The first supramolecular photosensitization of enantiodifferentiating bimolecular reaction: anti-Markovnikov photoaddition of methanol to 1,1-diphenylpropene sensitized by modified β-cyclodextrin†

Gaku Fukuhara,[a] Tadashi Mori,[a] Takehiko Wada[ab] and Yoshihisa Inoue*[ac]

Received (in Cambridge, UK) 3rd February 2006, Accepted 27th February 2006
First published as an Advance Article on the web 20th March 2006
DOI: 10.1039/b601674j

Enantiodifferentiating polar photoaddition of methanol to 1,1-diphenylpropene included and sensitized by cyanonaphthalene-modified β-cyclodextrin was examined for the first time to give optically active anti-Markovnikov adduct with accompanying inversion of the chiral sense of the photoproduct by temperature, which is entropic in origin.

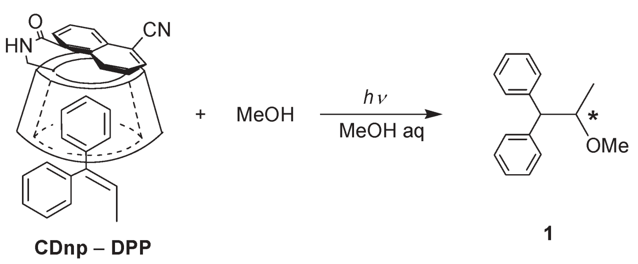
Photochirogenesis is one of the most crucial topics in current photochemistry,[1] providing us with an efficient and convenient access to optically active compounds through the electronically excited state, which is an alternative to the conventional catalytic or enzymatic methods. In conventional photochirogenesis in solution, it has been shown that the enantiomeric excess (ee) is critically influenced by environmental variants, such as temperature,[2] pressure[3] and solvent,[4] leading to the switching of product chirality in extreme cases. This enables us not only to optimize the ee but also to dynamically manipulate the chiral sense of photoproduct through the multiple entropy-related factors.[5] In contrast, the entropy term does not appear to significantly affect the product's ee in the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene included and sensitized by benzoate-appended β-cyclodextrins (CDs)[6] or sensitizer-immobilized zeolites.[7] This means that the supramolecular chiral environment is not suitable for the dynamic entropy control of photochirogenic processes, limiting the scope of the supramolecular approach. However, we have recently found that the ee and chiral sense of photoproduct again become highly sensitive to temperature in the same enantiodifferentiating photoisomerization by permethylating host CDs, for which the inherently flexible permethylated CD skeleton is responsible.[8] These contrasting results prompted us to further explore the scope and limitations of the entropy control concept in supramolecular photochirogenic systems.

In the present study, we also intend to expand the range of supramolecular photosensitization from uni- to bimolecular process. To these ends, we employed the enantiodifferentiating polar addition of methanol to 1,1-diphenylpropene (**DPP**) as a representative photochirogenic bimolecular reaction, which is well established in homogeneous solution,[9] and 6-(5-cyanonaphthyl-1-carboamido)-6-deoxy-β-cyclodextrin (**CDnp**) as a new sensitizing host (Scheme 1), and examined the temperature and solvent effects on the product's ee over a wide range of temperature and solvent.

CDnp† was synthesized in 31% yield by the condensation of 6-amino-6-deoxy-β-cyclodextrin[10] and 5-cyanonaphthalene-1-carboxylic acid[11] with a combination of 1,3-dicyclohexylcarbodiimide and 1-hydroxybenzotriazole. Aqueous methanol solutions (2 mL) in quartz cells (1 cm × 1 cm × 4 cm), containing **DPP** (0.1 mM) and **CDnp** (0.1 mM), were irradiated for 2 h under an Ar atmosphere at temperatures varying from 55 to −40 °C by using an ultra high-pressure mercury lamp fitted with a UV-29 glass filter, while methanol solutions (5 mL) in Pyrex tubes (1 cm i.d.), containing **DPP** (20 mM) and **CDnp** (1.0 mM), were irradiated at >320 nm for 16 h under Ar in the same temperature range by using a high-pressure mercury lamp fitted with a uranium glass filter. The conversion, yield and ee of photoadduct **1** were determined by capillary gas chromatography on an ASTEC B-PH column[9] to give the results shown in Table 1.

No photoadduct was obtained upon 2 h irradiation of a methanol solution of 1 mM **CDnp** and 0.1 mM **DPP**, probably due to the low binding of **DPP** by **CDnp** at this concentration, as proved by the lack of induced circular dichroism.[12] By increasing the **DPP** concentration up to 20 mM and the irradiation period to 16 h, a small but appreciable amount of **1** was obtained and subjected to the GC analysis to give low ee values, as shown in Table 1.

However, the use of aqueous methanol solutions greatly accelerated the photoreaction. As can be seen from Table 1, almost all of **DPP** was consumed after 2 h irradiation to give **1** in moderate yields in aqueous solutions containing 50% or 25% methanol. It is likely that this remarkable acceleration is accomplished through the enhanced binding of **DPP** by **CDnp**, followed by an efficient photoinduced electron transfer from **DPP** to an excited cyanonaphthalene moiety closely located within the CD cavity.



Scheme 1 Supramolecular enantiodifferentiating polar addition of methanol to **DPP** included and sensitised by **CDnp**.

---

[a] *Department of Applied Chemistry, Osaka University, 2-1 Yamada-oka, Suita 565-0871, Japan. E-mail: inoue@chem.eng.osaka-u.ac.jp; Fax: 81 6 6879 7923; Tel: 81 6 6879 7921*
[b] *PRESTO, JST, 2-1 Yamada-oka, Suita 565-0871, Japan*
[c] *Entropy Control Project, ICORP, JST, 4-6-3 Kamishinden, Toyonaka 560-0085, Japan*

† Electronic supplementary information (ESI) available: synthesis and spectroscopic data for **CDnp**. See DOI: 10.1039/b601674j

Table 1 Enantiodifferentiating polar photoaddition of methanol to **DPP** in the presence of **CDnp** in pure or aqueous methanol at various temperatures

Solvent	**DPP/CDnp**[a]	Temperature/°C	Conversion (%)	Yield (%)[b]	%ee[c]
100% MeOH[d]	0.1/1.0	25	[e]	[e]	[e]
100% MeOH[f]	20.0/1.0	25	<1	[g]	1.7
	20.0/1.0	−10	<1	[g]	−0.9
	20.0/1.0	−40	<1	[g]	−2.8
50% MeOH[d]	0.1/0.1	45	97	30	−2.1
	0.1/0.1	25	>99	43	1.4
	0.1/0.1	−10	>99	32	2.1
	0.1/0.1	−40	96	61	5.8
25% MeOH[d]	0.1/0.1	45	>99	15	6.5
	0.1/0.1	25	95	18	7.8
	0.1/0.1	15	>99	16	8.0
	0.1/0.1	0	>99	18	10.1
	0.1/0.1	−10	94	15	10.9

[a] Concentration in mM. [b] Yield based on conversion; error in yield <1%. [c] Enantiomeric excess of **1**; error in ee <0.5%. [d] Irradiated for 2 h with an ultra high-pressure Hg lamp fitted with a UV-29 glass filter [e] No reaction. [f] Irradiated for 16 h with a high-pressure Hg lamp fitted with a uranium glass filter. [g] Value not determined due to low conversion.

The low chemical yields of **1** particularly in 25% methanol solution may be attributed to the competitive attack of water to the radical cationic **DPP**, leading to the formation of water adduct, and also to the formation of varying amounts of benzophenone as an oxidation product. Indeed, ^{1}H NMR spectral examinations revealed the presence of hydroxyl-substituted photoadduct derived from the nucleophilic attack of water. Hence, the yield of **1** decreases from 30–60% to 15–18% with increasing water content from 50% to 75%.

It is not very surprising that the ee obtained in pure methanol is generally low and the product chirality is inverted by temperature, since in methanol the photoreaction occurs almost exclusively outside the CD cavity and the CD simply functions as a chiral auxiliary attached to the cyanonaphthalene sensitizer; the situation resembles the conventional photosensitization in homogeneous solutions.[9]

Interestingly, the absolute configuration of **1** was inverted from *S* to *R* in 50% methanol by simply lowering the irradiation temperature. This is rather unexpected for a native CD host with a rigid skeleton, in view of the previous observation in the supramolecular photosensitization of (*Z*)-cyclooctene with sensitizer-appended CDs, where the product ee is independent of the irradiation temperature but a linear function of the host occupancy.[6c]

Judging from the clear induced circular dichroism[12] and the almost quantitative consumption of **DPP** observed only in aqueous solutions, we may conclude that the chirality switching originates from the alteration of the photosensitization and enantiodifferentiation mechanisms from molecular to supramolecular regime. Thus, the acceleration of photoaddition and the better ee's obtained are reasonably attributed to the inclusion of **DPP** in the CD cavity, followed by the efficient photoelectron transfer from the closely located naphthalene moiety. It is interesting to note that the product chirality of **1** is critically manipulated by solvent polarity upon irradiation at a fixed temperature. For instance, at −10 °C, the product's ee varies from −0.9% to +2.1% and then to 10.9% by increasing the water content from 0% to 50% and then to 75%, behaviour very different from that observed in the supramolecular photosensitization of (*Z*)-cyclooctene.[6c]

In order to more quantitatively examine the enthalpic and entropic contributions to the enantiodifferentiating process, the obtained ee data were subjected to the Eyring analysis.[2–5,8] Thus, the natural logarithm of the relative rate constant for the formation of (*R*)- and (*S*)-**1**, *i.e.* $k_R/k_S = (100 + \%ee)/(100 - \%ee)$, was plotted against the reciprocal temperature. As illustrated in Fig. 1, all of the data points obtained in each solvent fall on a single straight line, indicating operation of the same enantiodifferentiation mechanism over the temperature range employed. From the slope and intercept of the plot, the differential activation enthalpy ($\Delta\Delta H^{\ddagger}_{R-S}$) and entropy ($\Delta\Delta S^{\ddagger}_{R-S}$) were calculated as shown in Table 2.

The oppositely-signed $\Delta\Delta H^{\ddagger}_{R-S}$, as well as $\Delta\Delta S^{\ddagger}_{R-S}$, values obtained in pure and aqueous methanol are consistent with the switching of the mechanism of chirality transfer, occurring outside or inside the CD cavity. The relatively low ee's obtained at ambient

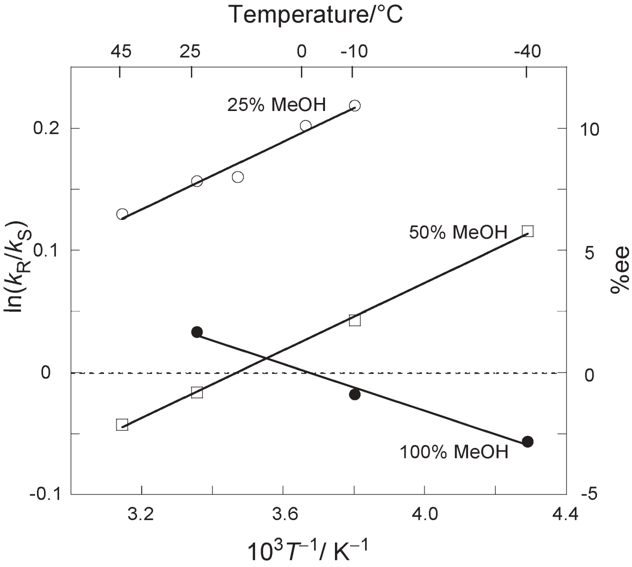


Fig. 1 Temperature dependence of %ee obtained in enantiodifferentiating polar addition of methanol to **DPP** included and sensitized by **CDnp** in methanol (●); correlation coefficient (*r*) 0.994, in 50% methanol (□); *r* 0.999 and in 25% methanol (○); *r* 0.984.

Table 2 Differential activation parameters obtained from the differential Eyring plots in pure and aqueous methanol solutions (T = 298 K)[a]

Solvent	$\Delta\Delta H^{\ddagger}_{R\text{-}S}$/ kJ mol^{-1}	$\Delta\Delta S^{\ddagger}_{R\text{-}S}$/ J mol^{-1} K^{-1}	$T\Delta\Delta S^{\ddagger}_{R\text{-}S}$/ kJ mol^{-1}
100% MeOH	0.8	2.9	0.9
50% MeOH	−1.1	−4.0	−1.2
25% MeOH	−1.1	−2.6	−0.8

[a] Error <0.1 kJ mol^{-1}.

temperatures are attributed to the comparable enthalpic ($\Delta\Delta H^{\ddagger}$) and entropic ($T\Delta\Delta S^{\ddagger}$) contributions in pure and 50% methanol, although (R)-**1** is enthalpically more favoured, or entropically less disfavoured, to give better ee's in 25% methanol. In any cases, the product chirality is sensitive to temperature and inverts at a specific (equipodal) temperature $T_0 = \Delta\Delta H^{\ddagger}/\Delta\Delta S^{\ddagger}$, since $\Delta\Delta G^{\ddagger} = \Delta\Delta H^{\ddagger} - T\Delta\Delta S^{\ddagger}$. Thus, at low temperature, the product chirality and ee ($\Delta\Delta G^{\ddagger}$) are determined predominantly by the $\Delta\Delta H^{\ddagger}$ value, but as the temperature increases the entropic term ($T\Delta\Delta S^{\ddagger}$) gradually grows to eventually overwhelm $\Delta\Delta H^{\ddagger}$ at T_0. Although such phenomena have been amply reported in conventional enantiodifferentiating photosensitizations,[2–5] similar behaviour has not been observed at least in the supramolecular photochirogenesis using native CDs that possess relatively rigid skeletons. In the present case, the CD skeleton is similarly rigid but the oversized cyanonaphthalene pendant and **DPP** guest do not appear to be tightly packed into the **CDnp** cavity even upon complexation, leaving some rotational and conformational freedom as is the case with the exciplex intermediates intervening in conventional photosensitizations. This result indicates that the chiral sense and ee of photoproduct can be critically manipulated by the environmental variants such as temperature and solvent even in the supramolecular photochirogenesis mediated by relatively rigid hosts and further demonstrates that we can expand the concept of entropy control to the supramolecular regime

Works for elucidating the detailed complexation and photosensitization mechanisms and the factors controlling the supramolecular photochirogenesis are currently in progress.

We are grateful to Dr Toshiko Muneishi for the measurement of the NMR spectra and the useful suggestions. G.F. appreciates the financial support by the COE program for the Creation of Integrated EcoChemistry, Osaka University.

Notes and references

1 For reviews, see: (*a*) A. G. Griesbeck and U. J. Meierthenrich, *Angew. Chem., Int. Ed.*, 2002, **41**, 3147; (*b*) Y. Inoue and V. Ramamurthy, *Chiral Photochemistry*, Marcel Dekker, New York, 2004.

2 (*a*) Y. Inoue, T. Yokoyama, N. Yamasaki and A. Tai, *J. Am. Chem. Soc.*, 1989, **111**, 6480; (*b*) Y. Inoue, N. Yamasaki, T. Yokoyama and A. Tai, *J. Org. Chem.*, 1992, **57**, 1332; (*c*) Y. Inoue, N. Yamasaki, T. Yokoyama and A. Tai, *J. Org. Chem.*, 1993, **58**, 1011.

3 (*a*) Y. Inoue, E. Matsushima and T. Wada, *J. Am. Chem. Soc.*, 1998, **120**, 10687; (*b*) M. Kaneda, S. Asaoka, H. Ikeda, T. Mori, T. Wada and Y. Inoue, *Chem. Commun.*, 2002, 1272; (*c*) M. Kaneda, A. Nakamura, S. Asaoka, H. Ikeda, T. Mori, T. Wada and Y. Inoue, *Org. Biomol. Chem.*, 2003, **1**, 4435.

4 Y. Inoue, H. Ikeda, M. Kaneda, T. Sumimura, S. R. L. Everitt and T. Wada, *J. Am. Chem. Soc.*, 2000, **122**, 406.

5 Y. Inoue, T. Wada, S. Asaoka, H. Sato and J.-P. Pete, *Chem. Commun.*, 2000, 251.

6 (*a*) Y. Inoue, S. Kosaka, K. Matsumoto, H. Tsuneishi, T. Hakushi, A. Tai, K. Nakagawa and L. -H. Tong, *J. Photochem. Photobiol., A*, 1993, **71**, 61; (*b*) Y. Inoue, F. Dong, K. Yamamoto, L. -H. Tong, H. Tsuneishi, T. Hakushi and A. Tai, *J. Am. Chem. Soc.*, 1995, **117**, 11033; (*c*) 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.*, 2000, **65**, 8041.

7 (*a*) V. Ramamurthy, *Chem. Commun.*, 1998, 1379; (*b*) A. Joy, R. Scheffer and V. Ramamurthy, *Org. Lett.*, 2000, **2**, 119; (*c*) T. Wada, M. Shikimi, Y. Inoue, G. Lem and N. J. Turro, *Chem. Commun.*, 2001, 1864.

8 G. Fukuhara, T. Mori, T. Wada and Y. Inoue, *Chem. Commun.*, 2005, 4199.

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

10 K. Hamasaki, H. Ikeda, A. Nakamura, A. Ueno, F. Toda, I. Suzuki and T. Osa, *J. Am. Chem. Soc.*, 1993, **115**, 5035.

11 (*a*) W. F. Short and H. Wang, *J. Chem. Soc.*, 1950, 991; (*b*) M. J. S. Dewar and P. J. Grisdale, *J. Chem. Soc.*, 1962, **84**, 35.

12 All of these aspects were elucidated from fluorescence (lifetime), UV/Vis and circular dichroism spectroscopy and will be published elsewhere. However, induced circular dichroism spectra in pure methanol (Fig. S1a) and 25% methanol aqueous solution (Fig. S1b) are shown in the ESI for clearly examining the complexation in the ground state.