Supramolecular enantiodifferentiating photoisomerization of cyclooctene with modified β-cyclodextrins: critical control by a host structure†

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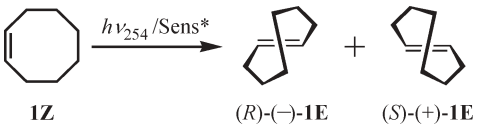
Enantiodifferentiating photoisomerization of (*Z*)-cyclooctene included and sensitized by *m*-methoxybenzoyl-β-cyclodextrin gave chiral (*E*)-isomers in up to 46% enantiomeric excess, which is the highest value ever reported for supramolecular photochirogenesis with analogous hosts, thus demonstrating the crucial role of the sensitizer-spacer moiety in supramolecular photochirogenic systems.

Supramolecular photochirogenesis has drawn considerable attention in recent years as an intriguing extension of chiral photochemistry.[1] In conventional chiral photosensitization, the transfer of chiral information occurs in an exciplex formed between an excited chiral sensitizer and a substrate, utilizing the weak excited-state interactions. In contrast, the chirality transfer in a supramolecular photochirogenic system can utilize the chiral host–guest interactions both in the ground and excited states. Various chiral hosts, such as chirally modified zeolites,[2] synthetic templates,[3] cyclodextrins (CDs),[4] proteins[5] and DNA[6] have been used as chirality sources to afford the photoproducts with good-to-excellent stereoselectivities. Of these chiral hosts, CDs are particularly attractive for the use in supramolecular photosensitization, possessing an inherently chiral hydrophobic cavity of appropriate size and, specifically, primary and secondary hydroxyl groups readily modifiable with a photosensitizer moiety.[7]

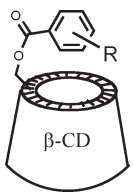
6-*O*-Modified CDs with benzoyl and isomeric phthaloyl groups have been used as chiral sensitizing hosts for the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1Z**) to give planar-chiral (*E*)-isomer (**1E**).[4e–f,8] These studies revealed that the enantioselectivity obtained upon supramolecular photosensitization of **1Z** with 6-*O*-benzoyl-β-CD is not sensitive to the temperature variation (due to the negligible contribution of the entropic term), but nicely correlates with the host occupancy.[1a,1c,4f,9] In contrast, the product's enantiomeric excess (ee) obtained upon sensitization with permethylated 6-*O*-benzoyl-β-CD regains the critical temperature dependence which is often reported for conventional photochirogenic reactions in homogeneous solution.[1c,e] Despite the intriguing mechanistic features revealed for supramolecular photochirogenesis with CD-based sensitizers, the enantioselectivity reported hitherto is rather modest (<25% ee) even as asymmetric synthesis in the excited state, which coincides with the fact that the CD's chiral recognition ability is low in general.



In the present study, we prepared a series of sensitizing β-CD hosts (Scheme 1) in order to fine tune the bulkiness of the sensitizer-spacer to be co-included with the substrate, and compared their behavior in supramolecular enantiodifferentiating photoisomerization of **1Z**, and found that the enantioselectivity is highly sensitive to the structural variation of the host as well as the temperature in this supramolecular photochirogenic system. Eventually, the use of *m*-methoxybenzoyl-β-CD as the sensitizing host doubled the highest enantioselectivity (23% ee) ever obtained for **1E** with a variety of sensitizer-appended CDs.

Modified β-CDs **3** and **4** were synthesized in 31.5% and 32.3% yield, respectively, by the reaction of β-CD with *m*- and *p*-methoxybenzoyl chlorides in dry pyridine and subsequent recrystallization.

We first investigated the complexation behavior of these modified β-CDs with **1Z** by means of circular dichroism spectral titrations. As exemplified in Fig. 1, host **3** exhibited a positive Cotton effect for the ^1L_a band (218 nm) but a negative effect for the ^1L_b band (234 nm) in 1 : 9 MeOH–H_2O. Interestingly, both the ^1L_a (219 nm) and ^1L_b (234 nm) bands showed negative Cotton effects in 1 : 3 MeOH–H_2O. According to the sector rule proposed by Kajtar *et al.*[10] (Scheme 2), this sign inversion of the ^1L_a band indicates that the chromophoric *m*-methoxybenzoyl moiety



1 R = H
2 R = *o*-OMe
3 R = *m*-OMe
4 R = *p*-OMe
5 R = *m*-CO_2Me

Scheme 1

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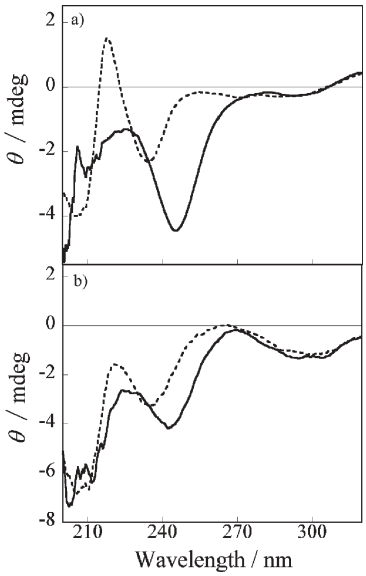
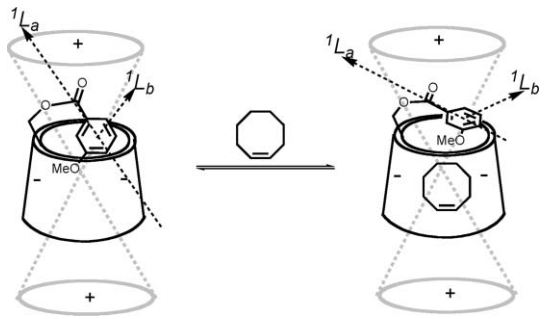


Fig. 1 Circular dichroism spectra of (a) 0.054 mM **3** in the absence (···) and presence (—) of 0.192 mM **1Z** in 10% MeOH, and (b) 0.071 mM **3** in the absence (···) and presence (—) of 0.192 mM **1Z** in 25% MeOH.



Scheme 2

penetrates more deeply into the chiral CD cavity in 10% MeOH than in more hydrophobic 25% MeOH.

Upon addition of **1Z**, the Cotton effect signals of both ^1L_a and ^1L_b bands became more negative, indicating that conformational changes are induced by the inclusion of **1Z** to make the *m*-methoxybenzoyl moiety more parallel, or the ^1L_b transition more perpendicular, to the axis of the CD cavity. From the differential circular dichroism spectral titration data obtained, the complex stability constants (K_s) for **1Z** in water–methanol mixtures were determined by using the least-squares fit. The K_s values for complexation of **1Z** with **3** are 23 100, 8200 and 4200 M^{-1} in 10%, 25% and 50% MeOH, respectively, and those for **4** are 20 200, 13 800 and 2430 M^{-1}, respectively.

Aqueous solutions (5 mL) of different methanol content, which contained **1Z** (1.5 mM) and a modified β-CD (0.054 to 0.108 mM), were irradiated at 254 nm in quartz tubes under an argon atmosphere at temperatures varying from +25 to −5 °C. The *E*/*Z* ratio and the ee of **1E** were determined by chiral capillary gas chromatography on a Shimadzu GC-2014 instrument fitted with a CBP-20 or a Supelco β-Dex225 column, respectively.[1b–c]

It turned out that the enantioselectivity is highly sensitive to the structure and position of the substituent introduced to the sensitizer moiety in modified β-CD. As shown in Table 1, sensitizer **3** which has a methoxy group at the *meta*-position gives **1E** in good (40.8%) ee in 10% MeOH at 25 °C, while its parent compound **1** and *ortho*- and *para*-isomers **2** and **4** afford only modest (4–10%) ee under identical conditions. It is also interesting to point out that the ee value falls drastically to 1.7% when the *meta*-substituent is altered from methoxy to methoxycarbonyl (host **5**). These observations reveal a clear dependence of the efficiency of chirality transfer on the structure of the sensitizer moiety in the supramolecular photosensitized isomerization system. The chromophore attached to modified β-CDs should act not only as a sensitizer but also as a space filler for adjusting the depth/position and orientation of guest penetration in the CD cavity so as to substantially affect the chirality induction in the guest substrate, and therefore the critical adjustment of the steric bulk and position of the substituent introduced to the chromophore is crucial as demonstrated in this work.

Upon prolonged irradiation, the *E*/*Z* ratio increased but the enantioselectivity slightly decreased. Both the *E*/*Z* ratio and the ee value increased on increasing the water content. Although the temperature effect upon the ee was only marginal, yet the irradiations at lower temperatures appreciably enhanced the ee value from −40.8% at 25 °C to −45.8% at −5 °C, which is much higher (almost doubled) than the prior highest (−23% ee) reported for the photosensitization with methyl phthaloyl-modified β-CD in 50% aqueous methanol at −40 °C.[4e] Such an enantioselectivity (*R*/*S* ratio = 2.7) is rather significant considering the fact that native β-CD and its derivatives bind various enantiomeric guests only with low enantioselectivities; the enantiomer ratio rarely exceeds 1.3.[11] Our finding is therefore indicative that the inherently poor chiral discrimination ability of β-CD in the ground state can be remarkably improved by utilizing the supramolecular interactions in both ground and excited states.

In this study, we have shown that the supramolecular photosensitized enantiodifferentiating isomerization of **1Z** is critically affected by an apparently small alteration of the host's substituent to give an unprecedentedly high ee of 46%, which is likely to be achieved by optimizing the ground- and excited-state chiral interactions within the CD cavity by fine-tuning the host structure, as well as the solvent and temperature. This investigation

Table 1 Enantiodifferentiating photoisomerization of **1Z** in the presence of modified β-CDs in methanol–water mixtures at various temperatures[a]

Host	Solvent (% MeOH)	Temperature/ °C	Irradiation time/min	*E*/*Z* ratio	% ee[b]
1[c]	0	25	5	0.05	−9.7
2[d]	50	25	5	0.19	4.3
3	10	25	5	0.07	−40.8
	10	0	5	0.19	−39.6
	10	−5	5	0.24	−45.8
	25	25	5	0.08	−33.3
	25	25	30	0.13	−31.1
	50	25	5	0.18	−30.2
	50	25	30	0.19	−26.3
4	10	25	5	0.12	−10.6
5[c]	50	25	2	0.21	−1.7

[a] Irradiated at 254 nm under argon in methanol–water mixture; [**1Z**] = 1.5 mM; [host] = 0.15–0.05 mM, varied depending on the solubility. [b] Sign of ee corresponds to that of the optical rotation of obtained **1E**. [c] Ref. 4*e*. [d] Ref. 9*b*.

will shed more light on the structure–enantioselectivity relationship and the strategy for enhancing the product's enantioselectivity in general supramolecular photochirogenesis.

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