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Ammonia-Driven Chirality Inversion and Enhancement in Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylate Mediated by Diguanidino-γ-cyclodextrin

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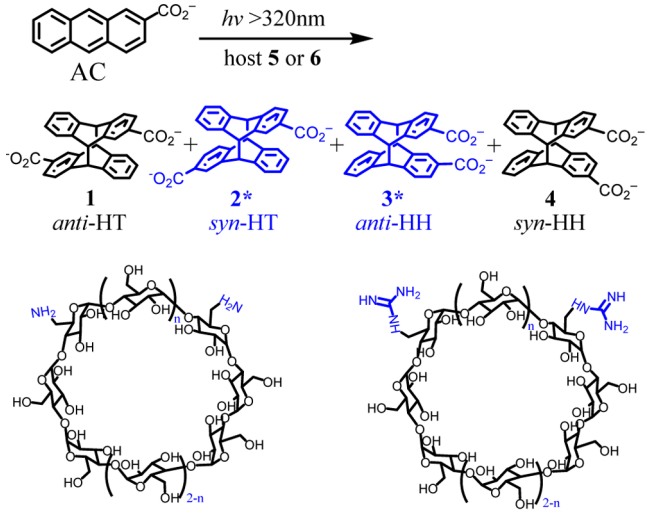
Supporting Information

ABSTRACT: In the supramolecular photocyclodimerization of 2-anthracenecarboxylate mediated by $6^A,6^D$-diguanidino-γ-cyclodextrin (CD), the chiral sense and enantiomeric excess of the photoproduct were dynamic functions of temperature and cosolvent to afford the (*M*)-*anti* head-to-head cyclodimer in 64% ee in aqueous methanol at −70 °C but the antipodal (*P*)-isomer in 86% ee in aqueous ammonia at −85 °C, while the corresponding diamino-γ-CD host did not show such unusual photochirogenic behaviors. The ee landscape was very steep against the temperature and sign-inverted against the ammonia content to reveal the opposite temperature dependence at low and high ammonia contents, for which an altered solvent structure and/or guanidinium−carboxylate interaction mode would be responsible.

Critical control of chiral sense and selectivity is a challenge in current photochemistry.[1] The low enantioselectivities often encountered in chiral photochemistry are ascribed in general to the short-lived weak interactions available in the excited state. The supramolecular approach, exploiting chirogenic interactions in both the ground and excited states, has greatly improved the stereochemical outcomes of photochirogenesis mediated by chiral hosts such as modified zeolites, hydrogen-bonding templates, self-assembled cages, cyclodextrins (CDs), and biomolecules.[2] However, obtaining the opposite enantiomer is not feasible, in principle, in the supramolecular photochirogenesis with naturally occurring hosts, for which no antipodal forms are available. Nevertheless, a few studies have succeeded in obtaining the opposite enantiomers by host modification[3a] or phase evolution,[3b,c] but only in low enantioselectivities. Here, we report a dramatic inversion of the product chirality with enhanced chemical and optical yields in a supramolecular photochirogenesis mediated by modified γ-CD, which was achieved by changing the solution temperature and the content of ammonia added as a cosolvent.

Enantiodifferentiating photocyclodimerization of 2-anthracenecarboxylate (AC; Scheme 1) has been investigated in various supramolecular systems.[4,5] AC forms a stable 1:2 complex with native γ-CD in aqueous solution, irradiation of which affords *head-to-tail* (HT) dimers **1** and **2** in 80% yield, with **2** in 41% enantiomeric excess (ee), and *head-to-head* (HH) dimers **3** and **4** in 20% yield, with **3** in <5% ee.[4a] To improve the HH yield by attractive electrostatic interactions (Figure S1, Supporting Information), two amino groups were introduced to the primary rim of γ-CD to give **5a**−**d**. Photoirradiation of AC with **5b** afforded **3** in 22% yield and −27% ee in aqueous methanol at −45 °C.[4c] However, the addition of organic cosolvent to the aqueous solution requires an intrinsic trade-off between the affinity decrease (to lower the ee) and the lowest available temperature (to enhance the ee). As a consequence, the ee of chiral photoproduct obtained in a mixed solvent is not greatly enhanced, even at low temperature. We now propose the use of ammonia as a less hydrophobic inorganic antifreezing cosolvent for supramolecular photochirogenesis.[6]

Scheme 1. Photocyclodimerization of 2-Anthracenecarboxylate (AC) Mediated by $6^A,6^X$-Diamino- and -Diguanidino-γ-CDs (*X* = B−E) 5a−d and 6a−d



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$6^A,6^X$-Diguanidino-γ-CDs **6a–d** (X = B–E) were synthesized by reacting the corresponding diamino-γ-CDs **5a–d** with 1*H*-pyazole-1-carboxamidine.[7] Photolysis of AC was run at 365 nm in the presence of **5** or **6** in NH_3–H_2O mixtures at +50 to −85 °C, and the photolysate was subjected to chiral HPLC analysis for chemical and optical yields.[7]

Upon irradiation in water at 0 °C, both of the diamino- and diguanidino-CDs gave the HH dimers in 25–30% combined yields, higher than that (11%) obtained with native γ-CD (Table S1, Supporting Information). This is due to anionic AC molecules being HH-preoriented in the CD cavity by attractive electrostatic interactions with the cationic substituents on the primary rim. Interestingly, the use of aqueous ammonia at −40 °C as a solvent led to contrasting photocyclodimerization behaviors for diamino- versus diguanidino-CD. As shown in Table 1, diamino-CDs **5a–d** gave **1–4** in ratios similar to that obtained with native γ-CD, suggesting a loss of the attractive electrostatic interactions. This is reasonable since protonation of the amino groups of **5** (pK_{a1} = 7.78, pK_{a2} = 8.82 for **5c**) is hindered in aqueous ammonia (pK_a = 9.2).[6] Nevertheless, **5d** gave appreciably higher ee's for both **2** and **3** than γ-CD or **5a–c**, indicating some steric contribution of the neutral amino substituents, even in a 30% NH_3 solution.

Table 1. Photocyclodimerization of AC Mediated by Native γ-CD, $6^A,6^X$-Diamino-γ-CDs 5a–d, and $6^A,6^X$-Diguanidino-γ-CDs 6a–d in NH_3–H_2O (3:7 w/w) at −40 °C[a]

	yield (%)[b]				ee (%)[b]			*anti/syn*	
host	**1**	**2**	**3**	**4**	**2**	**3**	HH/HT	**1/2**	**3/4**
γ-CD	57	23	15	5	33	−16	0.3	2.5	2.8
5a	58	25	12	5	36	−20	0.2	2.3	2.4
5b	61	19	14	5	30	−8	0.2	3.2	2.7
5c	58	24	12	6	30	−19	0.2	2.4	2.1
5d	60	24	12	4	42	−36	0.2	2.5	3.1
6a	33	19	22	27	−7	−7	0.9	1.7	0.8
6b	33	20	28	19	12	10	0.9	1.7	1.5
6c	28	19	37	16	−1	6	1.1	1.5	2.2
6d	25	20	44	12	−22	−1	1.3	1.3	3.8

[a][AC] = 0.4 mM; [CD] = 2 mM; irradiated at 365 nm under Ar. [b]Determined by chiral HPLC; the positive/negative ee value for **2** and **3** indicates predominant formation of the first/second-eluted (*M*)/(*P*)-enantiomer (ref 4f); error in yield <±1%; error in ee <±3%.

In contrast, diguanidino-CDs **6a–d** gave more HH dimers (HH/HT = 0.9–1.3) than **5a–d** (HH/HT = 0.2), and the **3**/**4** (*anti*/*syn*) ratio gradually increased from 0.8 to 3.8 with increasing interguanidinium distance in **6a–d**. These results indicate that the guanidinium ion survives even in 30% NH_3 solution to enhance the HH preference through the electrostatic and/or dual hydrogen-bonding interactions between the guanidinium–carboxylate pair in the less hydrophilic CD cavity.[8]

To further elucidate the role of NH_3 as a cosolvent, the photocyclodimerization of AC mediated by **6d** was run in aqueous solutions of various NH_3 contents (C_{NH_3}) at 0 °C. As shown in Table 2, the addition of NH_3 consistently enhanced the HH/HT and *anti*/*syn* ratios to make *anti*-HH dimer **3** the main product at 30% NH_3, for which enhanced electrostatic/hydrogen-bonding interactions and decreased solvophobic effect at higher C_{NH_3} are jointly responsible.

The enantioselectivities of both **2** and **3** showed steady decreases with increasing C_{NH_3} to give antipodal **2** at 30% NH_3. The inversion of product chirality by solvent composition, though not unprecedented,[9] is of mechanistic interest and synthetic importance, enabling us to obtain both enantiomers without using the antipodal CD host that is virtually inaccessible. Formation of a stable 1:2 complex of **6d** with AC was proven by UV–vis, circular dichroism, and NMR spectral studies (Figures S2–S6).[7] In 25% NH_3 solution at 20 °C, **6d** binds two ACs with stepwise association constants of K_1 = 850 M^{-1} and K_2 = 8200 M^{-1}, significantly higher than those for native γ-CD (K_1 = 240 M^{-1}, K_2 = 5900 M^{-1}), supporting the guanidinium–carboxylate interaction in 25% NH_3. On the other hand, **6d** showed a much larger overall association

Table 2. Photocyclodimerization of AC Mediated by 6d in Aqueous Ammonia and Methanol Solutions at Various Temperatures[a]

			yield (%)				ee (%)			*anti/syn*	
cosolvent (%)		T (°C)	**1**	**2**	**3**	**4**	**2**	**3**	HH/HT	**1/2**	**3/4**
none[b]		0	28	42	19	11	25	36	0.4	0.7	1.7
NH_3	10	0	35	32	23	10	12	27	0.5	1.1	2.3
	30	0	27	26	36	11	−10	16	0.9	1.0	3.3
		−20	28	22	39	11	−16	8	1.0	1.3	3.5
		−40	25	20	44	11	−22	−1	1.2	1.3	4.0
		−70	31	17	43	9	−30	−24	1.1	1.8	4.8
	80	−40	13	10	62	15	−45	−69	3.3	1.3	4.3
		−70	9	8	68	15	−49	−80	4.9	1.2	4.7
		−85	7	6	72	15	−52	−86	6.7	1.2	4.8
MeOH	60	−20	40	17	34	9	18	24	0.7	2.3	3.9
		−55	34	19	40	8	17	53	0.9	1.7	5.3
		−70	32	14	46	8	15	64	1.2	2.3	5.8

[a]For irradiation conditions and product analyses, see the footnotes of Table 1. [b]Aqueous phosphate buffer (pH 9).

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constant in pure water (K_1 = 360 M^{-1}, K_2 = 43000 M^{-1}), which confirms reduced solvophobic interactions in less polar NH_3. Indeed, the absorption maximum of Reichardt's dye exhibited a systematic bathochromic shift upon gradual addition of NH_3 (Figure S7), indicating decrease of the solvent polarity.[8b,c] These results reveal that NH_3 plays two contradictory roles to augment the guanidinium−carboxylate interaction and reduce the solvophobic interaction, counterbalance of which determines the relative stability of diastereomeric 1:2 complexes of **6d** with AC and should be the origin of the solvent composition-induced chirality switching.

Temperature (T) turned out to be another crucial factor. Upon photocyclodimerization of AC mediated by **6d** in 30% NH_3 (Table 2), lowering T from 0 to −70 °C led to chirality inversion and significant ee enhancement for **3**, while the ee of **2** simply increased from −10% to −30%. This result prompted us to exploit the synergetic effect of T and C_{NH_3}, which eventually allowed us to obtain **3** of −86% ee in 72% yield (Table 2).

Remarkably, the addition of 60% methanol, in lieu of NH_3, gave *antipodal* **2** and **3** in 15% and 64% ee, respectively, at −70 °C (Table 2), indicating that the solvent polarity is not the only factor that controls the ee; also the solvent structure and basicity, preferential solvation, and solvophobic effects jointly play crucial roles in the enantiotopic face-differentiating complexation of AC with **6d** as well as the subsequent photocyclodimerization.[10] The exceptionally wide range of ee variation (from +64% to −86%) achieved by a single chiral host (**6d**) proves the versatile and decisive role of the environmental factors in supramolecular photochirogenesis.

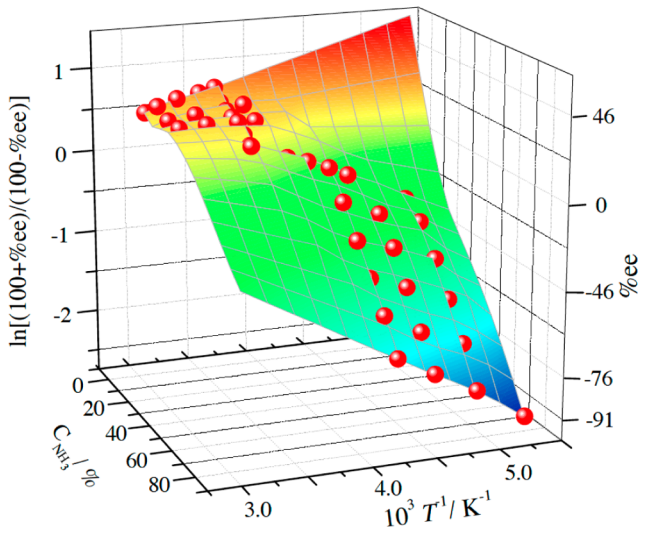

Figure 1. Enantiomeric landscape for **3** obtained by mapping the experimental ee values as a function of temperature (T) and NH_3 content (C_{NH_3}).

Figure 1 maps the ee landscape for **3** (Table S4)[7] as a function of T and C_{NH_3}, which demonstrates the synergetic nature of the ee enhancement to reach −86%, the highest value ever reported for a CD-mediated photochirogenesis. The ee landscape is not flat but unusually steep against T and is even twisted against C_{NH_3} to give a folded surface. Thus, by lowering T, the ee becomes more positive at C_{NH_3} = 10% but more negative at $C_{NH_3} \geq$ 30% (Table S4). To elucidate the origin of this unprecedented phenomenon, the temperature dependence of the relative rate constant (k_+/k_-) for giving (*M*)- and (*P*)-enantiomers[4f] was analyzed by using the differential Eyring equation: $\ln(k_+/k_-) = -\Delta\Delta G^{\ddagger}/RT = -\Delta\Delta H^{\ddagger}/RT + \Delta\Delta S^{\ddagger}/R$, where k_+/k_- = (100 + %ee)/(100 − %ee).[10] Plots of $\ln(k_+/k_-)$ against $1/T$ gave excellent straight lines for both **2** and **3** at all the employed C_{NH_3} values of 0−80% (Figures S10 and S11),[7] indicating operation of a single enantiodifferentiation mechanism in each solvent. The activation parameters obtained (Table S5)[7] indicate that the simultaneous sign inversion of the differential enthalpic ($\Delta\Delta H^{\ddagger}$) and entropic changes ($\Delta\Delta S^{\ddagger}$) is responsible for the dramatic chirality inversion of **3** in 30% NH_3 solution. Closer examinations of the whole parameters (Table S5)[7] revealed a unique feature of this diguanidino-CD-mediated photochirogenesis in NH_3−H_2O. Thus, the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values for both **2** and **3** are inverted in sign (from negative to positive) by increasing C_{NH_3}, but the changing profile is not straightforward, displaying a rapid growth at 30−40% NH_3 and a sudden decline at 40−50%, which is followed by a more moderate change (Table S5).[7]

To gain further insights into the possible mechanism switching by solvent composition, we plotted the $\Delta\Delta H^{\ddagger}$ as a function of the $\Delta\Delta S^{\ddagger}$ to examine whether the compensatory enthalpy−entropy relationship is held or not. In general, the $\Delta\Delta H^{\ddagger}$−$\Delta\Delta S^{\ddagger}$ plot affords a single straight line when the same enantiodifferentiation mechanism operates despite the change in host, guest, sensitizer, substituent, or solvent.[10] As shown in Figure 2, the compensation plot is obviously discontinuous

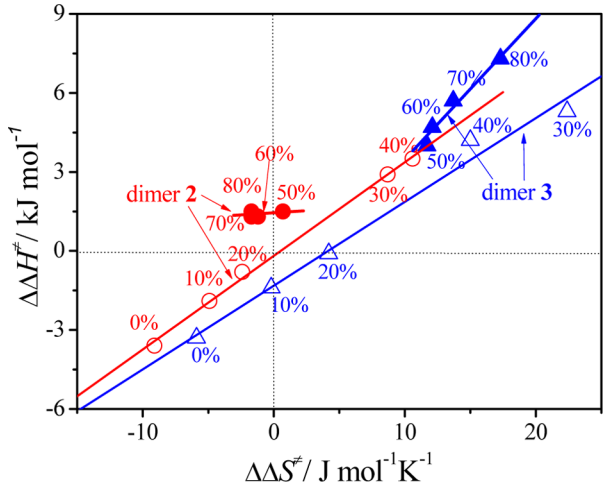

Figure 2. Enthalpy−entropy compensation plot for **2** (circle) and **3** (triangle) obtained for the photocyclodimerization of AC mediated by **6d** in aqueous solutions containing 0−40% (open symbols) and 50−80% NH_3 (solid symbols).

between 40% and 50% NH_3, to give seemingly two distinct straight lines for each of **2** and **3**, suggesting some mechanism switching caused by NH_3 content.

We deduce that the nature of the CD cavity and portals is altered between 40% and 50% NH_3 to provide totally different chiral environments for the enantiotopic face-differentiating 1:2 complexation and subsequent photocyclodimerization. In nice agreement with the behavior of ee, the CD spectrum of AC and **6d** showed a sudden shape change between 40% and 50% NH_3

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(Figure S9b),[7] suggesting significant change in complexation mode, for example, from electrostatic guanidinium−carboxylate interaction to hydrogen-bonding guanidine−carboxylic acid interaction (Figure S44) as a consequence of decreased polarity and increased basicity at higher NH_3 contents.

In conclusion, the product distribution and ee were critically controlled by temperature and ammonia content to give the *anti*-HH dimer **3** of −86% ee in 72% yield in the photocyclodimerization of AC mediated by 6^A,6^E-diguanidino-γ-CD through the more hydrogen-bonding guanidine−carboxylic acid interaction enhanced by the less polar, more basic cosolvent ammonia. Knowledge of the critical roles of external factors found in the present system provides a new versatile handle for manipulating the stereochemical outcomes of supramolecular photochirogenic reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization of synthesized hosts (Figures S13−S43), complexation models (Figures S1 and S44), spectroscopic studies of complexation (Figures S2−S7 and S9), binding constants (Table S2), and a full table and analyses of the photoreaction results (Figures S8 and S10−S12 and Tables S1, S3, and S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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