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γ-Cyclodextrin-Directed Enantioselective Photocyclodimerization of Methyl 3-Methoxyl-2-naphthoate

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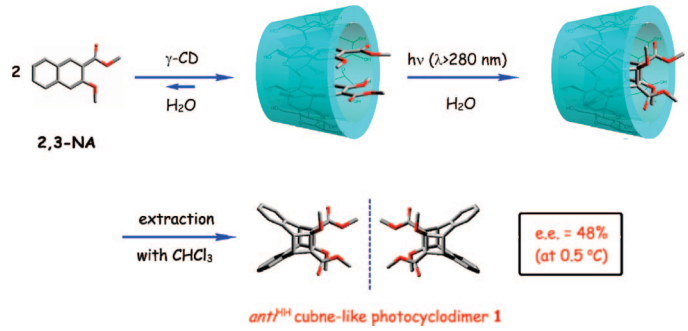

Irradiation of methyl 3-methoxyl-2-naphthoate (**2,3-NA**) in methanol solution with light $\lambda > 280$ nm produces *anti*-head-to-head cubane-like photocyclodimer **1** and [4+4] intermediate **2**, which is, to the best of our knowledge, the first incidence of directly obtaining the intermediate in photocyclodimerization of naphthalene analogues. X-ray crystal structural analysis has realized the chirality of **1**, and the optically pure enantiomers $\mathbf{1_a}$ and $\mathbf{1_b}$ have been achieved by HPLC resolution. To understand the fundamental photocyclodimerization of naphthalene analogues mediated by native γ-CD, the neutral **2,3-NA** was selected as a typical reactant in this work. UV−vis, fluorescence, and ^{1}H NMR analysis reveal that γ-CD can encapsulate **2,3-NA** to make a stable 2:1 inclusion complex **2,3-NA**@γ-CD both in aqueous solution and in the solid state. Irradiation of **2,3-NA**@γ-CD results in photocyclodimerization with remarkable selectivity and efficiency, whereas no photocyclodimers could be detected in host-free aqueous solution and the neat solids. More importantly, the use of native γ-CD as a chiral reaction vessel turns out to be an effective and versatile strategy for the enantioselective photocyclodimerization of **2,3-NA**. The ee values of 48% in aqueous solution and up to 34% in the solid state for *anti*-head-to-head photocyclodimer **1** have been achieved upon irradiation of the inclusion complex of **2,3-NA**@γ-CD under ambient temperature and pressure. All of the observations indicate that native γ-CD with hydrophobic interaction only is capable of regulating the orientation of naphthalene analogue **2,3-NA** within the cavity of γ-CD, and thereby leading to the highest ee value of 48% obtained so far for the photocyclodimerization with native γ-CD in solution.

Introduction

Enantioselectivity of chemical reactions has always been an important concern of chemists. While many elegant and efficient strategies have been developed for a variety of thermal reactions, there are few examples in photochemical transformations.[1] Short excited state lifetime and low activation energy for reactions in excited states leave little room for manipulating the diastereomeric transition state when a photochemical reaction is carried out in solution. It has therefore long been believed that the critical and precise control of asymmetric photochemical reactions is rather challenging.

Following the communication by Hammond and Cole in 1965,[2] several groups have dedicated themselves to the im-

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provement of the enantio- and diastereoselective phototransformations both in solution and in the solid state.[1−5] The use of supramolecular chiral systems was recently demonstrated to be an intriguing access to chiral phototransformation. By virtue of multiple intermolecular interactions, supramolecular chiral systems are able to associate with the substrate in both the ground and excited states, and thus photochemically deliver chiral information from a chiral entity to a prochiral substrate.[1,6−14] As exemplified in the literature, Toda and Tanaka et al.[6] applied chiral organic hosts to make host−guest cocrystals and then obtained high enantiodifferentiation of achiral compounds. Scheffer et al.[7] introduced the ionic chiral auxiliary concept to solid asymmetric photochemistry. Ramamurthy et al.[8] reported a series of photochemical reactions in chirally modified supercages of zeolites. Bach et al.[9] took advantage of hydrogen bonding interactions of Kemp's chiral triacid derivatives with prochiral substrates to achieve a high stereoselectivity. Inoue et al.[10−14] made use of native and modified cyclodextrin (CDs), and even DNA and protein as chiral hosts to improve the stereoselective phototransformations. Their achievements demonstrate that the chirality control in the excited state is a fascinating subject even though the enantiomeric excesses (ee) obtained in solution under ambient temperature and pressure are still low.

Cyclodextrin (CD) represents an important class of molecular reaction vessels that are cyclic oligosaccharides consisting of six, seven, and eight D-glucose units joined by α-1,4-linkages for α-, *β*-, and *γ*-CD, respectively. Owing to unique characteristics of good solubility in water, ready availability, inherent chirality, and transparence in UV−vis regions, CD has the remarkable property of accommodating various organic molecules in an aqueous solution by hydrophobic interaction and has been extensively used to improve the efficiency and selectivity of chemical reactions.[15−22] Since *γ*-CD is able to accommodate two molecules of aromatic compound within its chiral cavity, regio- and stereoselective photocyclodimerization between two substrates both in solution and in the solid have been achieved in the presence of *γ*-CD.[12−14,19−21] The most representative example is the enantioselective [4+4] photocyclodimerization of 2-anthracenecarboxylic acid by using *γ*-CD as a template.[12−14] Tamaki[13] realized in 1984 that the prochiral 2-anthracenecarboxylic acid was photodimerized to form dimers including chiral forms in a *γ*-CD aqueous solution, but until 2003 Nakamura and Inoue[12] reported in detail that the irradiation of 2-anthracenecarboxylic acid affords four configurational isomers, among which *syn*-head-to-tail and *anti*-head-to-head cyclodimers are chiral, while *syn*-head-to-head and *anti*-head-to-tail cyclodimers are achiral. It is important that they succeeded in chromatographic resolution of chiral photocyclodimers of 2-anthracenecarboxylic acid photochemically produced in the presence of native *γ*-CD. The enantiomeric excess (ee) value of *syn*-head-to-tail photocyclodimer was 32% in aqueous solution at 25 °C but was enhanced to 41% at 0 °C, while the ee of *anti*-head-to-head photocyclodimer was always less than 5%. Native *γ*-CD with hydrophobic interaction only was believed to be insufficient for precisely regulating the orientation of guests within the CD cavity. To achieve a high level of control of the photocyclodimerization, the framework of *γ*-CD was modified with rigid and flexible caps or cationic side arms to manipulate the preorganization of two 2-anthracenecarboxylic acid molecules by multiple intermolecular interactions.[14] The results demonstrate that even a trivial modification of native *γ*-CD can critically manipulate the stereochemical outcomes of the photocyclodimerization of 2-anthracenecarboxylic acid.

These successful examples stimulated us to initiate a study on the photocyclodimerization of naphthalene derivatives. Although the photocyclodimerization of anthracenes derivatives is one of the most established photochemical reactions,[1,12−14] the photochemical cyclodimerization of naphthalene analogues is quite limited in scope. Unlike anthracene, naphthalene itself does not undergo photocyclodimerization. Only some substituted naphthalene derivatives have been reported to give cubane-like photocyclodimers,[23−27] which may provide an effective protocol for making the strained cage of functionalized cubane molecules[28] that cannot be directly obtained by thermal reaction. Very recently, we found that the rigid cubane-like photocyclodimer of methyl 2-naphthoate[26] is actually a new type of

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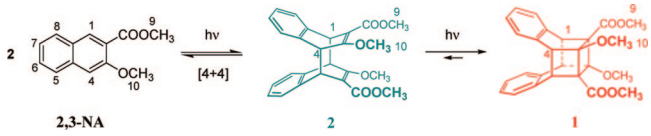
C_2-symmetric-chiral compound. Particular interest in the chirality control in the excited state prompted us to examine whether γ-CD could be used as a template for enantioselective photocyclodimerization of naphthalene derivatives. Much to our surprise, although the remarkably enhanced excimer formation of naphthylacetate derivatives in γ-CD and modified γ-CD has been realized,[29] the γ-CD-induced photocyclodimerization of naphthalene analogues has never been reported.

To understand this photocyclodimerization mediated by γ-CD, methyl 3-methoxyl-2-naphthoate (**2,3-NA**) was selected as a typical reactant in this work because (1) a reasonable solubility of neutral **2,3-NA** in an aqueous solution may allow a deep penetration to facilitate the interaction between the substrate and γ-CD, (2) the size of **2,3-NA** in longitude is shorter than that of 2-anthracenecarboxylic acid, and as a consequence, the interaction between the substrate and the chiral source, as well as stereoselectivity of the photocyclodimerization are expected to be different from those of 2-anthracenecarboxylic acid, and (3) the neutral feature renders the possibility to examine whether native γ-CD with hydrophobic interaction only can regulate the orientation of guests within the CD cavity, and hence direct the photocyclodimerization of **2,3-NA** to the desired products. In the present work, we report that this is indeed the case. The use of native γ-CD as a chiral reaction chamber turns out to be an effective and versatile strategy for the efficient and enantioselective photocyclodimerization of **2,3-NA**. The ee values of 48% in aqueous solution and up to 34% in the solid state for *anti*-head-to-head photocyclodimer **1** have been achieved upon irradiation of the inclusion complex of **2,3-NA**@γ-CD under ambient temperature and pressure, whereas no photocyclodimer could be detected in host-free aqueous solution and the neat solids.

Results and Discussion

1. Photocyclodimerization of 2,3-NA in Organic Solvents: Formation and Chirality of Cubane-like Photocyclodimer 1. Methyl 3-methoxyl-2-naphthoate (**2,3-NA**) was reported to form a photocyclodimer in 1976.[24] On the basis of the MS, IR, and ^{1}H NMR spectra, Sasse and co-workers assigned the cubane-like structure **1** to the photocyclodimer (Scheme 1). Since then, there has been no detailed reference to this reaction. Considering that neutral **2,3-NA** has a better solubility in an aqueous solution,[24] we reinvestigated this photochemical reaction in organic solution.

SCHEME 1. The Two-Photon Photocyclodimerization of 2,3-NA



The photochemical reaction was carried out at room temperature in a Pyrex tube with a 500-W high-pressure mercury lamp as a light source. As the irradiation of **2,3-NA** in degassed methanol (0.25 M) with $\lambda > 280$ nm was going on, white solids were gradually precipitated from the solution. Upon 3 h of irradiation, the reaction mixture was separated by column chromatography on silica eluted with petroleum ether/ethyl acetate (20/1 in volume) and dichloromethane to afford unreacted starting material of **2,3-NA** and photoproducts, respectively. The obtained products were subject to separation by HPLC on an achiral Intersil ODS-3 semipreparative column. As shown in Figure 1, compounds **1** (r.t. $\approx$ 21 min) and **2** (r.t. $\approx$ 23 min) were obtained as the photoproducts except for a small remnant of the starting material **2,3-NA** (r.t. $\approx$ 27 min). Table 1 listed the product distribution of the photocyclodimerization. In methanol the conversion of the starting material (**2,3-NA**) was close to 37% upon 3 h of photolysis, and the yield of **1** and **2** was 55% and 45%, respectively. The material balance was greater than 95%.

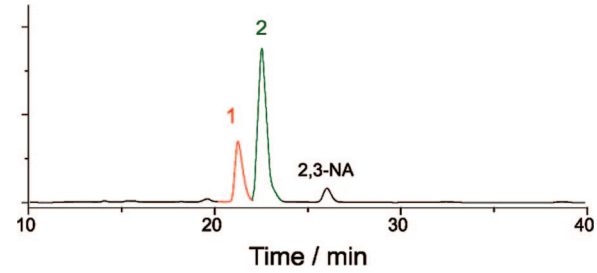


FIGURE 1. Typical HPLC chromatogram on an Intersil ODS-3 semipreparative column: the photoproducts resulted from irradiation of **2,3-NA** in methanol (UV detection at 260 nm; eluent 6:4 acetonitrile/water; flow rate 2 mL/min).

TABLE 1. The Conversion and Yield, Quantum Yield, and Enantiomeric Excess (ee) Value of Photocyclodimerization of 2,3-NA in Methanol and Aqueous Solution and in the Solid State

conditions		T_{irr} [h]	connversion[f] [%]	Φ_1[g] [%]	yield [%][h] 1	2	3	4	ee of 1 [%]
25 °C	methanol[a]	3	37	0.6	55	45			0
25 °C	aqueous[b]	3	0						
25 °C	neat solid[c]	6	0						
25 °C	aqueous[d]	3	74	8.2	85	12	<2		27
	solid[e]	6	68		78	10	<2	8	23
15 °C	aqueous[d]	3	70		87	11	<2		34
	solid[e]	6	69		76	11	<2	9	26
5 °C	aqueous[d]	3	79		84	12	<2		45
	solid[e]	6	67		80	10	<2	8	32
0.5 °C	aqueous[d]	3	72		83	13	<2		48
	solid[e]	6	66		79	9	<2	9	34

[a] **2,3-NA** in methanol solution (0.25 M). [b] **2,3-NA** in aqueous solution (ca. 1.8×10^{-4} M). [c] Neat **2,3-NA** in the solid state was irradiated for 6 h. [d] **2,3-NA**@γ-CD in an aqueous solution (4.4×10^{-4} M **2,3-NA** and 8.8×10^{-4} M γ-CD). [e] **2,3-NA**@γ-CD in the solid state. [f] Conversion of **2,3-NA** after irradiation; it can be calculated in terms of the change of absorbance in UV−vis spectra or HPLC separation. [g] The quantum yields for photocyclodimer **1** formation were determined by using the conversion for the photodimerization less than 15% at room temperature. [h] The relative yield of product can be determined according to the relatively integral area of corresponding peak by HPLC.

The parent ion peak ([M+Na$^+$], 455) in the MS (ESI) establishes the dimeric nature of products **1** and **2** (Supporting Information). The NMR investigation and crystal structural analysis (Figures S1, S2, and S12, Supporting Information) evidence that photocyclodimer **1** has a cubane-like framework with C_2-symmetry similar to that of methyl 2-naphthoate,[26] while **2** does not. Examination of ^{1}H NMR spectra reveals that **2** contains 16 aliphatic and 8 aromatic protons (Figure 2, also Figure S3 in the Supporting Information). A comparison with **1** reveals that the signal peaks for the 8 aromatic protons of **2** are upfield shifted from 6.99 to 6.76 ppm, while those for the 12 aliphatic prontons (H9$_{a,b,c}$, H9′$_{a,b,c}$ and H10$_{a,b,c}$, H10′$_{a,b,c}$) as well as the 4 bridged protons (H1, H1′, H4, H4′) are downfield shifted from 3.81−3.09 ppm and 4.42−4.20 ppm to 3.99−3.76

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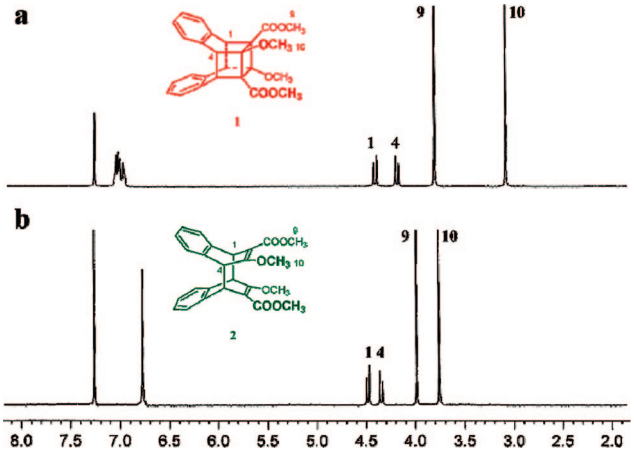


FIGURE 2. ^{1}H NMR spectra in $CDCl_3$ of (a) cubane-like *anti*-head-to-head photocyclodimer **1** and (b) *anti*-head-to-head [4+4] intermediate **2**.

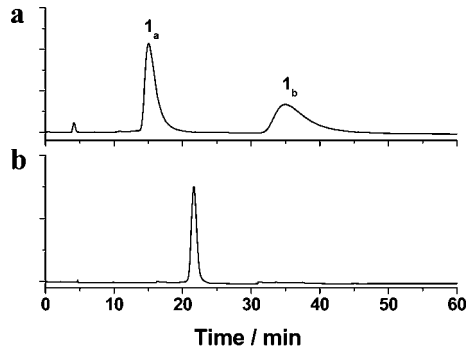


FIGURE 3. Typical HPLC chromatograms of (a) photocyclodimer **1** on a chiralcel OJ-H analytic column (UV detection at 220 nm; eluent 7:3 *n*-hexane/isopropanol; flow rate 0.8 mL/min) and (b) photocyclodimer **1** on an ODS-3 semipreparative column (UV detection at 260 nm; eluent 6:4 acetonitrile/water; flow rate 2 mL/min).

ppm and 4.48−4.34 ppm, respectively. Since **2** was unstable and could decompose to starting material of **2,3-NA**, combined with the fact that some of **1** was transformed to **2** caused by storing for 1−2 months in organic solution, we speculated that **2** should be an intermediate of **1**, namely *anti*-head-to-head [4+4] photocyclodimer, during the photoirradiation of **2,3-NA**. This is coincident with the claim that the formation of the cubane-like photocyclodimer of naphthalene analogue is a two-photon process.[25] That means **2,3-NA** absorbs the first photon to give a [4+4] cycloaddition product **2**, which subsequently either undergoes thermal dissociation to give **2,3-NA** or produces the cubane-like photocyclodimer **1** through absorption of the second proton, as shown in Scheme 1. This is, to the best of our knowledge, the first incidence of directly obtaining the intermediate of cubane-like photocyclodimer from the naphthalene analogue.

It is of significance that the optically pure enantiomers of **1** can be obtained by HPLC resolution. The resolution was carried out on a chiralcel OJ-H column (UV detection at 220 nm; eluent 7:3 *n*-hexane/2-propanol; flow rate 0.8 mL/min). Figure 3 shows two product peaks of **1** (first eluting $\mathbf{1_a}$ and second eluting $\mathbf{1_b}$) with identical peak areas in magnitude within experimental error. The chromatogram displays only one product peak when the acetonitrile solution of **1** is analyzed by HPLC with use of an achiral Intersil ODS-3 semipreparative column. The isolated enantiomers of $\mathbf{1_a}$ and $\mathbf{1_b}$ show near mirror image behavior in

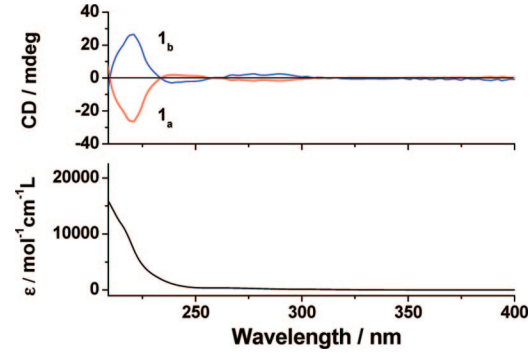


FIGURE 4. The circular dichroism (top) and absorption (bottom) spectra of enantiomers $\mathbf{1_a}$ (5.2×10^{-5} M) and $\mathbf{1_b}$ (6.0×10^{-5} M) in acetonitrile/water (6:4 in volume), respectively.

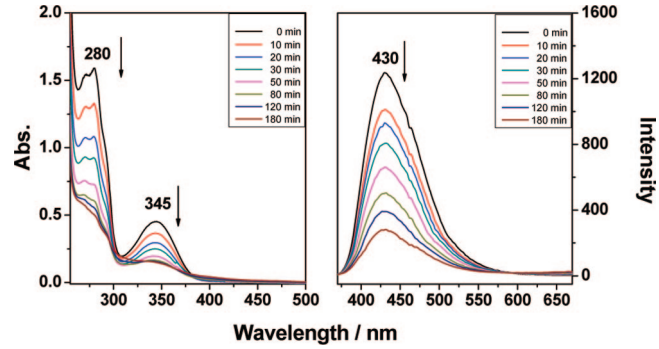


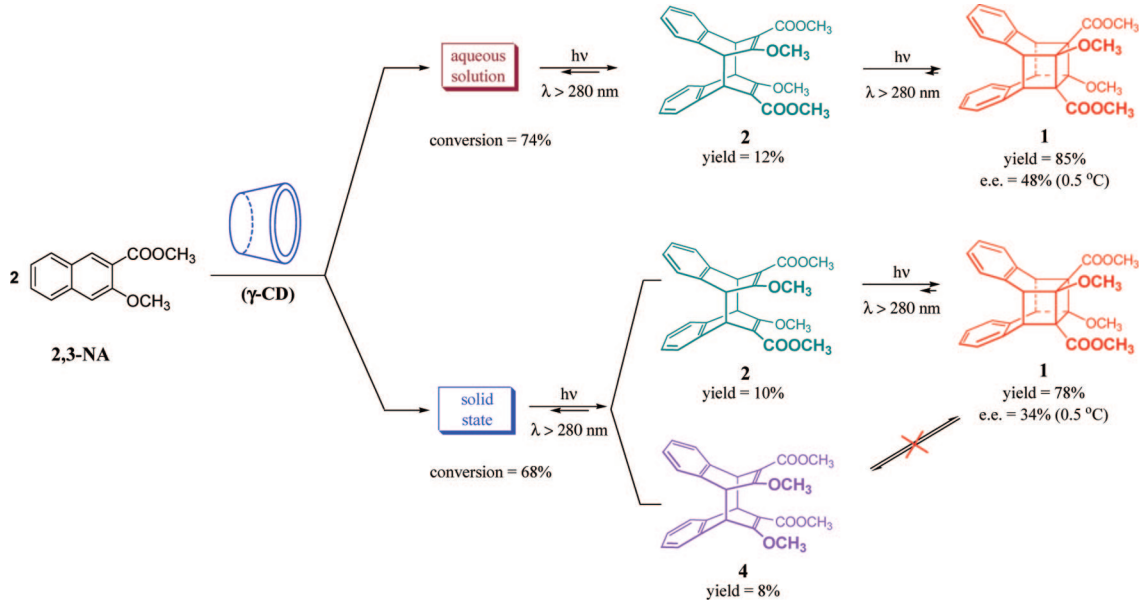
FIGURE 5. The absorption spectra (left) and emission spectra (right) of **2,3-NA** (2.2×10^{-4} M) with γ-CD (4.4×10^{-4} M) in an aqueous solution as a function of irradiation time.

the circular dichroism (CD) spectra, while their UV−vis absorption spectra are not distinguishable from each other (Figure 4). These results inerrably bear out the chirality of **1**.[30] Moreover, the optically pure enantiomers of **1** [$\mathbf{1_a}$ $[\alpha]^{20}_D$ −34.3 (*c* 5.8 mg/mL, acetonitrile), $\mathbf{1_b}$ $[\alpha]^{20}_D$ +34.2 (*c* 6.1 mg/mL, acetonitrile)] have been successfully obtained by HPLC resolution.

2. Photocyclodimerization of 2,3-NA in γ-CD Aqueous Solution. To examine whether γ-CD can direct the enantioselective photocyclodimerization of naphthalene series, we prepared an inclusion complex of **2,3-NA**@γ-CD by sonication of **2,3-NA** with 2 equiv of γ-CD aqueous solutions for 2 h. After filtering the solids, the saturated solution was purged with nitrogen and then irradiated with light $\lambda > 280$ nm in order to protect photocyclodimers from decomposition. The photochemical transformation was followed by UV−vis and fluorescence spectra. The absorbance and fluorescent intensity at the typical bands for **2,3-NA**@γ-CD quickly decreased along with irradiation. Figure 5 shows the absorption and fluorescence spectra of the aqueous solution of **2,3-NA**@γ-CD as a function of irradiation time at room temperature. Generally after 3 h of irradiation the conversion was determined to be 74% based on the decrease of the absorbance or fluorescent intensity, and the combined yield of the products was greater than 95% based on the consumption of the starting materials. The reaction mixture was extracted with chloroform and subject to HPLC separation on an achiral ODS-3 semipreparative column. As shown in Figure 6, the product analyses before and after irradiation clearly

(30) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994.

SCHEME 2. γ-CD-Directed Photocyclodimerization of 2,3-NA in Aqueous Solution and in the Solid State



show that **2,3-NA** undergoes photocyclodimerization to afford the cubane-like photocyclodimer **1**, [4+4] intermediate **2**, and unknown compound **3** (r.t. $\approx$ 32 min) in the presence of γ-CD. With respect to the correlations of the product distribution, the influence of γ-CD on the photocyclodimerization is indeed crucial. It is evident that the yield of photocyclodimer **1** is much improved from 55% in methanol to 85% in an aqueous solution by γ-CD, while that of **2** decreases from 45% to 12% (Table 1). In spite of the ratios changing with the media, **1** and **2** were obtained exclusively throughout the irradiation. On the basis of the consumption of the starting material, the yield of **1**, **2**, and **3** was determined by HPLC separation being 85:12:<2 upon 3 h of irradiation. ^{1}H NMR and UV−vis spectroscopic investigations suggest that **3** is derived from the rearrangement of **2,3-NA** (Figures S4 and S16, Supporting Information); however, its proportion is too small (<2%) to be identified. The quantum yield for photocyclodimer **1** formation in the presence of γ-CD is ca. 14 times higher than that obtained in methanol (Table 1). The difference in the ratio of **1** to **2** (ca. 8:1 in γ-CD aqueous solution but 1:1 in methanol) indicates that irradiation of **2,3-NA** in γ-CD aqueous solution results in photocyclodimerization with remarkable selectivity and efficiency (Scheme 2). γ-CD not only enhances the efficiency of photocyclodimerization but also facilitates the photochemical transformation from *anti*-head-to-head [4+4] intermediate **2** to cubane-like photocyclodimer **1**.

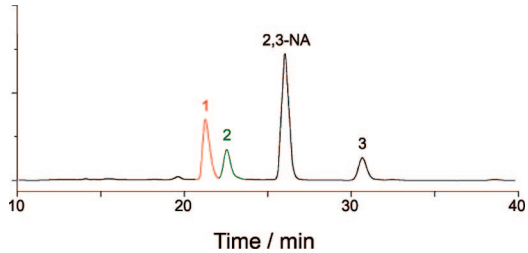


FIGURE 6. Typical HPLC chromatogram on an Intersil ODS-3 semipreparative column: the reaction mixture extracted with chloroform upon irradiation of **2,3-NA@**γ-CD in aqueous solution for 3 h (UV detection at 260 nm; eluent 6:4 acetonitrile/water; flow rate 2 mL/min).

More importantly, the photocyclodimerization of **2,3-NA** in the presence of γ-CD is enantioselective, as indicated in Figure 7. In contrast to the results of host-free solution, the ee value of photocyclodimer **1**, determined by HPLC on a chiral OJ-H column, was obvious. Despite the conversion changing with irradiation time, the ee value of **1** remained almost constant throughout the irradiation periods under the conditions employed and was independent of the concentration of **2,3-NA@**γ-CD. Photolysis of **2,3-NA** in γ-CD aqueous solution at a lower temperature affords enantiomer $\mathbf{1_b}$ as the major product in addition to the decreasing amounts of the other enantiomer $\mathbf{1_a}$ (Figure 7). A significant enhancement of ee value from 27% at 25 °C to 48% at 0.5 °C in aqueous solution was observed (Table 1). By contrast, irradiation of a saturated γ-CD-free aqueous solution of **2,3-NA** led to no photocyclodimer formation, thus excluding the possibility that the asymmetric induction observed in aqueous solution is due to optical resolution of racemic **1** formed during the reaction. From these results, it is clear that the environment of **2,3-NA** during irradiation is a major factor in both the efficiency and selectivity of photocyclodimerization.

3. Inclusion Complex of 2,3-NA@γ-CD Formation. The interaction of γ-CD with **2,3-NA** in aqueous solution was confirmed in terms of fluorescence, UV−vis, and ^{1}H NMR

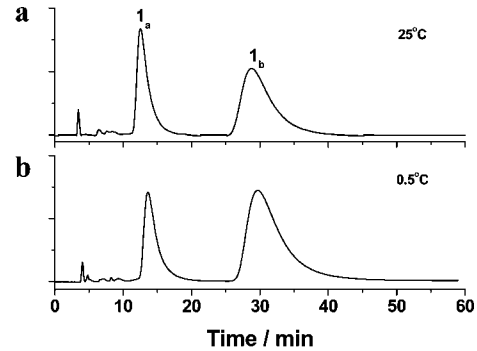


FIGURE 7. Typical HPLC chromatogram of **1** generated from photochemical transformation of inclusion complex **2,3-NA@**γ-CD in aqueous solution at (a) 25 °C and (b) 0.5 °C (OJ-H analytic column; UV detection at 220 nm; eluent 7:3 *n*-hexane/isopropanol; flow rate 0.8 mL/min).

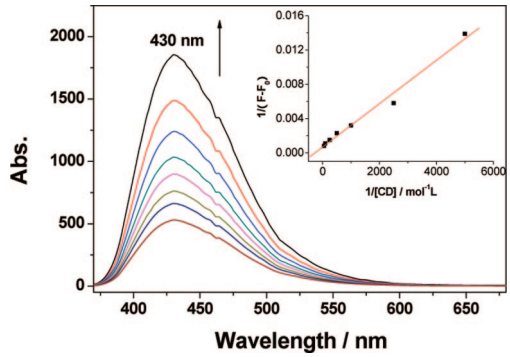


FIGURE 8. The family of fluorescence spectra of 2.0×10^{-7} M of **2,3-NA** aqueous solution at various concentrations of γ-CD ($10^{3}-10^{5}$ M). The insert: plot of the $1/\Delta F_i$ vs. $1/[\gamma\text{-CD}]$.

analysis. Benefiting from the reasonable solubility of **2,3-NA** in water, we carried out the titration experiments in an aqueous solution directly.

The changes in the fluorescence response of **2,3-NA** toward γ-CD were found to be pronounced. In the absence of γ-CD, the fluorescence spectra showed the typical bands of **2,3-NA** centered at 430 nm in an aqueous solution. Introduction of γ-CD into the dilute solution of **2,3-NA** (2.0×10^{-7} M) led to an increase in the fluorescent intensity as excited at 345 nm, while the shape and energy remained unchanged. The family of fluorescence spectra taken in the course of titration is given in Figure 8. The inset in Figure 8 shows the plot[31] of $1/\Delta F_i$ vs $1/[\gamma\text{-CD}]$, where ΔF_i refers to the difference in fluorescence intensity of **2,3-NA** at 430 nm in the presence and absence of γ-CD; [**2,3-NA**] and [γ-CD] are the concentrations of **2,3-NA** and γ-CD, respectively; K_1 is the primary binding constant. A straight line of $1/\Delta F_i$ vs. $1/[\gamma\text{-CD}]$ confirms that the interaction ratio of γ-CD and **2,3-NA** is 1:1. According to eq 1, the primary binding constant K_1 was determined to be 275 M^{-1}.[31]

$$\frac{1}{\Delta F_i} = \frac{1}{K_1 \alpha [2,3\text{-NA}]} \frac{1}{[\gamma\text{-CD}]} + \frac{1}{\alpha [2,3\text{-NA}]} \qquad (1)$$

$$\frac{[2,3\text{-NA}]^2[\gamma\text{-CD}]}{\Delta d} = \frac{1}{K_2 \Delta\varepsilon} + \frac{[2,3\text{-NA}]([2,3\text{-NA}] + 4[\gamma\text{-CD}])}{\Delta\varepsilon} \qquad (2)$$

Similar to the observations by Inoue for the formation of a 2:1 (2-anthracenecarboxylate:γ-CD) inclusion complex,[12] addition of γ-CD to a solution of **2,3-NA** (1.0×10^{-4} M) resulted in a decrease in the absorbance (Figure 9a). A Job plot[13] of the change in the absorption intensity at 345 nm shows a peak at 0.65 meaning that the ratio of [**2,3-NA**]:[γ-CD] = 2:1, when [γ-CD] + [**2,3-NA**] = 0.1 mM (Figure 9b). The spectral features suggest that the major species in this concentration region is 2:1 inclusion complexes. The binding constant K_2 was estimated to be 6.7×10^{6} M^{-2} based on eq 2 developed by Tamaki,[13] where [**2,3-NA**] and [γ-CD] are initial concentrations of **2,3-NA** and γ-CD, respectively. $\Delta\varepsilon$ is the difference of molar extinction coefficients ($\varepsilon_C - 2\varepsilon_{NA}$), and Δd is the absorption intensity change induced by the inclusion complex formation.

The 2:1 inclusion complex of **2,3-NA**@γ-CD in an aqueous solution was also verified by ^{1}H NMR spectroscopic investigation (Figure 10). All the signal peaks for both the aromatic protons of **2,3-NA** and the protons of C3 and C5 in the γ-CD inner cavity in ^{1}H NMR spectra are shifted upfield upon the complexation, indicating that two **2,3-NA** molecules are trapped into the same cavity of γ-CD, and **2,3-NA** is associated with γ-CD intimately. This is also reflected in its ROESY spectrum, in which the correlations between the protons of H3 and H5 in

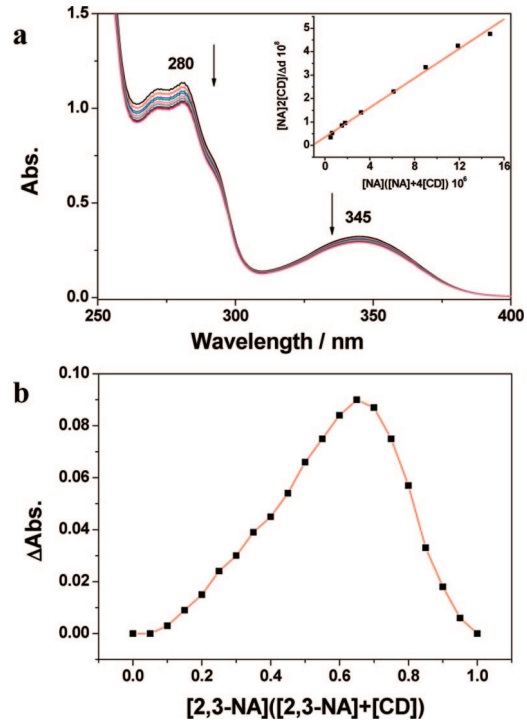


FIGURE 9. (a) UV−vis absorption spectra of a 1.0×10^{-4} M aqueous solution of **2,3-NA** at various concentrations of γ-CD (0.1−10 equiv); the inset is the plot for the estimation of the binding constant for the 2:1 inclusion complexes in aqueous solution. (b) Job plot of the change in the UV−vis absorption spectrum at 345 nm, [**2,3-NA**] + [γ-CD] = 0.1 mM.

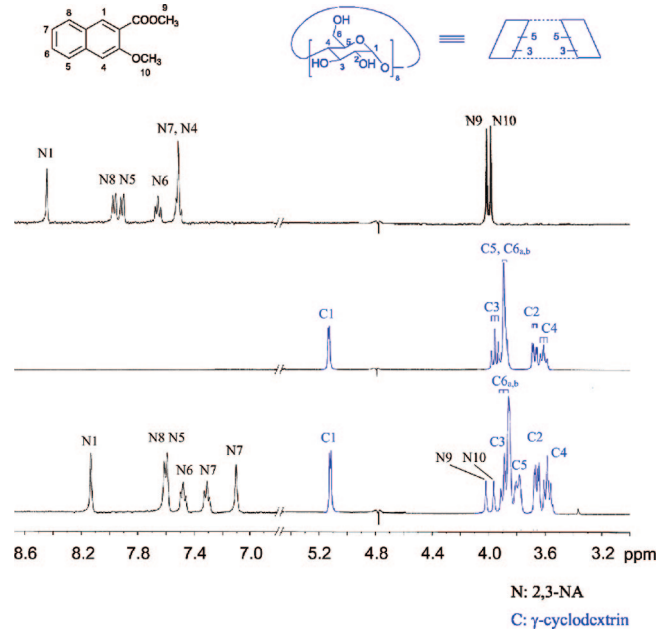


FIGURE 10. The ^{1}H NMR spectra of (a) **2,3-NA** in D_2O; (b) γ-CD in D_2O; and (c) **2,3-NA**@γ-CD in D_2O (4.4×10^{-4} M **2,3-NA**, and 2.4×10^{-4} M γ-CD).

(31) Conners, K. A. *Binding Constants: The Measurement of Molecular Complex Stability*; John Wiley & Sons: New York, 1987.

γ-CD with those of H1, H4 and H5, H8 of **2,3-NA**, respectively, were clearly observed (Figure S7, Supporting Information).

From the binding constants obtained,[31] we can calculate the distribution of free, 1:1 and 2:1 species of **2,3-NA** in the γ-CD aqueous solution (4.4×10^{-4} M **2,3-NA**, and 8.8×10^{-4} M γ-CD), where the 2:1 inclusion complex accounts for more than 93% of the total **2,3-NA** molecules in aqueous solution. Therefore, it is reasonable to consider that the photocyclodimer **1** predominantly derives from the 2:1 inclusion complex of **2,3-NA**@γ-CD. Because (i) no photocyclodimer **1** can be obtained in a γ-CD-free saturated aqueous solution of **2,3-NA** and (ii) the photocyclodimerization from the 1:1 complex should be inhibited by the γ-CD wall, at the same time the photocyclodimerization of **2,3-NA** occurs in the presence of γ-CD even at low concentration, we may deduce that the chiral environment of γ-CD is responsible for this enantioselective photocyclodimerization of **2,3-NA**.

4. Photodimerization of 2,3-NA@γ-CD Inclusion Complex in the Solid State. In principle, solid complexes do not dissociate as they do in solution, and thus the motions of the guest molecules in the cavity of solid complexes should be attenuated. The removal of mobile solvent molecules around the dissolved complex probably imposes additional constrains upon the direction of substrate inclusion in a solid complex. To provide more evidence on the γ-CD-directed enantioselectivity, we investigated the photochemical reaction of the **2,3-NA**@γ-CD inclusion complex in the solid state.

The inclusion complex was precipitated from an aqueous solution of **2,3-NA** with γ-CD. Typically, when a concentrated solution of **2,3-NA** (0.09 mmol/0.2 mL of chloroform) was added to a concentrated solution of γ-CD (0.04 mmol/10 mL) in water and stirred for 24 h, a fine white precipitate formed, which was isolated after thorough washing with ether and cold water to remove the uncomplexed **2,3-NA** and γ-CD, and then dried under vacuum at 60 °C. The white precipitate was believed to be the **2,3-NA**@γ-CD inclusion complex for the following reasons: (i) The **2,3-NA**@γ-CD molar ratio of 1:1.9, measured by dissolving the white precipitate in DMSO-d_6 and integrating their ^{1}H NMR proton signals from the glucose units in the γ-CD (δ 3.5∼3.6 ppm) and the methyl hydrogen of **2,3-NA** (δ 3.9 ppm) (Figure S6, Supporting Information), was highly reproducible from batch to batch; (ii) The **2,3-NA** component could not be removed by extensive washing with ether; (iii) The fluorescence maximum of the solid inclusion complex appeared in 24 nm red shifts as compared with that of neat **2,3-NA** (**2,3-NA**@γ-CD: $\lambda_{max} = 430$ nm; **2,3-NA**: $\lambda_{max} = 406$ nm). The excitation spectra for the neat solid and the inclusion complex, monitored at $\lambda_{em} = 406$ and 430 nm, respectively, are generally similar. However, as shown in Figure S18 in the Supporting Information, the spectra for the **2,3-NA**@γ-CD is evidently red-shifted, indicating that the pairs of naphthalene groups exist prior to the excitation; (iv) the vibration frequency of carbonyl from the IR spectra of the solid complex differs from those of **2,3-NA** (**2,3-NA**@γ-CD: $\upsilon_{C=O} = 1716$ cm^{-1}; **2,3-NA**: $\upsilon_{C=O} = 1730$ cm^{-1}, see Figure S19 in the Supporting Information). All of the observations suggest inclusion complex formation rather than a mechanical mixture of **2,3-NA** and γ-CD.

Irradiation of the solid inclusion complex of **2,3-NA**@γ-CD resulted in photocyclodimerization. For precise comparison, a new batch of **2,3-NA**@γ-CD complex was prepared and divided into two samples. The first sample was used to determine the host/guest ratio. The second sample was transferred to a quartz vessel and irradiated in a self-made reactor at $\lambda > 280$ nm. Generally, after 6 h of irradiation, the reaction sample was dissolved in deionized water, extracted with chloroform by sonication, and then subject to the HPLC analysis similar to that described in γ-CD aqueous solution. As indicated in Figure 11, the four products of **1**, **2**, **3**, and **4** (r.t. ≈ 18 min) were obtained when the reaction mixture was analyzed on an Intersil ODS-3 semipreparative column. In addition to the formation of **1**, **2**, and **3**, **4** could be obtained in a yield of 8% (Table 1). The identity of **4** was supposed to be a photocyclodimer of **2,3-NA** based on the same molecular ion peak of 455.0 observed in HPLC-MS (ESI) (Figure S10, Supporting Information). In view of the fact that (i) **1** stored for a long time cannot convert to **4**; (ii) only irradiation of the inclusion complex of **2,3-NA**@γ-CD in the solid state can afford **4** that is unstable and can transform to the starting material (Scheme 2); (iii) no signal could be read from **4** in the circular dichroism spectra, while the UV−vis spectra of **2** and **4** are quite similar (Figures S15 and S17, Supporting Information), **4** should be an isomeric compound of [4+4] photocyclodimer **2** with a *syn*-head-to-head structure.

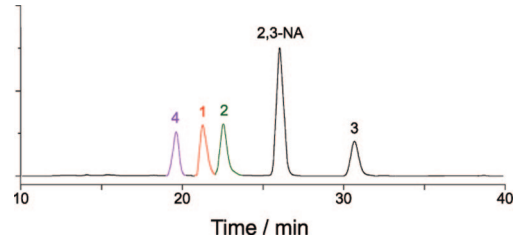


FIGURE 11. Typical HPLC chromatogram on an Intersil ODS-3 semipreparative column: the reaction mixture extracted by chloroform after irradiation of **2,3-NA**@γ-CD in the solid state (UV detection at 260 nm; eluent 6:4 acetonitrile/water; flow rate 2 mL/min).

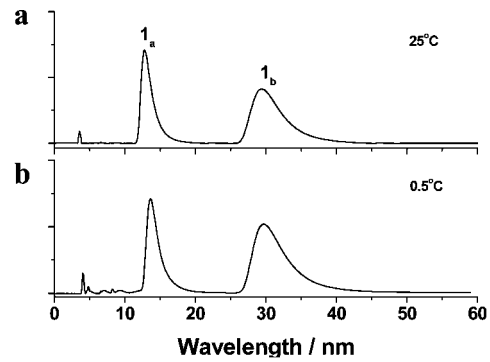
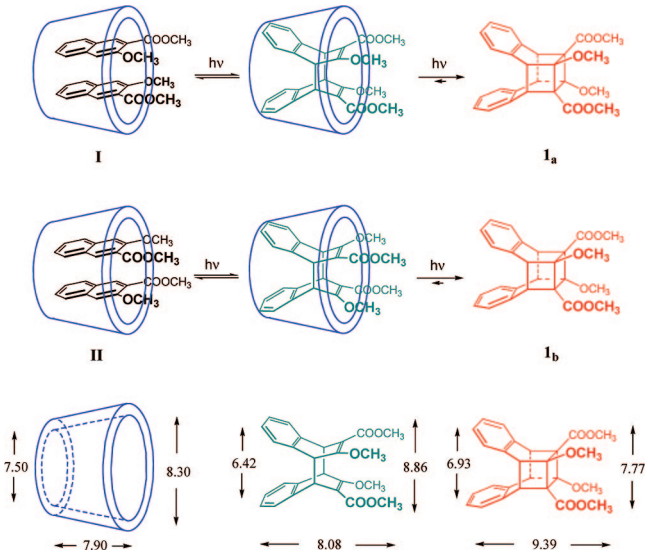


FIGURE 12. Typical HPLC chromatogram of **1** generated from photocyclodimerization of **2,3-NA**@γ-CD in the solid state at (a) 25 °C and (b) 0.5 °C (OJ-H analytic column; UV detection at 220 nm; eluent 7:3 *n*-hexane/isopropanol; flow rate 0.8 mL/min).

The photodimerization of **2,3-NA** in the solid complexes of γ-CD is also enantioselective. Enantiomer $\mathbf{1_b}$ was formed with 23% ee at 25 °C detected by HPLC on a chiral OJ-H column. At lower temperature, photolysis of the inclusion complex of **2,3-NA**@γ-CD affords enantiomer $\mathbf{1_b}$ as the major product in addition to decreasing the amounts of the other enantiomer $\mathbf{1_a}$ (Figure 12). Significant enhancement of the ee from 23% at 25 °C to 34% at 0.5 °C in the solid complex was observed. However, the conversion averages around 68% when irradiation of the solid complex of γ-CD takes place for 6 h, which was more or less reproducible from batch to batch. The relatively low conversion of the photocyclodimerization, determined by

SCHEME 3. The Arrangements of 2,3-NA and 2 in γ-CD



the integral of unreacted **2,3-NA** in HPLC chromatogram, may be rationalized by the fact that not all **2,3-NA** molecules located at the sites within the γ-CD cavity are suitable for the dimerization occurrence. Relative studies[1,15−17] have also shown that the molecular orientation within the cavity of γ-CD can be very complicated. In fact, each inclusion complex should have an average of several orientations. If the orientations of the pair of ground state chromophores in a solid inclusion complex were not suitable for the reaction, the reaction would be suppressed because the motion of **2,3-NA** is highly suppressed. Since photolysis of the neat solids of **2,3-NA** afforded no photocyclodimers, it may be reasonable to conclude that in the inclusion complex with the ratio of 2:1, **2,3-NA** are positioned in close proximity and in fixed orientation to each other. If oriented appropriately, such complexes can lead to efficient photocyclodimer formation upon irradiation.

5. A High Enantioselectivity of Photocyclodimerization of 2,3-NA. The enantiomeric excess of *anti*-head-to-head photocyclodimer **1** induced by native γ-CD obtained during irradiation in an aqueous solution was higher than that reported on the photocyclodimerization of 2-anthracenecarboxylic acid.[12] The improvement of *anti*-head-to-head photocyclodimer from <5% ee for 2-anthracenecarboxylic acid to 48% ee for **2,3-NA** implies that even a small structural difference of substrate, the size of **2,3-NA** in longitude is shorter than that of 2-anthracenecarboxylic acid, can significantly modulate the interaction between the substrate and γ-CD and enables us to obtain unique stereochemical outcomes upon irradiation.

The enantioselectivity of **1** caused by native γ-CD template in this work may be illustrated in Scheme 3. The cavity of γ-CD accommodates two molecules of **2,3-NA** and aligns them in a geometry favorable for the occurrence of photocyclodimerization. As described above, the photocyclodimerization of **2,3-NA** occurs only between the substituted rings and the substitutes in the photocyclodimer are in head-to-tail orientation, there are, hence, only two kinds of isomers orientating either two substituted groups to the open face or the closed face of γ-CD suitable for the photocyclodimerization. On the other hand, the size of **1** (6.93 × 7.77 × 9.39 Å^3) from crystal structure suggests that **1** should tightly fit in the cavity of γ-CD (7.50 × 8.30 × 7.90 Å^3), and can only be accommodated in the cavity from the more open face of γ-CD since the 7.50 Å closed face is too

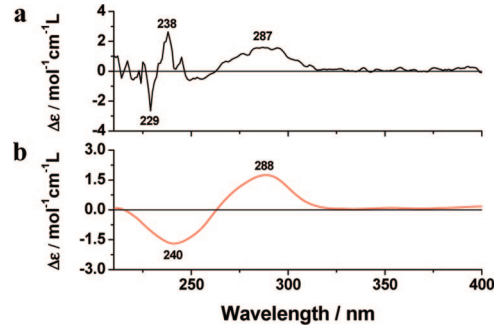


FIGURE 13. The circular dichroism spectra of **2,3-NA**@γ-CD in aqueous solution (a) before irradiation and (b) after 3 h of irradiation ([**2,3-NA**] = 1.1 × 10^{-4} M; [γ-CD] = 5.5 × 10^{-5} M, at room temperature).

narrow for its formation. In this situation, there are two possible arrangements for the substituted groups of adjacent monomers (**I** and **II**).

To shed more light on the interaction between a pair of **2,3-NA** and γ-CD, the circular dichroism spectra before and after irradiation were investigated and are shown in Figure 13. When 2 equiv of **2,3-NA** was added into γ-CD aqueous solution, the induced circular dichroism signal was clearly observed, suggesting that the chiral information of γ-CD was delivered to the included guest molecules. Upon irradiation the circular dichroism signal split and displayed an intense exciton coupling. This finding is therefore indicative that the orientation of the chromophores in the inherent chiral cavity is critically altered during irradiation. The distinct cotton effect reflects much stronger interaction between γ-CD and the photoproduct, in line with the fact that photocyclodimer **1** fits tightly in the cavity of γ-CD.

As illustrated as Scheme 3, the enantioselectivity obtained in this work may originate from (i) the difference in the stability of the stereomeric pairs of orientation isomers of **2,3-NA** in the ground sate and that of the intermediate **2** as well, (ii) the tight fit of photoproducts of **1** and **2** (Figure S13, Supporting Information) with the chiral cavity of γ-CD, and (iii) the fact that the photocyclodimerization occurs between the substituted rings and the substitutes are in the *anti*-head-to-head orientation. Considering the interaction between **2,3-NA** and native γ-CD, as well as the tight confinement of photoproducts with γ-CD, the *in situ* formation of the interacting hydrophobic moiety requires a more precise fit to the CD cavity and is easily hindered by a small size/shape alternation in guest structure. A slight difference in the relative location of **2,3-NA** and **2** may greatly affect the enantioselectivity of the photocyclodimerization. This rationalization may be supported by the fact that irradiation of the inclusion complex in the solid state at different temperatures led to different enantiomeric excess. As compared with those in the solid state, the two molecules of **2,3-NA** with hydrophobic interaction could penetrate deeper within the cavity of γ-CD in aqueous solution to cause the higher ee value in aqueous solution than that obtained in the solid state at the same temperature. The 48% ee obtained in this work is the highest value ever reported for the photocyclodimerization with native γ-CD under ambient temperature and pressure.

Conclusion

In summary, we have demonstrated that irradiation of **2,3-NA** in methanol with light λ > 280 nm produces *anti*-head-to-

head cubane-like photocyclodimer **1** and *anti*-head-to-head [4+4] intermediate **2**. Spectroscopic characterization reveals that γ-CD can engulf two molecules of **2,3-NA** into its cavity to make a stable 2:1 inclusion complex both in aqueous solution and in the solid state. Irradiation of **2,3-NA**@γ-CD results in photocyclodimerization with remarkable selectivity and efficiency, whereas no photocyclodimers could be detected in host-free aqueous solution and the neat solids. Studies on the product distributions clearly show that γ-CD not only enhances the efficiency of photocyclodimerization but also facilitates the photochemical transformation from the [4+4] intermediate **2** to cubane-like photocyclodimer **1**. More importantly, the use of native γ-CD as a chiral reaction vessel turns out to be an effective and versatile strategy for the enantioselective photodimerization of **2,3-NA**. The native γ-CD with hydrophobic interaction only is capable of regulating the orientation of **2,3-NA** within the cavity of γ-CD, thereby leading to the highest ee value of 48% obtained for the photocyclodimerization with native γ-CD in solution under ambient temperature and pressure. From the asymmetric photochemistry point of view, the photocyclodimerization of **2,3-NA** is attractive because no concurrent photochemical reaction of free substrates takes place both in an aqueous solution and in the solid state, which is desirable for a chiral host for executing a highly stereospecific transformation of the prochiral substrate bound at the chiral site. These results would stimulate us for further understanding the population of the stereomeric pair of inclusion complexes, reaction mechanisms, and the driving forces operating in the chiral supramolecular systems.

Experimental Section

HPLC Columns. The following columns were used: OJ-H analytic column, Daicel Chemical Industries, Ltd. 5 μm, 250 × 4.6 mm; OJ-H semipreparative column, Daicel Chemical Industries, Ltd. 5 μm, 250 × 10 mm; and Intersil ODS-3 semipreparative column, GL Sciences Inc. 5 μm, 250 × 10 mm.

Materials. γ-Cyclodertrin was purchased from TCI and used as received. All the solvents were of HPLC grade. Methanol was dried before used. Deionized water was used throughout this work. **2,3-NA** was prepared according to the literature method,[24] and its identity was confirmed by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, ppm) δ 8.31 (s, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.35−7.40 (t, J = 7.5 Hz, 1H), 7.21 (s, 1H), 4.00 (s, 3H), 3.96 (s, 3H). MS-ESI (+Na^+) 239.

Photocyclodimerization of 2,3-NA in Methanol. Irradiation of **2,3-NA** in degassed methanol (0.25 M) with light wavelength longer than 280 nm for 3 h can produce a white precipitate, which was recrystallized from petroleum ether/dichloromethane (v/v 3/1) to give crystals of photocyclodimer **1**. The reaction mixture was separated by column chromatography on silica eluted with petroleum ether/ethyl acetate (20/1 in volume) and dichloromethane to afford unreacted starting material of **2,3-NA** and photoproducts, respectively. The obtained product was subject to separation by HPLC on an achiral Intersil ODS-3 semipreparative column (UV detection at 260 nm; eluent 6:4 acetonitrile/water; flow rate 2 mL/min; see Figure 1). Compounds **1** (r.t. ≈ 21 min) and **2** (r.t. ≈ 23 min) were obtained as the main photoproducts except for a small remnant of the starting material **2,3-NA** (r.t. ≈ 27 min). **1** and **2** were directly collected by HPLC, and evaporation of the solvent afforded cubane-like photocyclodimer **1** and the [4+4] intermediate **2** as white solids.

^{1}H NMR of **1** ($CDCl_3$, ppm) δ 6.95−7.26 (m, 8H), 4.42 (d, J = 12.6 Hz, 2H), 4.20 (d, J = 12.6 Hz, 2H), 3.81 (s, 3H), 3.09 (s, 3H); ^{13}C NMR of **1** ($CDCl_3$, ppm) δ 169.4, 135.3, 134.5, 129.1, 128.2, 127.5, 127.4, 79.3, 56.6, 52.4, 52.1, 49.0, 44.0; X-ray crystal structure analysis of photocyclodimer **1** has confirmed its cubane-like structure. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. CCDC703661.

^{1}H NMR of **2** ($CDCl_3$, ppm) δ 6.76 (s, 8H), 4.47−4.49 (d, J = 11.0 Hz, 2H), 4.34−4.36 (d, J = 11.0 Hz, 2H), 3.99 (s, 3H), 3.76 (s, 3H). The ^{1}H NMR of **2** shown in Figure S3 in the Supporting Information indicates a small quantity of **2,3-NA** involved.

Resolution of Photocyclodimer 1. The enantiomeric separation of photocyclodimer **1** (resolved in alcohol) was performed by HPLC on a chiralcel OJ-H semipreparative column (UV detection at 220 nm; eluent 7:3 *n*-hexane/2-propanol; flow rate 1.0 mL/min). The obtained fractions were analyzed by analytic HPLC on a chiralcel OJ-H analytic column (Figure 3a).

Preparation of the 2,3-NA@γ-CD Inclusion Complex.

a. Aqueous Inclusion Complex. Deionized water (100 mL) was added to the mixture of **2,3-NA** (20 mg) and γ-CD (240 mg) and then sonicated in an AutoScience (AS)-3120 ultrasonic cleaner at 50 °C for 2 h. Filtration through 0.2 μm membrane afforded the desired inclusion complex of **2,3-NA**@γ-CD.

b. Solid Inclusion Complex. γ-CD aqueous solution (50 mL, 0.025 M) was added to a concentrated dichloromethane solution of **2,3-NA** (1.5 mmol) and the mixture was stirred for 24 h until no dichloromethane existed in this system; a fine white precipitate formed, which was isolated after thorough washing with ether and cold water to remove the uncomplexed **2,3-NA** and γ-CD, and then dried under vacuum at 60 °C.

Photoirradiation of the Inclusion Complex of 2,3-NA@γ-CD.

a. Aqueous Solution. A saturated aqueous solution of **2,3-NA**@γ-CD (60 mL) was sealed in a Pyrex tube under an argon atmosphere, then was irradiated with a 500 W high-pressure mercury lamp. The Pyrex tube was used as a light filter to cut off light below 280 nm and guarantee irradiation with $\lambda > 280$ nm. A quartz jacket with water circulation was used to cool the lamp. The irradiation was followed by UV−vis and fluorescence spectra. Generally after 3 h of irradiation, the conversion was greater than 70%. The reaction mixture was extracted with chloroform for further analysis.

b. Solid State. Irradiation of inclusion complexes in the solid state (15 mg) was accomplished in a self-made reactor, where the sample sealed in the quartz vessel was transferred to a Pyrex tube, and the tube was immersed into a water bath. The samples were exposed to the radiation for 3 h with two different sides, respectively. After irradiation for 6 h, the mixture was dissolved in water and extracted with chloroform for further analysis.

HPLC Separation of the Photoproducts. After evaporation of the solvent, the reaction mixture extracted with chloroform was dissolved in 0.5 mL of acetonitrile, which was filtered through 0.22 μm membrane and then subject to HPLC separation (see Figures 6 and 11). All of photoproducts were collected at their corresponding retention time (**1**: 21 min; **2**: 23 min; **3**: 32 min) for further analysis.

Photoproduct **3** was accumulated and then detected by UV−vis and NMR spectroscopic investigations, which suggest that **3** was derived from starting material **2,3-NA**; however, its yield was too small (<2%) to be identified. Photoproduct **4** was obtained upon irradiation of the inclusion complex in the solid state. The identify of **4** was supposed to be the *syn*-head-to-head [4+4] photocyclodimer of **2,3-NA**.

^{1}H NMR of **4** ($CDCl_3$, ppm) δ 7.21−7.23 (d, J = 7.0 Hz, 2H), 7.13−7.17 (m, 2H), 7.10−7.11 (d, J = 4.0 Hz, 4H), 4.39−4.41 (d, J = 10.8 Hz, 2H), 4.21−4.24 (d, J = 10.8 Hz, 2H), 3.60 (s, 3H), 3.57 (s, 3H).

Enantiomeric Excess (ee) Determination. The ee value of photocyclodimer **1** was determined by HPLC on an achiral Intersil ODS-3, and then Chiralcel OJ-H column. It should be mentioned that photocyclodimer **1** resulting from irradiation of the inclusion complex has been purified 3 times by HPLC on an achiral ODS-3

column in order to guarantee the exact ee measurement. After evaporation of solvent, the obtained fractions were resolved in alcohol and further analyzed on a chiralcel analytic OJ-H column (UV detection at 220 nm; eluent 7:3 *n*-hexane/2-propanol; flow rate 0.8 mL/min).

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Supporting Information Available: NMR spectra of all photoproducts and solid inclusion complex; LC-MS(ESI) of reaction mixture and enantiomers $\mathbf{1_a}$ and $\mathbf{1_b}$; structures of photocyclodimer **1** (crystal structural data) and the [4+4] intermediate **2** (AM1 optimized structural parameters); the circular dichroism and UV−vis spectra of **1** and **2** resulting from irradiation of **2,3-NA**@γ-CD in aqueous solution; UV−vis spectra of **3** and **4**; and fluorescence and IR spectra of **2,3-NA** and **2,3-NA**@γ-CD in the solid state. This material is available free of charge via the Internet at http://pubs.acs.org.

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