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Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylic Acid via Competitive Binary/Ternary Hydrogen-Bonded Complexes with 4-Benzamidoprolinol

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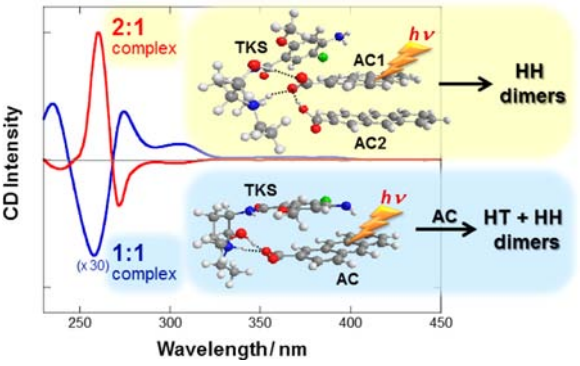
ABSTRACT



Circular dichroism (CD) spectral examinations at various host/guest ratios revealed that 2-anthracenecarboxylic acid (AC) forms not only 1:1 but also novel 2:1 hydrogen-bonded/π-stacked complexes with a chiral 4-benzamidoprolinol template (TKS159). The 2:1 complexation is a minor process but causes significant CD spectral changes as a consequence of the exciton coupling interaction of two AC chromophores and greatly accelerates the head-to-head photocyclodimerization to significantly affect the stereochemical outcomes.

Of several photochemical approaches to asymmetric synthesis, supramolecular photochirogenesis is of particular interest and has attracted much attention in recent years.[1] Thus, chiral supramolecular hosts, such as chirally modified zeolites,[2] cyclodextrins,[3] and proteins,[4] have been employed to confine prochiral substrate(s) in their chiral

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Table 1. Enantiodifferentiating Photocyclodimerization of 2-Anthracenecarboxylic Acid (AC) through Competitive 1:1 and 2:1 Complexation with Hydrogen-Bonding Template 4-Benzamidoprolinol (TKS159)[a]

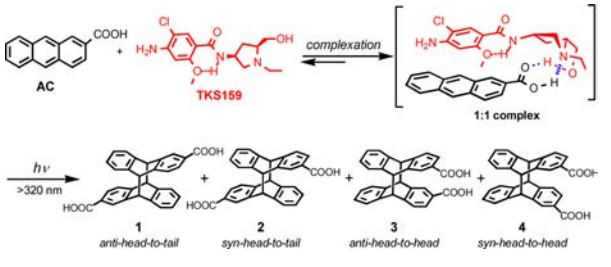
	% AC-TKS complex[b]				product distribution/%				% ee[c]		
$[TKS]_0/[AC]_0$	1:1	2:1	irradiation time/min	% conversion	**1**	**2**	**3**	**4**	**2**	**3**	HH/HT[d]
0	0	0	3.0	9	33	23	24	20	0	0	0.79
0.25	11	0.24	3.5	12	31	20	26	23	−2	−1	0.96
0.5	20	0.40	3.0	11	30	20	28	22	−8	−3	1.00
1.0	35	0.56	3.0	12	29	19	29	23	−14	−6	1.08
1.6	48	0.61	2.8	10	28	17	29	26	−20	−4	1.22
2.4	60	0.58	2.8	8	28	17	28	27	−21	−5	1.22
4.0	73	0.48	3.0	10	28	20	27	25	−25	−10	1.08
10	88	0.25	3.0	6	32	20	28	20	−30	−8	0.92
40	97	0.07	5.0	11	35	25	26	14	−30	−18	0.67
120	99	0.02	6.0	12	40	28	24	8	−28	−24	0.47

[a] $[AC]_0 = 0.25$ mM; irradiated at >320 nm in CH_2Cl_2 at 25 °C. [b] Composition of 1:1 and 2:1 complexes calculated by using $K_1 = 3400\ M^{-1}$ and $K_2 = 100\ M^{-1}$; see Figure S8 and Table S3 in the Supporting Information. [c] Enantiomeric excess determined by chiral HPLC (error in ee ≤2%); the negative ee indicates the favored formation of the second-eluted enantiomer; for the absolute configurations of **2** and **3**, see: Wakai, A.; Fukasawa, H.; Yang, C.; Mori, T.; Inoue, Y. *J. Am. Chem. Soc.* **2012**, *134*, 4990 and 10306. [d] HH/HT = ([**3**] + [**4**])/([**1**] + [**2**]).

environment in the ground state and then to control the stereochemical fate of confined substrate(s) in the excited state. The chiral H-bonding template is a simpler, yet effective, tool for manipulating the stereochemical outcomes of photochirogenic reactions.[5−7] In this strategy, the chiral template shields one of the enantiotopic faces of a prochiral substrate to block the intra- or intermolecular attack of a built-in or external reagent, facilitating the attack from the open face to give chiral photoproduct(s) often in good−high optical yields.[5,7]

In our recent work on enantiodifferentiating photocyclodimerization of 2-anthracenecarboxylic acid (AC) mediated by 4-amino-5-chloro-2-methoxy-*N*-((2*S*,4*S*)-(1-ethyl-2-hydroxymethyl-4-pyrrolidinyl))benzamide (TKS-159) (Scheme 1),[7] we have shown that TKS forms a 1:1 complex with AC through a unique hydrogen-bonding motif incorporating the TKS's prolinol and the AC's carboxyl. In the photocyclodimerization experiments, we used high TKS/AC ratios of 3 to 120 in order to secure the >99% complexation and obtained cyclodimers **2** and **3** in comparable enantiomeric excesses (ee) of 40% upon irradiation at >320 nm in dichloromethane at −50 °C.[7b] Further photophysical studies revealed the existence of diastereomeric *re*- and *si*-[AC•TKS] precursor complexes, which differ in fluorescence maximum and lifetime.[7b]

Scheme 1. Complexation and Photocyclodimerization of AC with Chiral Hydrogen-Bonding Template TKS159



In our effort to elucidate the detailed complexation and photochirogenic behaviors of AC with TKS, we examined the effects of AC:TKS stoichiometry on product ratio and ee, which led us to the unexpected results shown in Table 1 (where the conversion was kept low (≤12%) to avoid any significant deviation from the initial stoichiometry). As anticipated, the absolute ee of **2** smoothly increased with increasing concentration of TKS, more exactly the concentration of the [AC•TKS] complex or % AC complexed. However, the ee of **3** stayed low (<10%) until 90% of the AC in the solution formed the complex; see Table 1 and Figure S1a in the Supporting Information (SI). The ratio of head-to-head (HH) and head-to-tail (HT) dimers, ([**3**] + [**4**])/([**1**] + [**2**]), also exceeded unity at 20−80% complexation despite the steric repulsions in HH dimers, showing a bell-shaped dependence on % AC complexed (Figure S1b in SI). These results indicate that, at TKS/AC = 0.5−10, some additional AC-TKS species is formed in the solution to predominantly afford HH dimers, in paticular racemic or antipodal **3**, upon irradiation.

In our previous study,[7b] we determined the complex stoichiometry as 1:1 by the Job analysis of the ellipticity (θ) induced at the 0−0 band of the AC's ^1L_b band upon

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complexation with TKS in dichloromethane at a total concentration of 1 mM. Under the conditions employed, the CD spectral examination was feasible only up to the AC fraction (x) of 0.7, due to the precipitation of AC at higher x. Although the θ value at $x = 0.7$ was slightly smaller than expected, the Job plot gave a peak at $x = 0.5$, indicating the 1:1 complexation; see Figure S2 in SI.

In the present study to gain further insight into the AC-TKS species involved in this system, we reexamined the complex stoichiometry by performing the Job analysis of the ellipticity changes caused at the main band of AC at two different total concentrations. This enabled us to disclose the existence of an unprecedented 2:1 AC-TKS complex, which is practically "invisible" by conventional UV−vis, fluorescence, or NMR spectral examination due to the low abundance, but detectable spectroscopically by inspecting the CD spectral changes at the main band and also photochemically by closely examining the photochirogenic behavior, both of which are exaggerated by the proximity of two ACs in the 2:1 complex.

First, the CD spectral Job experiment was run at a low total concentration of 0.3 mM by changing x from 0 to 1 to afford the spectral changes shown in Figure 1a. Although TKS showed positive inherent Cotton effects at 255 and 304 nm, the addition of AC induced much stronger CD signals at the ^1B_b band (230−285 nm) as a result of exciton coupling of AC with TKS, while the CD signals induced at the $^1L_a/^1L_b$ bands (320−400 nm) were much weaker. The normalized CD spectra at $x = 0.2$−0.8 were superimposable to each other (Figure S3 in SI), indicating the predominant contribution of a single species, which is assignable to the stoichiometric 1:1 complex, as the Job plot (Figure 1a, inset; for the original data, see Table S1 in SI) reached the extremum at $x = 0.5$.

Unexpectedly, the Job analysis at a higher total concentration of 0.75 mM led to significantly different results. Thus, the CD spectral profile critically varied with x. As shown in Figure 1b (for a full series of the spectral changes, see Figure S4 in SI), the CD spectrum was identical in shape to that obtained at 0.3 mM (Figure 1a) at least up to $x = 0.33$, but intriguingly the negative extremum at 259 nm gradually blue-shifted to reach 253 nm at $x = 0.67$−0.8, leaving a shoulder at ca. 267 nm. This unusual CD spectral change and the irregular Job plot (Figure 1b, inset), specifically at higher x, are explainable by postulating the coexistence of an AC-rich complex species in the system.

It is also crucial to compare the Job plots obtained by monitoring the ellipticity changes at different wavelengths. In sharp contrast to the irregular shape change observed at the main band, the CD spectrum in the $^1L_a/^1L_b$ region never changed shape (Figure S5a in SI) and the Job plot monitored at 388 nm showed a normal symmetrical shape with a maximum at $x = 0.5$ (Figure S5b in SI), indicating the 1:1 stoichiometry, under exactly the same conditions. This apparent discrepancy is rationalized by assuming that the AC-rich species is low in quantity and detectable only through the exciton coupling of the allowed AC transitions.

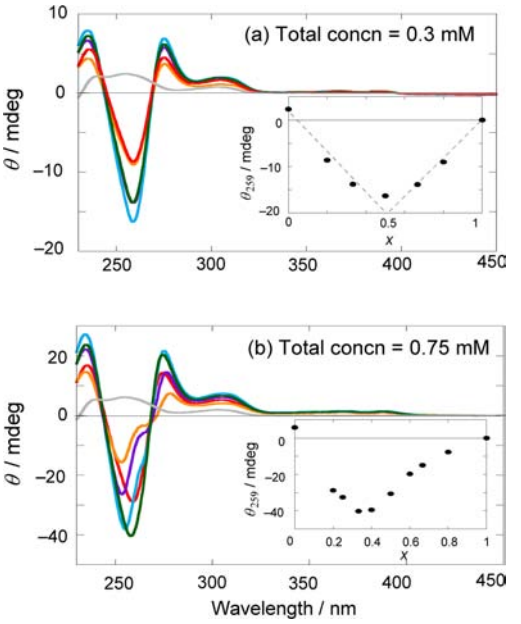

Figure 1. (a) CD spectra of AC/TKS mixtures in dichloromethane (25 °C) at various AC fractions (x) of 0 (gray), 0.2 (red), 0.33 (green), 0.5 (blue), 0.67 (purple), and 0.8 (orange); initial total concentration $[AC]_0 + [TKS]_0 = 0.3$ mM (fixed). (b) CD spectra obtained at $[AC]_0 + [TKS]_0 = 0.75$ mM (fixed). Insets: Job plots of the ellipticity monitored at 259 nm.

In order to elucidate the stoichiometry and quantity of the AC-rich species existing in the solution, we calculated the CD intensity of the 1:1 complex to be formed at each x by using the 1:1 binding constant ($K_1 = 3400\ M^{-1}$),[7b] without taking into account the AC-rich species. This allowed us to obtain a hypothetical Job plot for the 1:1 complex at 0.75 mM (Figure 2a, triangle), which differed substantially from the experimental one (Figure 2a, circle) as a consequence of the significant contribution of the exciton-coupling interaction in the AC-rich species. The hypothetical CD intensity of a 1:1 complex was subtracted from the experimental one to give a Job plot for the AC-rich species (Figure 2a, square; see Table S2 in SI for the original data) with a maximum at 0.67, indicating the 2:1 AC-TKS stoichiometry for the AC-rich species. More crucially, subtraction of the hypothetical from the experimental spectrum enabled us to speculate the CD spectrum of the 2:1 complex at each x (Figure 2b), which is opposite in sign to that of the 1:1 complex. The spectra thus obtained were practically identical in shape (Figure 2b, inset) despite the total ignorance of the 2:1 species in the calculation, revealing its marginal quantity in the solution.

In order to more quantitatively discuss the amount of the 2:1 complex, CD spectral titration of a dichloromethane solution of AC with TKS was performed (Figure S7) and the ellipticity changes obtained were analyzed using a sequential 1:1 and 2:1 complexation model with K_1 fixed at $3400\ M^{-1}$[7b] to afford the second binding constant: $K_2 = 100 \pm 600\ M^{-1}$. By using these equilibrium constants, the

abundance of a 2:1 complex was evaluated to be < 1% under the irradiation conditions (Table 1), which however significantly affects the stereochemical outcomes of photocyclodimerization affording more HH dimers and antipodal **3**.

Although the low concentration of the 2:1 complex did not allow us to directly determine the structure by conventional methods, the inverted HH/HT preference and the deviation of the ee of **3** from that of **2** at the intermediate AC/TKS ratios indicate that two AC molecules are oriented head-to-head and the enantioface selectivity of two facing ACs is significantly lowered or even inverted in the 2:1 complex. These implications allowed us to build a plausible model of the 2:1 complex derived from the hydrogen-bonding and $\pi-\pi$ stacking interactions of a 1:1 complex with a second AC (for representative conformers, see Figure S9). DFT-D3 calculations at the B-LYP/def2-TZVP level on all possible conformers of the 2:1 complex revealed that the *si-si* conformer, a precursor to the first-eluted **3** ($\mathbf{3}_+$), and the *si-re* conformer, a precursor to **4**, account for 59% and 38% of the populated conformers, while the *re-re* conformer accounts for only 2% (Table S4). Thus, the major enantiomer ($\mathbf{3}_-$) is derived from the *re-re* attack of the 1:1 complex, while the antipodal $\mathbf{3}_+$ is formed from the intracomplex *si-si* attack in the 2:1 complex, the contribution of which becoming more significant to cause the deviations of the ee of **3** and the HH/HT ratio at the intermediate AC/TKS ratios (Table 1). It is interesting to note that the photodimerization of the 1:1 complex is bimolecular in nature, while the reaction is unimolecular for the 2:1 complex. This difference in molecularity could be exploited as a more general tool to enhance one of the reactions over the other.

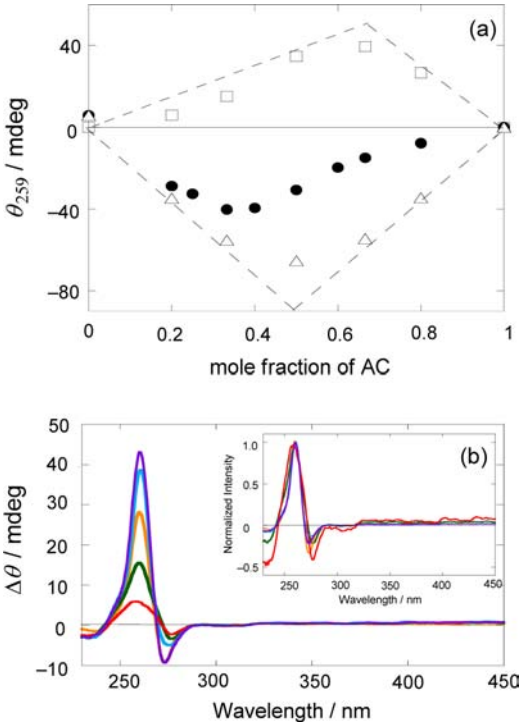

Figure 2. (a) Job plots of the experimental θ_{259} (circle) and the hypothetical θ_{259} (triagle) calculated for the 1:1 complex to be formed at 0.75 mM by using K_1 (3400 M^{-1})[7b] and the experimental θ obtained at 0.3 mM, where only a 1:1 complex is formed; for the details of the calculation, see Table S2. The subtraction of the former from the latter value at each x afforded the Job plot for the AC-rich species (square), which shows a peak at $x = 0.67$, indicating the 2:1 stoichiometry. (b) The CD spectra of the 2:1 complex obtained by spectral subtraction of the hypothetical CD spectrum of the 1:1 complex calculated by using K_1 as above from the experimental θ at each x; the inset shows the normalized subtraction spectra, which are practically identical to each other in shape, validating the calculation without taking into account the 2:1 species.

In this study, the existence of the 2:1 complex of AC with 4-benzamidoprolinol TKS159 was revealed by the observation of the unusual CD spectral and photochirogenic behavior, both of which are highly sensitive to the interchromophore distance, leading to the exciton coupling as well as the accelerated photocyclodimerization. The formation of such a higher order hydrogen-bonding complex has not been reported and is interesting and advantageous from stereochemical and photochirogenic points of view as a tool for accelerating and sterically controlling the photocyclodimerization of various arenecarboxylic acid substrates through the formation of an HH-oriented 2:1 substrate−host complex. This strategy is expandable to other chiral host−guest systems, and work along this line is currently in progress.

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Supporting Information Available. Experimental details, spectral examinations, and DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.