Supramolecular Photochirogenesis. 2. Enantiodifferentiating Photoisomerization of Cyclooctene Included and Sensitized by 6-*O*-Modified Cyclodextrins[⊥]

Yoshihisa Inoue,*[,†,‡] Takehiko Wada,[†] Norimitsu Sugahara,[†] Keiko Yamamoto,[†] Koichi Kimura,[†] Lin-Hui Tong,[§] Xing-Ming Gao,[§] Zhi-Jie Hou,[§] and Yu Liu[||]

Department of Molecular Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan, Inoue Photochirogenesis Project, ERATO, JST, 4-6-3 Kamishinden, Toyonaka 565-0085, Japan, Lanzhou Institute of Chemical Physics, Academia Sinica, Lanzhou 730000, China, and Department of Chemistry, Nankai University, Tianjin 300071, China

inoue@chem.eng.osaka-u.ac.jp

Received August 18, 2000

Supramolecular enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1Z**) to the chiral (*E*)-isomer (**1E**) via inclusion and sensitization by modified α-, *β*-, and/or *γ*-cyclodextrin derivatives, possessing benzoate (**2a**, **3a**, **4a**), isomeric phthalates (**3b**−**d**), and tethered benzamide (**3e**) chromophores, has been investigated in aqueous methanol solutions at varying temperatures. The photostationary-state **1E**/**1Z** ratios obtained upon sensitization with **2**−**4** in 1:1 water−methanol reached 0.4−0.8, which are higher than the value of ca. 0.25 reported for sensitizations by conventional alkyl benzoates in hydrocarbon solvents, although the ratio was reduced to 0.2−0.4 in water or methanol. The sensitizations of **1Z** by α- and *γ*-cyclodextrin benzoates (**2a**, **4a**) with size-mismatched cavities gave **1E** of poor enantiomeric excesses (ee's) smaller than 3 and 5%, respectively. In contrast, *β*-cyclodextrin derivatives (**3a**−**e**) afforded much higher ee's of up to 24%, depending on the solvent composition. Thus, the modification of cyclodextrin with a sensitizing group successfully enhanced the product through the excited-state supramolecular interaction within the cavity. Interestingly, the product ee's obtained with benzoate **3a** and methyl phthalate **3b** are not a simple function of either temperature or solvent, but are nicely correlated with the host occupancy or the percentage of occupied host. This means that the entropy factor plays an insignificant role in this supramolecular photochirogenesis system, which is in sharp contrast to the decisive role of entropy in the conventional (nonsupramolecular) counterpart performed in homogeneous solutions, where an inversion of product chirality by temperature variation is reported to occur.

Introduction

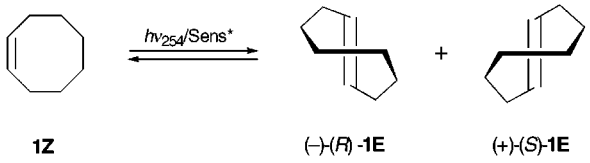
Asymmetric photochemistry has recently attracted much attention as a unique alternative route to optically active compounds,[1−3] which are difficult or tedious to obtain in conventional thermal and enzymatic asymmetric syntheses. To induce chirality in a prochiral substrate through a photochemical reaction, a chiral source able to selectively generate or discriminate one of the enantiomeric excited states should exist in the system. The chiral induction in the substrate may occur either upon enantioselective excitation by circularly polarized light (CPL) or through intra- and intermolecular interactions with an optically active moiety or compound.[2] Absolute asymmetric synthesis with CPL leads, in general, to poor enantiomeric excess (ee) at least in the initial stages of reaction. However, the excited-state diastereodifferentiation by a chiral auxiliary introduced at the substrate gives good-to-excellent diastereomeric excesses but requires an equimolar amount of chiral source. In this context, photochemical chirality transfer and multiplication, which may correspond to the catalytic asymmetric synthesis in the ground state, can be materialized only through enantiodifferentiating photosensitization with optically active compounds. However, the excited-state interaction between substrate and sensitizer is not expected to be strong and long-lived enough to control effectively and precisely the stereochemical course of intervening excited sensitizer−substrate complex (exciplex), even if formed.[2] The difficulty has been amply illustrated by several unsuccessful attempts[1,2] to surpass even the 6.7% ee reported originally by Hammond and Cole in 1965 for the enantiodifferentiating photoisomerization of 1,2-diphenylpropane.[4] Nevertheless, we have recently demonstrated that the photosensitized enantiodifferentiating isomerizations of cyclooctene[5−7] (Scheme

[†] Osaka University.
[‡] ERATO.
[§] Lanzhou Institute of Chemical Physics.
[||] Nankai University.
[⊥] This paper is dedicated to Professor Emeritus Hiroshi Sakurai on the occasion of his 80th birthday.

(1) Rau, H. *Chem. Rev.* **1983**, *83*, 535.
(2) Inoue, Y. *Chem. Rev.* **1992**, *92*, 741. Everitt, S. R. L.; Inoue, Y. *Organic Molecular Photochemistry*; Ramamurthy, V., Schanze, K. S., Ed.; Marcel Dekker: New York, 1999; pp 71−130.
(3) Pete, J.-P. *Adv. Photochem.* **1996**, *21*, 135.
(4) Hammond, G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256.
(5) Inoue, Y.; Yokoyama, T.; Yamasaki, N.; Tai, A. *J. Am. Chem. Soc.* **1989**, *111*, 6480. Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* **1992**, *57*, 1332. Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* **1993**, *58*, 1011. Tsuneishi, H.; Hakushi, T.; Tai, A.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2057.
(6) Inoue, Y.; Matsushima, E.; Wada, T. *J. Am. Chem. Soc.* **1998**, *120*, 10687.

10.1021/jo001262m CCC: $19.00
Published on Web 10/06/2000

Scheme 1. Enantiodifferentiating *Z*−*E* Photoisomerization of Cyclooctene Sensitized by a Chiral Sensitizer



1), cyclooheptene,[8] and cyclohexene,[9] as well as the enantiodifferentiating photoaddition of alcohols to 1,1-diphenylpropene,[10] not only afford good product ee's of up to 77%[8] but also lead to the unusual switching of product chirality simply by changing irradiation temperature,[5−10] pressure,[6] and/or solvent.[7] Each of these entropy-related factors plays the decisive role in determining the product chirality and ee.[11]

In addition to the asymmetric photochemistry utilizing the chiral light−molecule and molecule−molecule interactions mentioned above, there is yet another methodology available to photochemically induce chirality in prochiral substrates, through excited-state supramolecular chiral interactions. Apart from the solid-state asymmetric photochemistry in crystal or in zeolite supercage,[12,13] supramolecular asymmetric photochemistry, particularly photosensitization, in solution has not been extensively investigated thus far.[14,15] In the present study, a series of α-, *β*-, and *γ*-cyclodextrin derivatives **2**−**4** modified with benzoate or benzamide group were synthesized (Chart 1) and employed as sensitizing host molecules with a chiral cavity. The basic concept and mechanism of supramolecular asymmetric photosensitization using modified cyclodextrins as chiral sensitizing hosts are illustrated in Scheme 2. In principle, the substrate molecule located in the bulk solution is not accessible to the excited sensitizer group which is occluded in the chiral cavity. Upon inclusion of the substrate into the cavity, the sensitizer moiety, which is situated very close to the included substrate, can transfer its energy to the substrate which is in a chiral conformationally restricted environment, ultimately realizing the efficient supramolecular asymmetric photosensitization. There are several advantages of using cyclodextrin as a host: (1) the cavity is inherently chiral, (2) the tethered sensitizing group acts as a spacer that promotes tight packing and conformational fixation of the substrate/sensitizer in the cavity, and most importantly (3) undesirable sensitization outside the chiral cavity is thought to be automatically prohibited by the occlusion of the sensitizing group in the absence of included substrate, and therefore the efficient photosensitization is designed to occur only in the chiral cavity.

Experimental Section

General. Melting points were measured with a YANACO MP-21 apparatus and are uncorrected. Mass spectra were obtained on a JEOL JMS-DX-303 instrument. ^{1}H and ^{13}C NMR spectra were recorded in dimethyl sulfoxide-d_6 (DMSO-d_6) or in a 1:1 mixture of deuterated methanol and water (CD_3OD−D_2O) by a JEOL GSX-400 spectrometer. IR and UV spectra were obtained on JASCO IR-810 and Ubest-50 spectrophotometer, respectively. Circular dichroism (CD) spectra were measured in a cylindrical quartz cell (light path 1 cm; volume 2.7 mL) or a conventional quartz cell (light path 1 cm) on a JASCO J-720 or J-720W spectropolarimeter equipped with a PTC-348WI temperature controller.

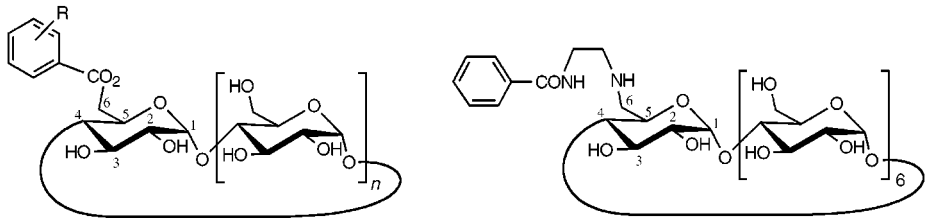
Gas chromatographic (GC) analyses of photolyzed samples were performed on a Shimadzu CBP-20 column (0.25 mm ϕ × 20 m) at 60 °C and Supelco *β*-DEX 120 and 225 columns (0.25 mm ϕ × 20 m) at 60 °C, using a Shimadzu GC-14AM instrument equipped with a C-R6A integrator. Relatively low injection temperatures of 100−120 °C were employed in the GC analyses in order to avoid possible thermal *E*−*Z* isomerization of product **1E** in the injection port. The conventional and chiral capillary columns gave satisfactory separations of geometric and enantiomeric isomers of cyclooctene (**1Z** and (*R*)- and (*S*)-**1E**) as well as of cycloheptane added as an internal standard.

Materials. Deionized and distilled water and methanol distilled from magnesium turnings were used as solvents throughout the work. (*Z*)-Cyclooctene (**1Z**) (Nakarai) was purified by the treatment with 20% aqueous silver nitrate followed by fractional distillation. (*E*)-Cyclooctene (**1E**) of >99.5% purity was prepared by the sensitized photoisomerization of **1Z** as reported previously.[16] α-, *β*-, and *γ*-Cyclodextrins (Kanto) were dried in vacuo for 5 h at 80 °C prior to use.

Modified α-, *β*-, and *γ*-cyclodextrins **2a**, **3a**, **3b**, **3e**, and **4a** were prepared as reported previously.[17−19] Novel 6-*O*-(*m*- or *p*-methoxycarbonylbenzoyl)-*β*-cyclodextrins (**3c** and **3d**) were synthesized by the reaction of *β*-cyclodextrin with methyl isophthaloyl or terephthaloyl chloride, according to the similar procedures, and recrystallized repeatedly from methanol and water.[17−19] **3c**: Yield 4.3%; mp 302−305 °C (dec); FAB-MS(NaI) *m*/*z* 1319 (M + Na^+); UV (CH_3OH) λ_{max} (ϵ/M^{-1} cm^{-1}) 229.0 (12600, sh), 281.0 (900), 289.0 nm (900); UV (H_2O) λ_{max}(ϵ) 236.0 (9000, sh), 282.0 (650), 289.0 (600); IR (KBr) *ν* 3350(s), 2950(m), 1730(m), 1640(w), 1260(m), 1160(s), 1080(s), 1040(s), 950(m), 860(w), 760(w), 740(w), 710(w), 580(w) cm^{-1}; ^{1}H NMR (DMSO-d_6) *δ* 8.5 (s, 1H), 8.2 (dd, 2H), 7.6 (t, 1H), 5.5−5.8 (m, 14H), 4.7−4.9 (m, 7H), 4.3−4.6 (m, 6H), 3.9 (br, 1H), 3.8 (s, 3H), 3.2−3.7 (m, 40H); ^{13}C NMR (CD_3OD−D_2O) *δ* 168.59, 167.54, 135.51, 135.36, 131.76, 131.37, 131.22, 130.62, 104.01, 103.48, 103.32, 103.13, 83.60, 82.64, 82.52, 82.24, 74.66, 74.56, 73.67, 73.54, 73.41, 71.17, 66.29, 61.60, 61.47, 61.24, 54.06. Anal. Calcd for $C_{51}H_{76}O_{38}$·$5H_2O$: C, 44.15; H, 6.25. Found: C, 43.64; H, 5.77. **3d**: Yield 5.0%; mp 315−318 °C (dec); FAB-MS(NaI) *m*/*z* 1319 (M + Na^+); UV (MeOH) λ_{max}(ϵ/M^{-1} cm^{-1}) 242.0 (19360), 286.0 (1700), 294.0 (1400); UV (H_2O) λ_{max}(ϵ/M^{-1} cm^{-1}) 244.5 (12400), 288.0 (1360), 299.0 nm (1100); IR (KBr) *ν* 3350(s), 2900(m), 1720(m), 1630(w), 1280(m), 1150(s), 1080(s), 1020(s), 940(m), 860(w), 750(w), 700(w), 580(w) cm^{-1}; ^{1}H

(7) Inoue, Y.; Ikeda, H.; Kaneda, M.; Sumimura, T.; Everitt, S. R. L.; Wada, T. *J. Am. Chem. Soc.* **2000**, *122*, 406.
(8) Hoffmann, R.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10702.
(9) Asaoka, S.; Horiguchi, H.; Wada, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 737.
(10) Asaoka, S.; Kitazawa, T.; Wada, T.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8486.
(11) Inoue, Y.; Wada, T.; Asaoka, S.; Sato, H.; Pete, J.-P. *Chem. Commun.* **2000**, 251.
(12) Ramamurthy, V. *Photochemistry in Organized and Constrained Media*; VCH Publishers: New York, 1991.
(13) Leibovitch, M.; Olovsson, G.; Sundarababu, G.; Ramamurthy, V.; Scheffer, J. R.; Trotter, J. *J. Am. Chem. Soc.* **1996**, *118*, 1219. Joy, A.; Scheffer, J. R.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 119. Joy, A.; Uppili, S.; Netherton, M. R.; Scheffer, J. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 728.
(14) For a review on asymmetric reactions with cyclodextrins, see Takahashi, K.; Hattori, K. *J. Incl. Phenom. Mol. Recogn. Chem.* **1994**, *17*, 1.
(15) Inoue, Y.; Dong, F.; Yamamoto, K.; Tong, L.-H.; Tsuneishi, H.; Hakushi, T.; Tai, A. *J. Am. Chem. Soc.* **1995**, *117*, 11033.
(16) Yamasaki, N.; Yokoyama, T.; Inoue, Y.; Tai, A. *J. Photochem. Photobiol., A: Chem.* **1989**, *48*, 465.
(17) Tong, L.-H.; Hou, Z.-J.; Inoue, Y.; Tai, A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1253.
(18) Gao, X.-M.; Tong, L.-H.; Inoue, Y.; Tai, A. *Synth. Commun.* **1995**, *25*, 703.
(19) 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.

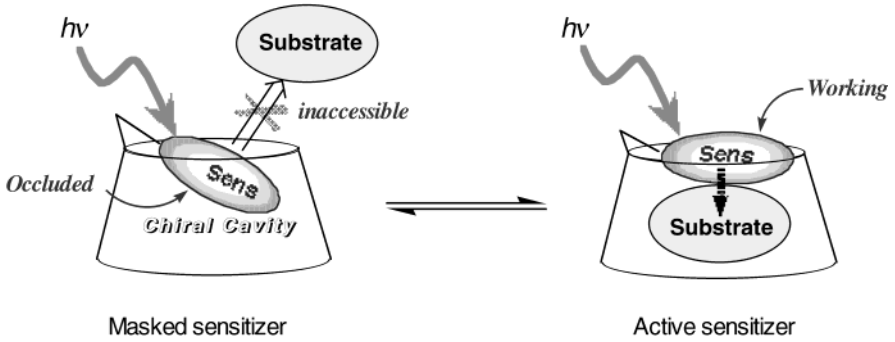
Chart 1. Modified Cyclodextrins as Chiral Sensitizing Hosts



2a $n = 5$, R = H
3a $n = 6$, R = H
3b $n = 6$, R = *o*-CO_2Me
3c $n = 6$, R = *m*-CO_2Me
3d $n = 6$, R = *p*-CO_2Me
4a $n = 7$, R = H

3e

Scheme 2. Concept of Inclusion Enhanced Supramolecular Asymmetric Photosensitization with Modified Cyclodextrin



NMR (DMSO-d_6) δ 8.0 (q, 4H), 5.5−5.9 (m, 14H), 4.7−5.0 (m, 7H), 4.3−4.6 (m, 6H), 4.0 (br, 1H), 3.8 (s, 3H), 3.2−3.7 (m, 40H); ^{13}C NMR (CD_3OD-D_2O) δ 169.87, 167.75, 134.82, 130.96, 130.86, 130.71, 104.11, 103.57, 103.29, 82.72, 82.57, 82.51, 82.30, 74.72, 74.63, 74.57, 73.76, 73.63, 73.49, 73.42, 71.32, 61.64, 61.46, 61.42, 53.98. Anal. Calcd for $C_{51}H_{76}O_{38}\cdot 5H_2O$: C, 44.15; H, 6.25. Found: C, 43.55; H, 5.84.

Complexation. Inclusion complexation behavior of the chromophoric cyclodextrin derivatives **2**−**4** was most clearly and conveniently investigated by CD spectrometric titration, as has been demonstrated in previous papers.[17,19] The CD spectra of **2**−**4** (0.05 mM) were recorded in the presence of **1Z** or **1E** at varying concentrations in aqueous solutions of various methanol contents at 25 °C and at 5−35 °C for **3b**. The differential CD spectra were obtained by subtracting the original CD spectrum in the absence of guest from that in the presence of guest. Under the same conditions, no significant changes were observed in the absorption spectra upon addition of **1Z**.

Photolysis. All irradiations were performed in a temperature-controlled water or methanol bath, using a 30 W mercury resonance lamp fitted with a Vycor sleeve. Aqueous solutions (5 mL) containing **1Z** (2 mM) and one of the cyclodextrin derivatives **2**−**4** (0.2 mM) were irradiated in quartz tubes under an argon atmosphere at +55 to −40 °C. The photolyzed solution was added to 10% aqueous KOH solution (5 mL) for decomplexation, and the resultant mixture was extracted with pentane (1 mL). The pentane extract was washed with water, analyzed by GC on a Shimadzu CBP-20 (PEG) column for *E*/*Z* ratio, and then extracted with 20% aqueous silver nitrate solution at <5 °C. The aqueous extract containing Ag^+−**1E** complex was washed twice with pentane and added with stirring to 28% aqueous ammonia solution at 0 °C, and the liberated **1E** was extracted with pentane. The enantiomeric excess of **1E** isolated (chemical purity >99%) was determined by chiral GC on Supelco β-DEX 120 and/or 225 columns.

Results and Discussion

CD Spectra. Possessing a variety of chromophoric groups attached to the primary side of cyclodextrins, modified cyclodextrins **2**−**4** gave distinctly different CD spectra in aqueous solutions. As shown in Figure 1, β-cyclodextrin derivatives **3a**−**e** gave strong and very weak CD extrema which correspond in wavelength to the absorption ^1L_a and ^1L_b bands, respectively, with analogous CD spectra obtained for α- and γ-cyclodextrin benzoates **2a**−**4a**. According to the sector rule proposed by Kajtar et al.,[20] the negative Cotton effects observed for both ^1L_a and ^1L_b bands indicate that the benzoyl group in **3a**−**d**, being directly connected to β-cyclodextrin through a short ester linkage, is just perched on the rim of the cavity.[17] In contrast, the benzoyl group in **3e**, which is tethered by an ethylenediamine chain to cyclodextrin, is deeply included in the cavity, affording strong positive ^1L_a and weak ^1L_b CD bands, as shown in Figure 1. These conformations are schematically illustrated in Figure 2, where both of the ^1L_a and ^1L_b axes of the benzoate derivatives **3a**−**d** lie in the negative region, while the ^1L_a and ^1L_b axes of *N*-benzoyl group in **3e** are in the positive and negative regions, respectively.

Inclusion Complexation of 1Z and 1E by Modified Cyclodextrins. The complexation behavior of the modified cyclodextrins with **1Z** and **1E** was quantitatively investigated in aqueous solutions by means of the differential CD spectrometry. As illustrated in Figure 3, the CD intensity of the ^1L_a band increased significantly (**3a**) or slightly (**3c**, **3d**) or decreased dramatically (**3b**, **3e**) upon gradual addition of the guest (**1Z** or **1E**), reflecting

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

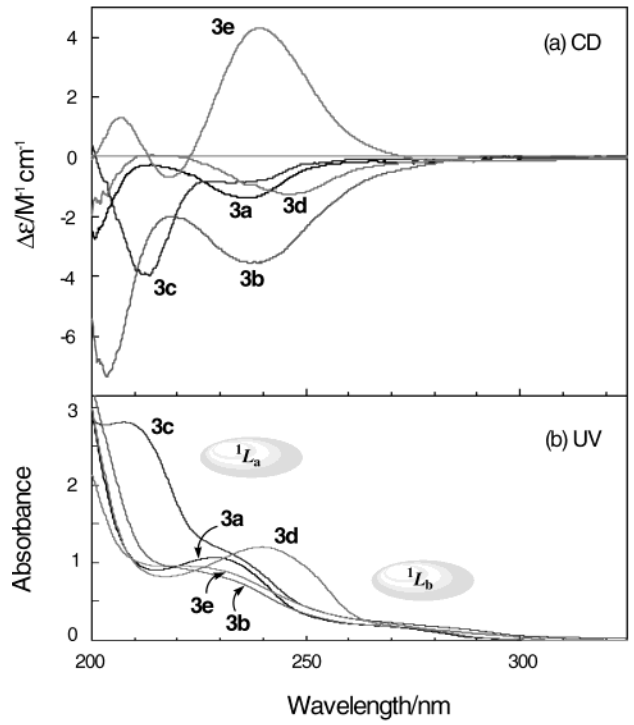


Figure 1. (a) Circular dichroism and (b) absorption spectra of *β*-cyclodextrin 6-*O*-benzoate (**3a**), methyl phthalate (**3b**), methyl isophthalate (**3c**), and methyl terephthalate (**3d**) and *N*-benzoylaminoethyl derivative (**3e**) in 1:1 water−methanol (0.05 mM); the absorbances were calculated from the high voltage applied to the photomultiplier tube of CD spectrometer and were not calibrated.

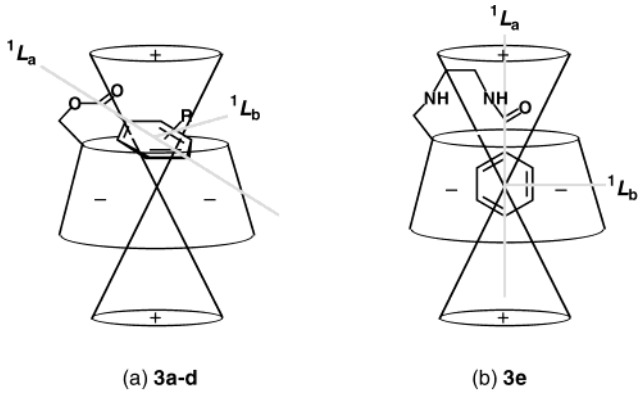


Figure 2. Schematic drawing of the sector rule applied to *β*-cyclodextrin derivatives **3a**−**d** (a) and **3e** (b); the axis of transition moment located in the double cone gives a positive Cotton effect peak, while that in the other direction leads to negative one (ref 20). However, the sector rule cannot quantitatively predict the relative intensity of induced CD signal among **3a**−**d**, which is a critical function of the orientation and penetration depth of relevant chromophore.

the extent of conformational changes of the chromophore upon guest inclusion. On the other hand, only negligible changes were observed for **2a**, indicating extremely weak binding of the guest by this smaller-sized α-cyclodextrin derivative.

Using the same procedure reported previously,[19] the CD spectral changes were quantitatively analyzed by the nonlinear least-squares method to give the complex stability constants (K_s) in aqueous solutions of varying methanol contents at 25 °C and a number of other temperatures. As can be seen from the results shown in Table 1, the cyclooctene guests are much better accommodated in *β*-cyclodextrins **3a**−**e** than in α-cyclodextrin derivative **2a** as expected, and the K_s values for **3a**−**e** vary widely with the substituent introduced, solvent composition, and temperature. Interestingly, the introduction of a methoxycarbonyl group at the ortho position of **3a** reduces the complex stability of **3b** with **1Z** and **1E** by factors of 1.2−2.2 (**1Z** in water or 50% aqueous methanol) and 4.4 (**1E** in water). Similarly, the K_s values for **3e** with **1Z** and **1E** are 2.1−4.8 times smaller than the corresponding values for **3a**. In contrast, the extra methoxycarbonyl group at the meta or para position enhances the K_s of **3c** and **3d** for **1Z** by a factor of 1.9−3.7 (in 50% aqueous methanol) or 6.2−8.5 (in water). The reduced K_s for **3b** and **3e** may be attributed to the competitive self-inclusion of the *o*-methoxycarbonyl in **3b**, or of the *N*-benzoyl in **3e**. On the other hand, the extended cavities of **3c** and **3d**, which are created by the hindered self-inclusion of the aromatic group due to the meta or para substitution, may be responsible for the enhanced K_s values. This view is compatible with the extensive CD spectral changes observed for **3a**, **3b**, and **3e** upon addition of the guest, and the much smaller CD changes for **3c** and **3d** (Figure 3). Thus, it is deduced that the aromatic moieties of **3a**, **3b**, and **3e** are more deeply embedded into the cavity than those of **3c** and **3d**.

Table 1. Complex Stability Constant (K_s) and Free Energy Change ($-\Delta G°$) for 1:1 Inclusion Complexation of (*Z*)- and (*E*)-Cyclooctene (1Z and 1E) with Modified *β*-Cyclodextrins (3a−d) in Methanol−Water Mixture at Varying Temperatures

host	guest	solvent	temp/°C	K_s/M^{-1}	$-\Delta G°$/kJ mol^{-1}
3a	**1Z**	50% MeOH	25	1440	18.0
		H_2O	25	20100	24.5
	1E	50% MeOH	25	2850	19.7
		H_2O	25	38100	26.1
3b	**1Z**	MeOH	15	31	8.5
			25	22	7.7
			35	13	6.4
		75% MeOH	25	103	11.5
		50% MeOH	5	2020	18.9
			15	1420	18.0
			25	650	16.0
			35	580	15.8
		25% MeOH	25	3250	20.0
		H_2O	25	16700	24.1
	1E	H_2O	25	8610	22.4
3c	**1Z**	50% MeOH	25	5390	21.3
		H2O	25	170000	29.8
3d	**1Z**	50% MeOH	25	2680	19.6
		H_2O	25	124000	29.1
	1E	H_2O	25	7400	22.1
3e	**1Z**	H_2O	25	9660	22.7
	1E	H_2O	25	7880	22.2

As can be seen from Table 1, the complex stability dramatically decreases with increasing methanol content in the aqueous solution. A plot of log K_s, or $\Delta G°$, for the complexation of **1Z** with **3b** against the methanol content gives an excellent straight line shown in Figure 4. This result indicates that no specific solvation by water or methanol of the cyclodextrin derivative occurs, and the water−methanol mixture behaves as a bulk solvent of continuously changing polarity/hydrophilicity. Hence, the K_s values for **3b**, as well as **3a**,**c**,**d**, at any methanol contents can be reasonably estimated by extrapolating the straight lines in Figure 4. The slope of the plot likely reflects the self-binding ability of the aromatic substituent in aqueous methanol: terephthaloyl < isophthaloyl ≈ phthaloyl < benzoyl.

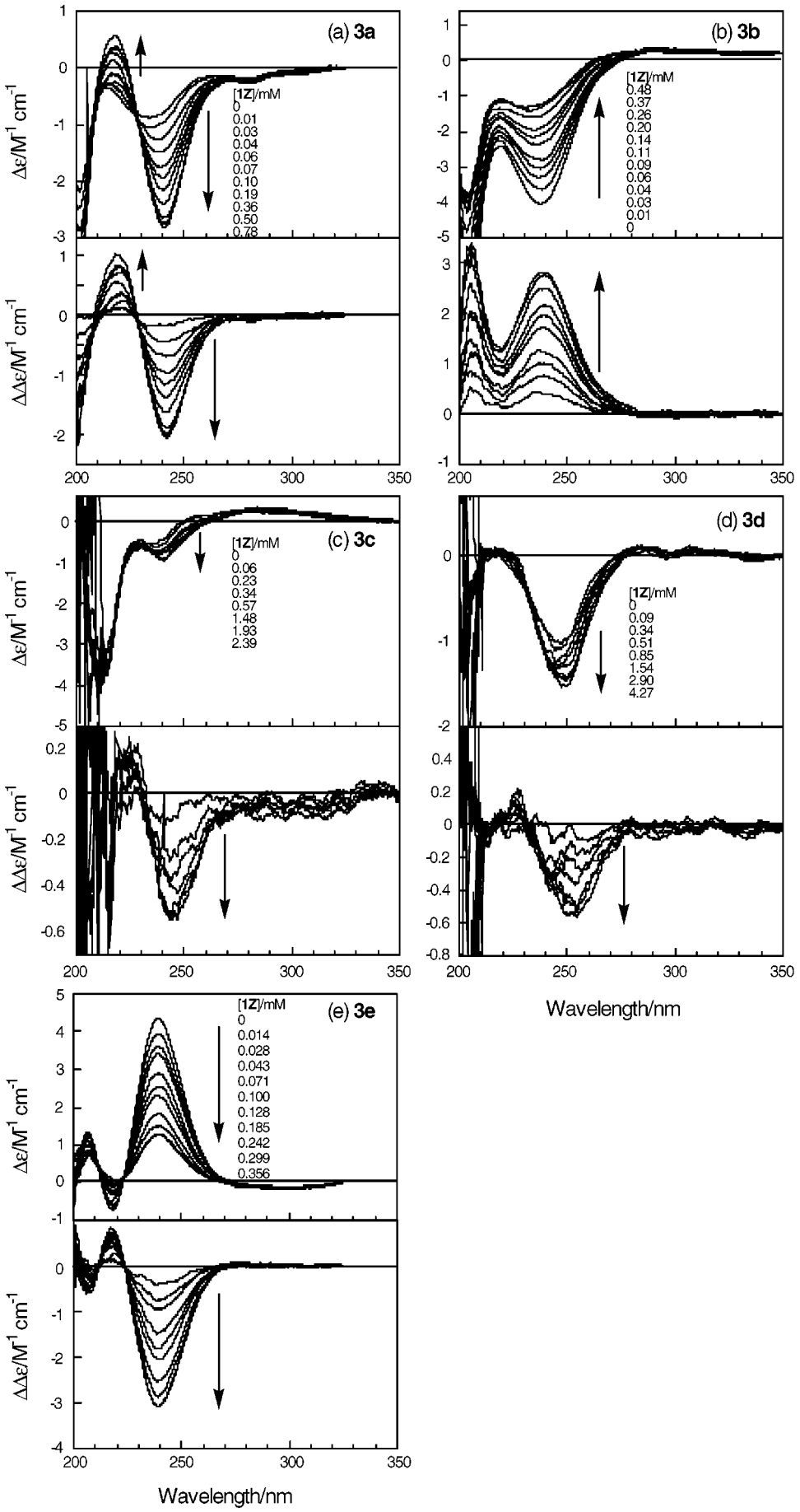


Figure 3. Circular dichroism (upper traces) and differential CD (lower traces) spectral changes of (a) **3a**, (b) **3b**, (c) **3c**, and (d) **3d** (0.05 mM) in water upon addition of varying amount of **1Z** as a guest.

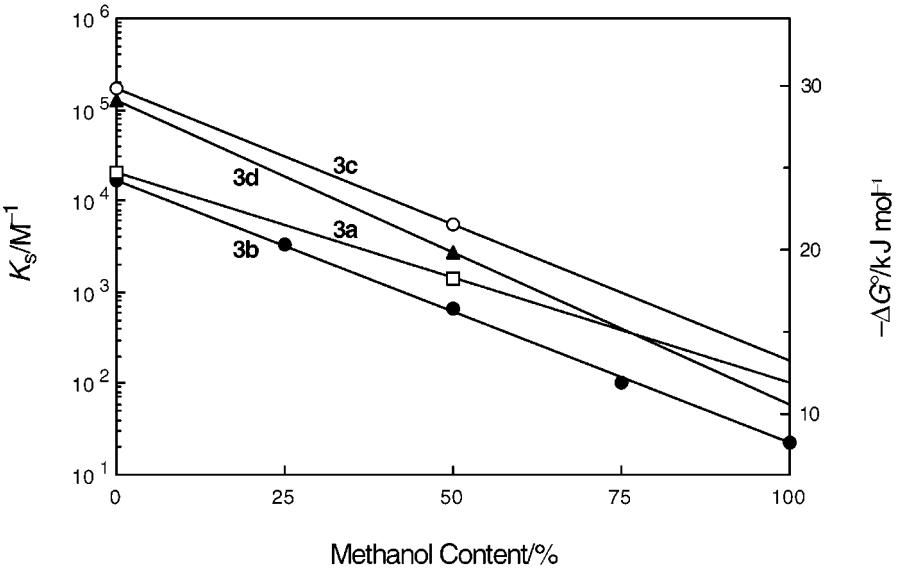


Figure 4. Complex stability constants (K_s) and free energy changes ($-\Delta G°$) for complexation of **1Z** with **3a** (□), **3b** (●), **3c** (○), and **3d** (▲) as a function of methanol content in aqueous methanol.

Table 2. Thermodynamic Parameters for Inclusion Complexation of (*Z*)-Cyclooctene (1Z) with *β*-Cyclodextrin Phthalate (3b) in Methanol and 1:1 Water−Methanol Mixture

solvent	$\Delta H°$/kJ mol^{-1}	$\Delta S°$/J mol^{-1} K^{-1}
MeOH	−30.8	−78.5
50% MeOH	−31.8	−51.1

The temperature effect on complex stability was also investigated for the complexation of **1Z** with **3b** in methanol at 15−25 °C, and in 50% methanol at 5−25 °C (Table 1). The logarithms of obtained K_s are plotted against the reciprocal temperature to give good straight lines in both solvents. From the slope and intercept of the plot, we obtain the thermodynamic parameters listed in Table 2. The complexation is clearly exclusively driven by the large negative enthalpy changes ($\Delta H°$) in both solvents, which overwhelm the considerably negative entropy changes ($\Delta S°$). The higher complex stability in 50% methanol originates from the much smaller entropy loss, probably attributable to more extensive desolvation upon inclusion of **1Z**. Using these thermodynamic parameters, we can calculate the extrapolated K_s values at lower temperatures.

Attempted Optical Resolution of 1E by Inclusion Complexation. Inclusion complexes are readily prepared by the addition of guests to an aqueous solution of cyclodextrin.[21] Using this conventional method, we first evaluated the chiral recognition abilities of native and modified *β*-cyclodextrins in the ground state. An ethereal solution of racemic **1E** was added to a near saturated aqueous solution of *β*-cyclodextrin, **3a**, or **3b** resulting in white precipitates, which were collected by filtration, washed repeatedly with ether and water, and finally decomplexed by adding to a 10% aqueous potassium hydroxide solution. The liberated **1E** was extracted with pentane, and the extract analyzed by chiral GC for enantiomeric purity. However, none of these native and modified cyclodextrins exhibited significant optical resolution; only benzoate **3a** gave an appreciable ee of −1.9% in favor of (*R*)-(−)-**1E**, while the ee's obtained with *β*-cyclodextrin and **3b** were respectively +0.5 and −0.6%, which are just outside of the experimental error (±0.3−0.5%). This reveals that the chiral cavity of native and modified *β*-cyclodextrins possesses very a poor chiral recognition ability for **1E**, at least in the ground state. Showing that the hydrophobic and van der Waals interactions within the cavity are not oriented enough to discriminate the enantiomers of **1E** accommodated in the cavity.

Photosensitization of 1Z with Modified Cyclodextrins. The geometrical photoisomerization of prochiral substrate **1Z** was efficiently sensitized by modified cyclodextrins **2**−**4** in aqueous methanolic solutions at 55 to −40 °C to give **1E** in good-to-excellent yields. The **1E**/**1Z** ratio and the enantiomeric excess (ee) of **1E** produced at each irradiation time and temperature are shown in Table 3 (see Supporting Information for the full version). Also included are the host occupancies, which are defined as percentages of host occupied by **1Z** under the initial conditions employed ([host] = 0.2 mM and [**1Z**] = 2 mM) and can be calculated from the solvent- and temperature-dependence of K_s shown in Figures 4 and 5.

To examine more clearly the effects of solvent composition, the host's cavity size and appended sensitizer group, the time dependent profiles of the *E*/*Z* ratio and % ee values at 25 °C are plotted as functions of irradiation time for α- to *γ*-cyclodextrin benzoates **2a**, **3a**, and **4a** in Figure 6, and also for *β*-cyclodextrin derivatives **3b**−**e** in Figure 7.

***E*/*Z* Ratio at the Photostationary State.** In all cases examined, the *E*/*Z* ratio increases with increasing irradiation time to give a plateau upon prolonged irradiations for up to 30−60 min, from which we determine the photostationary-state *E*/*Z* ratio, $(E/Z)_{pss}$. Naturally, the $(E/Z)_{pss}$ ratio is influenced more or less by the sensitizer appended to cyclodextrin, as was the case with the singlet photosensitization with conventional, noncomplexing, aromatic esters in homogeneous solutions.[5−8] However, it is intriguing that the $(E/Z)_{pss}$ ratio depends more critically on the methanol contents of aqueous solution. The highest $(E/Z)_{pss}$ of up to 0.4−0.8 are obtained

(21) Szejtli, J. *Cyclodextrin Technology*; Kluwer-Academic: Dordrecht, 1988.

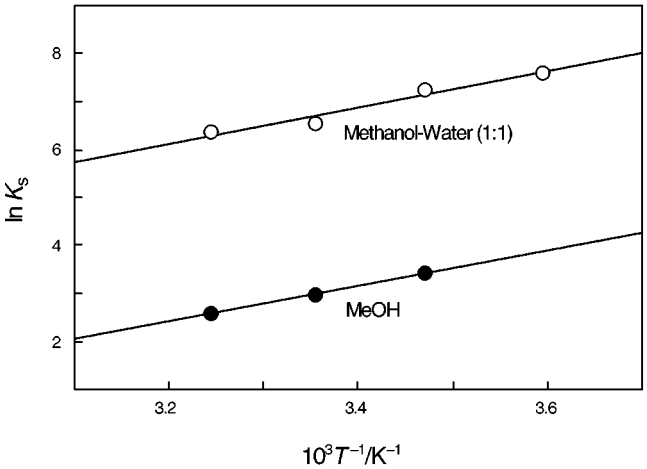


Figure 5. Temperature dependence of K_s for complexation of **1Z** with **3b** in methanol (●) and 1:1 methanol−water (○).

consistently in 50% aqueous methanol rather than in pure methanol or water, irrespective of the binding ability of host cyclodextrin used.

Typical $(E/Z)_{pss}$ ratios obtained in the singlet sensitization with methyl benzoate, phthalate, isophthalate, and terephthalate at 25 °C are 0.25, 0.06, 0.34, and 0.29, respectively.[22] Hence, the corresponding values of 0.6−0.8, 0.4, 0.7, and 0.7 for cyclodextrin benzoates **2a**−**4a**, phthalate **3b**, isophthalate **3c**, and terephthalate **3d** in 50% methanol are anomalously high for a medium-sized cycloalkene whose (*E*)-isomer is highly strained.[23,24] Furthermore, the $(E/Z)_{pss}$ ratio displays somewhat curious behavior as the methanol content further decreases to zero, giving a bell-shaped plot with a maximum at 50%, as can readily be recognized from the data for **3a** shown in Figure 6b. This unusual dependence of $(E/Z)_{pss}$ upon methanol content cannot simply be related to the inclusion complexation of **1Z**, since the host occupancy increases consistently with decreasing methanol content.

These much enhanced $(E/Z)_{pss}$ ratios could be accounted for in terms of the preferential complexation, and the subsequent excitation, of **1Z** rather than **1E**, as the $(E/Z)_{pss}$ ratio is expressed as a product of the excitation ratio (k_{qZ}/k_{qE}),[25] decay ratio (k_{dE}/k_{dZ}), and inclusion ratio (K_{sZ}/K_{sE}): i.e., $(E/Z)_{pss} = (k_{qZ}/k_{qE})(k_{dE}/k_{dZ})(K_{sZ}/K_{sE})$. However, this rationalization seems inadequate from the quantitative point of view, since the sensitization with **3a** in 50% methanol, despite the low K_{sZ}/K_{sE} of 0.5 and high host occupancy of 73%, gave the $(E/Z)_{pss}$ ratio as high as 0.8, which is comparable to or even higher than those for **3b**, **3d**, and **3e** which give much favorable K_{sZ}/K_{sE} ratios greater than unity (in water).

In the geometrical photoisomerization of **1Z** sensitized by various aromatic esters in organic solvents, where dynamic quenching dominates the energy transfer process, the energy transfer from excited aromatic ester to strained **1E** is almost diffusion controlled ($k_q = 0.9-1.3 \times 10^{10}$ s^{-1}); while that to **1Z** which possesses a higher singlet energy than **1E**, is slower by a factor of 3−8.[5] This accounts for the observed small $(E/Z)_{pss}$ ratios (<0.3) in homogeneous solutions, whereas the decay ratio (k_{dE}/k_{dZ}) is almost unity as far as the singlet mechanism is operative.[26] By contrast, in the present case where the sensitization and isomerization take place in a closely packed environment within the cavity, the rates of energy transfer to **1E** and **1Z**, and probably isomerization, must be affected distinctly differently by the position and

Table 3. The 1E/1Z Ratio and Enantiomeric Excess (ee) of 1E Obtained in Enantiodifferentiating Photoisomerization of (*Z*)-Cyclooctene (1Z) Sensitized by α-, β-, and γ-Cyclodextrin Derivatives (2a, 3a−e, and 4a) in Methanol−Water Mixture at Varying Temperatures[a]

host	solvent	temp/°C	host occupancy/%[b]	irradiation time/min	*E*/*Z*	% ee
2a	MeOH	25	c	5	0.16	0.3
				60	0.37	0.9
	50% MeOH	25	c	2	0.05	1.9
				60	0.73	1.7
	H_2O	25	c	5	0.10	2.3
				60	0.29	2.2
3a	MeOH	25	17	10	0.10	−2.1
				60	0.22	−0.9
	75% MeOH	25	42	2	0.04	−5.2
				60	0.57	−3.1
	50% MeOH	25	73	2	0.15	−9.4
				60	0.76	−5.0
	25% MeOH	25	91	2	0.06	−10.7
				60	0.58	−4.0
	H_2O	25	98	5	0.05	−9.7
				45	0.16	−5.7
3b	MeOH	55	1	5	0.07	10.5
				60	0.07	10.6
		25	4	2	0.03	9.4
				60	0.12	11.0
		−40	54	10	0.05	13.3
				60	0.24	16.5
	85% MeOH	−40	79	10	0.07	15.9
				60	0.41	17.0
	75% MeOH	25	20	2	0.05	9.3
				60	0.26	10.9
	50% MeOH	55	33	5	0.09	12.5
				60	0.44	12.0
		25	60	2	0.09	18.7
				40	0.42	17.5
		−40	98	10	0.05	c
				25	0.22	23.9
				60	0.29	23.5
3c	MeOH	25	24	2	0.03	0.0
				60	0.36	−0.7
	75% MeOH	25	54	2	0.06	0.6
				60	0.55	−0.4
	50% MeOH	25	91	2	0.21	−1.7
				60	0.60	0.3
3d	MeOH	25	10	2	0.08	−0.5
				40	0.55	0.2
	50% MeOH	25	83	2	0.22	c
				40	0.61	1.9
3e	MeOH	25	c	5	0.01	0.5
				60	0.05	0.2
	50% MeOH	25	c	5	0.07	4.3
				60	0.41	4.7
	H_2O	25	95	2	0.08	6.3
				30	0.35	8.1
4a	MeOH	25	c	2	0.00	2.1
				60	0.38	1.2
	50% MeOH	25	c	2	0.02	4.5
				60	0.54	3.0
	H_2O	25	c	2	0.05	3.9
				60	0.11	0.6

[a] Irradiated at 254 nm under argon atmosphere in methanol−water mixture; [**1Z**] = 2 mM, [host] = 0.2 mM. [b] Percentage of host occupied by **1Z** under the initial conditions employed. [c] Value not determined.

(22) Yamasaki, N.; Yokoyama, T.; Inoue, Y.; Tai, A. *J. Photochem. Photobiol., A: Chem.* **1989**, *48*, 465.
(23) Schleyer, P. v. R.; Williams, J. E.; Blanchard, K. R. *J. Am. Chem. Soc.* **1970**, *92*, 3181.
(24) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734.
(25) For the detailed description of the excitation and decay ratios as well as the sensitization and enantiodifferentiation mechanisms, see ref 5.
(26) Inoue, Y.; Takamuku, S.; Kunitomi, Y.; Sakurai, H. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1672.

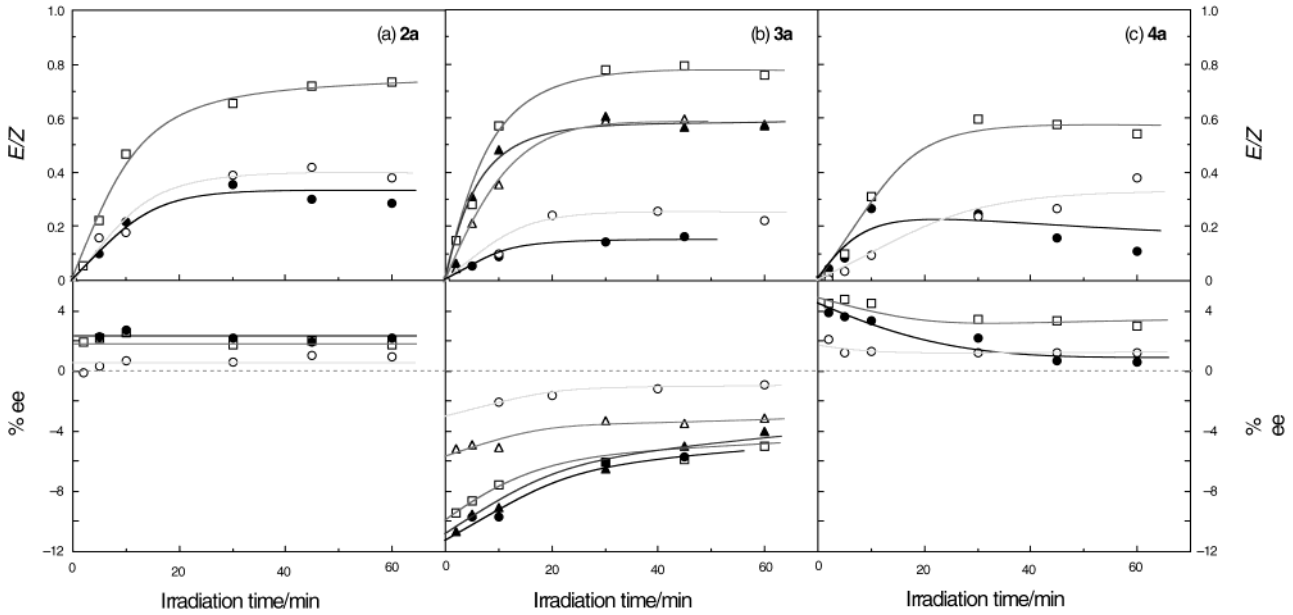


Figure 6. *E*/*Z* ratio and % ee obtained in the enantiodifferentiating photoisomerization of **1Z** sensitized by (a) **2a** in methanol (○), 50% methanol (□), and water (●) at 25 °C, (b) **3a** in methanol (○), 75% methanol (△), 50% methanol (□), 25% methanol (▲), and water (●) at 25 °C, and (c) **4a** in methanol (○), 50% methanol (□), and water (●) at 25 °C.

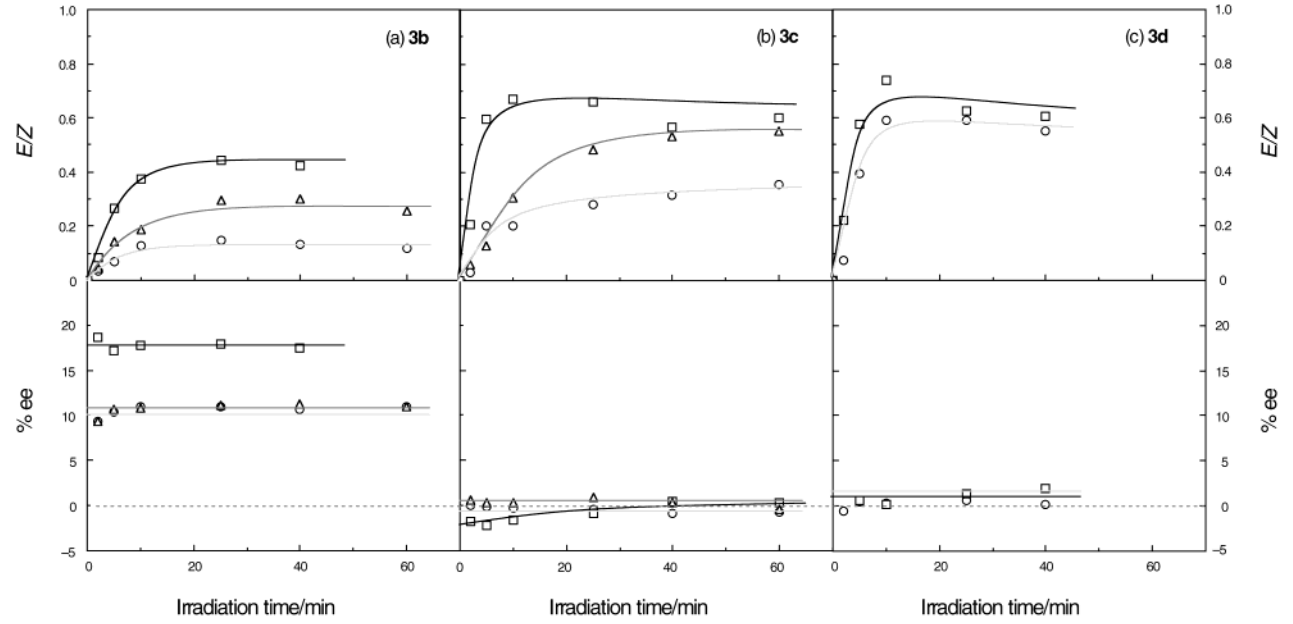


Figure 7. *E*/*Z* ratio and % ee obtained in the enantiodifferentiating photoisomerization of **1Z** sensitized by (a) **3b** in methanol (○), 75% methanol (△), and 50% methanol (□) at 25 °C, (b) **3c** in methanol (○), 75% methanol (△), and 50% methanol (□) at 25 °C, and (c) **3d** in methanol (○) and 50% methanol (□) at 25 °C.

orientation of guest in the cavity. However, the $(E/Z)_{pss}$ ratios shown in Figures 6 and 7 are not a simple function of the methanol content or host occupancy. As described above, the ratio is enhanced by increasing the water content up to 50%, but it decreases thereafter, regardless of the greater complex stabilities in the solvents of higher water contents. This may indicate that the guest orientation and distance to the sensitizing group, 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 $(E/Z)_{pss}$ ratio maximized 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**.

Effects of Cavity Size: Photosensitization with α-, *β*-, and *γ*-Cyclodextrin Benzoates (2a, 3a, 4a). The ee of photoproduct **1E** critically depends on the solvent and sensitizing host employed. As can be seen from Figure 6, only the *β*-cyclodextrin benzoate chiral sensitizer **3a** gave moderate ee's of up to 11%, while α- and *γ*-cyclodextrin benzoates **2a** and **4a** lead to much lower ee's of 1−3 and 1−5%, respectively. The extremely low ee's obtained with **2a** are not unexpected, since the cavity of α-cyclodextrin is too small to fully accommodate **1Z**, which is confirmed by no appreciable CD changes ob-

served upon addition of the guest to an aqueous solution of **2a**. Therefore, the sensitization with the benzoate moiety of **2a** must occur outside the cavity, where the cyclodextrin does not function as a *chiral host*, but simply behaves as a conventional *chiral auxiliary*. The low ee's obtained are within a typical ee range reported for a variety of optically active alkyl benzoates at 25 °C.[5]

The ee's obtained upon sensitization with γ-cyclodextrin benzoate **4a** are somewhat larger at the initial stages of photolysis but decrease appreciably with increasing irradiation time especially in aqueous solutions of higher water contents. The higher initial ee's of up to 5% and the subsequent gradual decrease of ee may be accounted for in terms of the preferential formation of (*S*)-(+)-**1E** in the enantiodifferentiating photosensitization within the chiral cavity, followed by the favored complexation and reverse photoisomerization of the same enantiomer upon longer irradiations.

The effects of water content and irradiation time upon ee are elucidated more clearly in the photosensitization with β-cyclodextrin benzoate **3a** in aqueous solutions of various methanol contents. As shown in Figure 6b (lower traces), the ee obtained with **3a** in each solvent depends not only on the methanol content, but also on the irradiation period. In all solvents employed, the ee decreases more or less with increasing irradiation period. The preferential inclusion (in 1.9% ee) and subsequent photoisomerization (to **1Z**) of (*R*)- rather than (*S*)-**1E** should be responsible for the gradual decrease in the product ee in the early stages of the photolysis, since the time dependence of the ee becomes more conspicuous as the water content increases, and the *E*/*Z* and ee show analogous time-profiles approaching a plateau upon prolonged irradiations.

The dependence of the ee on solvent composition is semiquantitatively accounted for in terms of the fraction of host occupied by **1Z** under the conditions employed ([**1Z**] = 2 mM; [**3a**] = 0.2 mM). As listed in Table 2, the initial host occupancy calculated from K_s increases from 17% in methanol to 73% in 50% methanol and then to 98% in pure water. Simultaneously, the product ee in the initial stages of irradiation is enhanced rapidly from 2 to 9% by increasing water content from 0 to 50%, but thereafter increases more slowly to 11% ee in close relation to the host occupancy. This parallel behavior clearly indicates that the enantiodifferentiating photoisomerization occurs primarily within the chiral host cavity. This confirms that the inclusion complexation by the modified cyclodextrin is essential in order to obtain the optimum ee of 11%, which is the highest ever obtained upon photosensitizations of **1Z** with a variety of optically active alkyl esters of unsubstituted benzoates.[5−7]

Effects of Sensitizer Modification: Photosensitization with Isomeric Phthalates of β-Cyclodextrin (3b−d). As described above, β-cyclodextrin benzoate **3a** gave high *E*/*Z* ratios and fairly good ee's as a chiral sensitizing host with a relatively simple structure. To elucidate in detail the role of inclusion complexation and the factors controlling enantiodifferentiating photoisomerization in the cavity, we further synthesized a series of isomeric phthalates **3b**−**d**, as well as the tethered benzamide **3e**. Under the comparable irradiation conditions, these modified cyclodextrins also efficiently sensitized the *Z*−*E* photoisomerization of **1Z** in aqueous methanol.

As can be seen from Figure 7, the product ee is substantially affected by the position of methoxycarbonyl group, although the geometrical photoisomerization proceeds quite smoothly in all cases. Of the three isomeric phthalates examined phthalate **3b** gave the highest ee's, up to 18% in 50% methanol at 25 °C. Conversely, iso- and terephthalates **3c** and **3d**, being effective sensitizers giving high *E*/*Z* ratios, entirely failed to give appreciable ee's in any solvent. These contrasting results are compatible with the original idea that only photosensitization within the cavity can efficiently transfer the host chirality to the included prochiral substrate; while sensitization outside the cavity should show much less efficient asymmetric induction. The very small CD spectral changes observed for **3c** and **3d** (Figures 3b,c) indicate that the aromatic chromophore is located away from the guest **1Z** accommodated in the cavity. Examinations with space-filling molecular models revealed that the meta and para substituents in **3c** and **3d** disturb the self-inclusion of the aromatic moiety, and therefore the intracavity sensitization of the included guest is no longer effective. In contrast, the *o*-methoxycarbonyl group introduced to **3b** has been revealed, by inspection of the NMR ROESY spectrum, to be originally included in the cavity in 50% methanol.[19] The appended *o*-methoxycarbonyl in **3b** probably works as a spacer in the cavity, promoting the conformational fixation of both guest and sensitizer in the chiral cavity to give ee's higher than those obtained with **3a**. The importance of the occluded sensitizing group is further demonstrated in the photosensitization with tethered benzamide **3e**. Upon sensitization with **3e** (Table 2), the ee of **1E** produced, not being as high as those found for **3b**, also increases from 1% in methanol to 4% in 50% methanol and then to 8% in water where the host occupancy approaches 95%.

Effects of Solvent and Temperature: Product ee as a Function of Host Occupancy. It has been demonstrated that the enantiodifferentiating photosensitizations of **1Z** and related compounds with chiral polyalkyl benzenepolycarboxylates are highly sensitive to temperature, and often exhibit temperature dependent switching of the product chirality, for which the entropy factor is solely responsible.[5−9,27,28] Consequently, the effects of temperature upon the product ee obtained in the supramolecular photosensitization of **1Z** with β-cyclodextrin phthalate **3b** was studied in aqueous methanol solutions.

Interestingly, it turned out that the product ee is not a function of temperature, but is governed predominantly by water content or more strictly by host occupancy. In Figure 8 the product ee's for **3a** and **3b**, obtained at temperatures ranging from −40 to +55 °C, are plotted as a function of host occupancy which is determined by the solvent composition and temperature employed. The plot of ee for **3a** at 25 °C versus the host occupancy gives an excellent straight line (Figure 8a). The extrapolation of the regression line to zero occupancy gives the ee value expected for the exterior sensitization, while the extrapolated ee at 100% occupancy is the maximum value for the interior sensitization. Thus, the sensitization outside the cavity leads to an extremely low ee of −1%, whereas the sensitization exclusively within the cavity gives −10% ee. From the maximum ee obtained at 100% occupancy, one can evaluate the inherent enantiodifferentiating ability of modified cyclodextrin in the excited state.

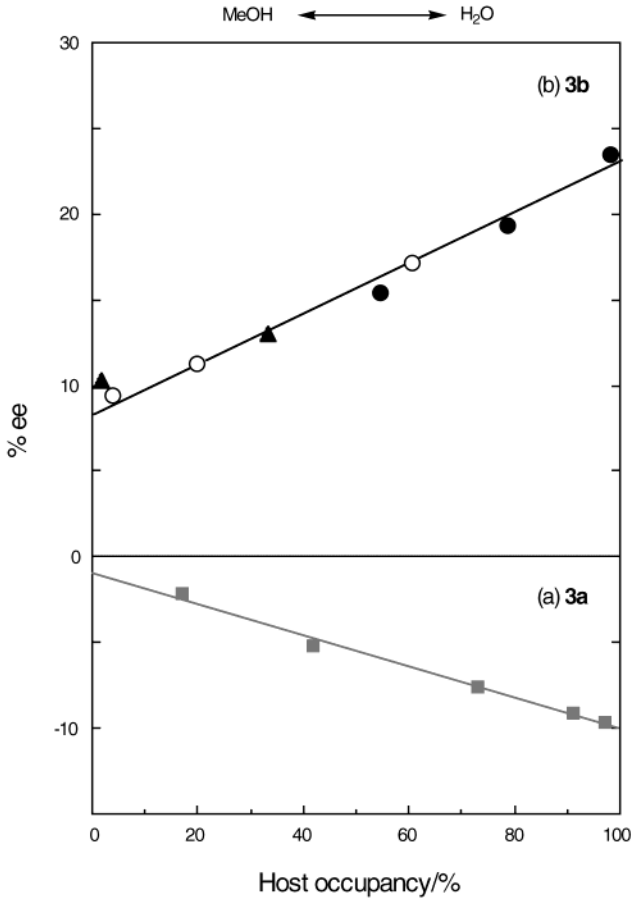


Figure 8. % ee as a function of host occupancy for the enantiodifferentiating photosensitization of **1Z** with (a) **3a** at 25 °C (■) and (b) **3b** at 55 (▲), 25 (○), and −40 °C (●) in methanol−water mixture of various compositions.

The photosensitization with **3b** in aqueous methanol at temperatures ranging from +55 to −40 °C exhibited quite interesting behavior. As expected, the product ee is apparently a critical function of both temperature and solvent composition employed. Nevertheless, all the ee values obtained upon sensitization with **3b**, when plotted against the host occupancy, fall on a *single* straight line irrespective of the temperature employed. The extrapolation of the regression line to 100% occupancy gives an ee of 24%. This maximum value, which is inherent to sensitizing host **3b**, is absolutely independent of the temperature. This unexpected observation clearly indicates that the temperature, and therefore the entropy factor, do not play any essential role in the supramolecular photochirogenesis within the cyclodextrin cavity, which may be compared to the photochemistry in solid state.

Conclusions

In this study, we have demonstrated that supramolecular photochirogenesis, employing modified cyclodextrins as sensitizing hosts, is a promising strategy not only for efficiently transferring the environmental chirality of the cyclodextrin cavity to the molecular chirality of photoproduct through the excited-state interactions, but also for enhancing the original photoenantiodifferentiating ability of native cyclodextrins. Indeed, we have successfully enhanced the extremely poor ee's of <1% obtained upon direct irradiation at 185 nm of **1Z** accommodated in native β-cyclodextrin[28] up to 24% ee. This supramolecular strategy is not restricted to cyclodextrin host but is applicable widely to a variety of chiral as well as achiral supramolecular systems by introducing a (chiral) chromophore.

An aspect of significant importance, revealed by this work, is that the entropy factor does not appear to play a significant role in the supramolecular photochirogenic process. This phenomenon, which is totally unexpected from the vital role of entropy demonstrated quite widely in the conventional (nonsupramolecular) asymmetric photosensitization reactions,[5−10,27] is tentatively rationalized by the greatly reduced motional freedom of guest substrates in supramolecular complexes. The scope of this phenomenon is currently being extended to other supramolecular systems.

Acknowledgment. L.H.T. is grateful to the Chinese Natural Science Foundation for financial support (No. 29873062).

Supporting Information Available: The full verson of Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

JO001262M

(27) Tsuneishi, H.; Hakushi, T.; Tai, A.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2057.

(28) Inoue, Y.; Tsuneishi, H.; Hakushi, T.; Tai, A. *J. Am. Chem. Soc.* **1997**, *119*, 472.

(29) Inoue, Y.; Kosaka, S.; Matsumoto, K.; Tsuneishi, H.; Hakushi, T.; Tai, A.; Nakagawa, K.; Tong, L.-H. *J. Photochem. Photobiol., A: Chem.* **1993**, *71*, 61.