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Entropy-Controlled Supramolecular Photochirogenesis: Enantiodifferentiating *Z*−*E* Photoisomerization of Cyclooctene Included and Sensitized by Permethylated 6-*O*-Modified *β*-Cyclodextrins

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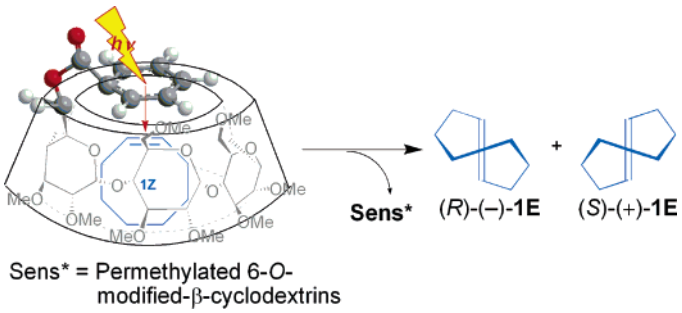

Permethylated 6-*O*-modified *β*-cyclodextrins **2a**−**2d** were synthesized as novel photosensitizing hosts with a flexible skeleton. Circular dichroism (CD) and 2D NMR spectral examinations of benzoate **2a** revealed that the benzoate moiety is deeply included into its own cavity in aqueous solution. Upon addition of (*Z*)-cyclooctene (**1Z**) to a 50% aqueous methanol solution of **2a** at 25 °C, the benzoate moiety of **2a** was gradually excluded from the cavity as indicated by the CD spectral changes; the Job's plot revealed the formation of a 1:1 complex of **2a** with **1Z**. The binding constants for the complexation of **1Z** by **2a** were determined by CD spectral titration in 50% aqueous methanol at various temperatures. The van't Hoff analysis of the obtained data afforded the thermodynamic parameters ($\Delta H° = -3.1$ kJ mol^{-1}, $\Delta S° = 48.5$ J mol^{-1} K^{-1}), demonstrating the entropy-driven complexation by the permethylated cyclodextrin. This is in sharp contrast to the complexation of **1Z** by nonmethylated *β*-cyclodextrin benzoate that is driven by enthalpy ($\Delta H° = -31.8$ kJ mol^{-1} and $\Delta S° = -51.1$ J mol^{-1} K^{-1}). Upon supramolecular photosensitization with **2a**−**2d**, **1Z** isomerized to the (*E*)-isomer (**1E**) in moderate enantiomeric excesses (ee's), which however displayed significant temperature dependence with accompanying switching of the product's chirality in an extreme case. Such dynamic behavior of ee is very different from that reported for the photosensitization with nonmethylated cyclodextrin benzoate, where the product's ee is controlled by host occupancy. Eyring treatment of the ee obtained at various temperatures (<0 °C) gave the differential activation parameters for the enantiodifferentiation process occurring in the supramolecular exciplex, revealing the crucial role of entropy, as indicated by the $\Delta\Delta S^{\ddagger}$ value changing dynamically from +4 to −24 J K^{-1} mol^{-1}. The origin of the contrasting behavior of permethylated versus nonmethylated cyclodextrin hosts is inferred to be the conformational flexibility of the former host, which enables the entropy-driven guest complexation in the ground state and the entropy-controlled enantiodifferentiation in the excited state.

Introduction

Photochirogenesis,[1] or asymmetric synthesis through an electronically excited state, provides a unique access to optically active compounds, which is alternative to the well-established thermal and enzymatic methods,[2] although the reported optical yields had been low since the very first work by Hammond and Cole.[3] Our previous studies on the enantiodifferentiating geometrical photoisomerization of (*Z*)-cyclooctene (**1Z**) with an optically active sensitizer (Scheme 1) revealed a dramatic temperature dependence of the enantiomeric excess (ee) of

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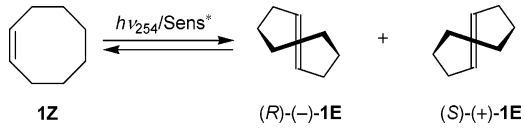
SCHEME 1. Enantiodifferentiating Geometrical Photoisomerization of 1Z Sensitized by Chiral Photosensitizer



produced (*E*)-isomer (**1E**), often accompanying an inversion of the product's absolute configuration.[4] This unprecedented chirality switching by temperature was accounted for in terms of the difference in activation entropy between the diastereomeric transition states formed from **1Z** and an excited chiral sensitizer.[4] More recent studies have led to the concept of multidimensional entropy control of photochirogenesis,[5] in which the entropy-related factors, such as temperature,[4,6] solvation,[7] and pressure,[8] are jointly used to enhance the product's ee.[6]

From the entropic point of view, supramolecular hosts are of particular interest[9,10] because of their well-defined nanopores that have inherently low-entropy environment. Hence, we have focused on the supramolecular photochirogenesis using native and modified cyclodextrins.[1h,11] In the enantiodifferentiating photoisomerization of **1Z** included and sensitized by β-cyclodextrin benzoates, **1E** was obtained in moderate ee's of up to 24%,[11d] which are significantly higher than the practically zero ee obtained upon direct irradiation at 185 nm of **1Z** accommodated in native β-cyclodextrin.[11b] Intriguingly, the product's ee does not depend on the irradiation temperature or solvent but is nicely correlated with the host occupancy or the percentage of occupied host. This unexpected behavior, which is in sharp contrast to the dynamic temperature dependence of ee in the conventional photosensitization with chiral compounds,[4−7] is thought to be an intrinsic feature of the supramolecular photochirogenesis in confined media, where the molecular motions and freedoms of both host and guest are greatly reduced. Such an idea is reinforced by the similar observation in supramolecular photochirogeneses within rigid supercages of chirally modified zeolites.[12] This seems reasonable since the role of entropy is much reduced in inherently low-entropy nanopores, which on the other hand does not allow us to manipulate the supramolecular photochirogenic processes by the external factors.

However, more recently we have found that the supramolecular photosensitization of **1Z** with permethylated 6-*O*-benzoyl-β-cyclodextrin **2a** (Chart 1) displays a critical dependence of product's ee upon temperature to give a large differential entropy of activation (-11 J K^{-1} mol^{-1}), for which the flexible host skeleton, as a consequence of the loss of the hydrogen-bond network around the cyclodextrin's secondary rim,[13] is likely to be responsible.[11j] Through this new strategy to use a flexible host in supramolecular photochirogenesis, we can retrieve the unique ability of photochemistry to dynamically manipulate the stereochemical outcomes of photochirogenesis by environmental variants without losing the advantage of potentially enantioface- or enantiotopos-discriminating complexation with chiral host in the ground state prior to the enantiodifferentiating photochemical process.

In the present study to explore the scope and limitations of this new idea of "entropy-controlled supramolecular photochirogenesis" and also to elucidate the mechanism and factors that control such processes, we synthesized a series of flexible permethylated cyclodextrin derivatives with tethered aromatic moieties (**2a**−**2d**; see Chart 1), examined their complexation behavior with the substrate (**1Z**), and performed the supramolecular enantiodifferentiating *Z*−*E* photoisomerization of **1Z** sensitized by **2a**−**2d** under a variety of conditions. The results are discussed to elucidate the complexation and photochirogenesis behavior of the flexible chiral cavity of methylated cyclodextrins, as well as the positive role of entropy-related factors.

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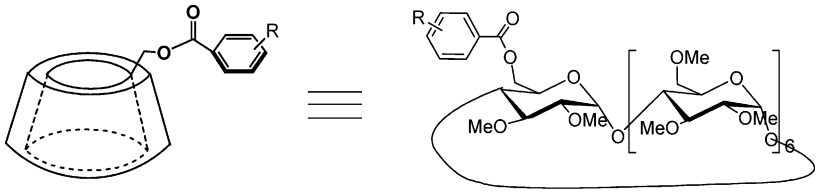
CHART 1. Permethylated 6-*O*-Modified β-Cyclodextrins as Novel Sensitizing Hosts



2a R = H
2b R = *o*-CO_2Me
2c R = *m*-CO_2Me
2d R = *p*-CO_2Me

Results and Discussion

Sector Rule Applied to Permethylated Cyclodextrin. Inclusion of a chromophoric compound in the cyclodextrin cavity leads in general to appreciable induced circular dichroism (ICD) at its absorption band, a sign of which can be used as a convenient tool for elucidating the orientation of the included chromophoric moiety.[14] An aromatic moiety appended to cyclodextrin also displays ICD signals upon inclusion, from which we can assess the relative location and orientation of the chromophore tethered to cyclodextrin.[11d,15,16] Permethylated 6-*O*-benzoyl-β-cyclodextrin **2a** showed strong and weak ICD extrema at wavelengths corresponding to the ^1L_a and ^1L_b bands, respectively. We wanted to determine the orientation of the benzoate moiety in the permethylated cyclodextrin cavity by expanding the sector rule, which was originally proposed for native cyclodextrins by Kajtar et al.,[17] to these ICD signals. However, to the best of our knowledge, the sector rule has not been applied to the sign of ICD caused by permethylated cyclodextrins. Recently, Mieusset et al. elucidated the structure of a permethylated β-cyclodextrin complex with *endo*-8-azibicyclo[3.2.1]octan-3-ol in solution by the NMR ROESY technique but did not discuss the ICD signals.[18] We therefore decided to investigate the CD spectral behavior of benzoic acid included in permethylated β-cyclodextrin, which was related to the complex structure determined by ROESY to test the validity of the sector rule. As can be seen from the ROESY spectrum of a permethylated β-cyclodextrin−benzoic acid complex in a highly acidic D_2O solution (Figure 1a), the aromatic H*o* and H*m* protons gave clear cross-peaks and H*p* a weak one with the cyclodextrin's H_3 protons located near the secondary rim, while only the H*o* protons showed appreciable NOE contact with H_5 protons near the primary rim. These results reveal that benzoic acid is deeply included into the cyclodextrin cavity, and its long axis is aligned along the cavity axis with the carboxylic acid moiety pointing to the primary rim, as illustrated in Figure 1c. The strong positive and weak negative ICD signals observed at the ^1L_a and ^1L_b bands (Figure 1b) are exactly the same as those observed with native cyclodextrins,[19] thus confirming that the sector rule is applicable to permethylated cyclodextrins.

Conformation of 2a. The CD intensity and *g* factor of the ^1L_a transition of **2a** gradually increased to the positive side as the solvent polarity was increased from methylcyclohexane to aqueous methanol of different compositions (Figure 2a), while the corresponding UV−vis peak showed appreciable bathochromic shifts in more polar solvents. Very similar trends were observed for the variable temperature UV−vis, CD, and *g* factor profiles of **2a** (Figure 2b). Thus, the λ_{max} shifted from 229 nm in methylcyclohexane to 232 nm in 25% MeOH, and a similar, but less-pronounced, bathochromic shift was observed for the VT UV−vis spectroscopy of the ^1L_a band (Figure 2).

More polar solvent or lower temperature facilitates inclusion of the benzoate moiety into the cavity, leading to a bathochromic shift and a positive ICD signal at the ^1L_a band (according to the expanded sector rule), whereas less polar solvent or higher temperature accelerates exclusion of the chromophore from the cavity, resulting in a hypsochromic shift and a negative ICD. Now, the apparently strange CD "couplet"[20] is better rationalized by a spectral sum of the mutually equilibrating "phenyl-in" and "phenyl-out" complexes, which produce a positive ICD at longer λ and a negative ICD at shorter λ, respectively, as illustrated in Scheme 2. Their population can be manipulated by changing the hydrophilicity and temperature of solvent. Indeed, the equilibration shift was confirmed by the 2D NMR technique (Supporting Information S2). The ROESY spectrum of **2a** in a 1:1 mixture of CD_3OD and D_2O showed NOE contacts of H*m* and H*p*, but not H*o*, of the benzoate moiety with the inner H_5, indicating the shallow penetration from the primary side of cyclodextrin. The equilibrium constant (*K*) for the phenyl-in

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(20) The detailed discussion was given in Supporting Information (S1).

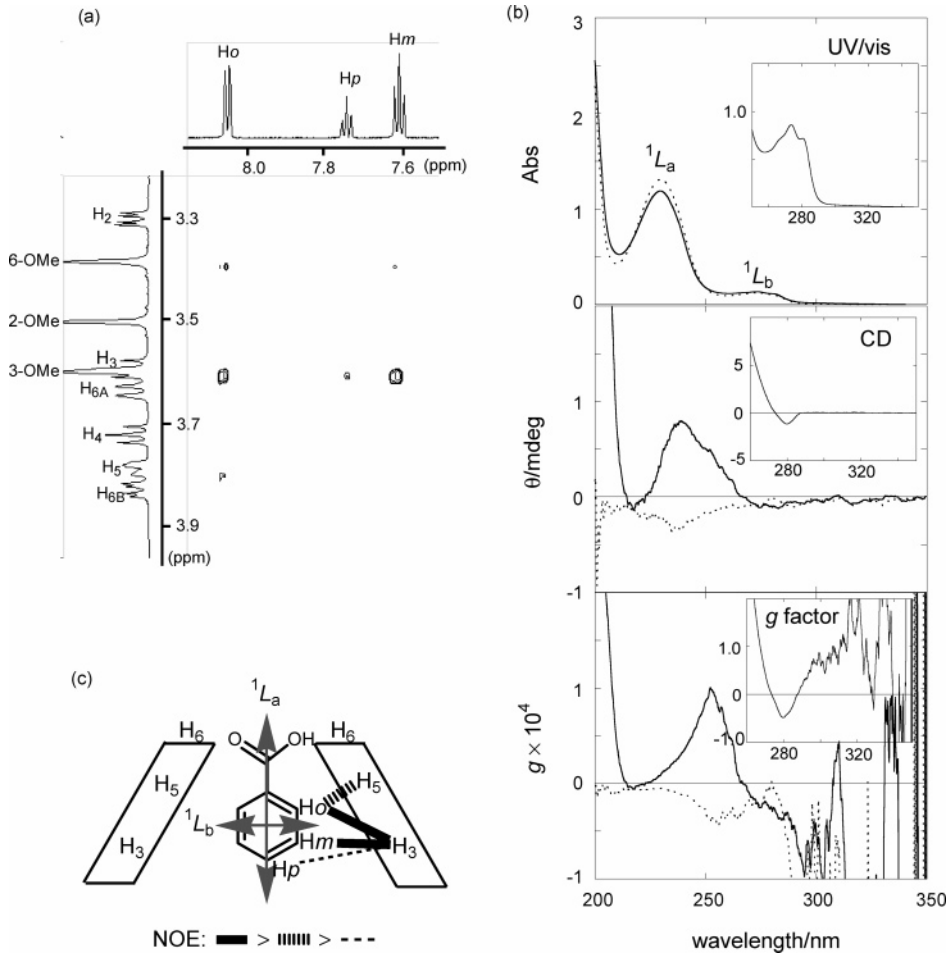

FIGURE 1. (a) ROESY spectrum of a equimolar mixture of benzoic acid (12.4 mM) and permethylated β-cyclodextrin (12.1 mM) in a D_2O solution containing 0.01 M DCl (mixing time = 1.0 s). (b) UV−Vis and CD spectra and anisotropy (g) factor profile of an aqueous benzoic acid solution (0.12 mM) in the absence (dotted line) and presence of a large excess amount of permethylated β-cyclodextrin (solid line) in an aqueous HCl (0.01 M) solution at 25 °C, using a 1 cm quartz cell; the inset shows the spectra of a benzoic acid solution (8.43 mM) containing a large excess amount of permethylated β-cyclodextrin, measured with a 1 mm quartz cell under the same conditions. Note that a negative dip is clearly seen at 280 nm. (c) A plausible structure of the complex of permethylated β-cyclodextrin with benzoic acid, elucidated from the ROESY spectrum. Although overlapping of H_3 and 3-OMe peaks made the assignment of the ROESY peaks difficult, we could correlate the two major cross-peaks to H*o* and H*m*, taking into account the structural features of relevant cyclodextrin protons and that the 3-OMe substituent is located outside the cavity and therefore difficult to reach the H*o* or H*m* protons, while H_3 located inside the cavity is readily accessible to the aromatic protons.

complexation can be written as follows:

$$\text{phenyl-out} \overset{K}{\rightleftharpoons} \text{phenyl-in}$$

$$K = [\text{phenyl-in}]/[\text{phenyl-out}] = \alpha(\Delta\epsilon_{245}/|\Delta\epsilon_{225}|) \quad (1)$$

where the $\Delta\epsilon_{245}/|\Delta\epsilon_{225}|$ ratio is used as a quantitative measure of the relative concentration of phenyl-in versus phenyl-out complex and α is an operational parameter for adjusting the difference in molar circular dichroism of the two species at each λ. By combining eq 1 with the Gibbs−Helmholtz equation ($\Delta G = \Delta H° - T\Delta S° = -RT\ln K$), we obtain

$$\ln(\Delta\epsilon_{245}/|\Delta\epsilon_{225}|) = -\Delta H°/RT + \Delta S°/R - \ln\alpha \quad (2)$$

According to eq 2, natural logarithms of the $\epsilon_{245}/|\Delta\epsilon_{225}|$ ratios obtained at 10−45 °C were plotted against the reciprocal temperature to give a good straight line, as shown in Figure 3. Although K and $\Delta S°$ cannot be determined due to the unknown α, the enthalpic change is determined from the slope of the plot as $\Delta H° = 9.9$ kJ mol^{-1}. Despite the positive $\Delta H°$, obviously the phenyl-in complex is formed in polar solvents, and hence the inclusion of the phenyl moiety into the permethylated cyclodextrin cavity should induce an entropic gain large enough to overcome the enthalpic loss. One of the most plausible sources of such a large entropic gain is the extensive desolvation from the permethylated cyclodextrin cavity, which is deeper than the native one.

Inclusion Complexation of 1Z with 2a. The complexation stoichiometry of **1Z** with **2a** was determined in 50% aqueous methanol by the Job's analysis.[23] Eight solutions, containing **2a** and **1Z** in different ratios, were prepared, keeping the total concentration at 0.148 mM. UV−vis spectral changes at 225 nm of these samples were plotted as a function of the mole fraction of **2a** to give a peak at 0.5 (Figure 4), indicating the

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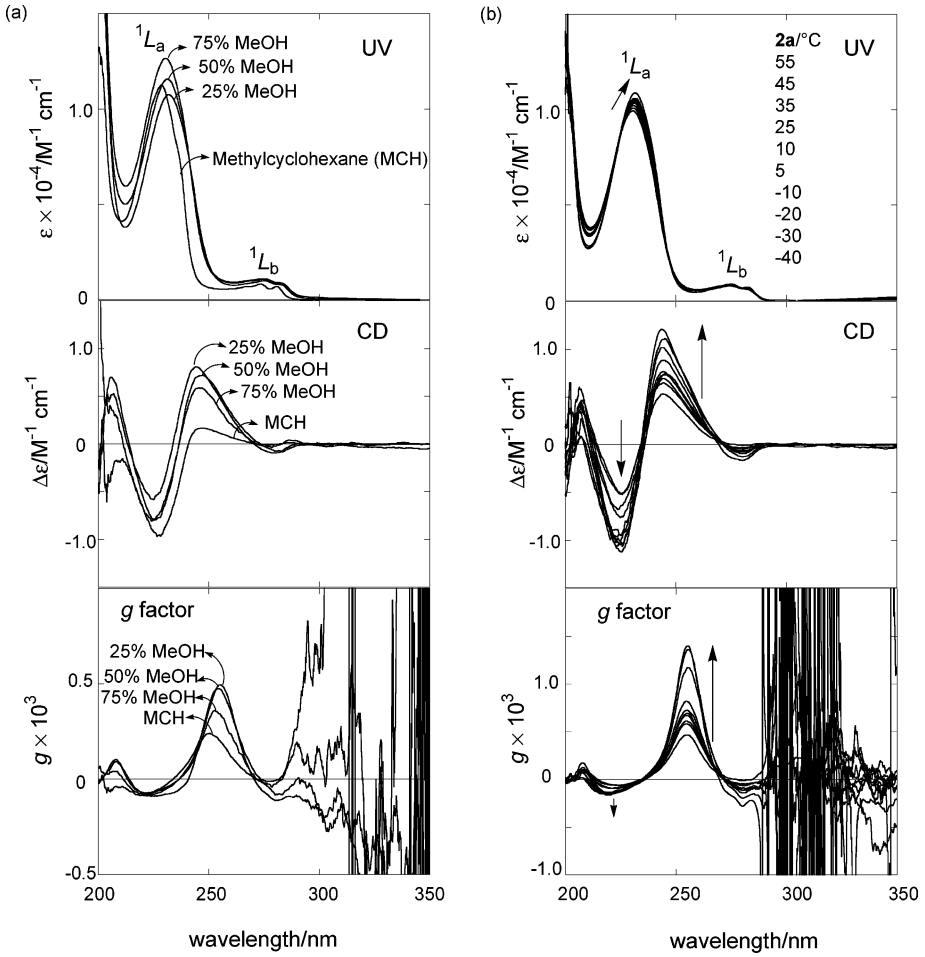


FIGURE 2. (a) UV−vis and CD spectra and *g* factor profile of **2a** in methylcyclohexane ([**2a**] = 0.193 mM), 3:1 MeOH−H_2O (0.074 mM), 1:1 MeOH−H_2O (0.078 mM), and 1:3 MeOH−H_2O (0.198 mM) at 25 °C and (b) of **2a** (0.2 mM) in 1:1 MeOH−H_2O at temperatures varying from 55 to −40 °C.

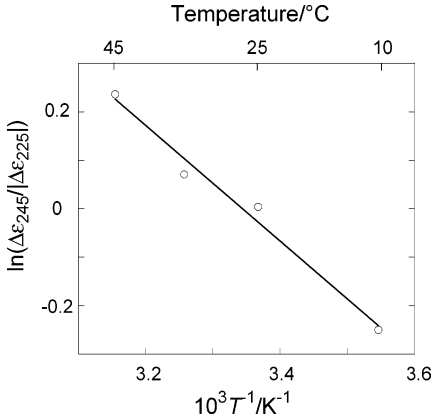


FIGURE 3. van't Hoff plot for the equilibrium between phenyl-in and phenyl-out conformers (correlation coefficient *r* 0.991).

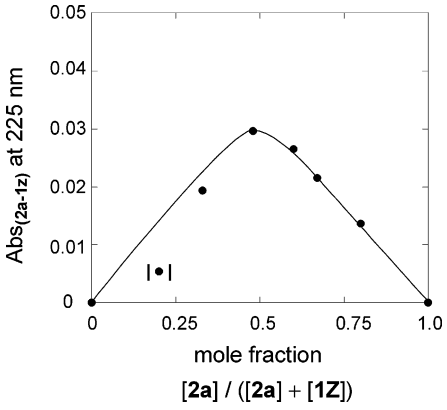
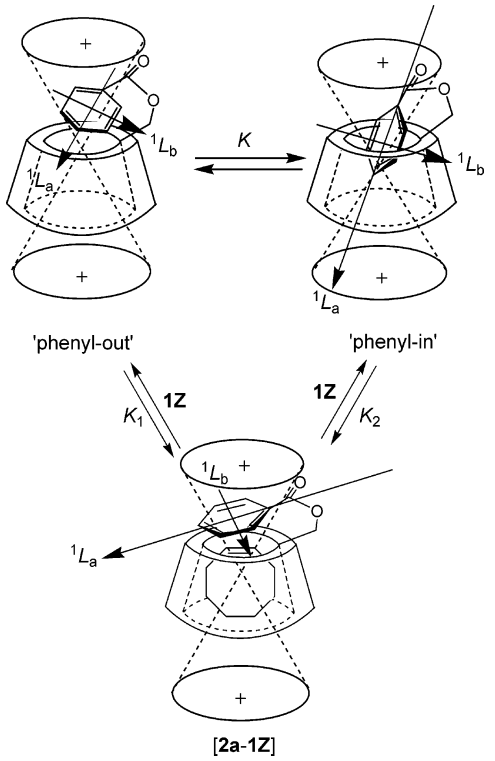


FIGURE 4. Job's plot of the absorbance changes at 225 nm upon complexation of **1Z** with **2a** in 50% aqueous methanol at 25 °C. [**2a**] + [**1Z**] = 0.148 mM. The deviation on the low [**2a**]/([**2a**] +[**1Z**]) side is likely to be responsible for the absorption by an increasing amount of **1Z** at the observing wavelength of 225 nm.

formation of a 1:1 complex. This is consistent with the stoichiometry obtained upon complexation of **1Z** with native *β*-cyclodextrin[11b] and 6-*O*-benzoyl-*β*-cyclodextrin reported previously,[11d] despite the permethylated *β*-cyclodextrin's more flexible skeleton and deeper cavity.

The inclusion of a guest by **2a** is somewhat complicated, as there is a pre-equilibrium between the phenyl-in and phenyl-out conformers. Thus, the 1:1 complexation of **1Z** with **2a** would proceed through the two routes via phenyl-in or phenyl-out conformer with different equilibrium constants (K_1 and K_2), as shown in Scheme 2. However, the inclusion of **1Z** is energetically much easier for the phenyl-out host with a vacant cavity than for the phenyl-in host with a cavity filled with the benzoate moiety. It is likely therefore that the major path of complexation

SCHEME 2. Sector Rule Applied to the ^1L_a and ^1L_b Transitions of 2a in Phenyl-in and Phenyl-out Conformations and of a 1:1 [2a−1Z] Complex



by **2a** involves the phenyl-out host and the phenyl-in mostly serves as a reservoir that supplies the phenyl-out, and the direct path from the phenyl-in will be negligible. Furthermore, the NMR data indicated that the in−out interconversion is fast on the NMR time scale. Thus, the VT NMR spectra of a 1:1 mixture of **2a** and **1Z** in 1:1 CD_3OD-D_2O at 25 to −40 °C did not show any coalescence behavior or peak separation at least in this temperature range; see Figure S3a (25 °C) and S3b (−40 °C) in Supporting Information. Hence, it is reasonable to assume that the phenyl-out conformer more readily forms a complex with the guest than the sterically hindered phenyl-in conformer.

Indeed, the CD and differential CD spectra and *g* factor profile of **2a** smoothly change their shape/intensity upon gradual additions of **1Z** with accompanying isodichroic point at 235 nm, as shown in Figure 5. The dramatic decreases in CD intensity at 225 and 245 nm upon addition of **1Z** are attributed to the losses of both phenyl-in and phenyl-out conformers, while the weak positive and negative CD peaks at 220−240 and 260−280 nm, remaining at high **1Z** concentrations, may be assigned to the [**2a**−**1Z**] complex.

Nonlinear least-squares calculations of the CD intensity changes upon addition of **1Z** give the complex stability constants (K_1), as exemplified for the [**2a**−**1Z**] complex in Figure 5d (for a similar treatment with [**2a**−**1E**] complex, see Supporting Information S4−9). In the case of [**2a**−**1Z**] complex formation in methanol, the modified Beneshi−Hildebrand[24] eq 3 was used for determining the very low complex stability constant K_1 (see Supporting Information S10). The stability constants (K_1) and the free energy changes ($-\Delta G°$) thus obtained are listed in Table 1. Compared to nonmethylated 6-*O*-benzoyl-*β*-cyclodextrin, permethylated **2a** exhibits slightly lower affinities to both of **1Z** and **1E** guests in 50% aqueous methanol at 25 °C.

$$\mathrm{H} + \mathrm{G} \overset{K_1}{\rightleftharpoons} \mathrm{HG}$$

$$\frac{[\mathrm{H}]_0}{\theta_{\mathrm{HG}}} = \frac{1}{K_1 \Delta\epsilon'_{\mathrm{HG}}[\mathrm{G}]} + \frac{1}{\Delta\epsilon'_{\mathrm{HG}}}$$

$$([\mathrm{G}] \gg [\mathrm{H}]_0,\ \Delta\epsilon'_{\mathrm{HG}} = \Delta\epsilon_{\mathrm{HG}} \times 32980) \qquad (3)$$

Thermodynamic Parameters. The complexation behavior of **2a** with **1Z** in aqueous solution containing 25 and 50% methanol was also investigated at 5 and 45 °C, and the natural logarithms of obtained K_1 were plotted against the reciprocal temperature to give good straight lines, as shown in Figure 6. From the slope and intercept of the plot, we obtained the thermodynamic parameters listed in Table 2, along with the data for nonmethylated 6-*O*-(*o*-methoxycarbonylbenzoyl)-*β*-cyclodextrin.[11d] Intriguingly, the temperature dependence of K_1 is very small in both solvents, and hence the enthalpy changes are only slightly negative. In contrast, the entropy changes are highly positive, dominating the complex stability. Thus, the inclusion complexation by **2a** is totally entropy-driven, which is quite different from the enthalpy-driven complexation by nonmethylated cyclodextrins (see Table 2). The large positive entropic gain for the permethylated host is tentatively attributed to the extensive desolvation upon complexation and/or the induced fit, dynamic structural changes of the flexible host skeleton upon guest inclusion. It is to note that the entropic contributions are much more important upon guest inclusion by permethylated cyclodextrins than that by native ones.

Enantiodifferentiating Photoisomerization. Enantiodifferentiating geometrical photoisomerization of **1Z** included and sensitized by permethylated sensitizing hosts **2a**−**2d** (Scheme 3) was performed under a variety of solvent and temperature conditions, and the results are listed in Table 3. Although the enantiomeric excesses (ee's) of obtained **1E** are low in general, photosensitizations with **2a** clearly indicate that solvent and temperature are the crucial factors that determine the product's ee. Thus, the use of methanol as a solvent leads to almost racemic product, irrespective of the irradiation temperature. However, the photosensitization with **2a** in aqueous methanol solutions gave **1E** in better ee's of up to 8.9%, and more interestingly, the product's ee did not depend on the host occupancy and the product chirality was switched in 50% aqueous methanol just by changing the temperature. The latter observations are in sharp contrast to those reported previously for the enantiodifferentiating photoisomerization of **1Z** included and sensitized by nonmethylated sensitizer-modified cyclodextrins, in which the product's ee was determined only by the host occupancy.[11d] More recently, we have revealed the temperature switching of product chirality in enantiodifferentiating

(22) (a) Petter, R. C.; Salek, J. S.; Sikorski, C. T.; Kumaravel, G.; Lin, F.-T. *J. Am. Chem. Soc.* **1990**, *112*, 3860. (b) McAlpine, S. R.; Garcia-Garibay, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4269. (c) Bügler, J.; Sommerdijk, N. A. J. M.; Visser, A. J. W. G.; van Hoek, A.; Nolte, R. J. M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1999**, *121*, 28. (d) Liu, Y.; Fan, Z.; Zhang, H.-Y.; Diao, C.-H. *Org. Lett.* **2003**, *5*, 251. (e) Liu, Y.; Fan, Z.; Zhang, H.-Y.; Yang, Y.-W.; Ding, F.; Liu, S.-X.; Wu, X.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 8345. (f) Miyauchi, M.; Harada, A. *J. Am. Chem. Soc.* **2004**, *126*, 11418.

(23) (a) Job, P. *Ann. Chim.* **1928**, *9*, 113. (b) Gil, V. M. S.; Oliveira, N. C. *J. Chem. Educ.* **1990**, *67*, 473. (c) Djedaïni, F.; Lin, S. Z.; Perly, B.; Wouessidjewe, D. *J. Pharm. Sci.* **1990**, *79*, 643.

(24) (a) Beneshi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703. (b) Person, W. B. *J. Am. Chem. Soc.* **1965**, *87*, 167.

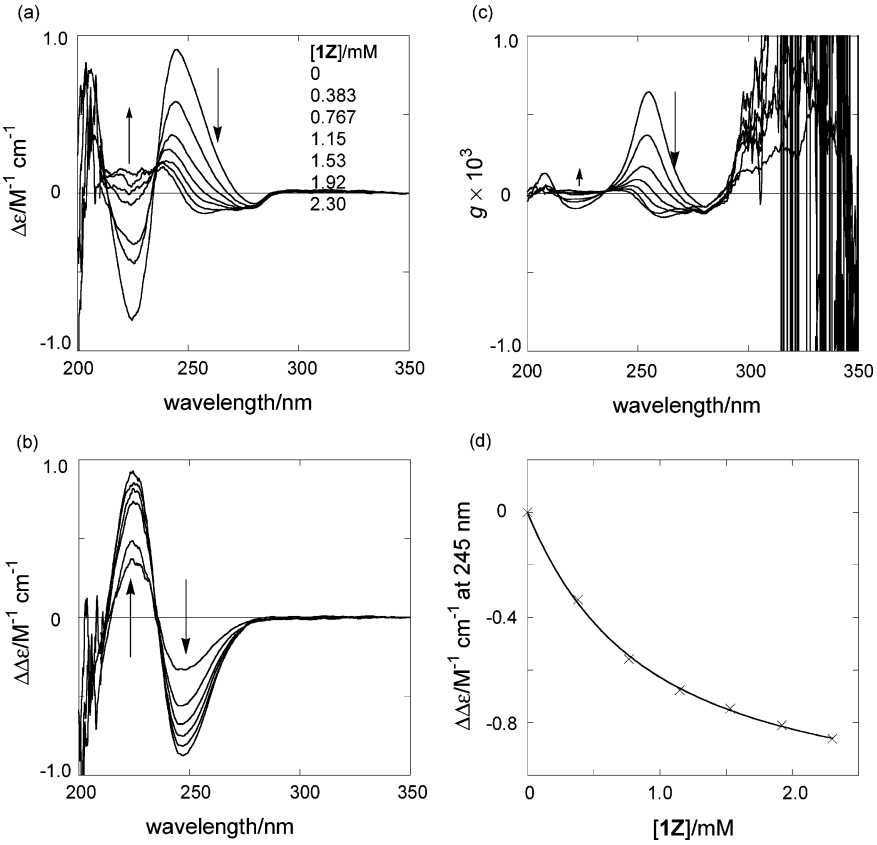


FIGURE 5. (a) CD spectra, (b) differential CD spectra, and (c) *g* factor profiles of a 50% aqueous methanol solution of **2a** (0.148 mM) upon addition of 0−2.3 mM **1Z** in 50% aqueous methanol at 5 °C. (d) Plot of the differential CD intensity at 245 nm as a function of [**1Z**], from which the complex stability constant was determined as 1300 ± 80 M^{-1} by using the nonlinear least-squares fitting technique.

TABLE 1. Complex Stability Constants (K_1) and Free Energy Changes ($-\Delta G°$) for 1:1 Inclusion Complexation of (*Z*)-Cyclooctene (1Z) and (*E*)-Cyclooctene (1E) with Permethylated 6-*O*-Benzoyl-*β*-cyclodextrin (2a) and Nonmethylated 6-*O*-Benzoyl-*β*-cyclodextrin in Methanol−Water Mixtures at 5−45 °C

host	guest	solvent	temp (°C)	K_1 (M^{-1})	$-\Delta G°$ (kJ mol^{-1})
2a	**1Z**	MeOH	5	4.58[a]	3.77[a]
		50% MeOH	45	1100	18.5
			25	1180	17.5
			5	1300	16.6
		25% MeOH	45	4070	22.0
			25	4890	21.0
			5	5420	20.0
	1E	50% MeOH	25	1580	18.2
6-*O*-benzoyl-*β*-cyclodextrin[b]	**1Z**	50% MeOH	25	1440	18.0
	1E	50% MeOH	25	2850	19.7

[a] Calculated by the modified Beneshi−Hildebrand eq 3. [b] From ref 11d.

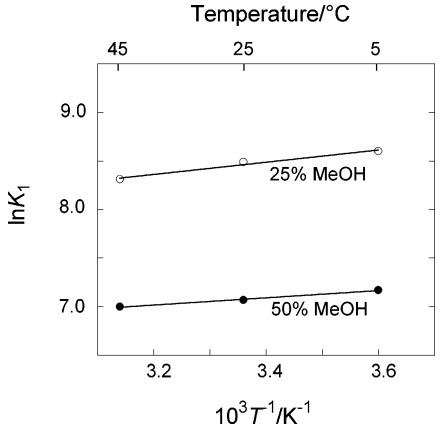


FIGURE 6. van't Hoff plots of stability constant K_1 in 50% MeOH (●) and 25% MeOH (○) at 5, 25, and 45 °C; correlation coefficient: 0.997 (50% MeOH); 0.987 (25% MeOH).

[4 + 4] photocyclodimerization of 2-anthracenecarboxylate mediated by modified *γ*-cyclodextrin, for which the larger, more flexible, skeleton of *γ*-cyclodextrin could be responsible.[11i] In the present study, the remarkable temperature dependence of ee and the product chirality switching were observed for a smaller (6-*O*-modified) *β*-cyclodextrin system, clearly demonstrating for the first time the significant role of entropy even in the supramolecular environment, as was the case with the enantiodifferentiating photoisomerization of **1Z** by chiral benzenepolycarboxylates[4−8] and with the enantiodifferentiating photoaddition of methanol to 1,1-dyphenylpropene[5,25] in homogeneous solutions.

Upon sensitization with *o*-, *m*-, and *p*-methoxycarbonylbenzoyl-modified *β*-cyclodextrins **2b**−**2d**, the product ee's were again highly temperature dependent, and the product chirality switching was observed for **2c** within the experimental temperature range employed.

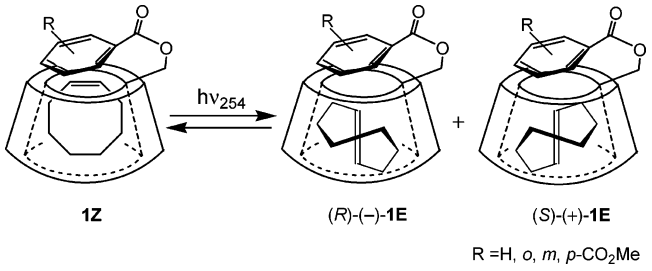
(25) (a) Asaoka, S.; Kitazawa, T.; Wada, T.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8486. (b) Asaoka, S.; Wada, T.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 3008.

TABLE 2. Thermodynamic Parameters for Inclusion Complexation of (*Z*)-Cyclooctene (1Z) with Permethylated 6-*O*-Benzoyl-*β*-Cyclodextrin (2a) in Methanol−Water Mixture

	6-*O*-(*o*-Methoxycarbonylbenzoyl)-*β*-Cyclodextrin[a]		**2a**	
solvent	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J mol^{-1} K^{-1})	$\Delta H°$ (kJ mol^{-1})	$\Delta S°$ (J mol^{-1} K^{-1})
MeOH	−30.8	−78.5		
50% MeOH	−31.8	−51.1	−3.1	48.5
25% MeOH			−5.2	52.8

[a] From ref 11d.

SCHEME 3. Supramolecular Enantiodifferentiating Photoisomerization of 1Z Sensitized by 2a−2d



Irradiation Time Dependence of Enantiomeric Excess and *E*/*Z* Ratio. As shown in Figure 7, the ee value did not show any dependence on irradiation time in pure methanol and in 50% aqueous methanol. This means that no appreciable kinetic resolution occurred in the reverse photoisomerization of produced **1E** to **1Z**. However, in 25% methanol solution, the product's ee showed clear deterioration upon prolonged irradiations, indicating that the reverse photoreaction is enantioselective with a preference for the same enantiomer produced in the forward reaction. This is probably because stronger binding in this more hydrophilic solvent enhances the chiral recognition of **1E** by the cyclodextrin cavity.

In all examined cases, the *E*/*Z* ratio increased with increasing irradiation time to reach a plateau after 30−60 min, from which we determined the photostationary state *E*/*Z* ratio, $(E/Z)_{pss}$. The $(E/Z)_{pss}$ ratio was a critical function of solvent and increases with increasing solvent polarity (water content). The relatively low $(E/Z)_{pss}$ ratios (0.08−0.29) and the very low ee values (≤1.1%) obtained in pure methanol are attributable to the photosensitization outside the cyclodextrin cavity since the aromatic moiety appears to remain outside of the cavity of **2a** even at −40 °C as indicated by the extremely weak CD signals. These values are sensible for "outside" photosensitization caused by "free host", in which permethylated *β*-cyclodextrin functions as a simple chiral auxiliary appended to the benzoate sensitizer, as the conventional photosensitizations with optically active alkyl benzoates are known to give comparable $(E/Z)_{pss}$ ratios of 0.1−0.2 and ee's of 0−3%.[6a] On the other hand, the much higher $(E/Z)_{pss}$ ratios (0.43−0.80) obtained in 50 and 25% methanol solutions are comparable to those obtained with nonmethylated modified cyclodextrins, which was accounted for in terms of the much accelerated energy transfer particularly to **1Z** in the confined environment.[11d]

Confirmation of "Free" and "Occupied" Host. To more clearly demonstrate the existence of free and occupied host, we examined the UV−vis (not shown) and CD spectra and *g* factor profile of **2a** (0.2 mM) in the presence of **1Z** (2.0 mM) under the conditions employed in photoirradiation (Figure 8). By lowering the temperature from 55 to 35 °C, the positive ICD signal at the ^1L_a band attributed to the phenyl-in host is slightly increased in intensity, probably due to the equilibrium shift from the phenyl-out to the phenyl-in conformer. However, further cooling to −40 °C led to significant decrease in intensity to eventually give a negative ICD peak, which is attributable to the [**2a**−**1Z**] complex. This temperature-dependent chiroptical property switching behavior is more clearly seen from the *g* factor profiles shown in Figure 8 (bottom). These results are fully compatible with the inclusion mechanism shown in Scheme

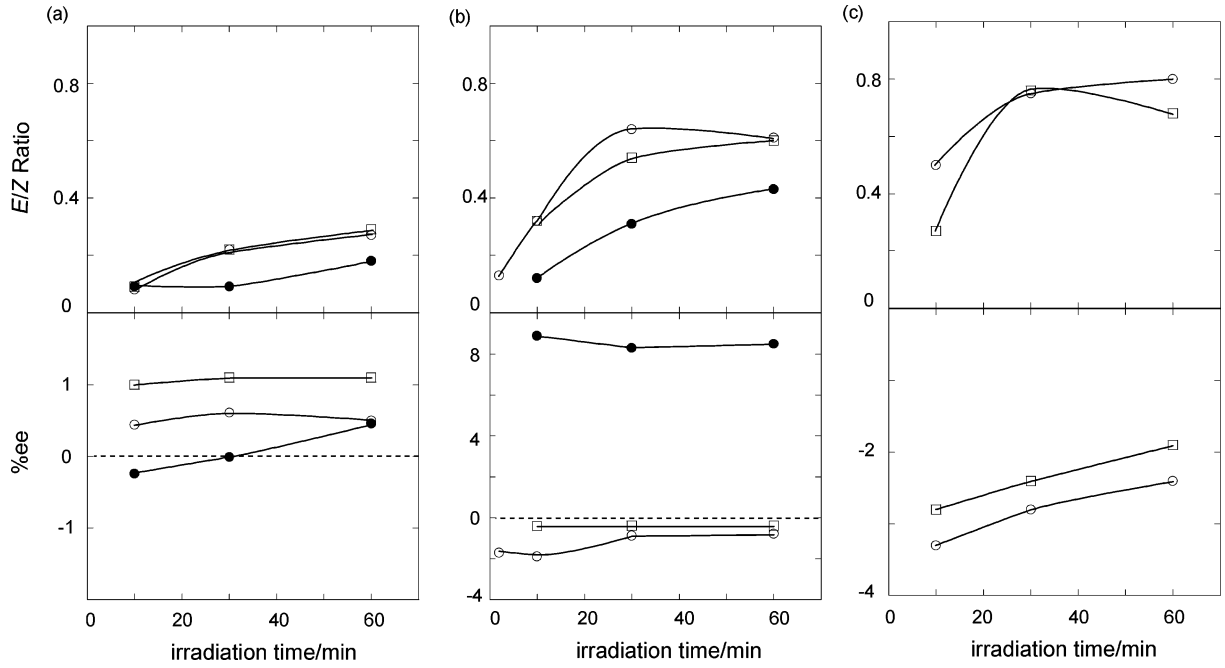


FIGURE 7. *E*/*Z* ratio and ee obtained in the supramolecular enantiodifferentiating photoisomerization of **1Z** sensitized by **2a**: (a) in methanol at 55 °C (□), at 25 °C (○), and at −40 °C (●), (b) in 50% methanol at 55 °C (□), at 25 °C (○), and at −40 °C (●), and (c) in 25% methanol at 55 °C (□) and at 25 °C (○).

TABLE 3. 1E/1Z Ratio and % Enantiomeric Excess of 1E Obtained in Supramolecular Enantiodifferentiating Photoisomerization of 1Z Sensitized by 2a−2d in Methanol−Water Mixture at Various Temperatures[a]

host	solvent	temp (°C)	host occupancy (%)[b]	irradiation time (min)	*E*/*Z* ratio	%ee[e]
2a	MeOH	55	*d*	10	0.09	1.0[f]
				30	0.22	1.1
				60	0.29	1.1
		25	*d*	10	0.08	0.4[f]
				30	0.22	0.6
				60	0.27	0.5
		−20	*c*	10	0.13	0.0[f]
				60	0.25	0.1
		−40		10	0.09	−0.2[f]
				30	0.09	0.0
				60	0.18	0.5
	50% MeOH	55	66	10	0.32	−0.4[f]
				30	0.54	−0.4
				60	0.60	−0.4
		45	67	10	0.29	−0.2[f]
				60	0.61	−0.9
		35	68	10	0.36	−1.8[f]
				60	0.69	−1.5
		25	69	2	0.13	−1.7
				10	0.32	−1.9[f]
				30	0.64	−0.9
				60	0.61	−0.8
		10	70	10	0.32	−1.5[f]
				60	0.76	−1.6
		5	71	10	0.21	−1.6[f]
				60	0.71	−1.4
		0	71	10	0.30	−0.8[f]
				60	0.77	−0.7
		−20	73	10	0.27	2.7[f]
				60	0.30	1.6
		−30	74	10	0.12	6.7[f]
				60	0.66	7.1
		−40	76	10	0.13	8.9[f]
				30	0.31	8.3
				60	0.43	8.5
	25% MeOH	55	88	10	0.27	−2.8[f]
				30	0.76	−2.4
				60	0.68	−1.9
		40	89	10	0.49	−3.5[f]
				60	0.71	−3.0
2a	25% MeOH	25	90	10	0.50	−3.3[f]
				30	0.75	−2.8
				60	0.80	−2.4
		10	91	10	0.37	−2.5[f]
				60	0.69	−1.9
		0	91	10	0.71	−0.7[f]
				60	0.70	−0.5
		−10	95	10	0.43	1.8[f]
				30	0.18	c
				60	c	c
2b	50% MeOH	25	*c*	10	0.43	3.1
		10		10	0.35	4.6
				10	0.38	5.3
		−10		10	0.36	5.8
		−20		10	0.37	5.4
		−30		10	0.21	4.7
				30	0.28	4.4
		−40		10	0.18	3.2
				30	0.35	3.5
				60	0.49	4.2
2c	50% MeOH	25	*c*	10	0.72	0.7
		10		10	0.48	−0.8
		0		10	0.33	−0.6
		−10		10	0.31	−0.3
		−20		10	0.24	−0.1
		−30		10	0.19	1.1
		−35		10	0.25	1.9
		−40		10	0.16	7.4
				30	0.26	7.4
				60	0.49	7.6
2d	50% MeOH	25	*c*	10	0.71	0.7
		10		10	0.53	1.2
		0		10	0.19	3.2
		−10		10	0.30	5.5
		−20		10	0.43	6.3
		−30		10	0.35	8.1
		−40		10	0.22	9.0
				30	0.19	10.6
				60	0.34	8.3

[a] Irradiated at 254 nm under argon atmosphere in methanol−water mixture; [**1Z**] = 2.0 mM, [**2**] = 0.2 mM. [b] Percentage of host occupied by **1Z** under the initial conditions employed. [c] Value not determined. [d] No complexation behavior was observed. [e] Error in ee: ±0.5%. [f] From ref 11j.

2 and reveal that the real "supramolecular" photosensitization occurs only in highly hydrophilic solvent at low temperatures.

Temperature Dependence of Enantiomeric Excess and the Activation Parameters. To obtain the activation parameters for the supramolecular enantiodifferentiating photoisomerization sensitized by **2a**−**2d**, the ee data obtained at various temperatures were subjected to the Eyring analysis.[4−8] Thus, the $\ln(k_S/k_R)$ values, calculated by the equation $k_S/k_R = (100 + \%ee)/(100 - \%ee)$,[4−8] were plotted against the reciprocal temperature to give good straight lines only at low temperatures (Figure 9), except for the pure methanol case, where practically no complexation occurs. The deviation from the straight line at higher temperatures is ascribed to a serious contamination by the outside sensitization by free host (despite the low efficiency[11d]). From the slope and intercept of the straight line obtained at low temperatures, the differential activation enthalpy ($\Delta\Delta H^{\ddagger}_{S-R}$) and entropy ($\Delta\Delta S^{\ddagger}_{S-R}$) are calculated for each sensitizing host (Table 4).

It is noted that **2a** is a poor (conventional) sensitizer in pure methanol, where the host cannot include the substrate and hence gives almost racemic product throughout the entire temperature range, but **2a** functions as an efficient sensitizing host in aqueous methanol to give highly temperature-dependent ee's, which allows us to manipulate the product's ee and chiral sense by external factors, such as temperature, as shown in our previous report.[11j] This is exactly the case with **2c**, which gave the largest $\Delta\Delta H^{\ddagger}_{S-R}$ and $\Delta\Delta S^{\ddagger}_{S-R}$ values of the same sign and indeed exhibited a switching of the product chirality at −20 °C in 50% aqueous methanol solution (Table 4 and Figure 9). It is likely that the lack of hydrogen-bonding network around the secondary rim endows skeletal flexibility to a permethylated cyclodextrin, which in turn allows the dynamic motion of cyclodextrin's chiral walls synchronized with the rotational relaxation of the olefinic double bond of **1Z**[4−8] in the supramolecular exciplex.

These observations reveal the unique nature of flexible sensitizing hosts **2a**−**2d** for the use in the excited state, although similar behavior in the ground state has been reported by other groups.[13] We may further conclude that, by using flexible hosts, we can combine the advantage of well-defined intimate interactions in a supramolecular system with the ability of dynamic control by multiple entropy-related factors.

Enthalpy−Entropy Compensation. It has been demonstrated that not only the thermodynamic parameters for inclusion complexation[10a−c,e,f] but also the differential activation param-

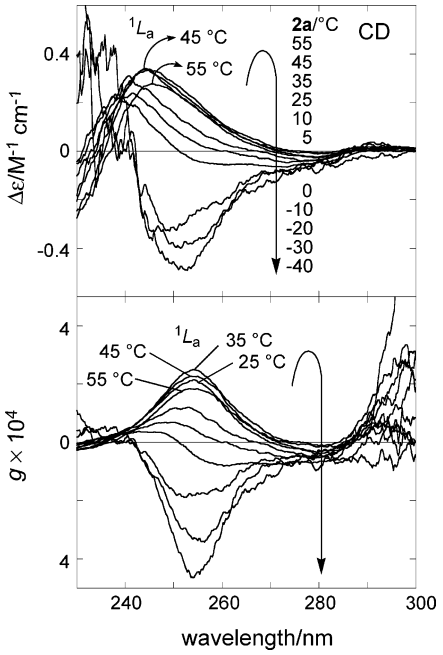


FIGURE 8. CD spectral and *g* factor profile changes of a 50% aqueous methanol solution of **2a** (0.2 mM) and **1Z** (2.0 mM) at temperatures ranging from 55 to −40 °C.

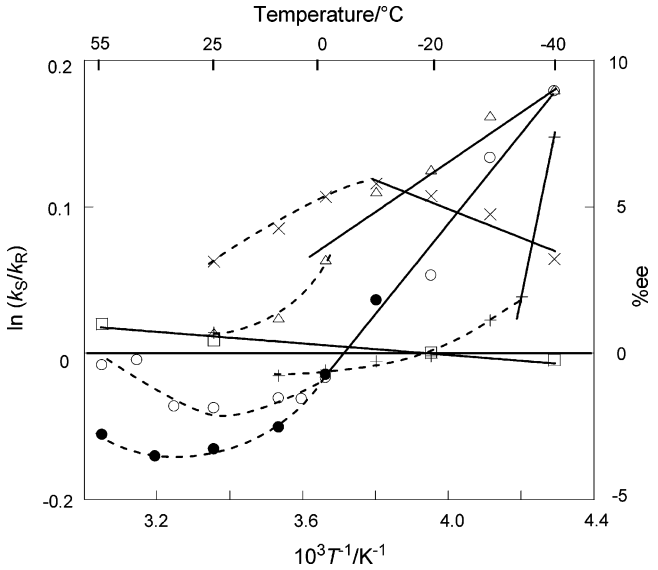


FIGURE 9. Temperature dependence of ee obtained in supramolecular enantiodifferentiating photoisomerization of **1Z** sensitized by **2a** in pure methanol (□), 50% methanol (○), and 25% methanol (●) (data from ref 11j), by **2b** in 50% methanol (×), by **2c** in 50% methanol (+), and by **2d** in 50% methanol (△).

eters for enantiodifferentiating photosensitization[5,6] exhibit a compensatory relationship between ΔH° ($\Delta\Delta H^\ddagger$) and $T\Delta S^\circ$ ($T\Delta\Delta S^\ddagger$). The differential activation parameters obtained in this study (Table 4), although the number of data sets is obviously too small, also display an excellent enthalpy−entropy compensation to give a good straight line in Figure 10: $\Delta\Delta H^\ddagger = 0.237\Delta\Delta S^\ddagger - 0.25$ (r 0.99). This immediately indicates that the same enantiodifferentiation mechanism operates in these supramolecular photosensitization systems, affording approximately the same ee at the isoenantiodifferentiating temperature of 237 K (−36 °C).

TABLE 4. Differential Activation Parameters Calculated from the Eyring Plots for 2a−2d in 50% Aqueous Methanol

host	critical temperature (°C)[a]	$\Delta\Delta H^\ddagger_{S-R}$ (kJ mol^{-1})	$\Delta\Delta S^\ddagger_{S-R}$ (J mol^{-1} K^{-1})
2a	<0	−2.9	−11
2b	<−10	0.9	4
2c	<−35	−5.9	−24
2d	<0	−1.5	−5

[a] Below this temperature, the Eyring plot gave a straight line.

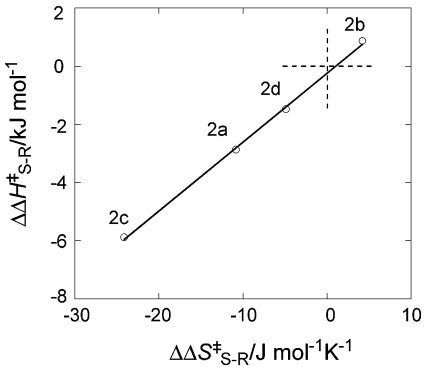


FIGURE 10. Enthalpy−entropy compensation plot for the differential activation parameters obtained in the supramolecular photochirogenesis with **2a**−**2d**.

Conclusions

In this study, we have revealed the effects of a host's flexibility on the inclusion complexation in the ground state and also on the supramolecular enantiodifferentiation in the excited state. The enthalpy-driven complexation by native cyclodextrins is dramatically switched to an entropy-driven process by simply increasing the host's flexibility through permethylation of the host. The same strategy may be applicable to other rigid hosts and useful in creating "soft" hosts with higher tunability and sensibility to the external factors. Also in the excited state, the increased flexibility of permethylated cyclodextrin leads us to an entropy-controlled enantiodifferentiating photoisomerization, which shows a critical dependence of the product's ee on temperature and solvent. The present strategy is different from the conventional supramolecular way, where the exact fitting to a particular guest in shape and size, that is, rigid host, is intended. However, the present study may indicate that, by affording flexibility to a host, we can more dynamically control the system without losing the well-defined supramolecular interactions. Hence, designing a host skeleton with tunable flexibility is crucial for efficiently and dynamically manipulating the stereochemical outcome of a supramolecular photochirogenesis system. Works toward entropy-controlled supramolecular photochirogenesis, using other modified cyclodextrins, are currently in progress.

Experimental Section

Method. The phenyl-in−phenyl-out equilibrium of **2a** at 5.30 × 10^{-5}−1.48 × 10^{-3} M concentration was determined by UV−vis and CD spectra and g ($= \Delta\epsilon/\epsilon$) factor profiles in aqueous methanol and methylcyclohexane at temperatures ranging from −40 to 55 °C. This equilibrium was also monitored by 2D NMR technique. The stoichiometry and inclusion complexation behavior of **1Z** with **2a** was investigated by the Job's analysis[23] as well as the CD spectrometric titration reported previously.[11d,f,15] All ir-

radiations were performed in a temperature-controlled water or methanol bath, by using a low-pressure mercury lamp equipped with a Vycor sleeve. Aqueous methanol solutions (5 mL) containing **1Z** (2.0 mM) and one of the permethylated modified β-cyclodextrins **2a**−**2d** (0.2 mM) were irradiated in quartz tubes under an argon atmosphere at −40 to 55 °C. The photolyzed samples were poured into brine (1 mL), and the resultant mixture was extracted with pentane (1 mL). The organic layer was analyzed on a Shimadzu CBP-20 (PEG) column for the *E*/*Z* ratio and then extracted with 20% aqueous silver nitrate solution at <5 °C. The resultant aqueous solution containing the [Ag^+−**1E**] complex was washed twice with pentane (2 mL) and added to a 28% aqueous ammonia solution at 0 °C, and liberated **1E** was extracted with pentane (0.5 mL). The ee of **1E** was determined by chiral GC on a Supelco β-DEX 225 column. To test the possible deviation of ee by preferential inclusion of enantiomeric **1E** with **2** in the workup procedures, we performed the control experiment of optical resolution using permethylated β-cyclodextrin. Racemic **1E** was added to an aqueous solution saturated with permethylated β-cyclodextrin to give white precipitates, which were collected, washed repeatedly with water and ether, and dried. The complex stoichiometry was determined as 1:1 by the conventional method using ^{1}H NMR.[28] This complex was subjected to the workup procedures employed for the photoirradiated samples to give **1E** in 0.22% ee. This reveals that permethylated β-cyclodextrin cannot appreciably discriminate the enantiomers of **1E** upon complexation, and therefore, we anticipate that their derivatives **2a**−**2d** behave similarly and have no appreciable influence on the product's ee determined by this procedure.

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Supporting Information Available: The ROESY spectrum of **2a** in 1:1 CD_3OD-D_2O, the CD spectra and *g* factor profiles for the complexation of **1Z** and **1E** with **2a** under a variety of conditions, and the synthesis and characterization of compounds **2a**−**2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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