Entropy-controlled supramolecular photochirogenesis: enantiodifferentiating *Z–E* photoisomerization of cyclooctene included and sensitized by permethylated 6-*O*-benzoyl-β-cyclodextrin†

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In contrast to the photosensitization with a non-methylated analogue, supramolecular photochirogenesis with a novel permethylated mono(6-*O*-benzoyl)-β-cyclodextrin exhibited a critical dependence of the product's enantiomeric excess upon temperature, and possessed a large differential entropy of activation (-11 J K^{-1} mol^{-1}) for which the flexible host skeleton is likely to be responsible.

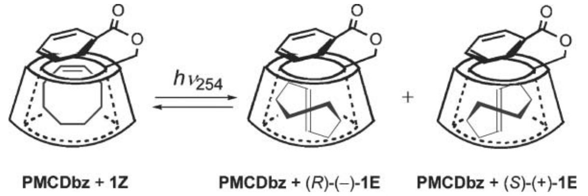
Photochirogenesis,[1] or photochemical asymmetric synthesis, provides us with unique and attractive access to optically active compounds through the electronically excited states, which is a powerful alternative to conventional catalytic or enzymatic approaches. Our recent studies revealed that the enantiomeric excess (ee) and the chiral sense of photoproduct are critically affected, or even switched in sign, by such entropy-related factors as temperature,[2] pressure[3] and solvation,[4] and hence by multidimensional control[5] achievable by combining these factors, resulting in more rational and effective methods of obtaining higher ee's under mild conditions. More recently, we have shown that the role of entropy is greatly reduced in supramolecular photochirogenesis, where the enantiodifferentiation occurs in inherently low-entropy (well-organized) environments. Thus, in the enantiodifferentiating photoisomerization of (*Z*)-cyclooctene (**1Z**) included and sensitized by mono(6-*O*-benzoyl)-β-cyclodextrin (**CDbz**),[6] the ee of the (*E*)-isomer (**1E**) does not depend on temperature or solvent, but is nicely correlated with the host occupancy, indicating an insignificant contribution of entropy to the supramolecular photochirogenesis. In a related manner, photochirogeneses in rigid nanopores of zeolites have also been reported.[7]

In this study to further elucidate the role of entropy and define the scope and limitations of the 'entropy control' concept in supramolecular photochirogenesis, we prepared the novel permethylated mono(6-*O*-benzoyl)-β-cyclodextrin (**PMCDbz**), which is expected to have a flexible skeleton as a consequence of the absence of the hydrogen-bond network on the CD's secondary side.[8] The enantiodifferentiating photoisomerization of **1Z** was performed in the presence of **PMCDbz** in aqueous methanol solution at various temperatures (Scheme 1), and the results were compared with those obtained previously with the non-methylated 6-*O*-benzoyl-β-cyclodextrin (**CDbz**). This allows us to assess the effects of the flexible host skeleton on the excited-state interactions within the host's cavity and eventually on the stereochemical outcome (both the ee and chiral sense of photoproduct) of the supramolecular photochirogenic process.

PMCDbz† was synthesized in 80% yield by the reaction of permethylated 6-*O*-tosyl-β-CD[9] with benzoic acid. Aqueous methanol solutions (5 mL) of different compositions, containing **1Z** (2 mM) and **PMCDbz** (0.2 mM), were irradiated at 254 nm for 10 min in quartz tubes under an argon atmosphere at temperatures varying from +55 to −40 °C (further examinations at lower temperatures were not done due to frozen solvent), and the *E*/*Z* ratio and the ee of **1E** were determined by capillary gas chromatography on Shimadzu CBP-20 and Supelco β-DEX225 column, respectively.[2,3]

As shown in Table 1, the *E*/*Z* ratio and ee values were critical functions of the solvent and temperature, both of which increase in general with increasing water content or decreasing temperature. The relatively low *E*/*Z* ratio (0.08–0.13) and the very low ee ($\leqslant 1\%$) obtained in pure methanol are attributable to the photosensitization outside the CD cavity, since practically no complexation of **1Z** by **PMCDbz** occurs in methanol, judging from the negligible circular dichroism in spectral examinations. These values are sensible for "outside" photosensitization, in which the **PMCD** moiety simply functions as a chiral auxiliary appended to the benzoate chromophore, as the conventional photosensitizations with optically active alkyl benzoates are known to give comparable *E*/*Z* ratios of 0.1–0.2 and ee's of 0–3%.[2b]

Interestingly, in aqueous solutions containing 50% and 25% methanol, the chiral sense of photoproduct was inverted by changing temperature, affording antipodal (*R*)-(−)- and (*S*)-(+)-**1E** above and below the equipodal temperature (*ca.* −5 °C). Similar



Scheme 1 Supramolecular enantiodifferentiating photoisomerization of **1Z** included and sensitized by **PMCDbz**.

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Table 1 Enantiodifferentiating photoisomerization of **1Z** in the presence of **PMCDbz** in methanol–water mixtures at various temperatures[a]

Solvent	Temperature/°C	*E*/*Z* ratio	%ee[b]
MeOH	55	0.09	1.0
	25	0.08	0.4
	−20	0.13	0.0
	−40	0.09	−0.2
50% MeOH	55	0.32	−0.4
	45	0.29	−0.2
	35	0.36	−1.8
	25	0.32	−1.9
	10	0.32	−1.5
	5	0.21	−1.6
	0	0.30	−0.8
	−20	0.27	2.7
	−30	0.12	6.7
	−40	0.13	8.9
25% MeOH	55	0.27	−2.8
	40	0.49	−3.5
	25	0.50	−3.3
	10	0.37	−2.5
	0	0.71	−0.7
	−10	0.43	1.8

[a] Irradiated at 254 nm for 10 min under argon in methanol–water mixture; [**1Z**] = 2 mM, [**PMCDbz**] = 0.2 mM. [b] Error in ee: ±0.5%.

product chirality switching is known to occur in the enantiodifferentiating photosensitization of **1Z** with chiral benzenepolycarboxylates[2] and in the enantiodifferentiating photoaddition of methanol to 1,1-diphenylpropene,[10] but have never been reported for a supramolecular photosensitization. This indicates that, despite the efficient inclusion of **1Z**, particularly in aqueous methanol solutions at low temperatures,[11] the supramolecular photochirogenic behaviour of **PMCDbz** is quite different from that of non-methylated **CDbz**[6] and instead resembles conventional enantiodifferentiating photosensitization, in which dynamic conformational changes in the exciplex intermediate and hence the entropic factors play a crucial role.[2–5]

In order to quantitatively evaluate the enthalpic and entropic contributions to the photoenantiodifferentiation process, the ee data in Table 1 were subjected to the Eyring analysis.[2–5] Thus, the natural logarithm of the relative rate constant for the formation of (*S*)- and (*R*)-**1Z**, k_S/k_R = (100 + %ee)/(100 − %ee), was plotted against the reciprocal temperature for each solvent. As can be seen from Fig. 1, all of the data points obtained in pure methanol fall on a single straight line, indicating operation of the same enantiodifferentiation mechanism in this solvent over the temperature range employed, where practically no complexation occurs and the photosensitization takes place almost exclusively outside of the CD cavity to give consistently low ee's ($\leqslant$1%).

In sharp contrast, when the water content was increased to 50% or 75% much improved ee's of up to 10% were obtained, presumably as a result of the supramolecular photosensitization within the CD cavity, and the $\ln(k_S/k_R)$ *versus* T^{-1} plots afforded steeper straight lines particularly at temperatures lower than 5 °C, exhibiting an inversion of the product chirality. However, the plot starts to deviate from the regression line above *ca.* 10 °C, apparently approaching the racemic line at higher temperatures. The deviation starts somewhat earlier and is more pronounced in 50% methanol than in 25% methanol, indicating appreciable contribution of the outside sensitization as a consequence of less efficient binding of **1Z** by **PMCDbz** under such conditions. These phenomena are quite reasonable for supramolecular photosensitizations, where the enantiodifferentiation process and the product's ee are governed by both the ground- and excited-state interactions. Thus, the contribution of the 'outside' sensitization by 'free' host in the bulk solution, which gives extremely low ee's irrespective of the temperature, increases with increasing temperature or methanol content.

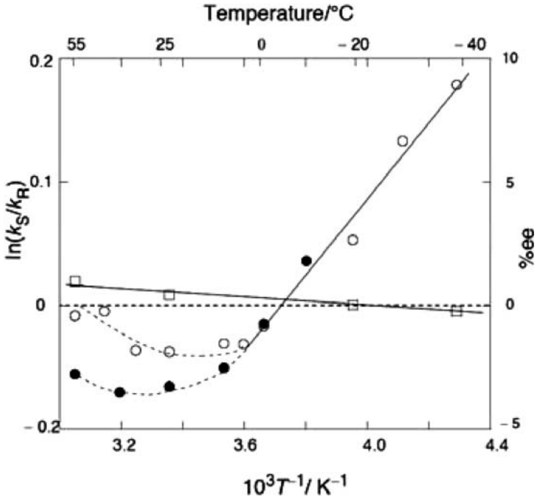

Fig. 1 Temperature dependence of %ee obtained in enantiodifferentiating photoisomerization of **1Z** sensitized by **PMCDbz** in methanol (□), 50% methanol (○) and 25% methanol (●).

It is noted that the supramolecular photosensitizations in 25% and 50% methanol afford practically the same regression line in the low temperature region; the differential activation enthalpy and entropy obtained are $\Delta\Delta H^{\ddagger}_{S-R} = -2.9$ kJ mol^{-1} and $\Delta\Delta S^{\ddagger}_{S-R} = -11$ J mol^{-1} K^{-1}. These are completely different from those obtained with non-methylated **CDbz**,[6] but are very similar to those reported for the conventional photosensitization in homogeneous solutions,[2] demonstrating the vital role of entropy even in the supramolecular environment. The major origin of such a large entropy contribution in supramolecular photochirogenesis is tentatively assigned to the increased conformational freedoms of **PMCDbz**, which allows both the efficient inclusion complexation and the subsequent dynamic quenching of excited benzoate by **1Z** included in the flexible **PMCD** cavity. These observations, for the first time, quantitatively reveal the unique nature of the flexible sensitizing host **PMCDbz** in the excited state, although similar behaviour in the ground state has been reported by other groups.[8]

In summary, we have demonstrated that the stereochemical outcome of supramolecular photochirogenesis can be critically controlled by environmental factors by employing a conformationally flexible chiral host, such as **PMCDbz**. This strategy allows us to utilize not only the advantage of supramolecular chemistry for enhancing specific substrate–host complexation, but also the unique ability of photochemistry for dynamically manipulating rates and equilibria in the excited state by temperature and other environmental variants. Work towards elucidating the detailed complexation/sensitization mechanisms and the factors operating in this entropy-controlled supramolecular photochirogenic system, as well as a search for other such systems, is currently in progress.

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Notes and references

1 For reviews, see: (*a*) H. Rau, *Chem. Rev.*, 1983, **83**, 535; (*b*) Y. Inoue, *Chem. Rev.*, 1992, **92**, 741; (*c*) 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**, 6450; (*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. Comm.*, 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. Comm.*, 2000, 251.

6 (*a*) Y. Inoue, F. Dong, K. Yamamoto, L.-H. Tong, H. Tsuneishi, T. Hakushi and A. Tai, *J. Am. Chem. Soc.*, 1995, **117**, 11033; (*b*) 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. Comm.*, 2001, 1864.

8 (*a*) T. Yamada, G. Fukuhara and T. Kaneda, *Chem. Lett.*, 2003, **32**, 534; (*b*) R. Nishiyabu and K. Kano, *Eur. J. Org. Chem.*, 2004, 4985.

9 T. Kaneda, T. Fujimoto, J. Goto, K. Asano, Y. Yasufuku, J. H. Jung, C. Hosono and Y. Sakata, *Chem. Lett.*, 2002, 514.

10 (*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.

11 The host occupancies, determined from circular dichroism spectral titrations upon addition of **1Z** to a solution of **PMCDbz** at 25 °C, were 69% and 90% in 50% and 25% methanol, respectively, while practically no spectral changes were observed in pure methanol.