	0.62	1.80	0.87
5b	40	40.7	31.7	14.3	13.4	1.0	26.5	0.38	1.28	1.07
	25	39.7	32.4	14.4	13.4	2.5	20.2	0.39	1.23	1.07
	12.5	35.7	32.3	17.0	15.0	−3.6	10.5	0.47	1.10	1.14
	0	35.2	32.1	16.1	16.6	−11.8	6.5	0.49	1.09	0.98
	−10	35.4	29.2	18.4	17.1	−17.1	−4.0	0.55	1.21	1.08
	−30	35.3	23.1	20.6	21.1	−18.9	−19.6	0.71	1.53	0.98
	−45	38.7	19.3	21.6	20.4	−15.9	−26.9	0.72	2.01	1.06
5c	55	36.3	37.6	15.9	10.2	3.2	10.1	0.35	0.97	1.56
	40	38.2	32.7	17.9	11.2	2.9	8.3	0.41	1.17	1.49
	20	39.2	31.6	18.2	11.0	1.7	4.9	0.41	1.24	1.66
	0	37.8	32.1	19.2	10.9	−0.8	−1.7	0.43	1.18	1.76
	−45	36.3	17.1	30.2	15.4	−0.7	−23.0	0.87	2.13	1.83
5d	55	37.8	35.2	18.1	8.9	3.4	9.4	0.37	1.07	2.03
	40	35.5	33.5	21.3	9.7	3.8	9.2	0.45	1.06	2.21
	0	36.4	33.5	21.2	8.9	4.1	−4.0	0.43	1.09	2.38
	−20	35.1	27.7	26.3	10.9	2.9	−16.6	0.59	1.27	2.41
	−30	34.7	25.1	28.7	11.6	3.0	−15.9	0.67	1.38	2.47
	−45	35.2	21.8	31.9	11.0	9.2	−19.8	0.75	1.61	2.90

[a] Photoirradiation was performed in 50% methanol aqueous. For other conditions, see Table 1.

havior was also found with the other three hosts **5a**, **5c** and **5d**. Although temperature-switching behavior have been reported for asymmetric isomerization of cycloalkenes sensitized by optically active alkylbenzenecarboxylates [18–21] and also been demonstrated in the sensitized bimolecular anti-Markovnikov photoaddition of alcohol to 1,1-diphenylpropene [22], the same phenomenon has never been observed for a direct, non-sensitized photoreaction.

Among the diamino-γ-CDs, AC-regioisomer **5b** is most effective in regulating the enantioselectivity and gives ee of cyclodimer **3** ranging from −26.9% to 31.8%. This is in sharply contrast to the case of dipyridino-γ-CDs, where the highest ee of ca. –15% was achieved by AE-regioisomer [10], revealing that the relative orientation of two ACA molecules within the γ-CD cavity is highly dependent on the nature of cationic species introduced.

To quantitatively analyze the temperature effect on the product ee of **3**, we plotted the natural logarithm of the relative enantiomer ratios of **3**, which were calculated from the experimental ee values, as a function of the reciprocal temperature, according to the Arrhenius or Eyring equations [18]. Fig. 1 illustrates the temperature dependence of the ee of **3** obtained upon irradiation of ACA with **5b** in aqueous solutions at various methanol contents over a temperature range of 0–55 °C. In all cases, good straight lines were obtained over the temperature range examined. From the slope and intercept of the regression line, the differential enthalpy ($\Delta\Delta H^{\ddagger}$) and entropy changes ($\Delta\Delta S^{\ddagger}$) were calculated; the results are listed in Table 4.

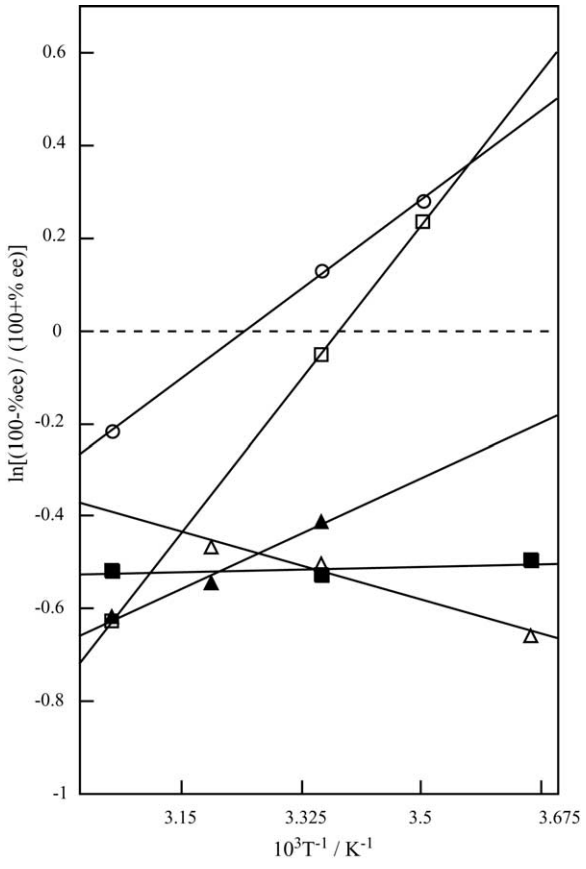


Fig. 1. Plots of the relative rate constants for the formation of enantiomers of **3** against the reciprocal temperature upon photocyclodimerization of ACA catalyzed by **5b** in a mixture of aqueous methanol containing 10% (○), 30% (□), 50% (▲), 60% (■) and 80% (△) methanol.

Table 4
The differential activation parameters for the formation of enantiomeric **3** upon photocyclodimerization of ACA mediated by **5a–d**

Host	Solvent (vol%)		$\Delta\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})
	Water	MeOH		
γ-CD	100	0	1.13	4.30
	50	50	−1.29	−3.52
5a	100	0	−0.83	−3.82
	75	25	−0.75	−3.07
	50	50	−1.91	−6.81
	25	75	−1.08	−3.66
	0	100	+0.11	−0.07
5b	100	0	−6.41	−22.01
	90	10	−9.16	−29.70
	80	20	−11.1	−38.02
	70	30	−15.7	−53.50
	60	40	−13.95	−49.00
	50	50	−5.70	−22.60
	40	60	−0.32	−5.32
	30	70	+4.11	+9.64
	20	80	+3.53	+7.51
	10	90	+6.19	+19.80
	0	100	+4.48	+15.30
5c	100	0	−1.58	−5.82
	75	25	−2.16	−6.65
	50	50	−2.41	−8.97
	25	75	+1.91	+5.00
	0	100	+1.33	+4.11
5d	100	0	−1.66	−5.40
	75	25	−3.16	−9.89
	50	50	−3.66	−12.63
	25	75	+4.57	+13.13
	0	100	+1.83	+5.40

To our surprise, the $\Delta\Delta S^{\ddagger}$ values are highly negative (−22 to −53 kJ mol^{-1} K^{-1}) in 0–50% methanol solution, but become less negative (−5 kJ mol^{-1} K^{-1}) in 60% methanol solution, and is even found to be inverted to a positive value of 10 kJ mol^{-1} K^{-1} in 70% methanol solution. This result unambiguously demonstrates that the temperature-switching behavior of cyclodimers **3** is intrinsically governed by the non-zero differential entropy in the enantiodifferentiating process, which is controllable by varying the solvent composition. This behavior significantly differs from the low entropy-dependence behavior reported for the photosensitized isomerization of (*Z*)-cyclooctene mediated by benzoate-appended β-CD derivatives, but may be rationalized in terms of the more flexible skeleton of γ-CD than its smaller α- and β-analogues. The unusual solvent-dependent entropy switching behavior, commonly observed with **5a**, **5c** and **5d**, confirms the crucial role played by solvation/desolvation in

the supramolecular enantiodifferentiating photocyclodimerization of ACA mediated by diamino-γ-CDs.

It should be emphasized that the ACA molecules bound in the γ-CD cavity are unable to exchange their orientation or position during the lifetime of the excited state, and as a consequence of the very high photocyclodimerization quantum yield, the difference in photoreactivity between the diastereomeric complex pairs should be negligible [8a]. Consequently, the product distribution and ee of the photocyclodimerization of ACA is essentially determined by the distribution of the diastereomeric precursor complexes in the ground state, with the differential kinetic parameters derived from the Eyring-type plot being correlated to the stability differences between the ground-state diastereomeric complexes. Taking this into account, we attribute the dramatic switch of the $\Delta\Delta S^{\ddagger}$, associated with the variation of methanol content, to the combined effects of the electrostatic and hydrophobic interactions, which counterbalance each other depending on the methanol content and the fine-tuning of the geometry of two ACA molecules within the cavity of γ-CD.

3.2.4. Enthalpy–entropy compensation

It has been demonstrated that the thermodynamic parameters for the inclusion complexation of various organic guests with cyclodextrins exhibit a compensatory relationship between ΔH° and $T\Delta S^{\circ}$ [14]. In the present study, the enantiomeric excess of photoproduct **3** is essentially governed by the complexation step, as discussed above. Consequently, the differential enthalpy and entropy changes obtained in this study are also expected to behave similarly, exhibiting a compensatory enthalpy–entropy relationship. In order to better understand the global mechanism and factors controlling the supramolecular photochirogenesis process, and also to examine the general validity of the compensatory enthalpy–entropy relationship, we made a compensation plot using all of the kinetic parameters in Table 4, to obtain an excellent straight line, passing through the origin, as illustrated in Fig. 2; $\Delta\Delta H^{\ddagger} = 0.300\Delta\Delta S^{\ddagger} + 0.29$ (correlation coefficient 0.997). From the slope, we can determine the "isoenantiodifferentiating" temperature (T_{iso}) [16] of this supramolecular enantiodifferentiating photocyclodimerization as 300 K. The consistent T_{iso} obtained for all of the hosts **5a**–**d** implies that the same enantiodifferentiation mechanism is active for the supramolecular photochirogenesis process in each case, and also that no significant change in the chiral environment of the γ-CD cavity occurs upon modification of the primary face.

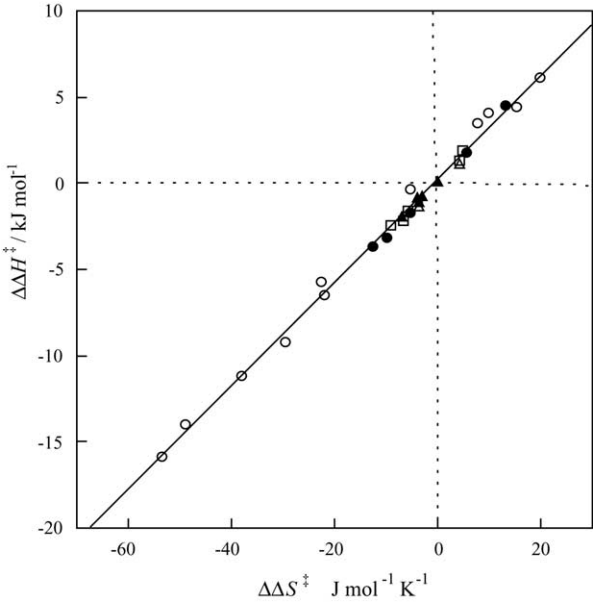


Fig. 2. Enthalpy–entropy compensation plot for the differential parameters of the enantiomers of **3** obtained in the photocyclodimerization of ACA catalyzed by γ-CD (△), **5a** (▲), **5b** (◯), **5c** (□) and **5d** (●).

4. Conclusions

In the present study, 6^{A},6^{X}-dideoxy-6^{A},6^{X}-diamino-γ-cyclodextrins **5a**–**d** (X = B, C, D and E) were prepared as catalysts for the enantiodifferentiating [4 + 4] photocyclodimerization of ACA. The electrostatic interactions between the amino groups of **5a**–**d** and the carboxylate group of ACA greatly improved the yields of HH cyclodimers **3** and **4**. The electrostatic interactions between the hosts and guests were enhanced either by lowering the temperature or by lowering the solvent polarity. The relative yields of cyclodimers **3** and **4** highly depended on the distance of the two amino groups in **5a**–**d**, with the **3**/**4** ratio gradually increasing on changing the host from **5a** to **5d**. The product's ee was affected, and even the sense of product chirality was dramatically switched, by varying the solvent polarity and the reaction temperature. The temperature-dependent inversion of product's ee was assigned to the non-zero differential entropy in the enantiodifferentiating process. This study verified, for the first time, that an entropy-controlled chirality inversion occurs in a direct non-sensitized asymmetric photoreaction. The differential entropy was dramatically influenced by the composition of solvent, yet obeyed the compensatory relationship with the differential enthalpy, indicating that the enantiodifferentiation mechanism remains the same throughout the whole system.

The present study not only demonstrates that the entropic contribution to the enantiodifferentiating process is controllable through manipulation of entropy-related environmental factors, but also presents a new strategy for the multidimensional entropy control of supramolecular photochirogenesis.

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