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Dual Supramolecular Photochirogenesis: Ultimate Stereocontrol of Photocyclodimerization by a Chiral Scaffold and Confining Host

Cheng Yang,[†,‡] Chenfeng Ke,[§] Wenting Liang,[‡] Gaku Fukuhara,[‡] Tadashi Mori,[‡] Yu Liu,[§] and Yoshihisa Inoue*[,‡]

[†]PRESTO, Japan Science and Technology Agency (JST) and [‡]Department of Applied Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan

[§]Department of Chemistry, State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China

Supporting Information

ABSTRACT: In contrast to the brilliant success in thermal asymmetric synthesis, precise stereocontrol remains a great challenge in chiral photochemistry because of the lack of effective tools and methodologies for controlling the short-lived, weakly interacting, and highly reactive electronically excited species. In this work, we achieved this goal through the "dual-chiral, dual-supramolecular" photochirogenesis approach, which enabled us to realized dramatic acceleration and perfect stereocontrol in one of the most representative photoreactions. Thus, the [4 + 4] photocyclodimerization of 2-anthracenecarboxylate tethered to an α-cyclodextrin scaffold was accelerated by a γ-cyclodextrin or cucurbit[8]uril host and gave a single enantiomeric cyclodimer (out of four possible chiral and achiral stereoisomers) in up to 98% chemical and 99% optical yield.

Chiral photochemistry, or photochirogenesis, is a less-explored but most rapidly growing interdisciplinary area of chemical science.[1] Nevertheless, simultaneously achieving high chemical and optical yields is still a major challenge, and hence, precise manipulation of the orientation and conformation of short-lived, weakly interacting excited-state reactant molecules is currently the most crucial task in photochirogenesis. To this end, the supramolecular approach to photochirogenesis[2] is advantageous in several respects, as one can confine, preorganize/orient, and even accumulate reactant molecules in a chiral nanospace before and during the photoreaction.

We have shown the validity of this approach using the [4 + 4] photocyclodimerization of 2-anthracenecarboxylic acid (AC) mediated by several chiral supramolecular hosts (Scheme 1).[3] More recently, the same photochirogenic reaction was studied in chiral gels and liquid crystals, where it was found to give good to high stereoselectivities.[4] The idea of these foregoing studies was to locate two AC molecules stereospecifically in a chiral nanospace in order to shield one of the AC's enantiotopic faces in the ground state. Indeed, the conventional chiral auxiliary approach led to low stereodifferentiation without the use of supramolecular hosts or assemblies.[4a,b] These results have proven the advantage of the supramolecular approach but have also revealed that no single host is enough to gain the ultimate stereochemical outcome. For instance, native γ-cyclodextrin (γ-CD) forms a 1:2 complex with AC, photoirradiation of which afforded syn-head-to-tail (syn-HT) dimer **2** in 41% yield with 41% enantiomeric excess (ee) but almost-racemic anti-head-to-head (anti-HH) dimer **3** in low yield.[3a] Sophisticated modifications of γ-CD to incorporate a doubly charged or copper(II)-chelated diamino side chain greatly improved the stereoselectivity of **3** to −70% ee and the yield to 52% under the optimized conditions.[3b,e] We now propose a "dual-chiral, dual-supramolecular" strategy to achieve the ultimate chemical and optical yields. In this approach, two AC molecules anchored to an α-CD scaffold are accommodated in the cavity of γ-CD or cucurbit[8]uril (CB[8]) for more critical, highly synergetic stereodifferentiation in both the ground and excited states, which allowed us to selectively obtain anti-HH dimer **3** in 98% chemical and 99% optical yield using the γ-CD host and 97% chemical and 98% optical yield even with the achiral CB[8] host.

$6^A,6^X$-Dianthroyl-α-CDs **6**−**8** (X = B, C, D) were synthesized by reacting the corresponding $6^A,6^X$-dimesitylenesulfonyl-α-CDs[5] with sodium anthracenecarboxylate in dimethyl sulfoxide. In accordance with their substitution patterns, the ^{1}H NMR spectra of **6** and **7** exhibited two sets of AC proton signals, while symmetrical A,D-substituted **8** showed one (Figures S1−S6 in the Supporting Information).[6] The AC proton signals of **6**−**8** significantly differed from each other in chemical shift and coupling pattern, indicating distinctly different conformations of the AC moieties in these modified α-CDs. This was further verified by electronic spectroscopy studies. As shown in Figure 1a, the UV−vis spectra of **7** and **8** exhibited bathochromic shifts relative to monoanthroyl-α-CD **5** at the absorption edge (^1L_b band) and the main (^1B_b) band. Although an analogous bathochromic shift of the ^1L_b band was observed for **6**, the main band behaved differently with accompanying peak broadening and suppression of the shoulder at 271 nm, which may reflect the parallel, more-stacked conformation of the two AC chromophores located at the 6^A and 6^B positions in **6**.[6]

Circular dichroism spectra of dianthroyl-α-CDs **6**−**8** showed strong exciton couplets having comparable amplitudes of the main band, in sharp contrast to the very weak signal of the monoanthroyl analogue **5** (Figure 1b). More crucially, the signs of the exciton couplets of A,B- and A,C-substituted **6** and **7** were totally opposite that of A,D-substituted **8**, being negative for the former two but positive for the latter one. The two AC moieties are apparently more separated on the α-CD scaffold in **8** than in **6** and **7**, but the couplet amplitudes (A) and the Davydov

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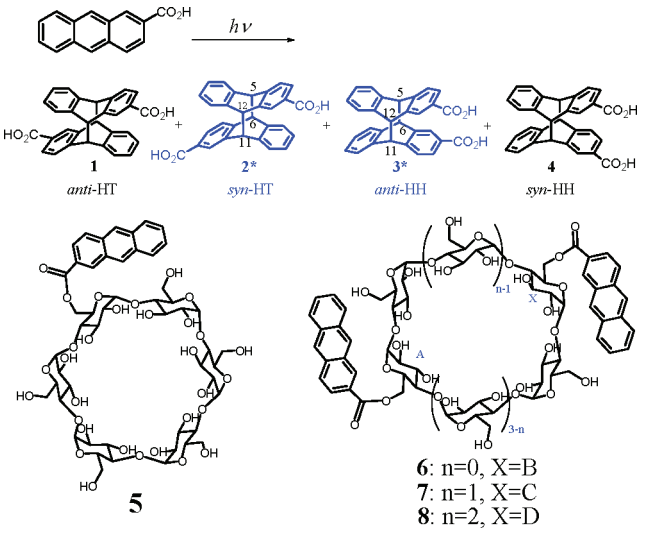
Scheme 1. [4 + 4] Photocyclodimerization of 2-Anthracenecarboxylate (AC) and Mono- and $6^A,6^B$-, $6^A,6^C$-, and $6^A,6^D$-Dianthroyl-α-cyclodextrins **5**−**8**



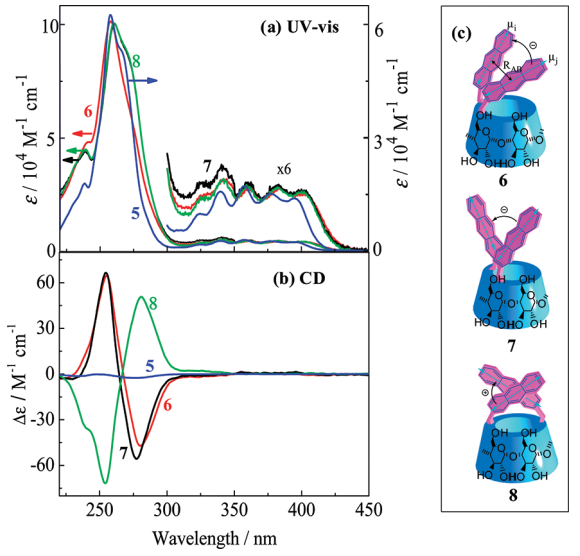


Figure 1. (a) UV−vis and (b) circular dichroism spectra of 0.03 mM methanol solutions of **5** (blue), **6** (red), **7** (black), and **8** (green). (c) Proposed AC conformations obtained by applying the exciton chirality theory[7] to the circular dichroism spectra of **6**−**8**.

splitting energies (ΔE) observed for **6**−**8** are comparable to each other (A = 112, 122, and 122 M^{-1} cm^{-1} and ΔE = 21, 19, and 22 kJ mol^{-1}, respectively). These facts indicate that despite the different substitution pattern, the inter-AC distance and absolute angle do not greatly differ in these dianthroyl-α-CDs, probably because of $\pi-\pi$ stacking and hydrophobic interactions. The only major difference is the chiral sense of AC stacking, which is left-handed in **6** and **7** but the opposite in **8**, according to the exciton chirality theory (Figure 1c).[7]

Mono- and dianthroyl-α-CDs **5**−**8** were photoirradiated at 365 nm under argon in methanol or water at 25 °C. The photolyzed samples were saponified to liberate cyclodimers **1**−**4** from the scaffold, and the mixture of retrieved cyclodimers was subjected to chiral HPLC analysis on a tandem column of ODS and Chiralcel OJ-RH. The photolysis of monoanthroyl-α-CD **5** in methanol gave less-hindered HT dimers **1** and **2** as the major products, while chiral products **2** and **3** were obtained with low ee (<10%) (Table 1).

Intriguingly, the population of cyclodimers obtained from dianthroyl-α-CDs **6**−**8** was a critical function of the inter-AC distance on the α-CD scaffold. Thus, both the A,B and A,C isomers (**6** and **7**) gave sterically hindered HH dimers in high combined yields (mostly >80%). However, a closer look revealed that the former favored syn-HH dimer **4** and the latter anti-HH dimer **3**. In sharp contrast, A,D isomer **8** afforded HT dimers **1** and **2** in ∼90% combined yield. The observed trends in the HH/HT and syn/anti ratios can be rationalized nicely in terms of the inter-AC distance on the scaffold, demonstrating the ability of α-CD skeleton to orient the ACs attached to the rim.

The enantioselectivity of the major chiral cyclodimer obtained upon irradiation in methanol was generally high (46−90% ee) even at 25 °C irrespective of the AC substitution pattern, but it was not greatly improved by lowering the temperature to −40 °C. Thus, photolysis of the A,B isomer **6** in methanol followed by saponification gave anti-HH dimer **3** with 60% ee at 25 °C, which slightly improved to 64% ee at −40 °C.[6] Significantly, the photolysis of A,C isomer **7** in methanol gave **3** in 90% ee at 25 °C and 92% ee at −40 °C, while A,D isomer **8** afforded syn-HT dimer **2** in 51% ee at 25 °C and in 63% ee at −40 °C. These consistently high ee's may indicate the highly stereospecific preorientation of two ACs on an α-CD scaffold, in nice agreement with the intense exciton couplets (Figure 1b).

We further examined the fluorescence behavior of **5**−**8** in methanol at 20 °C. Dianthroyl-α-CDs **6**−**8** showed fluorescence at ∼440 nm that was appreciably weaker, broadened, and red-shifted relative to that of monoanthroyl-α-CD **5** (Figure S13).[6] Spectral subtraction gave a rough estimate of the excimer emission at ∼490 nm for **6** and **7**, which was appreciably red-shifted for **8** (Figure S13). The fluorescence decay profiles of **6**-**8** were well-fitted by a sum of two exponential functions, from which we obtained two lifetimes of 2−4 and 14 ns (Table S1).[6] The longer lifetime was consistent with that of the AC monomer, while the shorter one, which became more abundant at longer wavelengths, was assigned to the excimer.[9]

In this dual supramolecular approach, we first examined an "allosteric" stereocontrol of the conformation and the subsequent photocyclodimerization, in which α-CD plays the dual role of a simple scaffold and a host. Thus, the guest binding to the α-CD cavity in **6**−**8** was expected to provide allosteric tuning of the AC photocyclodimerization. Indeed, the addition of hexanol, which binds well to α-CD (K = 3000 M^{-1}),[10] consistently and significantly improved the ee of the major chiral product, as exemplified by the enhancement of the ee of **3** at 25 °C from 28 to 44% for **6** and from 61 to 73% for **7** as well as the ee of **2** from 46% to 68% for **8** (see Table 1 for similar ee enhancements at lower temperatures), revealing the critical effect of the included hexanol guest on the conformational freedom of the AC moieties on the α-CD rim.

Alternatively, we can add another chiral or achiral host as a confining agent. Addition of γ-CD or CB[8] to an aqueous solution of dianthroyl-α-CDs **6**−**8** was obviously more effective in concurrently enhancing the chemical and optical yield of a specific product. Encapsulation of the two AC moieties in **6**−**8** by γ-CD or CB[8] greatly intensified the couplet amplitude.

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The low water solubility (<0.1 mM) of dianthroyl-α-CDs was greatly improved upon complexation with γ-CD. The rotational Overhauser effect spectroscopy (ROESY) NMR chart of a mixture of **7** and γ-CD (Figure S15)[6] showed cross-peaks between the aromatic protons of AC and the interior protons (H-3 and H-5) of γ-CD. This result, together with the enhanced couplet amplitude in the circular dichroism spectra (Figure 2a), confirmed the simultaneous inclusion of the two AC moieties in the cavity of γ-CD. The 1:1 stoichiometry of the complexation of **7** by γ-CD and CB[8] was demonstrated by Job analysis (Figure S16),[6] and the association constants with **7** were determined to be 6.5×10^3 M^{-1} for γ-CD and 7.6×10^5 M^{-1} for CB[8]. The relatively small K for γ-CD relative to that reported for the inclusion of a second AC in the native γ-CD cavity (3.9×10^4 M^{-1})[3a] is presumably due to the decreased flexibilities of the AC moieties attached to α-CD rim. Interestingly, the HH yield and the ee of **3** were drastically enhanced by addition of γ-CD or even achiral CB[8], regardless of the inter-AC distance on the α-CD rim. In the ultimate case, A,C isomer **7** gave **3** in 87% yield with 99% ee upon photolysis with γ-CD, while in the presence of CB[8], the ee remained high at 96% and the yield reached 95%, all attained in water at ambient temperature.

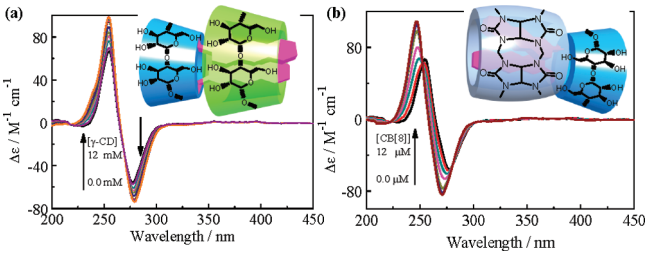

Figure 2. Circular dichroism spectral changes of 10 mM **7** with increasing concentrations of (a) γ-CD and (b) CB[8].

Decreasing the temperature further enhanced the stereoselectivity in all examined cases. Thus, photolysis of **6** in the presence of CB[8] gave **4** in 91% yield at 0 °C. In the photolysis of **7** with γ-CD, the yield of **3** increased from 87% at 25 °C to 94% at 0 °C and further improved to 96% in the presence of both hexanol and γ-CD while the ee remained high at 99%, demonstrating the synergetic fine-tuning effect of the hexanol guest. The photolysis of **7** with CB[8] at 0 °C also afforded **3** in 97% yield with 98% ee. These results prompted us to perform the photoreaction in 14% aqueous LiCl solution at −18 °C. The photolysis of **7** with CB[8] in LiCl solution at −18 °C resulted in a reduced yield and ee of **3** due to the competing ligation of Li^+ to the CB portals. However, the addition of γ-CD at −18 °C led to the ultimate stereochemical outcome, affording **3** in 98% yield with 99% ee.

In conclusion, we have shown that dual supramolecular photochirogenesis using α-CD as a chiral scaffold for aligning the substrates and γ-CD or CB[8] as a convenient yet powerful chiral or achiral confining host can achieve the ultimate chemo- and enantioselectivities. The preorganization and preorientation of the two AC moieties on the α-CD scaffold is primarily responsible for this, but the additional supramolecular confinement

Table 1. Photocyclodimerization of Mono- and Dianthroyl-α-CDs 5−8 in the Presence or Absence of Host and/or Guest Additive(s)[a]

					relative yield/% (ee/%)[c]			
α-CD	solvent	T/°C	additive[b]	conversion/%	**1**	**2**	**3**	**4**
5	methanol	25	none	69	38	43 (6)	12 (−9)	7
6	methanol	25	none	97	7	11 (6)	34 (60)	48
	water	0	none	82	1	2 (0)	31 (32)	66
			hexanol	70	1	1 (5)	30 (47)	68
			γ-CD	>99	0	1 (2)	23 (64)	76
			CB[8]	>99	1	1 (2)	7 (85)	91
7	methanol	25	none	84	7	4 (18)	81 (90)	8
	water	0	none	68	18	6 (49)	64 (69)	12
			hexanol	49	9	6 (45)	71 (77)	14
			γ-CD	>99	1	3 (2)	94 (99)	2
			γ-CD + hexanol	>99	1	1 (4)	96 (99)	2
			CB[8]	>99	0	1 (7)	97 (98)	2
		−18[d]	none	43	15	5 (49)	68 (73)	12
			hexanol	32	6	3 (41)	79 (82)	12
			γ-CD	>99	0	0 (−)	98 (99)	2
			CB[8]	>99	3	5 (7)	85 (83)	7
8	methanol	25	none	61	43	48 (51)	4 (8)	5
	water	0	none	52	46	49 (51)	3 (11)	2
			hexanol	36	38	37 (69)	14 (8)	11
			γ-CD	65	42	42 (46)	11 (60)	5
			CB[8]	71	15	24 (47)	50 (36)	11

[a] Conditions: aqueous or methanol solutions of **5**−**8** (0.02 mM) were irradiated for 1 h at 365 nm under an argon atmosphere. The products were saponified to liberate cyclodimers **1**−**4**. [b] Additive concentrations: [hexanol] = 2 mM; [γ-CD] = 2 mM; [CB[8]] = 0.02 mM. [c] The ee was determined by chiral HPLC (error <1%). The first-eluted enantiomers, assigned as (5*R*,6*R*,11*S*,12*S*)-**2** and (5*R*,6*S*,11*R*,12*S*)-**3**, were given a positive sign; for the absolute configuration determination, see ref 8. [d] In 14% aqueous LiCl solution.

of the host is absolutely needed. In the present system, the remaining conformational diversity of the AC moieties was forced to converge to a single, most favored, conformer upon encapsulation by the γ-CD or CB[8] host, which demonstrates that the critical control of entropy or freedom in the precursor complex is most crucial in obtaining a single enantiopure product. Similar dual supramolecular approaches should be applicable not only to other photochirogenic reactions but also to various supramolecular recognition and sensing systems.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details, synthesis and characterization data for **5**−**8**, spectral analysis of **5**−**8** and their complexation, and HPLC profiles of the photoproducts. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
inoue@chem.eng.osaka-u.ac.jp

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