

## Inclusion-Enhanced Optical Yield and *E/Z* Ratio in Enantiodifferentiating Photoisomerization of Cyclooctene Included and Sensitized by $\beta$ -Cyclodextrin Monobenzoate

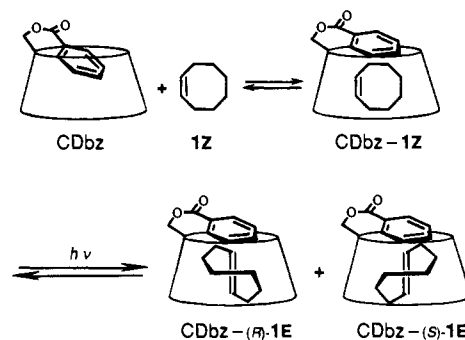
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Cyclodextrins (CDs), a series of cyclic oligomers of D-glucopyranose, are known to accommodate a variety of organic guests in their chiral hydrophobic cavities, forming inclusion compounds. Consequently, they have been applied widely to biomimetic chemistry as well as to separation science and technology, including chiral recognition.<sup>1–9</sup> In sharp contrast to the well-documented stoichiometric and catalytic thermal asymmetric syntheses utilizing the CD's chiral cavity,<sup>1,6,9–12</sup> little effort appears to have been devoted to the study of asymmetric photochemistry in the chiral cavity.<sup>9,13–15</sup> Only a few stoichiometric asymmetric photoreactions of CD complexes have hitherto been investigated in the solid state,<sup>13–15</sup> We have reported recently that the direct irradiation at 185 nm of a 1:1 complex of (*Z*)-cyclooctene (**1Z**) with  $\beta$ -CD in the solid state or in water suspension leads to prompt *Z*–*E* isomerization affording apparent photostationary-state (pss) *E/Z* mixtures, but that the (*E*)-isomer (**1E**) obtained is almost racemic: optical purity (op) < 1%.<sup>15,16</sup> It is then obvious that simple inclusion in CD is not sufficient to induce appreciable optical activity in the included prochiral guest during the photochemical transformation in the chiral cavity.

**Scheme 1.** Inclusion Complexation of (*Z*)-Cyclooctene (**1Z**) with  $\beta$ -Cyclodextrin 6-*O*-Monobenzoate (CDbz) and Sensitized Enantiodifferentiating Photoisomerization to **1E** within the Cyclodextrin Cavity



In the present study, we employed  $\beta$ -cyclodextrin 6-*O*-monobenzoate (CDbz)<sup>17</sup> as a novel photosensitizing host molecule carrying a chiral cavity. The use of the modified CD as a chiral sensitizing host in an aqueous solution leads to efficient energy transfer exclusively to the guest residing in the chiral cavity. In the absence of guest molecule, the benzoate appended as a potential sensitizer is embedded in the cavity<sup>17</sup> and is therefore protected from attack by substrate molecules that are placed outside in the bulk solution. Once included in the host cavity, a guest substrate is placed in close proximity to the benzoate moiety capping the cavity. Hence, both energy transfer to **1Z** and the subsequent enantiodifferentiating isomerization to **1E** are expected to be accomplished in much higher efficiency in the CDbz's chiral cavity (Scheme 1).

In a typical run, aqueous solutions (4 mL) containing **1Z** (2 mM) and CDbz<sup>17</sup> (0.2 mM) placed in quartz tubes were irradiated at 254 nm for given periods under an argon atmosphere in a water bath thermostated at 25 °C, using a 30-W mercury resonance lamp fitted with a Vycor filter. To each irradiated solution was added a 10% aqueous potassium hydroxide solution (1 mL), and the mixture was extracted with pentane (1 mL). The pentane extract, an aliquot of which was analyzed for *E/Z* ratio by gas chromatography (GC) on a 3-m  $\beta,\beta'$ -oxydipropionitrile column, was in turn extracted with a 20% aqueous silver nitrate solution (2 mL) at 0 °C. The aqueous extract was washed with pentane and then poured onto a concentrated aqueous ammonia solution at 0 °C to liberate **1E**, and the resultant mixture was extracted again with pentane (0.5 mL) (yield of **1E** based on consumed **1Z**: 80–95%; chemical purity, >99% by GC). The enantiomers of **1E** were separated satisfactorily by GC on a 30-m Supelco  $\beta$ -DEX 120 capillary column to give the enantiomeric excess (ee) of **1E** isolated; the GC response was calibrated with several mixed samples of (*R*)- and (*E*)-**1E** of known optical purities determined by using a polarimeter.

The *E/Z* ratios and ee values, obtained in the photosensitization in aqueous solutions of varying methanol–water compositions, are plotted as functions of irradiation time in Figure 1. As can be seen from the upper traces in Figure 1, **1Z** readily isomerizes to **1E** upon irradiation to afford distinctly different ultimate *E/Z* ratios at the photostationary state, (*E/Z*)<sub>pss</sub>, which depend critically on the solvent composition. The (*E/Z*)<sub>pss</sub> ratio increases with increasing water content up to 50% to give the highest value of 0.8 in 50% methanol solution and then decreases. It is noted that some of the (*E/Z*)<sub>pss</sub> ratios obtained in this study far exceed the typical values of 0.25–0.36 observed in the alkyl benzoate-sensitized photoisomerizations of **1Z** in

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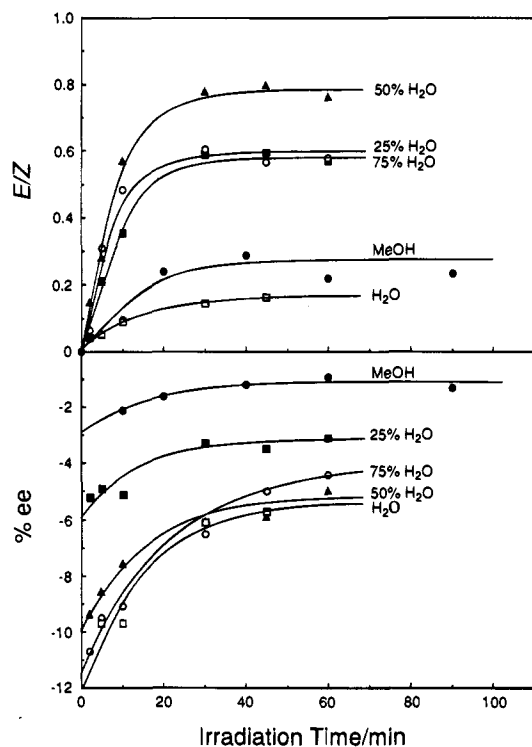
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**Figure 1.** *E/Z* ratios (upper traces) and % ee values (lower traces) obtained in enantiodifferentiating photoisomerizations of **1Z** sensitized by  $\beta$ -cyclodextrin 6-*O*-monobenzoate (CDBz) in water-methanol solutions of varying water content; 0% (●), 25% (■), 50% (▲), 75% (○), and 100% H<sub>2</sub>O (□). The sign of ee agrees with that of the optical rotation of **1E** produced; in this case, (*R*)-(–)-**1E** was obtained.

organic solvents<sup>18</sup> and are almost comparable to the highest *E/Z* ratio of 0.96 reported for the direct excitation in pentane at 185 nm.<sup>19</sup> These much enhanced (*E/Z*)<sub>ps</sub> ratios, though anomalously high<sup>18,19</sup> for a medium-sized cycloalkene whose (*E*)-isomer is highly strained,<sup>20</sup> would be accounted for in terms of the varied energy transfer rate from the excited benzoate moiety to included **1Z**, as the (*E/Z*)<sub>ps</sub> ratio is expressed as a product of the excitation ratio ( $k_{qZ}/k_{qE}$ ) and the decay ratio ( $k_{dE}/k_{dZ}$ ); i.e., (*E/Z*)<sub>ps</sub> = ( $k_{qZ}/k_{qE}$ )( $k_{dE}/k_{dZ}$ ).<sup>18,19</sup> However, this obvious dependence of (*E/Z*)<sub>ps</sub> upon solvent composition cannot be attributed to the preferential complexation and the subsequent excitation of **1Z** rather than **1E**, since **1E** shows a higher complex stability constant ( $K_s$ ) with CDBz than **1Z**. Thus the  $K_s$  values for **1Z** and **1E**, determined by titration using circular dichroism spectrometry,<sup>17</sup> are respectively 1440 and 2850 in 50% methanol and 20 100 and 38 100 in water.<sup>21</sup>

In the geometrical photoisomerization of **1** sensitized by various aromatic carboxylates in organic solvents where dynamic quenching dominates the energy transfer process, the energy transfer from the excited aromatic esters to strained **1E** is nearly diffusion controlled, while that to **1Z**, which possesses a higher singlet energy, is slower by a factor of 3–8.<sup>22</sup> That accounts for the observed small (*E/Z*)<sub>ps</sub> ratios of less than 0.35 in homogeneous solutions. By contrast, in the present case, where the sensitization and isomerization take place in a closely packed environment within the CD cavity, the rates of energy transfer, and probably isomerization, to **1E** and **1Z** must be affected

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distinctly differently by the guest's position and orientation in the cavity. However, the (*E/Z*)<sub>ps</sub> ratio shown in Figure 1 is not a simple function of the solvent composition or the complex stability; the ratio is enhanced substantially by increasing the water content up to 50%, but it dramatically decreases thereafter, regardless of the much greater complex stabilities in the solvents of higher water content. This indicates that the guest orientation and distance to the benzoate moiety, being different for **1E** and **1Z**, vary quite critically in the cavity depending upon the solvent composition. Probably these two parameters cannot always cooperate with each other, since deeper penetration leads in general to reduced freedom of the guest orientation in the cavity. Hence, the maximized (*E/Z*)<sub>ps</sub> ratio in 50% methanol solution is inferred to be materialized incidentally as a consequence of a trade-off between these two parameters for **1E** and **1Z**.

More interestingly, the ee value obtained in each solvent, shown also in Figure 1 (lower traces), not only depends on the solvent composition but also varies with the irradiation period. In all solvents employed, the % ee value decreases more or less with extending irradiation period, although the value is somewhat erratic especially at shorter irradiation periods, owing to the smaller sample size available at the early stages of reaction. Preferential inclusion and photoisomerization of (*R*)- rather than (*S*)-**1E** in the CD cavity<sup>23</sup> must be responsible at least in part for the gradual decrease in ee at the early stages of the photolysis, since the time dependence of ee becomes more conspicuous as the water content increases and the *E/Z* and ee values show analogous time profiles approaching a plateau upon prolonged irradiations.

On the other hand, the dependence of ee on the solvent composition is reasonably accounted for in terms of the CDBz's binding ability varying with the water content. The  $K_s$  value for **1Z** is estimated to be very small (<100 M<sup>-1</sup>)<sup>21</sup> in methanol but is much enhanced up to 1440 M<sup>-1</sup> in 50% aqueous methanol<sup>17</sup> and further to 20 100 M<sup>-1</sup> in water.<sup>21</sup> Accordingly, the proportions of the host occupied by guest **1Z** at the concentrations employed in the present study are calculated as <17, 73, and 98% in methanol, 50% methanol, and water, respectively. The product's ee developing rapidly with increasing water content from 0 to 50%, followed by the relatively slow growth thereafter, clearly indicates that the enantiodifferentiating photoisomerization occurs within the CDBz's capped chiral cavity, which seems essential to afford a high ee value.

Finally, it is emphasized that the ee's obtained in the present study, as high as 11%, are much higher than that (<0.5%) reported previously in the solid-state irradiation of the inclusion complex of **1Z** with  $\beta$ -CD,<sup>15</sup> and also that this photochemical enantiodifferentiating process is not stoichiometric but sensitized with a catalytic amount of the optically active host/sensitizer CDBz. We may conclude therefore that our strategy to append a chromophore to native CD and use it as a sensitizing chiral host in aqueous solution works well as a promising tool to enhance both the low (*E/Z*)<sub>ps</sub> ratio of the highly constrained cycloalkenes and the originally poor enantiodifferentiating ability of the CD's chiral cavity, and can be broadly applicable to asymmetric photochemistry using modified CDs.

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(23) The enantiodifferentiating complexation experiments with racemic (*E*)-cyclooctene (**1E**) were performed with  $\beta$ -CDBz as well as native  $\beta$ -CD. Addition of an equimolar amount of racemic **1E** to a saturated aqueous solution of CDBz produced a white precipitate of **1E**-CDBz complex, alkaline decomposition of which afforded (*R*)-(–)-**1E** of 1.88% ee, while similar complexation with native  $\beta$ -CD and the subsequent decomposition of the complex produced gave the antipodal (*S*)-(+)-**1E** of 0.46% ee.