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Enantiodifferentiating Photoisomerization of Cyclooctene Included and Sensitized by Aroyl-β-cyclodextrins: A Critical Enantioselectivity Control by Substituents

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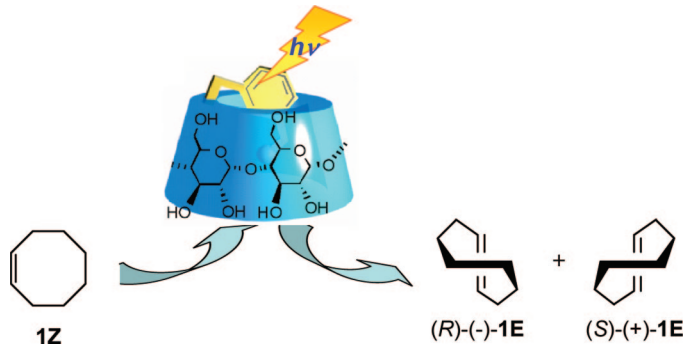

A series of 6-*O*-benzoyl-β-cyclodextrins (CDs) with methyl, methoxy, methoxycarbonyl, and bromo substituent(s) at the ortho-, meta-, and/or para-position(s) were synthesized as chiral sensitizing hosts for the use in supramolecular enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1Z**) to its chiral (*E*)-isomer (**1E**). The complex stability constants (K_S) of the modified β-CDs with **1Z** in aqueous methanol solutions were highly sensitive to the substituent(s) introduced to the benzoate moiety, and the log K_S values decreased linearly with slightly different slopes with increasing methanol content. The enantiomeric excess (ee) of **1E** obtained upon photosensitization with these hosts was a critical function of the size and position of the substituent, varying from almost zero to 46% ee. This indicates that even an apparently small structural difference between methyl and methoxy can critically affect the enantiodifferentiating photoisomerization of a guest included in the chiral cavity, probably through manipulation of both the orientation of ground-state **1Z** and the subsequent rotational relaxation of excited **1Z** inside the chiral cavity.

Introduction

Asymmetric photochemistry, or photochirogenesis, has attracted considerable attention in recent years.[1] Apart from the absolute asymmetric synthesis with circularly polarized light, photochirogenesis is achieved in general through intra- and/or intermolecular chiral interactions of a photosubstrate with an optically active moiety or compound,[1a,2] in which chirality transfer from the chiral source to the substrate is controlled by

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(1) (a) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741. (b) Inoue, Y.; Ramamurthy, V. *Chiral Photochemistry*; Marcel Dekker: New York, 2004. (c) Yang, C.; Fukuhara, G.; Nakamura, A.; Origane, Y.; Fujita, K.; Yuan, D.-Q.; Mori, T.; Wada, T.; Inoue, Y. *J. Photochem. Photobiol. A: Chem.* **2005**, *173*, 375. (d) Fukuhara, G.; Mori, T.; Wada, T.; Inoue, Y. *Chem. Commun.* **2005**, 4199. (e) Fukuhara, G.; Mori, T.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2006**, *71*, 8233. (f) Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 966.

(2) Everitt S. R. L.; Inoue, Y. In *Organic Molecular Photochemistry*, Ramamurthy, V., Schanze, K. S., Eds.; Marcel Dekker: New York, 1999; p 71.

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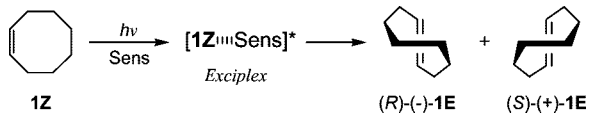
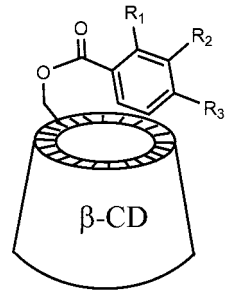
SCHEME 1. Enantiodifferentiating Geometrical Photoisomerization of 1Z Sensitized by Chiral Photosensitizers



relatively weak and short-lived interactions in the excited state. Recently, a supramolecular approach to photochirogenesis, which utilizes both the ground- and excited-state interactions between a chiral host and a prochiral guest, has emerged as an attractive extension of the conventional asymmetric photochemistry.[3] Various hosts, including chirally modified zeolites,[4] synthetic templates,[5] cyclodextrins,[1d,e,3a,e,d,6] proteins,[7] and DNA,[8] have been used as chirality sources to give the corresponding optically active photoproducts in good-to-excellent stereoselectivities.

Among these hosts, cyclodextrin (CD) is particularly attractive for application in supramolecular photochirogenesis because of its inherently chiral cavity, ready availability, and feasible modification.[9] Combining advantages of the catalytic nature of photosensitization and the intimate interactions in the supramolecular system, sensitizer-appended CDs provide an intriguing access to chiral photochemistry.[1,3,10] Benzoate and isomeric phthalate derivatives of β-CD have been used as chiral sensitizing hosts for the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1Z**) to give planar-chiral (*E*)-isomer (**1E**) (Scheme 1). Upon inclusion of **1Z** into the CD cavity in aqueous solution, the hydrophobic benzoate moiety is forced to move out of the cavity to some degree but still stays on the cavity rim covering the substrate, which upon irradiation facilitates the efficient energy and chirality transfer in a conformationally restricted chiral environment to give optically active **1E**. The photosensitization of **1Z** with 6-*O*-benzoyl-β-CD in aqueous methanol solutions gives **1E** in enantiomeric excess (ee) varying from 1% to 10%, depending on the methanol content. The use of slightly modified host, 6-*O*-(methyl phthaloyl)-β-CD, leads to much better ee values of 10−23%, which also varies with the methanol content but is totally independent of the reaction temperature, revealing that the entropy factor does not play a significant role in supramolecular photoisomerization of **1Z** included and sensitized by native CD-based hosts.[3a,e,d] Interestingly, we have recently found that the enantioselectivity of **1E** produced upon sensitization with *O*-permethylated 6-*O*-benzoyl-β-CD exhibits a critical dependence on temperature, indicating that the entropy-related factors become crucial again as a consequence of the flexible skeleton of permethylated CD.[1d,e] Despite these intriguing features, the enantioselectivity obtained by using CD-based sensitizing hosts still remained modest.

SCHEME 2. 6-*O*-Mono(benzoyl)-β-cyclodextrins As Chiral Sensitizing Hosts



	R_1	R_2	R_3
2	H	H	H
3a	CH_3	H	H
3b	H	CH_3	H
3c	H	H	CH_3
4a	OCH_3	H	H
4b	H	OCH_3	H
4c	H	H	OCH_3
5a	CO_2CH_3	H	H
5b	H	CO_2CH_3	H
5c	H	H	CO_2CH_3
6a	OCH_3	OCH_3	H
6b	H	OCH_3	OCH_3
7	H	H	Br

More recently, we have briefly reported that the photoisomerization of **1Z** sensitized by 6-*O*-(*m*-methoxybenzoyl)-β-CD gives chiral **1E** in up to 46% ee, which is the highest value ever reported for supramolecular photochirogeneses with analogous CD hosts.[11] This result clearly indicates that even an apparently trivial modification of the attached chromophore can critically manipulate the stereochemical outcomes of the supramolecular photochirogenesis within a CD cavity, and prompted us to synthesize a series of 6-*O*-benzoyl-β-CDs with methyl, methoxy, methoxycarbonyl, and bromo substituent(s) at the ortho-, meta-, and/or para-position(s) (Scheme 2) for use in the supramolecular enantiodifferentiating photoisomerization of **1Z** to elucidate the origin and the detailed mechanisms of this highly substituent-dependent enantioselectivity.

Results and Discussion

A series of sensitizer-appended β-CDs **3a**−**c**, **4b**−**c**, **6a**,**b**, and **7** (Scheme 2) were synthesized by the reactions of native β-CD with the corresponding benzoyl chlorides in pyridine and purified by repeated recrystallization. NMR and HR-MS spectral studies were performed to confirm the structure of these chiral sensitizing hosts. The solubilities of these hosts were poor in general in pure water, but were considerably improved by adding 5−50% methanol to the aqueous solutions.

Structure of Modified CDs. To elucidate the structural features of sensitizer-appended CDs **3**−**7**, in particular the orientation of the aromatic group introduced to the primary rim, we performed the circular dichroism spectral study in aqueous methanol solutions. As exemplified in Figure 1, these modified β-CDs mostly displayed negative induced circular dichroism (ICD) signals in the chromophore's ^1L_a (at shorter λ) and ^1L_b (at longer λ) regions, indicating that the benzoate moieties are only partly included or just perching on the primary rim, according to the sector rule.[12,13] This is

(3) (a) Inoue, Y.; Dong, F.; Yamamoto, K.; Tong, L.-H.; Tsuneishi, H.; Hakushi, T.; Tai, A. *J. Am. Chem. Soc.* **1995**, *117*, 11033. (b) Sugahara, N.; Kawano, M.; Wada, T.; Inoue, Y. *Nucleic Acids Symp. Ser.* **2000**, *44*, 115. (c) Inoue, Y.; Wada, T.; Sugahara, N.; Yamamoto, K.; Kimura, K.; Tong, L.-H.; Gao, X.-M.; Hou, Z.-J.; Liu, Y. *J. Org. Chem.* **2000**, *65*, 8041. (d) Gao, Y.-Y.; Inoue, M.; Wada, T.; Inoue, Y. *J Incl. Phenom. Macrocycl. Chem.* **2004**, *50*, 111. (e) Tong, L.-H.; Lu, R. H.; Inoue, Y. *Prog. Chem.* **2006**, *18*, 533.

(4) Chong, K.-C.-W.; Sivaguru, J.; Shichi, T.; Yoshimi, Y.; Ramamurthy, V.; Scheffer, J.-R. *J. Am. Chem. Soc.* **2002**, *124*, 2858.

(5) (a) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982. (b) Grosch, B.; Orlebar, C.-N.; Herdtweck, E.; Kaneda, M.; Wada, T.; Inoue, Y.; Bach, T. *Chem. Eur. J.* **2004**, *10*, 2179.

(6) (a) Rao, V.-P.; Turro, N.-J. *Tetrahedron Lett.* **1989**, *30*, 4641. (b) Koodanjeri, S.; Joy, A.; Ramamurthy, V. *Tetrahedron* **2000**, *56*, 7003. (c) Shailaja, J.; Karthikeyan, S.; Ramamurthy, V. *Tetrahedron Lett.* **2002**, *43*, 9335. (d) Koodanjeri, S.; Joy, A.; Ramamurthy, V. *Tetrahedron Lett.* **2002**, *43*, 9229. (e) Vizvardi, K.; Desmt, K.; Luyten, I.; Sandra, P.; Hoornaert, G.; Eycken, V. E. *Org. Lett.* **2001**, *3*, 1173.

(7) (a) Zandomeneghi, M. *J. Am. Chem. Soc.* **1991**, *113*, 7774. (b) Lhiaubet-Vallet, V.; Sarabia, Z.; Bosca, F.; Miranda, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 9538. (c) Wada, T.; Nishijima, M.; Fujisawa, T.; Sugahara, N.; Mori, T.; Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7492.

(8) Wada, T.; Sugahara, N.; Kawano, M.; Inoue, Y. *Chem. Lett.* **2000**, 1174.

(9) (a) Takahashi, K. *Chem. Rev.* **1998**, *98*, 2013. (b) Breslow, R.; Dong, S. *Chem. Rev.* **1998**, *98*, 1997.

(10) Yang, C.; Mori, T.; Wada, T.; Inoue, Y. *New J. Chem.* **2007**, *31*, 697.

(11) Lu, R.; Yang, C.; Cao, Y.; Wang, Z.; Wada, T.; Jiao, W.; Mori, T.; Inoue, Y. *Chem. Commun.* **2008**, *3*, 374–376.

(12) Kajtar, M.; Horvath-Toro, C.; Kuthi, E.; Szejtli, J. *Acta Chim. Acad. Sci. Hung* **1982**, *110*, 327.

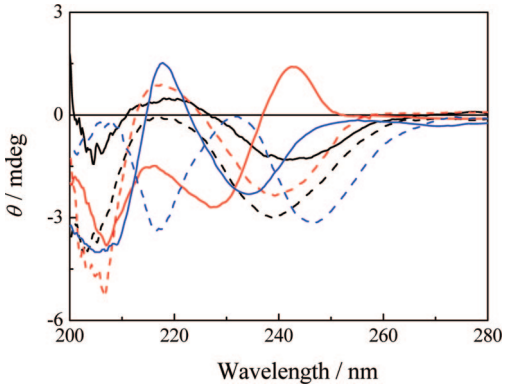
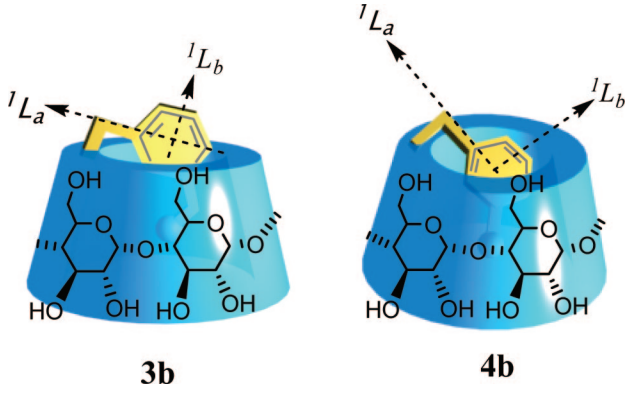


FIGURE 1. CD spectra of 0.1 mM **3a** (black), **3b** (red), and **4b** (blue) in aqueous solutions containing 10% (solid line) and 50% (dashed line) methanol.

SCHEME 3. Proposed Conformations of 3b and 4b in 10% Aqueous Methanol Solution



reasonable since the short ester linker may prevent deep penetration of the benzoate into the cavity. On the other hand, the aromatic moiety lying over the hydrophobic cavity can reduce the net surface area exposed to the solvent and enhance the hydrophobicity of the modified CD cavity. It should be noted that the chromophore conformation is not necessarily the same in different modified CDs, and the positive ICD observed in the ^1L_a region of *m*-methoxybenzoyl-modified **4b** in 10% methanol solution suggests that the benzoate moiety penetrates deeper into the cavity than the ortho- and para-substituted **4a** and **4c**, while the positive ICD observed at the ^1L_b band of **3b** indicates that the benzene plane is positioned oblique rather than flatly (Scheme 3). Such an exceptional behavior indicates that a small structural difference in substituting group and position can critically influence the orientation of chromophore in the cavity. The chromophore orientation is sensitive also to the solvent composition, as indicated by the fact that the circular dichroism signals go more negative upon increasing the content of methanol from 10% to 50%, probably due to shallower penetration into the cavity.

Complexation of 1Z with Modified CDs. The complexation behavior of **1Z** with modified β-CDs **3**, **4**, and **6** was studied in methanol−water mixtures by means of circular dichroism spectral titration, and the results were compared with those obtained previously with **2** and **5**.[3c] As shown in Figure 2, addition of **1Z** to a solution of **3a** caused a gradual increase in intensity of the negative ICD at 240 nm, while the same procedure with **4c** led to a switching of the positive ICD to a negative one at the ^1L_b band and a gradual decrease of ICD intensity at the ^1L_a band. These results clearly indicate that the chromophore orientation is critically manipulated to accommodate the incoming **1Z**.[11] The smooth CD spectral changes accompanied by isodichroic points suggest formation of stoichiometric 1:1 complex shown below:

$$\mathrm{CD} + \mathbf{1Z} \overset{K_s}{\rightleftarrows} [\mathrm{CD}\cdot\mathbf{1Z}]$$

Assuming the 1:1 stoichiometry, the differential circular dichroism spectral data were quantitatively analyzed by the nonlinear least-squares curve fitting method to give the complex stability constant (K_S) in aqueous solutions of varying methanol contents.[14] The K_S values obtained in 10−50% methanol, as well as those extrapolated to 0% methanol, are listed in Table 1. The K_S values reported previously for **2** and **5a**−**c**[3c] are also included in the table; note that the present measurements with **3**, **4**, and **6** were carried out at 18 °C due to the instrumental requirements, while the previous experiments with **2** and **5** were at 25 °C. Nevertheless, we dare to include the previous data to more broadly compare the stability constants for these structurally related CD hosts, since we know that the K_S for **5a** is roughly doubled from 650 to 1420 M^{-1} by reducing the temperature from 25 to 15 °C,[3c] and would expect not the same but similar, slightly smaller changes at 18 °C for other relevant CD hosts used in this study. Certainly, a direct comparison should be made for the data obtained for **3**, **4**, and **6**.

It is interesting to note that β-CDs **4b**,**c** with a methoxy substituent show stabilities obviously higher than methyl- and dimethoxy-substituted β-CDs **3a**,**b** and **6a**,**b** by factors of 2.1−4.6 in 10% methanol. This variation in K_S due to the very small structural difference in host structure suggests that the substituent plays a decisive role in adjusting the chromophore conformation upon synergic binding of **1Z**. The chromophores attached to CD reduce the surface area of included **1Z** exposed to the aqueous solution and enhance the van der Waals interaction within the cavity. In such a situation, it is likely that the substituent coincluded into the cavity critically influences the guest's position and orientation in the cavity and therefore the K_S value.

The significantly higher K_S values observed for methoxy-substituted **4b** and **4c** may suggest that the methyl group of **4b** and **4c**, possessing more conformational freedoms than that of **3a** and **3b**, can manipulate their spatial orientation to match the geometry of **1Z**. For dimethoxy-substituted **6a**, the bulkier chromophore may disturb its coinclusion with **1Z** in the cavity, not exhibiting as high a K_S value as those obtained with **4b** and **4c**. The substitution position on the benzene ring is also very important in affecting the complex affinity as the ortho-substituted **3a** shows much larger K_S than its meta-analogue **3b**.

Increasing methanol content significantly decreases the binding affinity of the hosts. To quantitatively analyze the effect of methanol on the complexation behavior, we plotted the natural logarithm of K_S as a function of the fraction of methanol F_M to give good straight lines $\ln K_S = aF_M + b$ for all of the β-CDs employed, as shown in Figure 3. The slope *a* indicates the

(13) Tong, L.-H.; Hou, Z.-J.; Inoue, Y.; Tai, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1253.

(14) Inoue, Y.; Yamamoto, K.; Wada, T.; Everitt, S.; Gao, X.-M.; Hou, Z.-J.; Tong, L.-H.; Jiang, S.-K.; Wu, H.-M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1807.

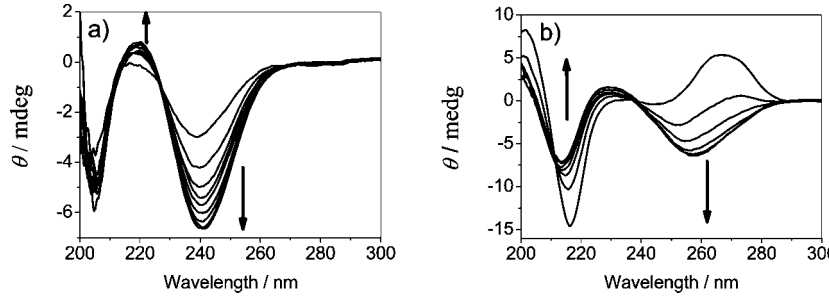


FIGURE 2. CD spectral changes of (a) 0.059 mM **3a** upon increasing the concentration of **1Z** from 0 to 2.8 mM and (b) 0.055 mM **4c** upon increasing the concentration of **1Z** from 0 to 2.5 mM in 10% aqueous methanol.

TABLE 1. Complex Stability Constant (K_S) and Free Energy Change ($-\Delta G°$) for the 1:1 Inclusion Complexation of 1Z with Modified CDs in Methanol−Water Mixtures

host	temp/°C	MeOH/%	K_S/M^{-1}	$-\Delta G°$/kJ mol^{-1}
2[b]	25	0	20100	24.5
		50	1440	18.0
3a	18	0	*12500*[b]	*22.8*[b]
		10	8960	20.7
		25	3580	18.6
		50	1530	16.6
3b	18	0	*9000*[b]	*22.0*[b]
		10	5000	19.3
		25	2790	18.0
		50	670	14.8
4b	18	0	*33900*[b]	*25.3*[b]
		10	23110	22.8
		25	11120	21.1
		50	4200	18.9
4c	18	0	*34900*[b]	*25.3*[b]
		10	20200	22.5
		25	9640	20.8
		50	2430	17.7
5a[a]	25	0	16700	24.1
		25	3250	20.0
		50	650	16.0
	15	50	1420	17.6
5b[a]	25	0	170000	29.8
		50	5390	21.3
5c[a]	25	0	124000	29.1
		50	2680	19.6
6a	18	0	*18400*[b]	*23.8*[b]
		10	10730	21.1
		25	6640	20.3
		50	1760	18.7
6b	18	0	*15600*[b]	*23.4*[b]
		10	10300	21.0
		25	6300	19.9
		50	1710	16.9

[a] Reference 3c; measured at 25 °C. [b] Value extrapolated from the data at higher methanol contents.

sensitivity of K_S to the methanol content, while the intercept b equals the K_S value extrapolated to pure water.

The Gibbs free energy change upon host−guest complexation is a function of the surface area change upon merger of two solvent voids containing a host and a guest (G) into a single solvent void of the complex. As formulated in eq 1, the total free energy change ($\Delta G°_{total}$) originates primarily from the desolvation of a guest G ($\Delta G°_{desol}$), the association of G with host CD ($\Delta G°_{ass}$), and the release of solvent molecules from the cavity ($\Delta G°_{rel}$).

$$\Delta G°_{total} = \Delta G°_{desol} + \Delta G°_{ass} + \Delta G°_{rel} \quad (1)$$

As a first approximation, we assume that the solvation effect is comparable for free CD and complex [CD·G] and

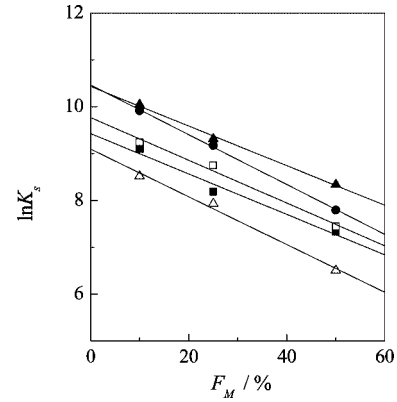


FIGURE 3. Logarithm of the complex stability constant (K_S) of **1Z** with **3a** (—), **3b** (□), **4b** (▲), **4c** (●), and **6b** (△) at 18 °C as a function of the methanol content (F_M) in methanol−water mixture.

is canceled out, so that only the solvation to G has to be seriously considered. The $\Delta G°_{desol}$ and $\Delta G°_{rel}$ are directly affected by the solvent composition. The $\Delta G°_{ass}$ should also be sensitive to the solvent composition in an indirect manner, since the chromophore conformation, being susceptive to the solvent, significantly influences the guest orientation in the cavity. We therefore divide the $\Delta G°_{ass}$ into two parts, i.e., one originating from the CD moiety ($\Delta G°_{CD}$) and the other from the chromophore ($\Delta G°_{chrom}$), to obtain eq 2, which is different from that for native β-CD only by $\Delta G°_{chrom}$:

$$\Delta G°_{total} = \Delta G°_{desol} + \Delta G°_{CD} + \Delta G°_{chrom} + \Delta G°_{rel} \quad (2)$$

In a methanol−water mixture, $\Delta G°_{total}$ is considered to be a weighted average of the contributions from methanol (M) and water (W), and we can rewrite eq 2 as:

$$\Delta G°_{total} = F_M \Delta G°_{desol(M)} + (1 - F_M)\Delta G°_{desol(W)} + \Delta G°_{CD} + \alpha[F_M \Delta G°_{chrom(M)} + (1 - F_M)\Delta G°_{chrom(W)}] + F_M \Delta G°_{rel(M)} + (1 - F_M)\Delta G°_{rel(W)} \quad (3)$$

where α is a correction factor for the solvation energy, reflecting the sensitivity of complexation affinity to the chromophore solvation. Equation 3 can then be rewritten as:

$$\ln K_S = -[F_M(\Delta G°_{desol(M)} - \Delta G°_{desol(W)} + \alpha\Delta G°_{chrom(M)} - \alpha\Delta G°_{chrom(W)} + \Delta G°_{rel(M)} - G°_{rel(W)}) + \Delta G°_{desol(W)} + \Delta G°_{CD} + \alpha\Delta G°_{chrom(W)} + \Delta G°_{rel(W)}]/RT = aF_M + b \quad (4)$$

where

$$a = -(\Delta G°_{desol(M)} - \Delta G°_{desol(W)} + \alpha\Delta G°_{chrom(M)} - \alpha\Delta G°_{chrom(W)} + \Delta G°_{rel(M)} - \Delta G°_{rel(W)})/RT \quad (5)$$

$$b = -(\Delta G^\circ_{\text{desol(W)}} + \Delta G^\circ_{\text{CD}} + \alpha\Delta G^\circ_{\text{chrom(W)}} + \Delta G^\circ_{\text{rel(W)}})/RT \quad (6)$$

Since $\Delta G^\circ_{\text{desol(M)}}$, $\Delta G^\circ_{\text{desol(W)}}$, $\Delta G^\circ_{\text{rel(M)}}$, and $\Delta G^\circ_{\text{rel(W)}}$ are considered to be approximately equal for all host molecules, the difference in *a* observed for various β-CD hosts is deduced to arise from the $\alpha(\Delta G^\circ_{\text{chrom(M)}} - \Delta G^\circ_{\text{chrom(W)}})$ value, the differential solvation energy of chromophore in water and methanol. On the other hand, the difference in *a* observed for various β-CD hosts is ascribed to the difference in solvation energy of the chromophore. Therefore, the $\alpha\Delta G^\circ_{\text{chrom(M)}} - \alpha\Delta G^\circ_{\text{chrom(W)}}$ for **3b** and **4c** are inferred to be more significant than the other modified β-CDs as suggested by their larger *a* values (Table 2).

TABLE 2. The Slope (*a*) and Intercept (*b*) Obtained from the Linear Fitting of the Data Shown in Figure 3 to ln $K_S = aF_M + b$ and the Estimated $K_{S(W)}$ Obtained by Extrapolating the Data to Pure Water and $K_{S(M)}$ Obtained by Extrapolating to Pure Methanol

host	*a*	b	$K_{S(W)} = \exp(b)$	$a + b$	$K_{S(M)} = \exp(a + b)$
3a	−4.32	9.43	12500	5.11	170
3b	−5.09	9.10	9000	4.81	60
4b	−4.23	10.43	33900	6.20	480
4c	−5.32	10.46	34900	6.14	170
6a	−4.60	9.82	18400	5.22	180
6b	−4.56	9.77	15600	5.21	180

The intercept *b* is the complex stability constant extrapolated to 0% methanol, or pure water. As can be seen from Table 2, the *b* value varies from 9.10 to 10.46, or K_S from 9000 to 34900 M^{-1}, indicating that all of these modified β-CDs can form very stable 1:1 complexes with **1Z** in pure water. The methoxy-substituted hosts **4b** and **4c** give the *b* values larger than any of the other modified CDs, revealing that they have the most positive (or least negative) $\alpha\Delta G^\circ_{\text{chrom(W)}}$ values.

We can estimate the complex stability constants in pure methanol from the sum of *a* and *b*. The K_S values thus obtained (60−480 M^{-1}) for complexation in pure methanol (Table 2) indicate that even in pure methanol, β-CDs can bind **1Z** moderately. The good linear relationship of ln K_S against F_M indicates that the chromophore conformation varies smoothly rather than abruptly upon increasing the methanol content.

Enantiodifferentiating Photoisomerization of 1Z with Modified CDs. Photoisomerization of **1Z** included and sensitized by modified β-CDs was performed in aqueous methanol solutions of varying methanol contents at different temperatures. The *E*/*Z* ratio and the enantiomeric excess (ee) of **1E** produced in the initial stage (2−5 min of irradiation) and the near photostationary state (pss) (30−60 min of irradiation) at each temperature are shown in Table 3, along with some of the relevant data previously reported for **2** and **5a**−**c**.[3c]

TABLE 3. 1E/1Z (*E*/*Z*) Ratio and Enantiomeric Excess (ee) of 1E Obtained in the Photoisomerization of 1Z Mediated by Modified CDs 2, 3a−c, 4a−c, 5a−c, 6a,b, and 7 in Aqueous Methanol[a]

host	MeOH/%	*T*/°C	*hν*/min	*E*/*Z*	ee/%	host	MeOH/%	*T*/°C	*hν*/min	*E*/*Z*	ee/%
2[b]	0	25	5	0.05	−9.7	**3c**	50	25	5	0.32	−13.4
			60	0.29	−5.7				10	0.58	−12.5
	25	25	2	0.06	−10.7				20	0.64	−10.8
			60	0.58	−4.0	**4a**[c]	50	25	5	0.19	4.3
	50	25	2	0.15	−9.4				30	0.44	3.5
			60	0.76	−5.0	**4b**	10	−5	5	0.24	−45.8
3a	10	0	5	0.01	−6.4			0	5	0.19	−39.6
			60	0.14	−1.5			25	5	0.07	−40.8
	25	0	5	0.13	−4.6				30	0.23	−32.8
			60	0.27	−3.7		25	25	5	0.08	−33.3
		25	10	0.14	−5.4				30	0.13	−31.1
			30	0.29	−5.1		50	25	5	0.18	−30.2
			60	0.39	−3.0				30	0.19	−26.3
	50	0	5	0.02	−3.6	**4c**	10	−5	5	0.12	−6.0
			60	0.27	−3.5			0	5	0.14	−9.4
		25	2	0.07	−4.3			25	5	0.12	−10.6
			10	0.17	−2.9				30	0.20	−10.3
			60	0.35	−3.3		25	25	5	0.24	−10.8
3b	10	0	5	0.11	−13.6				30	0.13	−7.3
			60	0.16	−1.2		50	25	5	0.21	−12.7
		25	10	0.13	−17.4				30	0.36	−9.1
			30	0.24	−18.1	**5a**[b]	50	25	2	0.09	18.7
	25	0	5	0.11	−15.4				40	0.42	17.5
			60	0.46	−7.1	**5b**[b]	50	25	2	0.21	−1.7
		25	5	0.09	−15.7				60	0.60	0.3
			10	0.15	−11.7	**5c**[b]	50	25	40	0.61	1.9
			30	0.30	−8.0	**6a**	10	0	5	[c]	
			60	0.20	−5.4			25	5	[c]	
	50	0	5	0.01	−12.2	**6b**	10	−5	5	0.11	−34.2
			60	0.49	−5.3			0	30	0.14	−38.9
		25	5	0.11	−11.8			25	5	0.11	−38.1
			10	0.25	−9.9		25	0	5	0.19	−31.9
			30	0.29	−6.7				30	0.20	−30.0
			60	0.38	−5.0		50	0	5	0.09	−7.0
3c	10	25	5	0.68	−13.1				30	0.11	−6.6
			10	0.65	−11.9	**7**	10	25	20	0.08	−6.9
			30	0.43	−3.8		50	25	5	0.05	−9.0
			60	0.38	−1.0				20	0.23	−7.3

[a] Irradiated at 254 nm under argon in aqueous methanol solution; [**1Z**] = 1.5 mM, [host] = 0.05−0.15 mM, depending on the host solubility. [b] Reference 3c. [c] Reference 3d. [d] **1E** not detected (*E*/*Z* < 0.01).

The *E*/*Z* ratio obtained at near pss appreciably increases in general with increasing methanol content from 10% to 50%. The ee at the initial stage (2−5 min of irradiation) decreases to some extent at higher methanol contents due to the increasing contribution of external sensitization in the bulk solution, which is inherently less enantiodifferentiating. Interestingly, the temperature does not appear to significantly influence the enantioselectivity at least at −5 to 25 °C, as exemplified by a small decrease (from 46% to 41% ee) for **4b** or even a small increase (from 34% to 38% ee) for **6b** by raising the temperature. These results are consistent with the previous observation with **2** and **5a**, demonstrating again the low-entropy environment of the rigid cavity of β-CD.[3c]

Substituent Effects on Enantioselectivity. As can be seen from Table 3, the *E*/*Z* ratio and the ee of **1E** are critically affected by the substituent and its position introduced to the benzene ring of the host. For example, the pss *E*/*Z* ratio in 50% aqueous methanol at 25 °C varies widely from the lowest 0.11 (for **6b**) or 0.19 (for **4b**) to the highest 0.76 (for **2**), and most of the hosts, except for **6a**, afford the ratio in a range of 0.4−0.6, which is an advantage of supramolecular photosensitization within a CD cavity for preparing highly strained **1E** in view of the much lower *E*/*Z* ratios (0.05−0.28) obtained by conventional photoisomerization of **1Z** with the same aromatic sensitizer (not incorporating β-CD) due to the less-efficient energy transfer to **1Z** than to **1E**. These observations indicate that the energy transfer from the sensitizer moiety to **1Z** within the CD cavity is highly dependent on both the type and position of the substituent introduced to the benzene ring. It is somewhat surprising that the brominated host **7** can give comparable *E*/*Z* ratios of up to 0.23 despite that bromine may accelerate the intersystem crossing to triplet, which is known to afford much smaller *E*/*Z* ratios (<0.1) in general.[13] The near pss *E*/*Z* ratio, as a measure of the efficiency of energy transfer, does not appear to be directly related to the complex stability constant K_S (Table 1), as demonstrated by the fact that the strongest binders **4b** and **4c** merely afford modest *E*/*Z* ratios around 0.2 in 10% methanol solution at 25 °C.

The product's absolute configuration and ee are even more critically affected by the type and position of substituent(s) introduced. In 10−50% methanol solutions, *o*-methylated host **3a** affords (*R*)-**1E** in low ee values (2−6%), while *o*-methoxylated **4a** and *o*-methoxycarboxylated **5a** give the antipodal product in better ee values (4−19%). In contrast, the use of meta-substituted **3b**, **4b**, and **6b** (excepting **5b**, which carries a sensitizer moiety located outside the cavity, and is less efficient in enantiodifferentiation, with the same being true for **5c**)[3c] leads to the formation of (*S*)-**1E** in much higher ee values of 18%, 46%, and 39%, respectively, in 10% methanol, which, however, deteriorated in 25% and 50% methanol due to the less efficient binding in these more hydrophobic solvents. The 46% ee obtained is the highest value ever reported for a supramolecular photosensitization with analogous hosts.[3c]

It shouold be noted that the ortho-, meta-, and para-isomeric sensitizing host series **3**, **4**, and probably **6** (again excepting **5** due to the conformational difference)[13] share the same trend in product's ee—the meta isomer always affords the highest value, the para the second best, and the ortho the lowest. This reveals that the enantiodifferentiation within the cavity is primarily controlled by the steric, rather than electronic, effects, which is in line with the circular dichroism spectral elucidation that the substituent on the benzoate moiety greatly affects its orientation in the cavity.

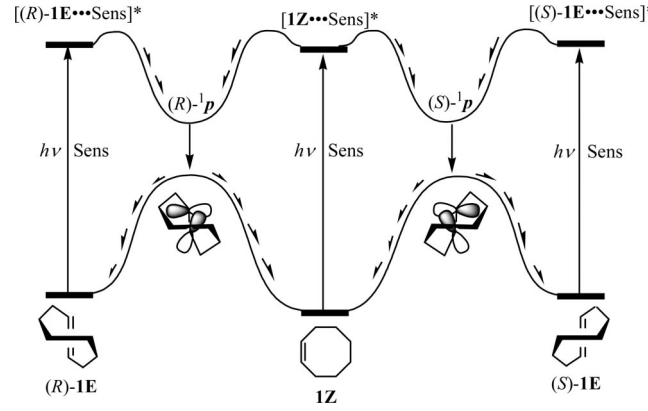


FIGURE 4. Schematic potential energy diagram for the ground and excited states of **1Z** and **1E**.

It is also interesting to compare the results obtained with methoxy-substituted hosts **4a**−**c** and **6a**,**b**. The higher ee values for **4b** and **6b** indicate that the *m*-methoxy is conformationally most favorable in enhancing the ee of **1E**. The additional methoxy introduced at the para position (**6b**) does not significantly alter the chiral environment of the original cavity of **4b**. Thus, the methoxy at the meta position should dominate the enantiodifferentiating processes in the cavity, since para-substituted host **4c** gives **1E** in only modest ee. However, the coexistence of meta- and ortho-substituents significantly reduces the sensitizing ability of host **6a**, indicating that **1Z** is included indeed (Table 1) but has little access to the sensitizer moiety in the cavity of **6a**.

The enantiodifferentiating photoisomerization of **1Z** mediated by a sensitizing host (Sens) is essentially reversible and may be illustrated as shown in Figure 4. In the initial stage of the reaction, the reverse isomerization from **1E** is negligible and the product's ee is determined by the relative rate of the rotational relaxation of **1Z**'s double bond to a pair of enantiomeric perpendicular singlets, i.e. (*R*)- and (*S*)-^{1}***p*** which are precursors to (*R*)- and (*S*)-**1E**, within the excited-state complex [**1Z**•••Sens]*. It is likely that both the rotational relaxation to (*R*)- and (*S*)-^{1}***p*** on the excited-state potential surface and the subsequent decay to (*R*)- and (*S*)-**1E** on the ground-state surface, occurring within the chiral cavity, are enantiodifferentiating in principle.

The 46% ee obtained with **4b** indicates that the CD cavity configured jointly by the inherently chiral glucopyranose walls and the *m*-methoxylbenzoate has an overall preference for the *R*-absolute configuration to the *S* by a factor of 2.7. As stated above, there are two distinct potentially enantiodifferentiating processes that are pivotal to the supramolecular photochirogenesis: (1) the rotational relaxation of **1Z** to (*R*)- and (*S*)-^{1}***p*** within the chiral host cavity to a pair of diastereomeric CD complexes, [(*R*)-^{1}***p***•••**4b**] and [(*S*)-^{1}***p***•••**4b**], and (2) the subsequent decay of these diastereomeric complexes to (*R*)- and (*S*)-**1E**, which can proceed at different rates. Thus, the geometrical matching of the enantiomers is crucial in both of these steps involving ^{1}***p*** and **1E**. The ^{1}***p*** enantiomer that is better induced fitted to the CD cavity upon rotational relaxation will be favored in the first step. If the rotation to the opposite direction is disfavored in the first step, further rotation to give the final product is anticipated to be highly discouraged, and hence the favored ^{1}***p*** enantiomer will have a better (or at least the same) chance to

decay to **1E** of the same absolute configuration. In this specific case, the cavity of **4b** is deduced to be matched to the dimensions of (*R*)-^{1}***p*** and (*R*)-**1E** much better than their antipodes. This rationalization may be supported by the fact that the ee of **1E** obtained gradually declines upon prolonged irradiation in all examined cases, which indicates that the preferentially produced **1E** enantiomer is better accommodated in the host cavity to revert to **1Z** at a rate faster than that for the less favored antipodal product. We may conclude therefore that the chiral CD cavity is exploited twice in a synergetic manner, first in the excited-state rotation to ^{1}***p*** and then in the ground-state rotation to the final product **1E**, which is a major advantage of the supramolecular photochirogenesis.

Conclusions

In this study, a series of substituted benzoate-modified CDs were synthesized and used as chiral sensitizing hosts for mediating the enantiodifferentiating photoisomerization of cyclooctene. The conformational variation of these modified CDs and their complexation behavior with **1Z** were examined by circular dichroism spectroscopy in water−methanol mixed solvents to reveal that the orientation of chromophore, and therefore the complex stability constant (K_S), are highly sensitive to both the type and position of the introduced substituents. The chromophore conformation is smoothly varied by changing the methanol content to give a linear relationship of ln K_S with the methanol fraction.

The supramolecular photosensitization of **1Z** mediated by the modified CDs gave chiral **1E**, enantiomeric excess of which was critically affected by the substituent introduced to the sensitizer moiety to give the highest ee values of 39−46% upon sensitization with *m*-methoxylbenzoate-appended β-CDs, which is attained by manipulating the excited-state rotational relaxation from prochiral substrate **1Z** to enantiomeric perpendicular singlet (*R*/*S*)-^{1}***p*** and the subsequent decay to the corresponding final product (*R*/*S*)-**1E**. Both of these successive processes are stereochemically driven to the same direction by the chiral CD cavity modified with the aromatic chromophore, featuring the supramolecular photochirogenesis.

Experimental Section

Complexation Study. The complexation behavior of **1Z** with **3a**−**c**, **4b**−**c**, **6a**,**b**, and **7** was investigated and the complex stability constants (K_S) were determined by circular dichroism spectrometric titration, according to the procedures reported previously.[3c–e,15]

Photolysis. Aqueous methanol solutions (5 mL) containing **1Z** (1.5 mM) and modified β-cyclodextrin (0.054−0.108 mM, determined by the solubility) were irradiated at 254 nm in quartz tubes under an argon atmosphere at temperatures ranging from −5 to 25 °C by using a 30-W low-pressure mercury lamp fitted with a Vycor filter. Each photolyzed sample was poured into a 10% aqueous KOH solution (5 mL), and the resulting mixture was extracted with pentane (1 mL). The organic extract was analyzed by gas chromatography on a Shimadzu CBP-20 (PEG) column for the *E*/*Z* ratio and then extracted with a 20% aqueous silver nitrate solution (2 mL) at 0 °C. The aqueous phase containing [Ag^+·**1E**] complex was washed twice with pentane (1 mL) and added to a 28% aqueous ammonia solution at 0 °C, and the liberated **1E** was extracted with pentane (0.5 mL). The ee of **1E** obtained was determined by chiral GC on a Supelco β-DEX 225 column.

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Supporting Information Available: Experimental details, syntheses, and ^{1}H and ^{13}C NMR spectra of **3a**−**c**, **4b**,**c**, **6a**,**b**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Tong, L. H. Inclusion Complextion and Photosensitization of Cyclooctene with β-Cyclodextrin 6-O-Benzeate. In *Final Rep. Inoue Photochirogenesis Project (ERATO, JST)* **2001**, *8*, 13.