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Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylic Acid Using a Chiral *N*-(2-Hydroxymethyl-4-pyrrolidinyl)benzamide Template

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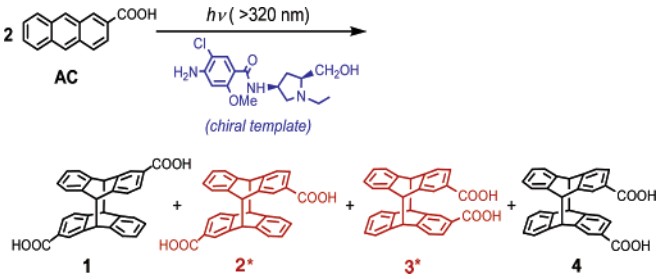
ABSTRACT



Supramolecular enantiodifferentiating photocyclodimerization of 2-anthracenecarboxylic acid (AC) was performed in the presence of (2*S*,4*S*)-4-amino-5-chloro-2-methoxy-*N*-(1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide (TKS159), and its stereoisomers were employed as chiral templates. The TKS template provides us with a novel hydrogen-bonding and shielding motif for enantioface-selectively binding an AC molecule. Chiral products 2 and 3 were obtained in good enantiomeric excesses (ee's) of 40% and 40%, respectively.

Photochirogenesis, or photochemical asymmetric synthesis, is one of the most intriguing topics in current photochemistry. Of several strategies employed in the photochirogenic reactions reported so far, the supramolecular approach, utilizing both the ground- and excited-state interactions, as well as the environmental variants, is of our particular interest.[1,2] Precise preorientation of prochiral substrate(s) in a chiral environment prior to photoirradiation is an essential task for achieving efficient photochirogenesis, which has been realized through chiral supramolecular interactions to afford moderate to high regio-[3−5] and enantioselectivities.[6,7]

Photocyclodimerization of anthracene derivatives is one of the most established photoreactions,[8−26] which is often

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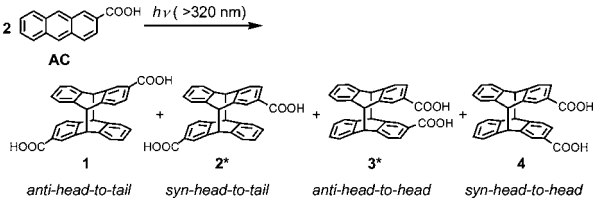
used as a photochemical tool for inter- and intramolecularly tethering two relevant moieties.[8,9] However, its photochirogenic aspect has only recently been investigated. Thus, the enantiodifferentiating [4+4] photocyclodimerization of 2-anthracenecarboxylic acid (AC) (Scheme 1) has been mediated

Scheme 1. Photocyclodimerization of 2-Antharacenecarboxylic Acid (AC) to Stereoisomeric Cyclodimers **1**−**4**



by γ-cyclodextrins,[21−24] and bovine serum albumin (BSA)[25] was added as chiral supramolecular hosts. In these cases, the stereochemical outcomes are governed by the "chiral environment" of the supramolecular host that simultaneously binds two (or more) ACs in a single binding site, and the subsequent photoirradiation fixes the enantioface selectivity determined in the diastereomeric precursor complexes.

To more explicitly define the substrate's enantioface in a precursor complex, it is advantageous to use a chiral template that binds the substrate through multipoint interactions. Bach et al. have succeeded in obtaining good enantiomeric excesses (ee's) in enantiodifferentiating [4+2] photocycloaddition and photocyclization reactions by using chiral Kemp's lactam derivatives that trap the complementary amide/lactam substrates through the dual hydrogen-bonding interactions.[7,27] Although the same template or strategy is not applicable to carboxylic acid substrates such AC, we incidentally found that (2*S*,4*S*)-4-amino-5-chloro-2-methoxy-*N*-(1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide (TKS159) (**5**), originally developed as a gastroprokinetic agent that has a strong affinity to a 5-hydroxytryptamine (5-HT$_4$) receptor,[28] binds an AC molecule through a new nine-membered dual hydrogen-bonding motif incorporating the carboxylic acid and 2-hydroxymethylpyrrolidine moieties. In this paper, we report the binding and photochirogenic behavior of AC with TKS159 (**5**) and its enantiomeric and diastereomeric isomers *ent*-**5**, **6**, and *ent*-**6** (Figure 1).

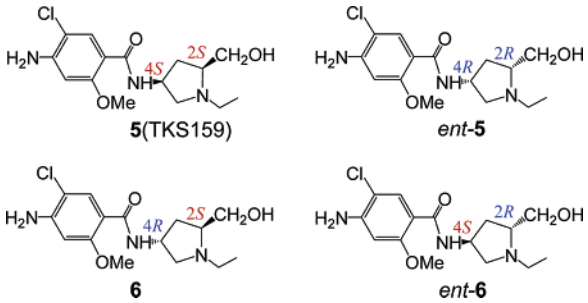


Figure 1. Chiral templates: (2*S*,4*S*)-, (2*R*,4*R*)-, (2*S*,4*R*)-, and (2*R*,4*S*)-4-amino-5-chloro-2-methoxy-*N*-(1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamides **5**, *ent*-**5**, **6**, and *ent*-**6**.

We first examined the interactions of AC with **5** and its epimer **6** in CD_2Cl_2 by ^{1}H NMR spectroscopy. Interestingly, AC at 5 mM concentration, which is hardly soluble in CD_2Cl_2, was smoothly dissolved upon addition of an equimolar amount (5 mM) of **5** or **6** to afford a clear solution. This

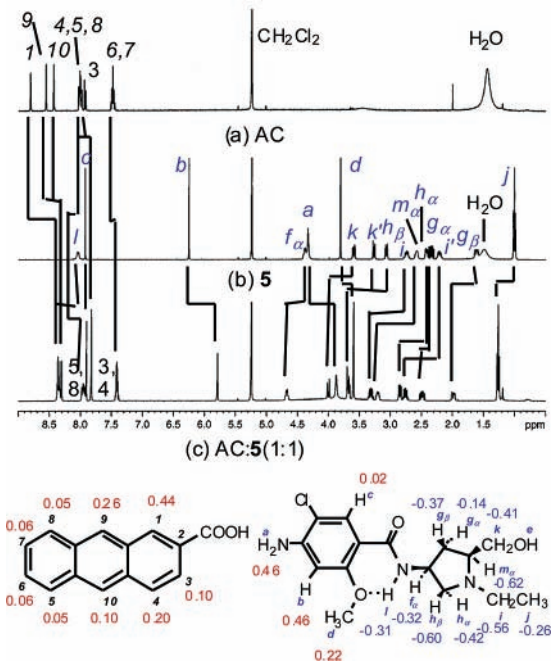


Figure 2. Top: ^{1}H NMR spectra of (a) AC (1 mM), (b) **5** (5 mM), and (c) a 1:1 mixture of AC and **5** (5 mM each) in CD_2Cl_2 at 30 °C. Bottom: Chemical shift changes (in ppm) of AC and **5** protons caused by complex formation. Red and blue figures indicate upfield and downfield shifts, respectively.

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indicates formation of a complex that has a higher solubility than AC. The NMR spectra of the CD_2Cl_2 solutions of AC, **5**, or **6** and a 1:1 mixture of AC and **5** or **6** are shown in Figures 2 and 3. All protons were assigned by using the H−H

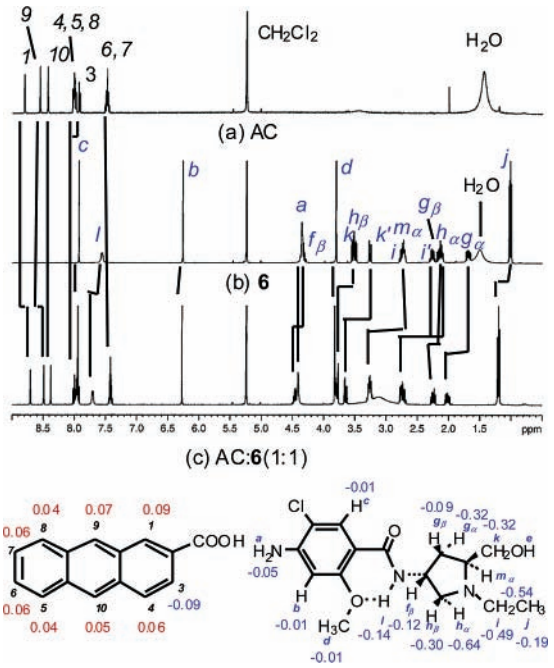

Figure 3. Top: ^{1}H NMR spectra of (a) AC (1 mM), (b) **6** (5 mM), and (c) a 1:1 mixture of AC and **6** (5 mM each) in CD_2Cl_2 at 30 °C. Bottom: Chemical shift changes (in ppm) of AC and **6** protons caused by complex formation. Red and blue figures indicate upfield and downfield shifts, respectively.

COSY, HOHAHA, and NOESY techniques (Supporting Information).

As summarized in Figures 2 and 3, AC's H1, H3, H4, H9, and H10 protons display large upfield shifts ($\Delta\delta$ 0.10−0.44 ppm) upon complexation with **5** but only small upfield shifts ($\Delta\delta$ 0.04−0.09 ppm) or even a downfield shift (H3) upon complexation with **6**. Similarly, the benzoyl's H*a*, H*b*, and H*d* protons of **5** show significant *upfield* shifts ($\Delta\delta$ 0.22−0.46 ppm) upon complexation with AC but noticeable *downfield* shifts ($\Delta\delta$ 0.01−0.05 ppm) for the corresponding protons of **6**.

In contrast, the pyrrolidine and nearby protons (particularly H*g*, H*h*, H*i*, H*k*, and H*m*) of both **5** and **6** are significantly downfield shifted ($\Delta\delta$ > 0.3 ppm). These observations led us to the complex structures, in which the AC's carboxylic group is dually hydrogen-bonded to the pyrrolidine's nitrogen and hydroxyl groups and the AC's two aromatic rings (particularly H1 and H9) cover part of the 2-methoxybenzoyl moiety (H*a*, H*b*, and H*d*) of **5**. However, no such stacking occurs with **6** because of its hydroxymethyl configuration anti to the benzamide, and hence, the significant downfield shifts are accounted for in terms of the deshielding by the ring current of AC placed edge-to-face against the pyrrolidine ring. In good agreement with the partially stacked conformation elucidated above, the ROESY spectrum of a 1:1 mixture of AC and **5** in CD_2Cl_2 at 25 °C (Figure 4) revealed clear

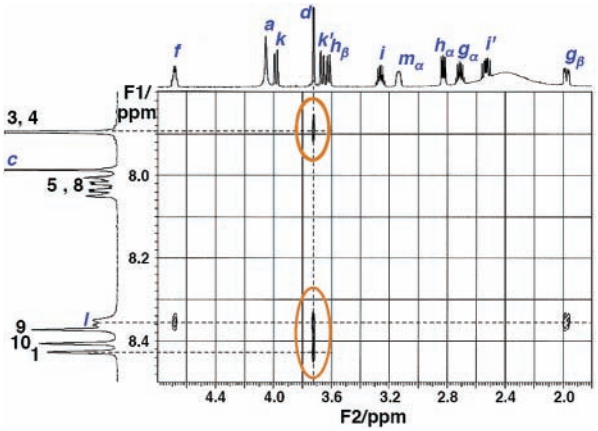

Figure 4. ROESY spectrum (part) of a 1:1 mixture of AC and **5** (5 mM each) in CD_2Cl_2 at 25 °C.

cross-peaks for the template's MeO protons (H*d*) with AC's H1, H3, and H4 (Supporting Information). We conclude therefore that template **5** (or *ent*-**5**) with 2*S*,4*S* (or 2*R*,4*R*) configuration forms a stacked complex with AC, in which one of the enantiofaces of AC is covered in part by the template's benzoyl moiety, whereas the diastereomeric **6** (or *ent*-**6**) with 2*S*,4*R* (or 2*R*,4*S*) configuration gives an unstacked complex due to the anti configuration at the pyrrolidine's 2- and 4-positions.

To gain further evidence for the new hydrogen-bonding motif proposed above, a single crystal of a stoichiometric complex of **6** with AC, obtained as a monohydrate by recrystallizing a 1:1 mixture of both components in dichloromethane, was subjected to X-ray crystallographic analysis. The X-ray structure (Figure 5) reveals the existence of a nine-

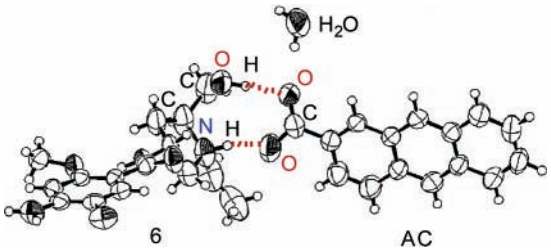

Figure 5. X-ray structure of an AC−**6** complex; the anisotropic ellipsoids for non-H atoms enclose 50% probability.

membered hydrogen-bonding network connecting the AC's carboxylic OH to the pyrrolidine's N (the proton is transferred to the nitrogen) and the carboxylic C═O to the hydroxyl proton of the pyrrolidine's side chain. However, attempts to obtain a single crystal of the AC−**5** complex

(from toluene, dichloromethane, acetonitrile, or methanol) were unsuccessful.

The above binding studies revealed that one of the AC's enantiofaces is covered with the template's benzoyl moiety in the AC−**5** complex, blocking the approach of other molecules, whereas both enantiofaces are exposed in the AC−**6** complex. This system provides us with a good opportunity to examine the photochirogenic performance of this new chiral template in the enantiodifferentiating photocyclodimerization of AC. Fortunately, we have the whole enantiomer and diastereomer series of TKS159.

Photoirradiation (λ > 320 nm) of a dichloromethane solution of AC (0.25 mM) with or without a chiral template (10 equiv) was performed for 2 h at 25 °C or −50 °C under an argon atmosphere. After workup,[26] the irradiated samples were analyzed by chiral HPLC[26] (on a tandem Cosmosil AR-II + Chiralcel OJ-R column) to determine the chemical yields of **1**−**4** and the enantiomeric excesses (ee's) of **2** and **3**. The results are shown in Table 1.

Table 1. Supramolecular Photocyclodimerization of 2-Anthracenecarboxylic Acid Using Chiral Templates[a]

template[b]	temp (°C)	conversion (%)	relative yield/% (ee[c]/%)				HT/HH
			1	**2**	**3**	**4**	
none	20	96	32	22 (0)	25 (0)	21	1.2
	−50	70	23	12 (0)	52 (0)	13	0.5
5	25	98	34	23 (−25)	25 (−10)	18	1.3
	−50	82	41	20 (−36)	31 (−40)	8	1.6
ent-**5**	25	98	35	21 (27)	24 (14)	20	1.3
	−50	78	42	19 (43)	28 (43)	11	1.6
6	25	98	30	21 (−2)	24 (0)	25	1.0
	−50	73	45	21 (−1)	23 (−3)	11	1.9
ent-**6**	25	98	29	20 (−3)	26 (−1)	25	1.0
	−50	82	42	21 (2)	24 (−1)	13	1.7

[a] AC (0.25 mM) in CH_2Cl_2 was irradiated for 2 h at λ > 320 nm under Ar in the presence (10 equiv) or in the absence of a chiral template. [b] [Template]/[AC] = 10. [c] Error in ee upon chiral HPLC analysis: <5%.

The chiral templates added to the AC solution significantly affect both the product distribution and the ee. In the absence of a template, where AC tends to form a hydrogen-bonded dimer, the head-to-head (HH) and anti products are favored in particular at low temperature.[26] In the presence of an excess amount (10 equiv) of the template, formation of the least-hindered anti head-to-tail (HT) product **1** is greatly accelerated at the expense of the syn products **2** and **4** at both temperatures, probably due to the steric hindrance of the template attached to AC.

There are striking differences in the ee's of **2** and **3** obtained upon photodimerization mediated by **5** (or *ent*-**5**) vs its epimer **6** (or *ent*-**6**), and the enantiomeric template pair **5** and *ent*-**5** (or **6** and *ent*-**6**) affords antipodal **2** and **3** in essentially the same absolute ee, as anticipated. Thus, **5** and *ent*-**5** (10 equiv) afford antipodal **2** in an absolute ee of 25−27% and **3** in 10−14% ee at 25 °C, both of which are enhanced up to 36−43% and 40−43% ee at −50 °C. These ee values are comparable or even superior to those obtained in the BSA-mediated photocyclodimerization in water at 25 °C.[25] The higher ee's, as well as the more pronounced preference for anti and HT dimers, observed at lower temperatures are likely to originate from the enhanced complexation of AC with the chiral template and also from the intrinsic temperature effect on the photochirogenic reaction.[1]

In sharp contrast, the enantiomeric template pair, **6** and *ent*-**6**, being diastereomeric to **5** and *ent*-**5**, respectively, affords poor ee's (<3%), irrespective of the irradiation temperature used. This result clearly indicates the importance of the partial overlap of the template with the AC plane in the AC complex with **5** and *ent*-**5**, which leads to the preferential attack from the open enantioface of the AC bound to the chiral template.

In this study, to expand the scope of template-mediated supramolecular photochirogenesis,[6,7,27] we have shown that TKS159, possessing a benzamide barrier connected to 2-hydroxymethylpyrrolidine, functions as a unique and effective chiral template for the enantiodifferentiating photocyclodimerization of AC. This was made possible by efficiently binding the substrate AC through the nine-membered hydrogen-bonding network and simultaneously shielding one of the AC's enantiofaces. The TKS template and its unique hydrogen-bonding motif should be applicable to a variety of organic carboxylic acids, and work along this line is currently in progress.

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Supporting Information Available: Crystallographic data in CIF format, experimental details, and spectral data are provided. This material is available free of charge via the Internet at http///pubs.acs.org.

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