Journal of Inclusion Phenomena and Macrocyclic Chemistry **50**: 111–114, 2004.

Original Article

Supramolecular Photochirogenesis. 3. Enantiodifferentiating Photoisomerization of Cyclooctene Included and Sensitized by 6-*O*-Mono(*o*-methoxybenzoyl)-*β*-cyclodextrin

YUNYAN GAO[1], MAKI INOUE[2], TAKEHIKO WADA[2] and YOSHIHISA INOUE[1,2]*
[1]*The ICORP Entropy Control Project, JST, 4-6-3 Kamishinden, Toyonaka 560-0085, Japan;* [2]*Department of Molecular Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan*

(Received: 15 October 2003; in final form: 22 November 2003)

Key words: asymmetric synthesis, cyclodextrin, cyclooctene, photochirogenesis, photoisomerization

Abstract

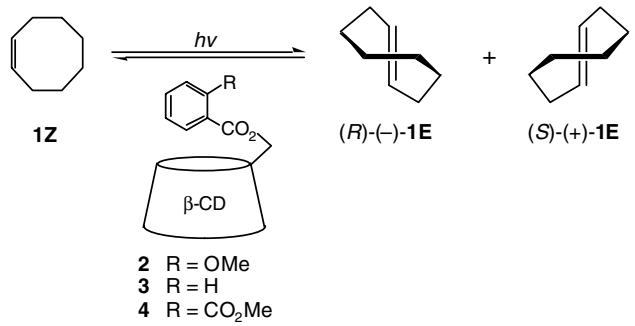
Supramolecular enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1***Z*) to chiral (*E*)-isomer (**1***E*) through inclusion and sensitization by 6-*O*-mono(*o*-methoxybenzoyl)-*β*-cyclodextrin (**2**) was investigated in water and in aqueous methanol solutions at various temperatures. A dramatic inversion of the product chirality was observed to occur by simply changing the solvent from water to methanol. Thus, the supramolecular photosensitization in aqueous solution gave (*R*)-(–)-**1***E* in 15% enantiomeric excess (ee), whereas in methanol the antipodal (*S*)-(+)-**1***E* was obtained in 5% ee. The temperature and solvent dependencies of the product ee are discussed.

Introduction

Recent developments in asymmetric photochemistry, or photochirogenesis, have attracted much attention [1–4]. Apart from the absolute asymmetric synthesis using circularly polarized light, the photochirogenic methodologies hitherto proposed may be classified into two major categories [2, 3]. The first one utilizes the intramolecular chiral interactions in the excited state to create a new stereogenic center in the substrate, where the chirality transfer occurs intramolecularly from a built-in chiral auxiliary to a prochiral moiety of the substrate. In this diastereodifferentiation strategy, one can count on the relatively strong intramolecular interactions and may expect a good high diastereomeric excess in general. On the other hand, the second methodology employs the intermolecular interactions between a chirogen and a substrate in the electronically excited state, where the chirality transfer occurs from a chiral sensitizer to a prochiral substrate in the photosensitization process. In this enantiodifferentiating photosensitization method, the intermolecular interactions in the excited state are usually weak and short-lived, so that one will not anticipate a very high enantiomeric excess (ee) in most cases. Nevertheless, this photochirogenic method is attractive as an alternative catalytic route to optically active compounds, which is unique to photoreaction and performed without using hazardous transition metals. In our recent studies [5], we have demonstrated that the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1***Z*) can be executed by using a catalytic amount of chiral sensitizers to give optically active (*E*)-cyclooctene (**1***E*) in good to high ee's upon sensitization with optically active alkyl benzene(poly)carboxylates.

More recently, we have proposed a unique supramolecular photochirogenesis strategy for transferring host chirality to a guest substrate by using a chiral sensitizing host [6]. This method, enabling us to amplify the amount of chiral compound through the sensitization process, differs from the conventional supramolecular photochemistry in crystals, zeolites, or cyclodextrins [6–10]. However, only limited efforts have hitherto been devoted to this field of supramolecular enantiodifferentiating photosensitization in solution. We have shown that cyclodextrins modified with benzoate and isomeric phthalates on the primary side function as chiral sensitizing hosts for the enantiodifferentiating photoisomerization of **1***Z*, and afford **1***E* in such ee's that moderately depend on the solvent composition, or more strictly, on the host occupancy [6]. Thus, the product ee varied from 1 to 10% upon sensitization with 6-*O*-benzoyl-*β*-cyclodextrin and from 10 to 23% with 6-*O*-(methyl phthaloyl)-*β*-cyclodextrin by increasing the water content in aqueous methanol. In the present study,

* Author for correspondence. E-mail: inoue@ap.chem.eng.osaka-u.ac.jp



Scheme 1. Enantiodifferentiating *Z–E* photoisomerization of cyclooctene (**1**) included and sensitized by 6-*O*-modified *β*-cyclodextrin derivatives (**2–4**).

we synthesized a new chiral sensitizing host, in which *o*-methoxybenzoyl unit is introduced to *β*-cyclodextrin at the 6-hydroxyl group, for the use in the enantiodifferentiating photosensitization of **1***Z*. The seemingly small difference in substituent in the sensitizing host caused an unexpected change in the sensitization behavior, inducing a dramatic switching of the product chirality by changing the solvent from water to methanol.

Experimental

General

Mass spectra were measured on a JEOL JMN-DX303 instrument. ^{1}H NMR spectra were recorded in DMSO-d_6 on a JEOL GSX-400 instrument. Electronic absorption spectra were obtained with a JASCO V-50 spectrometer. Circular dichroism (CD) spectra were measured in a quartz cell (1 cm light path) on a JASCO J-720WI spectrometer equipped with a PTC-343 temperature controller.

Gas chromatographic (GC) analyses of photolyzed samples were performed for the **1***E*/**1***Z* ratios on a Shimadzu CBP-20 column (0.25 mm $\phi \times 2$ m) at 60 °C and for the ee of **1***E* on a Supelco *β*-DEX225 column (0.25 mm $\phi \times 2$ m) at 55 °C, using a Shimadzu GC-17A instrument equipped with a CR7A integrator. A low injection port temperature of 100 °C was employed in order to avoid the thermal *E*-to-*Z* isomerization of the photoproduced **1***E* upon injection.

Materials

(*Z*)-Cyclooctene (purchased from Wako) was used as received. *β*-Cyclodextrin (Wako) was first recrystallized from water and then dried *in vacuo* at 70 °C for 12 h prior to use. Distilled water and HPLC-grade methanol were used throughout the work.

*6-O-Mono(o-methoxybenzoyl)-β-cyclodextrin (***2***)*

o-Methoxybenzoic acid (1.5 g) in dry pyridine (50 mL) was added at 0 °C in 30 min to a pyridine solution (500 mL) of *β*-cyclodextrin (15 g). To the mixture were added 6 g of dicyclohexylcarbodiimide and a small amount of 4-dimethylaminopyridine with continuing stirring. The resulting solution was stirred overnight at room temperature and then quenched by 1 mL of water. Petroleum ether (1 L) was added to the resultant mixture with stirring. After standing for 30 min, the precipitate was filtrated and extracted with acetone for 30 h by using a Soxhlet apparatus. The remaining solid was recrystallized from water and then purified by preparative HPLC. FAB-MS (KI) *m*/*z* 1307 ($M + K^+$); UV $\lambda_{max}(H_2O)$/nm (ε/M^{-1} cm^{-1}) 297 (3070), 237 (6890); λ_{max}(MeOH) 295 (2850), 235 (6080); ^{1}H NMR (DMSO-d_6) δ/ppm 7.7 (d, 1H), 7.5 (t, 1H), 7.1 (d, 1H), 7.0 (t, 1H), 5.6–5.7 (m, 14H), 4.8–4.9 (m, 7H), 4.0–4.5 (m, 7H), 3.9 (s, 3H); Anal. Calcd. for $C_{50}H_{76}O_{37} \cdot 8H_2O$ C, 42.45; H, 6.56. Found: C, 42.33; H, 6.04.

Complexation

Inclusion complexation behavior of 6-*O*-mono(*o*-methoxybenzoyl)-*β*-cyclodextrin **2** was investigated by CD spectrometric titration. The CD spectra of **2** (<0.1 mM) were measured in the presence of varying concentrations of **1***Z* in water–methanol mixed solvents. Assuming the 1:1 stoichiometry, the complex stability constants (K_S) were determined from the CD intensity changes caused by the addition of **1***Z* in water–methanol solutions of different compositions, by using the least-squares fitting procedure [6].

Photolysis

All irradiations were run in a temperature-controlled water or water-ethylene glycol bath, using a 60 W mercury resonance lamp fitted with a Vycor sleeve. An aqueous methanol solution (4 mL), containing **1***Z* (2 mM) and host **2** (0.2 mM), was placed in a quartz tube, purged with argon at 0 °C, and then irradiated for a given period of time. The photolyzed solution was poured onto a 10% aqueous KOH solution (5 mL) with stirring for decomplexation. The resultant mixture was extracted with pentane (1 mL), and an aliquot of the pentane extract was subjected to GC analysis on a CBP-20 column for the *E*/*Z* ratio. The rest of the pentane extract was extracted with 20% aqueous silver nitrate at 0 °C. The aqueous extract containing Ag^+-**1***E* complex was washed twice with pentane and then decomplexed with a 28% ammonia solution at 0 °C. The liberated **1***E* was extracted with pentane and the enantiomeric excess of isolated **1***E* was determined by chiral GC analysis on a Supelco *β*-DEX225 column.

Results and discussion

Complexation of **1***Z with* **2**

Circular dichroism spectrum of 6-*O*-mono(*o*-methoxybenzoyl)-*β*-cyclodextrin **2** was measured in aqueous

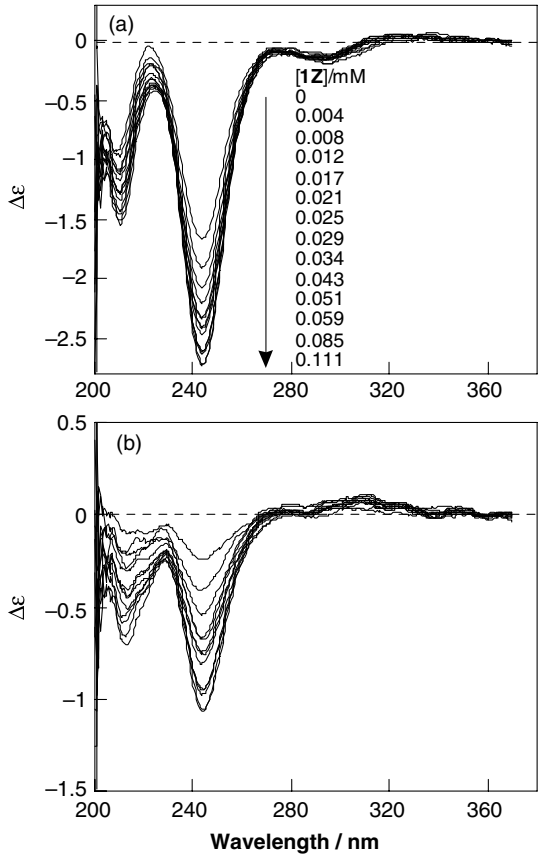


Figure 1. (a) Circular dichroism and (b) differential circular dichroism spectral changes of 6-*O*-mono(*o*-methoxybenzoyl)-*β*-cyclodextrin **2** (2.36×10^{-5} M) in water upon gradual addition of (*Z*)-cyclooctene **1***Z* as a guest.

Table 1. Complex stability constants (K_S) for 1:1 complexation of (*Z*)-cyclooctene **1***Z* with 6-*O*-mono(*o*-methoxybenzoyl)-*β*-cyclodextrin **2**, 6-*O*-monobenzoyl-*β*-cyclodextrin **3**, and 6-*O*-mono(methyl phthaloyl)-*β*-cyclodextrin **4** at 25 °C in water-methanol mixtures of different compositions

Host	% Methanol in water						
	0	20	25	30	50	75	100
2	276,200	25,249		20,332	2130	308	
3[a]	20,100				1440		
4[a]	16,700		3250		650	103	22

[a]Ref. [6].

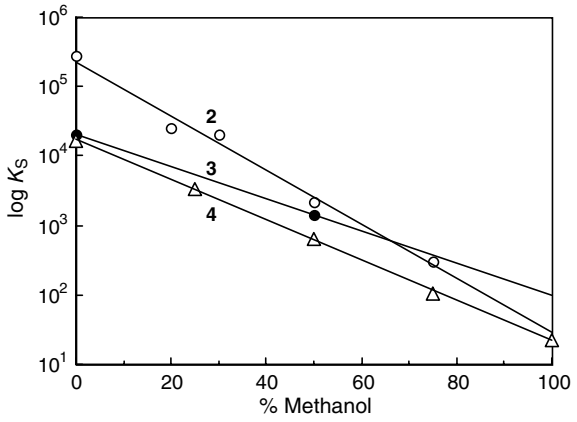


Figure 2. Log K_S for complexation of **1***Z* with 6-*O*-mono(*o*-methoxybenzoyl)-*β*-cyclodextrin **2**, 6-*O*-monobenzoyl-*β*-cyclodextrin **3**, and 6-*O*-mono(methyl phthaloyl)-*β*-cyclodextrin **4** at 25 °C as functions of methanol content in water.

solution at 25 °C. As can be seen from Figure 1a (top trace), *o*-methoxybenzoyl-modified cyclodextrin **2** exhibits its negative Cotton effect extrema for both of the ^1L_a (ca. 245 nm) and ^1L_b (ca. 295 nm) bands. According to the sector rule proposed by Kajter *et al.*, these CD spectral features are compatible with a shallow penetration of the chromophoric *o*-methoxybenzoyl moiety into the chiral cyclodextrin cavity, covering the narrower opening, as was reported previously for the benzoyl-analogue **3** [6].

Complexation behavior of (*Z*)-cyclooctene **1***Z* with host **2** was quantitatively examined in water–methanol mixtures by CD spectroscopy. Representative CD and differential CD spectral changes upon addition of varying amounts of **1***Z* to an aqueous solution of **2** at 25 °C are shown in Figure 1a and b. CD intensity of the ^1L_a band at 245 nm gradually increases with increasing **1***Z* concentration. From the differential CD spectral data obtained, we determined the complex stability constant (K_S) for **1***Z* in water–methanol mixtures of various compositions, by using the least squares curve fitting method. The obtained K_S values are listed in Table 1, along with the relevant values for **3** and **4** reported previously [6]. The *o*-methoxybenzoyl-modified cyclodextrin **2** shows much better binding for **1***Z* than benzoyl analogue **3** and methyl phthaloyl analogue **4** particularly at low methanol contents (<50%). This tendency may be accounted for in terms of the enhancement of hydrophobicity of the cavity by the introduced chromophore. In all cases, the binding constant steadily decreases with increasing methanol content in aqueous solution, and the log K_S values plotted against the methanol content gave good straight lines, as shown in Figure 2. This indicates that no specific solvation by water or methanol to the cyclodextrin occurs, and the water–methanol mixture behaves as a homogeneous solvent of continuously changing polarity/hydrophilicity.

Photosensitization of **1***Z* *with* **2**

Supramolecular enantiodifferentiating photoisomerization of **1***Z* included and sensitized by chiral host **2** was investigated in water-methanol mixtures at varying temperatures. The **1***E*/**1***Z* ratios and enatiomeric excesses (ee's) of **1***E* obtained at different temperatures and irradiation times are shown in Table 2.

The **1***E*/**1***Z* ratios of 0.18–0.62, obtained upon 30 min irradiation in water and aqueous methanol at 25 °C, are significantly higher than the ratio of 0.08 obtained in pure methanol. This is in accordance with the trend of

Table 2. **1***E*/**1***Z* ratio and enatiomeric excess (ee) of **1***E* obtained in enantiodifferentiating photoisomerization of (*Z*)-cyclooctene **1***Z* sensitized by 6-*O*-mono(*o*-methoxybenzoyl)-*β*-cyclodextrin **2** in water–methanol mixtures at various temperatures

Solvent	Temperature/°C	Irradiation time/min	**1***E*/**1***Z* ratio	% Ee
Water	50	1	0.12	−13.7
		5	0.53	−12.6
		10	0.82	−12.8
		30	0.62	−12.1
	25	1	0.05	−14.4
		3	0.19	−15.0
		15	0.42	−13.4
		30	0.60	−12.4
	10	1	0.05	−9.1
		3	0.09	−10.8
		5	0.10	−10.9
		10	0.28	−10.6
20% MeOH	25	5	0.25	−7.0
		30	0.32	−5.3
40% MeOH	25	30	0.45	2.5
50% MeOH	25	5	0.19	4.3
		15	0.28	3.4
		30	0.44	3.5
	−12	30	0.18	5.5
	−30	30	0.17	7.0
75% MeOH	25	5	0.06	4.2
		30	0.18	3.8
MeOH	25	5	0.025	5.0
		15	0.05	2.5
		30	0.08	2.5
		60	0.08	2.5

the complex stability constant, indicating that the supramolecular sensitization within the cyclodextrin cavity is much more efficient than the external sensitization in the bulk solution.

The product ee also depends critically on the methanol content in aqueous solution. In pure water, (*R*)-(−)-**1***E* was produced as the major enantiomer in −15% ee (the sign of ee is matched to that of optical rotation of **1***E* obtained), and in 20% methanol solution the product ee decreases to −7%. Further addition of methanol to the solution led to a dramatic switching of the product chirality, eventually affording the antipodal (*S*)-(+)-**1***E* in 5% ee in pure methanol. This means that we can switch the product chirality by simply changing the solvent. Although a similar phenomenon has been reported for the enantiodifferentiating photoisomerization of **1***Z* with conventional chiral sensitizers performed in polar and nonpolar solvents, such as pentane and ether, at low temperatures [12], this is the first example of the product chirality switching by solvent occurred at ambient temperature. More important is the mechanistic difference; thus, the solvation to the chiral auxiliaries of sensitizer is responsible for the chirality switching in the previous case, while the inclusion of the sensitizer moiety into the chiral cyclodextrin cavity in the present case.

Temperature effect on the product ee was also examined in water from 10 to 50 °C and in 50% methanol from −30 to 25 °C. However, the product ee obtained upon the supramolecular photosensitization of **1***Z* was not a critical function of the irradiation temperature in both solvents. This result is very different from the highly temperature-dependent ee's obtained in the conventional enantiodifferentiating photosensitization of the same substrate [5], but nicely coincides with the previous results obtained with monobenzoyl-*β*-cyclodextrin **3** and mono(methyl phthaloyl)-*β*-cyclodextrin **4** [6]. It may be concluded therefore that the product ee, as a measure of the supramolecular interactions, is less sensitive to temperature change in the inherently low-entropy environment of sensitizer-appended cyclodextrin cavity.

References

1. H. Rau: *Chem. Rev.* **83**, 535 (1983).
2. Y. Inoue: *Chem. Rev.* **92**, 741 (1992).
3. S.R.L. Everitt and Y. Inoue: In V. Ramamurthy and K.S. Schanze (eds.), *Organic Molecular Photochemistry*, Marcel Dekker, New York (1999), p. 71.
4. B.L. Feringa and R.A. van Delden: *Angew. Chem. Int. Ed.* **38**, 3418 (1999).
5. Y. Inoue, T. Yokoyama, N. Yamasaki, and A. Tai: *J. Am. Chem. Soc.* **111**, 6480 (1989); Y. Inoue, N. Yamasaki, T. Yokoyama, and A. Tai: *J. Org. Chem.*, **58**, 1011 (1993); Y. Inoue, E. Matsushima, and T. Wada: *J. Am. Chem. Soc.* **120**, 10687 (1998); Y. Inoue, T. Wada, S. Asaoka, H. Sato, J.-P. Pete: *Chem. Comm.* 251 (2000).
6. Y. Inoue, F. Dong, K. Yamamoto, L.-H. Tong, H. Tsuneishi, T. Hakushi, and A. Tai: *J. Am. Chem. Soc.* **117**, 11033 (1995); N. Sugahara, M. Kawano, T. Wada, and Y. Inoue: *Nucleic Acids Symp. Ser.* **44**, 115 (2000); Y. Inoue, T. Wada, N. Sugahara, K. Yamamoto, K. Kimura, L.-H. Tong, X.-M. Gao, Z.-J. Hou, and Y. Liu: *J. Org. Chem.* **65**, 8041 (2000).
7. V. Ramamurthy: *Photochemistry in Organized and Constrained Media*, VCH, New York, 1991.
8. M. Leibovitch, G. Olovsson, G. Sundarababu, V. Ramamurthy, J.R. Scheffer, and J. Trotter, *J. Am. Chem. Soc.* **118**, 1219 (1996); A. Joy, J.R. Scheffer, V. Ramamurthy , *Org. Lett.* **2**, 119 (2000).
9. S. Schailaja, S. Karthukeyan, and V. Ramamurthy: V. *Tetrahedron Lett.* **43**, 9335 (2002).
10. A. Nakamura and Y. Inoue: *J. Am. Chem. Soc.* **125**, 966 (2003).
11. M. Kajtar, C. Horvath-Toro, E. Kuthi, and J. Szejtli: *Acta Chim. Acad. Sci. Hung.* **110**, 327 (1982).
12. Y. Inoue, H. Ikeda, M. Kaneda, T. Sumimura, S.R.L. Everitt, and T. Wada: *J. Am. Chem. Soc.* **122**, 406 (2000).