Photochirogenesis

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Catalytic Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylic Acid Mediated by a Non-Sensitizing Chiral Metallosupramolecular Host**

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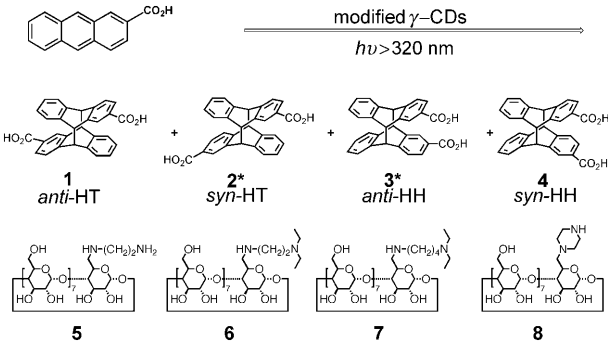
In remarkable contrast to the recent progress in asymmetric syntheses in the ground state, its counterpart in photochemistry, or "photochirogenesis", is still a challenge for chemists, mostly because of the short-lived weak interactions available in the excited state.[1] The success in conventional asymmetric synthesis owes largely to the use of chiral transition metal catalysts.[2] A similar approach seems to be applicable to the photochemical asymmetric synthesis, but chiral metal complexes have rarely been employed in chiral photochemistry, with the exception of a few attempts.[3] The lack of success is probably due to the photoinduced electron transfer occurring between metal and ligand or substrate in the complex, resulting in the quenching of excited substrate or dissociation of chiral ligand. The only method to achieve catalytic photochirogenesis is the use of a chiral sensitizing system.[4,5] Therefore, the development of a novel non-sensitizing, yet catalytic, photochemical route to chiral compounds should greatly expand the range of photochirogenesis. Herein, we report the first catalytic enantiodifferentiating photoreaction mediated by a metallosupramolecular host. This system enables us not only to critically control the orientation and enantioface selectivity of substrate accommodated in a chiral host, but also to accelerate the photoreaction with a catalytic amount of host, thus providing a convenient strategy to achieve the catalytic photochirogenesis without using the conventional chiral photosensitization.



Scheme 1. Metallosupramolecular photocyclodimerization of 2-anthracene carboxylate (AC) mediated by γ-cyclodextrin derivatives possessing a diamino side chain (**5**–**8**) in the presence and absence of $Cu(ClO_4)_2$ in aqueous methanol. * = chiral product; HH = head-to-head, HT = head-to-tail.

Enantiodifferentiating supramolecular [4+4] photocyclodimerization of 2-anthracenecarboxylic acid (AC) (Scheme 1) mediated by γ-cyclodextrin (CD) derivatives is known to give chiral *syn*-head-to-tail (*syn*-HT) dimer **2** and *anti*-head-to-head (*anti*-HH) dimer **3** in good enantiomeric excess (*ee*).[6] Thus, the photocyclodimerization mediated by native γ-CD gives **2** in 51% *ee*, whereas the same reaction mediated by dimethylaminoethylamino-γ-CD affords **3** in 41% *ee*. In spite of the good *ee* values obtained in these supramolecular photochirogenic reactions, an excess amount of chiral host has to be used to attain the highest *ee* values by minimizing the population and photoreaction of free AC in the bulk solution. In the present study, we synthesized a series of γ-CD derivatives **5**–**8** as chiral hosts by the reactions of 6-*O*-tosylated γ-CD with the corresponding amines.[7] The free and metal-coordinated diamino side chains introduced onto γ-CD are expected to enhance the complexation of AC and control its orientation and enantioface selectivity in the CD cavity through electrostatic interaction or ligation to a divalent metal cation. Therefore, this complexation should accelerate the subsequent photocyclodimerization of ACs accommodated in the cavity, eventually achieving the catalytic photochirogenesis with enhanced chemical and optical yields.

AC (0.2 mM) is soluble in a 1:1 mixture of methanol and an aqueous buffer solution (pH 5) at 20°C, but forms aggregates at lower temperatures in the absence of host, which was revealed by a bathochromic shift of the AC absorption (0-0 band) from 386 nm to 429 nm (Supporting Information, Figure S1). However, in the presence of γ-CD hosts, no AC aggregate was formed even at −50°C. The

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stepwise 1:1 and 1:2 association constants were determined for γ-CD derivatives **6** and **7** by UV/Vis spectroscopic titration in aqueous methanol solution at −50 °C (Table 1).[7]

Table 1: Association constants for the stepwise 1:1 and 1:2 complexation of AC with native and modified γ-CDs.

Host	Solvent[a]	T [°C]	K_1 [L mol^{-1}]	K_2 [L mol^{-1}]	K_1K_2 [10^6 L^2 mol^{-2}]	K_2/K_1
γ-CD[6a]	B	5	206	201000	41.4	976
6	B	0	275	25900	7.1	94
	BM	−50	838	2040	1.7	2.4
[**6**·Cu]	BM	−50	569	3200	1.8	5.6
7	B	0	1180	10200	12.0	8.7
	BM	−50	2800	1360	3.8	0.5

[a] Solvent B: aqueous phosphate buffer at pH 5; solvent BM: a 1:1 (w/w) mixture of phosphate buffer and methanol.

The K_1 values for **6** and **7** are much larger than that obtained in water at 0 °C (275 L mol^{-1}), for which the reduced temperature, stronger electrostatic interactions in the less polar solvent and the co-inclusion of methanol in 1:1 complex would be jointly responsible. The last factor may also rationalize the smaller K_2 values that are observed. Coordination of copper(II) to **6** appreciably reduces the K_1 value to 569 L mol^{-1}, but raises the K_2 value to 3200 L mol^{-1}, thus enhancing the contribution of 1:2 complex (K_2/K_1) without lowering the overall affinity (K_1K_2).

Photoirradiation of AC with and without native or modified γ-CDs **5**–**8** was carried out at wavelengths longer than 320 nm in a 1:1 methanol/aqueous buffer mixture at −50 °C to give the results shown in Table 2 (see also the Supporting Information, Table S2). In the absence of host, the photocyclodimerization was extremely slow because of the bimolecular nature of photodimerization and the AC aggregation mentioned above. However, the addition of the CD host led to a substantial acceleration of photocyclodimerization, and the irradiation of AC with **5** and **6** gave the sterically and electrostatically less-favored HH dimers as major products in 51–59 % combined relative yields, which are significantly higher than those (33–37 %) obtained with native γ-CD and the other modified CDs **7** and **8** as a result of the effective interaction of AC with the diamino side chain. The *ee* value with **3** also improved from −7 % with native γ-CD to −15 % with 2-aminoethylamino-γ-CD **5**, and up to −48 % with *N*,*N*-diethylaminoethylamino-γ-CD **6** by using a fivefold excess of CD relative to AC. Elongation of the inter-amino distance in **7** led to a decrease in HH yield but a comparable −47 % *ee* for **3**. In contrast, piperazine-modified γ-CD **8** gave the lowest HH yield and *ee* for **3**, which is probably due to the chair conformation of piperazine, in which the terminal amino group is oriented outward and thus cannot control the orientation of AC accommodated in the cavity.

Copper(II) perchlorate, stoichiometric to the CD host (that is, [AC]/[CD]/[Cu] = 1:5:5), was then added to the system to examine the effects of chelation of the diamino side chain in **5**–**8** to copper(II) on the photo- and stereochemical outcomes. As shown in Table 2, the addition of copper(II)

Table 2: Photocyclodimerization of AC in the presence of native and modified γ-CDs with and without added $Cu(ClO_4)_2$.[a]

Host	[Host]/[AC]	[Cu]/[AC]	Conversion [%][b]	Relative yield [%][c]						% *ee*[c]	
				1	**2**	**3**	**4**	HT	HH	**2**	**3**
none	0	0	1.9	38	22	27	13	60	40	0	0
		5	1.8	37	18	33	12	55	45	0	0
γ-CD	5	0	63	41	26	26	7	67	33	32	−16
		5	47	37	24	31	8	61	39	37	−7
5	5	0	88	27	14	21	38	41	59	5	−15
		5	–[d]	25	15	23	37	40	60	19	−26
6	5	0	86	32	17	21	30	49	51	1	−48
		5	56	19	12	30	39	31	69	−9	−60
	0.1	0	51	21	15	34	25	41	59	0	−45
		0.1	41	22	15	32	31	37	63	1	−49
		0.5	12	13	7	52	28	20	80	13	−70
			49[e]	13	8	53	26	21	79	13	−67
			83[f]	13	9	51	27	22	78	11	−64
	0.01	0	7[g]	21	12	34	23	33	57	1	−24
		0.5	3[g]	24	12	43	21	36	64	6	−43
7	5	0	90	45	18	20	17	63	37	−14	−47
		5	–[d]	28	16	31	25	44	56	−7	−42
8	5	0	84	40	24	23	12	64	35	31	−13
		5	[d]	31	19	33	17	50	50	31	−18

[a] Irradiation of AC (0.2 mM) performed at $\lambda > 320$ nm in a 1:1 mixture (w/w) of phosphate buffer (pH 5) and methanol at −50 °C. [b] Conversion after 1 h irradiation, unless noted otherwise. [c] Relative yield and *ee* (error in *ee* < 3 %) determined by chiral HPLC (ODS + Daicel OJ-RH); see Ref. [6]; the positive/negative *ee* value indicates the dominant formation of first/second-eluting enantiomer. [d] Not determined. [e] Conversion after 12 h irradiation. [f] Conversion after 40 h irradiation. [g] Conversion after 30 min irradiation.

moderately decelerated the photocyclodimerization, but significantly shifted the product distribution to the HH dimers in all examined cases. The enhanced HH preference may be attributed to the coordination of two ACs to copper(II) chelated by the side chain, and also to the reduced electrostatic repulsion in the CD cavity.

Intriguingly, the *ee* value of **3** was significantly enhanced from −48 % to −60 % upon addition of copper(II) to **6**, whereas the effect of copper(II) was almost negligible for **7** and **8**. This contrasting behavior is probably due to the less-efficient chelation of the diamino side chain of the latter two hosts. To achieve catalytic photoreaction, we reduced the amount of **6** down to a 0.1 equiv of AC to obtain the major product **3** in −45 % *ee*, which is comparable to that (−48 %) obtained with a fivefold excess of AC. The acceleration of photocyclodimerization in the cavity and possibly the suppression in the bulk solution owing to the aggregation of free AC would be jointly responsible for this efficient catalysis (Table 2 and the Supporting Information).

Upon addition of copper(II) (0.1 to 0.5 equiv of AC), the conversion was reduced from 51 % to 12 % owing to the decelerated photocyclodimerization both inside and outside the cavity. Meanwhile, both the relative yield and *ee* of **3** increased in the presence of 0.1 equiv of **6** upon addition of copper(II) (0.1 equiv to 0.5 equiv). Under the optimized conditions ([AC]/[CD]/[Cu] = 1:0.1:0.5), the relative yield and *ee* of **3** simultaneously reached the maxima (52 % and −70 %

ee at 12% conversion and 51% and −64% *ee* even at 83% conversion), achieving catalytic photochirogenesis with chemical and optical yields higher than those (30% and −60% *ee*) obtained with a fivefold excess of **6**. However, the photoreaction of AC in the presence of 0.1 equiv each of **6** and copper(II) ([AC]/[CD]/[Cu] = 1:0.1:0.1) afforded **3** in −49% *ee*, which is only slightly higher than that (−45% *ee*) obtained in the absence of copper(II), and is much smaller than that (−70% *ee*) obtained in the presence of 0.5 equiv of copper(II). This result clearly indicates that the coordination of the sidearm of **6** to copper(II) is not very strong, and a fivefold excess is needed for sufficient complexation of **6** with copper(II). Reducing of the amount of **6** down to 1% of AC led to a lower *ee* of −24%, which however recovered to −43% by adding a 0.5 equiv of copper(II) ([AC]/[CD]/[Cu] = 1:0.01:0.5). These observations unambiguously reveal the catalytic role played by the chiral metallosupramolecular host. Furthermore, the fact that only a slight reduction in *ee* was observed even at higher conversions may indicate that the product inhibition of AC binding is minimal under the conditions employed, probably because of the less efficient inclusion of butterfly-shaped photodimers and the acceleration of AC photodimerization in the CD cavity.

In this newly developed metallosupramolecular photochirogenesis system, copper(II) incorporated in diamino-CD plays dual crucial roles in achieving the concurrent enhancement of chemical and optical yields of HH dimer **3** by facilitating the formation of HH-oriented 1:2 complexes and simultaneously discouraging the formation and photocyclodimerization of the less-favored diastereomeric *syn*-HH complex (Figure 1).

In this study, we have developed a new strategy for realizing the catalytic photochirogenesis mediated by non-sensitizing metallosupramolecular host, which enabled us to achieve a 64–70% (or 43%) *ee* and a 51–52% (or 43%) yield for *anti*-HH dimer **3** by using a 0.1 (or even a 0.01) equiv of catalyst **6**·Cu^{II} in aqueous methanol at −50 °C. Further studies to elucidate the detailed mechanisms and to expand the scope of metal-assisted catalytic supramolecular photochirogenesis are in progress.

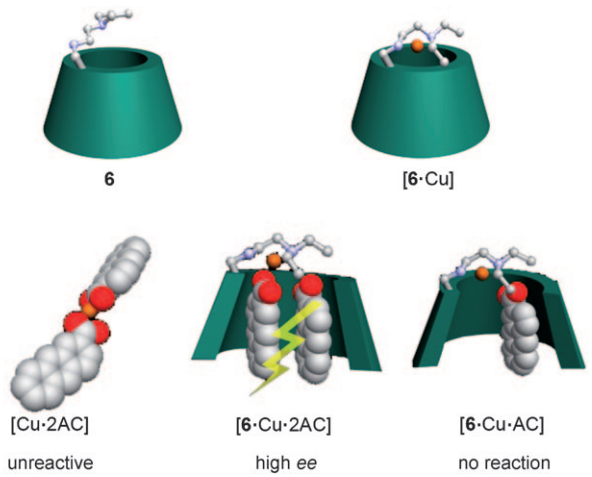

Figure 1. Photocyclodimerization of AC in the presence of **6**·Cu^{II}. Cu orange, O red, N blue.

Experimental Section

General procedure for the preparation of 6–8: 6-TsO-γ-CD (300 mg) was dissolved in alkanediamine or piperazine (5 mL), and the mixture was stirred at 80 °C under argon for 12 h. The resulting solution was added dropwise to 100 mL of acetone with stirring to give a precipitate. The white precipitate was collected by centrifugation, washed with acetone, dissolved in water, and freeze-dried to yield the pure product as a white powder. **6**: ^{1}H NMR (400 MHz, D_2O): δ = 4.88 (m, 8H), 3.63–3.32 (m, 46H), 3.16 (t, 1H, J = 9.2 Hz), 2.74 (d, 1H, J = 12 Hz), 2.49–2.42 (m, 8H), 0.82 ppm (t, 6H, J = 7.2 Hz). HR-ESI-MS: *m/z* 1395.5515 [*M* + H], calcd 1395.5507. **7**: ^{1}H NMR (400 MHz, D_2O): δ = 4.91 (m, 8H), 3.72–3.45 (m, 45H), 3,22 (t, 1H, J = 9.2 Hz), 3.08 (q, 1H, J = 12 Hz), 2.85 (d, 1H, J = 12 Hz), 2.60–2.41 (m, 8H), 1.36 (m, 4H), 0.94 ppm (t, 6H, J = 7.2 Hz). HR-ESI-MS: *m/z* 1423.5799 [*M* + H], calcd 1423.5819. **8**: ^{1}H NMR (400 MHz, D_2O): δ = 4.90 (m, 8H), 3.89 (m, 1H), 3.72–3.30 (m, 46H), 3.21 (t, 1H, J = 9.2 Hz), 2.91–2.67 (m, 4H), 2.42 ppm (m, 4H); HR-ESI-MS: *m/z* 1387.4855 [*M* + Na], calcd 1387.4856.

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[7] For details, see the Supporting Information.