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Enantiodifferentiation in the Photoisomerization of (*Z*,*Z*)-1,3-Cyclooctadiene in the Cavity of γ-Cyclodextrin−Cucurbit[6]uril-Wheeled [4]Rotaxanes with an Encapsulated Photosensitizer

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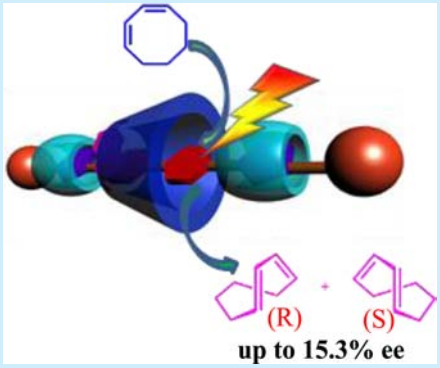
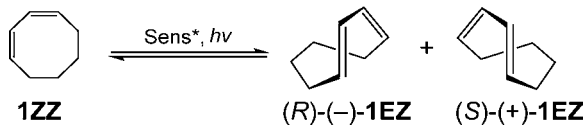
Supporting Information

ABSTRACT: A biphenyl photosensitizer axle was implanted into the cavities of native and capped γ-cyclodextrins through rotaxanation using a cucubit[6]uril-templated azide−alkyne 1,3-dipolar cycloaddition, resulting in the construction of highly defined chiral binding/sensitizing sites. The orientation and interaction of the axle and capping moieties at the ground and excited states were interrogated by NMR, UV−vis, circular dichroism, and fluorescence spectroscopic studies. In situ photoisomerization of (*Z*,*Z*)-1,3-cyclooctadiene sensitized in the cavity of these [4]rotaxanes afforded (*Z*,*E*)-1,3-cyclooctadiene in up to 15.3% ee, which represents the highest level of enantiodifferentiation obtained to date for this supramolecular photochirogenesis.



Chiral photochemistry, or photochirogenesis, which allows for the photogeneration of enantioenriched chiral compounds by activating thermally forbidden processes, represents one of the greatest challenges in modern photochemistry.[1] The short lifetime, weak interactions, and high reactivity of the electronically excited photosubstrates account for the poor stereochemical outcome commonly encountered in photochirogenesis.[2] Both internal and external factors, such as chiral inductors, temperature, solvent, and pressure, have proven to be crucial factors in photochirogenesis.[3] Recently, supramolecular photochirogenesis has emerged as a promising tactic, as it benefits from relatively long and strong supramolecular interactions exerting their influence on both the ground and excited states.[4] A variety of chiral hosts, including cyclodextrin (CD) derivatives,[5] chiral zeolite supercages,[6] chiral templates,[7] chiral cages,[8] and biomacromolecules,[9] have been exploited for mediating stereoselective photoreactions. Photosensitization of (*Z*)-cyclooctene with β-CD tethered to a sensitizer represents the seminal example of sensitized supramolecular photochirogenesis[10] and produces good to excellent enantioselectivities for the planar chiral (*E*)-cyclooctene. The enantioselectivity for the photoisomerization (*Z*,*Z*)-1,3-cyclooctadiene **1ZZ** to (*E*,*Z*)-1,3-cyclooctadiene **1EZ** (Scheme 1), in contrast, remains poor, reflecting the very different stereochemical requirements for these two related transformations. Very recently, improved ee values of up to 13% were achieved by using a relatively rigid matrix of amyloid-based nanofibers or hydrogels formed by CD-based polymers.[10c,11]

Scheme 1. Enantiodifferentiating Photoisomerization of (*Z*,*Z*)-1,3-Cyclooctadiene



While CDs possess the advantages of being readily available, UV transparent, and inherently chiral, their ability to serve as enantiodifferentiation agents in photochirogenesis is generally insignificant. The round shape and hydrophobic interior of CDs can accommodate a wide variety of binding organic guests, but with typically poor specificity.[12] The negligible stereoinduction is particularly pronounced for γ-CD due to its relatively flexible framework and larger cavity. In the present letter, we describe a new strategy to build up a highly confined chiral sensitizing cavity by implanting an aromatic sensitizer into the cavity of γ-CD through rotaxanation. This strategy takes advantage of the large cavity size of γ-CD to simultaneously accommodate the photosensitizer and substrate. Once the biphenyl sensitizer/axle is anchored through

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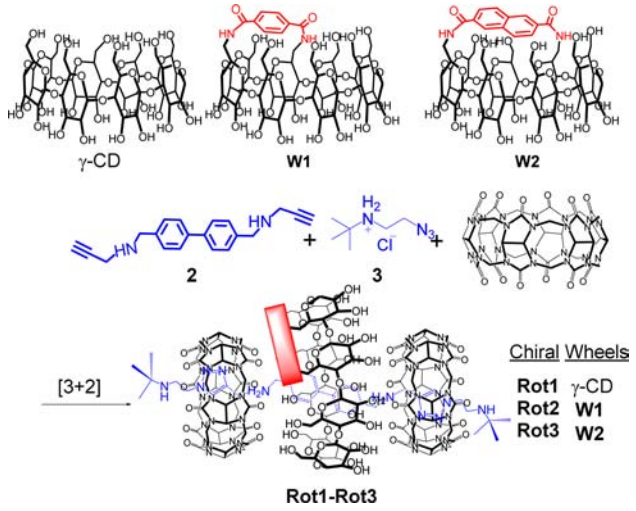
rotaxanation, the remaining space inside the CD cavity no longer possesses a symmetrically round shape. Accordingly, the in situ photosensitization is expected to affect chirality transfer more efficiently than conventional γ-CD derivatives.

Capped γ-CDs **W1** and **W2** (Scheme 2) were synthesized by reacting $6^A,6^C$- or $6^A,6^D$-diamino γ-CDs[12] with the correspond-

Scheme 2. Supramolecular Chiral Photosensitizers



ing aromatic dicarboxylic acids, respectively.[13] γ-CD-cucurbit[6]uril (CB[6])-wheeled [4]rotaxanes **Rot1**−**Rot3** were constructed by mixing the appropriate γ-CD, the CB[6] end caps, the biphenyl-based bis-terminal alkyne "axle" **2**, and the azide "stopper" **3** in an aqueous solution at room temperature followed by a CB[6]-templated azide−alkyne 1,3-dipolar cycloaddition.[14] All rotaxanes were obtained in good yields, partially due to the supramolecular interactions organizing all of the components into the appropriate arrangement.[15]

The ^{1}H NMR spectra of **Rot1**−**Rot3** clearly show two sets of proton signals for the CB[6] end caps, corresponding to CB[6] located at the primary and secondary rims of γ-CD (Figure 1). Similarly, four unique biphenyl protons were seen with the rotaxanes due to the loss of symmetry along the longitudinal axis. **Rot1** shows only one set of glucose protons with the nonanomeric protons all packed in the narrow region between 3.8 and 3.4 ppm, suggesting that the biphenyl axle is centrally positioned in the CD cavity and exerts relatively equal shielding and deshielding effects on each glucose unit. Compared to the ^{1}H NMR spectra of **Rot1**, the nonsymmetrical aryl protons in the biphenyl units of **Rot2** and **Rot3** (a, a′, b, and b′) are all shifted more upfield, as well as being more separated from each other, as a result of the shielding effect arising from the aromatic capping moieties on the CD rims (Figure 1b,c). Moreover, the proton signals in the CD units of **Rot2** and **Rot3** are distributed over a much wider range versus **Rot1**, with some of the nonanomeric protons shifted as far upfield as 2.4 ppm (**Rot2**) or 2.2 ppm (**Rot3**). This can be explained in terms of the anisotropic shielding and deshielding effects jointly exerted by the capping moiety and the biphenyl axle. The unequal shielding and deshielding effects received by the different glucose units in the CD units of **Rot2** and **Rot3** suggest that the biphenyl axle is located off-center of CD cavity, most likely due to the presence of capping groups.

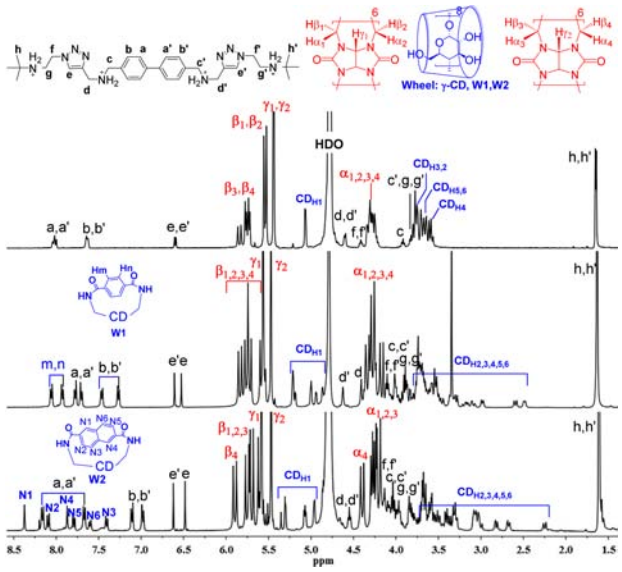


Figure 1. ^{1}H NMR spectra (400 MHz, D_2O, 298 K) of the hetero[4]rotaxanes (a) **Rot1**, (b) **Rot2**, and (c) **Rot3**.

The UV−vis and circular dichroism spectra of the capped CDs and [4]rotaxanes were studied in aqueous solutions (Figure 2). The capped γ-CDs **W1** and **W2**, whose aromatic

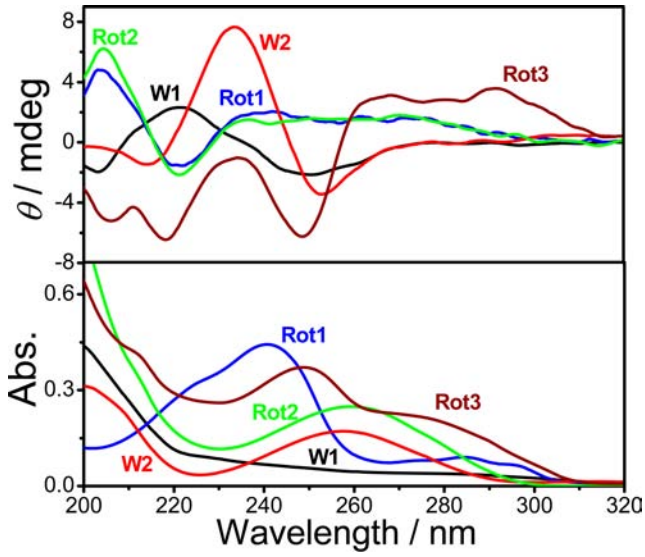


Figure 2. Circular dichroism (top) and UV−vis (bottom) spectra of 10 μM **W1** (black), **W2** (red), **Rot1** (blue), **Rot2** (green), and **Rot3** (brown) measured in water at 25 °C.

caps are fixed in a *trans*-annular manner on the primary rim of the CDs, show positive induced circular dichroism (ICD) signals at the main UV−vis absorption bands. According to the "sector rule" proposed by Kajtar and co-workers,[16] such an ICD implies that the aromatic planes are more parallel to the longitudinal axis of the CD ring. Negative exciton coupling circular dichroism (ECCD) was seen at the short wavelength of **Rot1**, suggestive of a left-handed screw arrangement for the two conjoined benzene rings in the biphenyl axle. **Rot2** showed a circular dichroism spectrum very similar to that of **Rot1**, rather than a simple sum of **Rot1** and **W1**. **Rot3**, on the other hand, has a circular dichroism spectrum significantly deviating from the sum of **Rot1** and **W2**, and it shows an improved positive

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signal at longer wavelengths and negative signals below 250 nm. Moreover, the UV–vis spectrum of **Rot3** is broadened with a significant bathochromic shift compared to **W2**. These results indicate an alternation of capping moiety's orientation in the rotaxanes and an electronic interaction between the biphenyl axle and the capping moieties at the ground state.

The fluorescence emission of the biphenyl unit in **Rot1** is stronger than that of the free biphenyl unit **2** (Figure 3); this

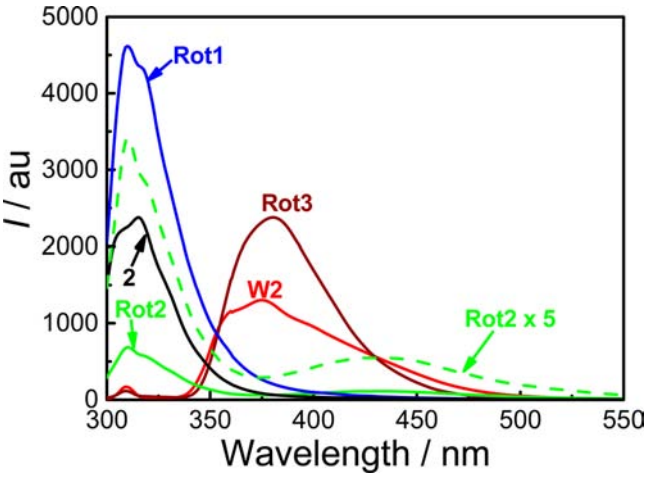

Figure 3. Fluorescence spectra of 10 μM **2** (black), **W2** (red), **Rot1** (blue), **Rot2** (green), and **Rot3** (brown) in water at 25 °C, λ_{ex} = 280 nm.

can be attributed to protection from the CD wall. Fluorescence from the biphenyl unit in **Rot3** was not observed. Instead, only fluorescence emission at a longer wavelength closer to that of **W2** was observed, suggesting an efficient energy transfer from the higher energy biphenyl axle to the naphthalene capping moiety. Interestingly, the fluorescence spectra of **Rot2** contained two fluorescence peaks, one at 310 nm and a very broad emission at the longer wavelength of 433 nm. The former, having a lifetime (7.7 ns) similar to that for **Rot1** (7.6 ns), corresponds to emission from the biphenyl axle. The latter signal is assigned as the exciplex fluorescence between the terephthalamide cap on the CD rim and the biphenyl axle. The formation of this rarely observed benzene–biphenyl exciplex could be ascribed to the noncovalent interlocked nature of the rotaxane, which leads to a high local concentration of the two components with adjustable stacking via slipping of the wheel along the axle. Two lifetime decays of 2.7 and 8.9 ns, respectively, were observed with the exciplex fluorescence, suggesting the presence of conformational isomers of the exciplex. The above results indicate that the capping moiety and the axle interact with each other in both the ground and excited states and therefore are expected to further confine the binding sites.

The complexation of **1ZZ** with the rotaxanes **Rot1**–**3** was studied by circular dichroism and fluorescence titration. Addition of **1ZZ** did not cause an apparent change in the circular dichroism spectra, suggesting that no significant conformational changes occurred in the rotaxanes. Binding of **1ZZ** by the rotaxanes did result in fluorescence quenching in the latter, most likely due to energy transfer from the excited biphenyl axle to the introduced diene **1ZZ**. Job's plots consistently demonstrated a 1:1 stoichiometry for the complexation of **1ZZ** with the various modified CDs and rotaxanes, with association constants of 2130, 2510, 3820, 8170, and 10330 M^{-1} for **W1**, **W2**, **Rot1**, **Rot2**, and **Rot3**, respectively. The remarkably improved binding affinity observed for the rotaxanes **Rot2** and **Rot3** versus the capped CDs **W1** and **W2** clearly demonstrates a more intimate interaction jointly originating from the CD wall, the biphenyl axle, and the aromatic capping moieties.

Photoisomerization of **1ZZ** using 280 nm light was carried out in an aqueous solution of a CD-based chiral sensitizers under a nitrogen atmosphere. The enantioselectivity varied considerably with the chiral host employed. With the capped γ-CDs **W1** and **W2**, the observed enantioselectivity was negligible even though the sensitizer moiety was rigidly fixed on the primary rim of CD (Table 1). This result confirms that the

Table 1. Enantiodifferentiating Photoisomerization of 1ZZ Sensitized by Chiral Hosts[a]

host	temp (°C)	1EZ/1ZZ	1EZ % ee
W1	25	0.16	1.1
W2	25	0.14	0.8
Rot1	25	0.09	3.9
	0.5	0.06	4.7
Rot2	25	0.08	12.8
	0.5	0.05	15.3
Rot3	25	0.06	8.3
	0.5	0.04	9.2

[a]Irradiation at 280 nm under nitrogen in a methanol–water mixture for 30 min; [**1ZZ**] = 0.5 mM; [host] = 0.1 mM.

cavity of γ-CD is too large to realize efficient chiral delivery. With **Rot1**, **1ZZ** should be coincluded with the biphenyl sensitizer in the cavity of γ-CD during sensitization. However, the modest enantioselectivity (4.7% ee) obtained suggests that the chiral cavity thus formed is still not specific enough for efficient chirality transfer. On the other hand, the enantioselectivity was significantly improved with the rotaxanes wheeled with capped γ-CDs **W1** and **W2**. Thus, the ee values were improved to 12.8% and 8.3% with **Rot2** and **Rot3**, respectively, at 25 °C. This unambiguously demonstrated the effect of the capping moiety on further confining the complex. Since both the capping moieties and the biphenyl axle could play the role of a sensitizer, they individually are expected to contribute to the photoisomerization, though it is not immediately clear which part dominates the photosensitization. For all of the rotaxane-based sensitizers investigated, lowering the temperature led to a further increase in enantioselectivity. At 0.5 °C, **Rot2** afforded **1EZ** in 15.3% ee, which is the highest value obtained to date for the supramolecular photoisomerization of **1ZZ**.

In summary, we have established a new strategy to construct highly confined chiral cavities by implanting a biphenyl species into the round and large chiral cavity of γ-CD via rotaxanation. Capping the inner rim of the CD host with rigid aromatic rings, which interact with the biphenyl axle at both ground and excited states, induced increased conformational restraint in the chiral cavity. The enantioselective sensitized photoisomerization of **1ZZ** with these rotaxanes gives **1EZ** with an enhanced ee of up to 15.3%. This study opens a new window for building highly specific chiral binding sites from naturally occurring chiral hosts

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00057.

Experimental details and analytical data (NMR, ESI-HRMS, fluorescence lifetime analyses) (PDF)

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Notes

The authors declare no competing financial interest.

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