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Enantioselective [2 + 2]Photodimerization Reactions of Coumarins in Solution

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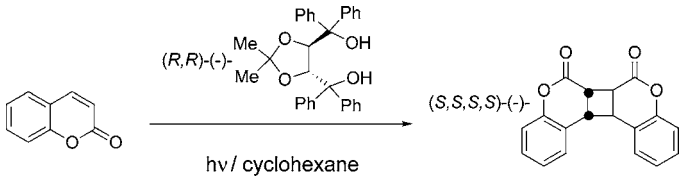
ABSTRACT



The [2 + 2]photodimerization reactions of coumarin to an optically active anti-head-to-head dimer in the presence of an optically active host compound in cyclohexane solution proceeded with high enantioselectivity.

The [2 + 2]photodimerization reaction of coumarin and its derivatives has attracted considerable interest in recent years and has been studied extensively.[1] Recently, we have reported a highly enantioselective photodimerization reaction of coumarin in inclusion crystals with optically active host compounds that proceeds in a *single-crystal-to-single-crystal* manner.[2] We have now found that the enantioselective photodimerization reactions of coumarin (**3a**) and 6-methylcoumarin (**3b**) to the corresponding *anti-head-to-head* dimers (**4a** and **4b**) proceed efficiently even in a homogeneous solution in the presence of an optically active host (**1** and **2**) in high enantioselectivity.

Table 1. Photodimerization Reaction of Coumarin in Solution[a]

	crystalline product[b]		dissolved product[c]	
solvent	yield(%)	ee (%)	yield(%)	ee (%)
MeOH	0		trace	
acetone	0		trace	
AcOEt	0		trace	
THF	0		trace	
cyclohexane	69	48 (−)	trace	
methylcyclohexane	50	59 (−)	trace	
benzene	20	91 (−)	12	56 (+)
toluene	18	89 (−)	10	98 (+)

[a] Photoreaction was carried out at 40 °C for 24 h. [b] Precipitated 1:2 inclusion crystals of (−)-**1** with coumarin dimer. [c] Products in solution.

When a solution of an equimolar mixture of host (*R*,*R*)-(−)-**1**[3] and coumarin (**3a**) in cyclohexane was irradiated by a 100 W high-pressure Hg lamp through a Pyrex filter at 40 °C, a crystalline 2:1 inclusion complex of (−)-**1** and (*S*,*S*,*S*,*S*)-(−)-**4a** was gradually precipitated as the reaction proceeded, and the product of 48% ee was obtained in 69% yield after 24 h of irradiation. The optical purity was determined by

(1) (a) Xiuling, Y.; Scheller, D.; Rademacher, O.; Wolff, T. *J. Org. Chem.* **2003**, *68*, 7386. (b) Narasimha, J.; Venkatesan, K.; Weiss, R. G. *J. Org. Chem.* **1992**, *57*, 3292. (c) Klaus, C. P.; Thiemann, C.; Kopf, J.; Margaretha, P. *Helv. Chim. Acta* **1995**, *78*, 1079. (d) Tanaka, K.; Toda, F. *J. Chem. Soc., Perkin Trans. 1* **1992**, 943. (e) Moorthy, J. N.; Venkatesan, K. *J. Org. Chem.* **1991**, *56*, 6957. (f) Frederich, D. L.; Barancyk, S. V. *J. Am. Chem. Soc.* **1989**, *111*, 8653. (g) Meng, J. B.; Fu, D. C.; Yao, X. K.; Wang, R. J.; Matsuura, T. *Tetrahedron* **1989**, *45*, 6979. (h) Suginome, H.; Kobayashi, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3782. (i) Gnanaguru, K.; Ramasubbu, N.; Venkatesan, K.; Ramamurthy, V. *J. Org. Chem.* **1985**, *50*, 2337. (j) Kato, S.; Seki, T.; Katsuura, Y.; Kobayashi, T.; Komatsu, K.; Fukushima, S. *Toxicol. Appl. Pharm.* **1985**, *81*, 295. (k) Leenders, L. H.; Schouteden, E.; deSchriver, F. C. *J. Org. Chem.* **1973**, *38*, 95. (l) Hoffman, R.; Well, P.; Morrison, H. *J. Org. Chem.* **1971**, *36*, 102. (m) Hammond, G. S.; Stout, C. A.; Lamola, A. A. *J. Am. Chem. Soc.* **1964**, *86*, 3103.

(2) (a) Tanaka, K.; Mochizuki, E.; Yasui, N.; Kai, Y.; Miyahara, I.; Hirotsu, K.; Toda, F. *Tetrahedron* **2000**, *56*, 6853. (b) Tanaka, K.; Toda, F.; Mochizuki, E.; Yasui, N.; Kai, Y.; Miyahara, I.; Hirotsu, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 3523.

(3) (a) Toda, F.; Tanaka, K. *Tetrahedron Lett.* **1988**, *29*, 551. (b) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Rogg, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954.

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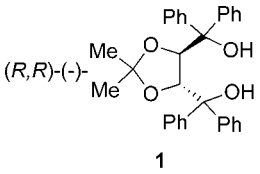
chiral HPLC (Chiralcel OD, hexane/2-propanol 95/5). From the solution left after separation of the inclusion complex, only a trace amount of **4a** was detected. Similar photoirradiation in methylcyclohexane gave the inclusion complex of (−)-**1** and (*S*,*S*,*S*,*S*)−(−)-**4a** of 59% ee in 50% yield. When the reaction was carried out in aromatic solvents such as toluene or benzene, (−)-**4a** was obtained from the inclusion complex crystal, and the opposite enantiomer (+)-**4a** was obtained from the solution. (Table 1) However, no photodimerization product was formed in polar solvents such as MeOH, acetone, ethyl acetate, or THF, which form a stable complex with host (−)-**1**.



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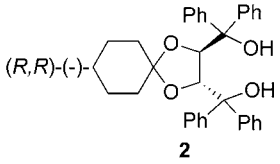

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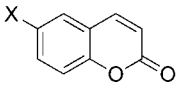
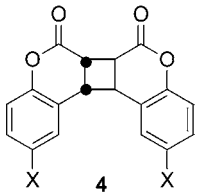


3 a: X = H
b: X = Me



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One possible explanation of this reaction is as follows: The photodimerization of coumarin occurs in all solvents but is reversible. In hydrocarbon and aromatic solvents, one enantiomer of the dimer complexes with the host, precipitates as inclusion crystals, and is protected from reverse reaction. Another enantiomer is decomposed to monomer by further irradiation in solution. In aromatic solvents, the solvent protects the dimer from photodecomposition, which would explain why one enantiomer of the dimer precipitates with the host and another enantiomer remains in solution. In hydrogen bonding solvents such as MeOH, no crystallization occurs and the solvent is transparent, so the product is decomposed to monomer. In fact, a 2:1 inclusion complex of (−)-**1** and (*S*,*S*,*S*,*S*)-(−)-**4a** gave a mixture of (−)-**1** and a coumarin monomer upon photoirradiation for 3 h in MeOH solution. However, the possibility that the enantioselective photodimerization reactions occur via the 2:1 complex of (−)-**1** and coumarin through hydrogen bonding in nonpolar solvents cannot be excluded, since the addition of coumarin to a solution of (−)-**1** shifts the OH protons in the ^{1}H NMR spectrum in benzene-d_6.

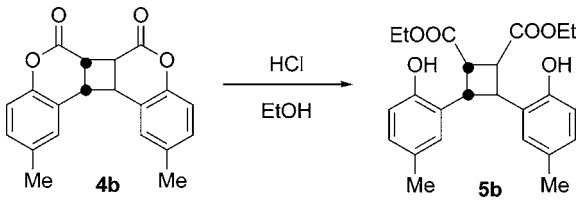
At lower temperatures, the optical purity of dimer (**4**) was improved and (−)-**4a** of higher ee was obtained. For example, when an equimolar mixture of (*R*,*R*)-(−)-**1** and coumarin (**3a**) in cyclohexane was irradiated at 20 °C for 24 h, a 2:1 inclusion complex of (−)-**1** and (*S*,*S*,*S*,*S*)-(−)-**4a** of 85% ee was formed as colorless prisms in 70% yield. (Table 2) Further recrystallization of the inclusion complex from toluene afforded the enantiopure inclusion complex in 31% yield. Treatment of the inclusion complex with DMF/H_2O (5/1) gave a 1:1 complex of (−)-**1** and DMF in 99% yield. The filtrate left after separation of the 1:1 complex of (−)-**1** and DMF was concentrated in vacuo to give (*S*,*S*,*S*,*S*)-(−)-**4a** of >99% ee in 26% yield.

Table 2. Photodimerization Reaction of Coumarins (**3a** and **3b**) in Solution[a]

		crystalline product		dissolved product	
host	guest	yield(%)	ee (%)	yield (%)	ee (%)
(−)-**1**	**3a**	70 (**4a**)	85 (−)	trace	
(+)-**1**	**3a**	59 (**4a**)	85 (+)	trace	
(−)-**2**	**3b**	60 (**4b**)	95 (+)	0	
(+)-**2**	**3b**	46 (**4b**)	96 (−)	0	

[a] Photoreaction was carried out at 20 °C for 24 h. [b] Precipitated 1:2 inclusion crystals of (−)-**1** with coumarin dimer. [c] Products in solution.

Similarly, a 2:1 inclusion complex of (*R*,*R*)-(−)-**2** and (*S*,*S*,*S*,*S*)-(+)-**4b** of 95% ee was obtained in 60% yield upon photoirradiation of a cyclohexane solution of an equimolar mixture of (−)-**2** and 6-methylcoumarin (**3b**). Treatment of the inclusion complex with DMF/H_2O gave (*S*,*S*,*S*,*S*)-(+)-**4b** of >99% ee in 27% yield. The optical purity of **4b** was not determined directly by HPLC. Thus, the dimer (+)-**4b** was transformed to the diester (+)-**5b** according to the literature method,[1a,j] the optical purity of which was successfully determined by chiral HPLC (Chiralcel OD, hexane/2-propanol 95/5).



4b **5b**

The absolute stereochemistry of (*S*,*S*,*S*,*S*)-(−)-**4a** was determined by comparison with the literature data,[2a] and that of (*S*,*S*,*S*,*S*)-(+)-**4b** was determined by X-ray crystal structure analysis of a 2:1 inclusion complex of (−)-**1** and (*S*,*S*,*S*,*S*)-(+)-**4b**. (Figure 1)[4]

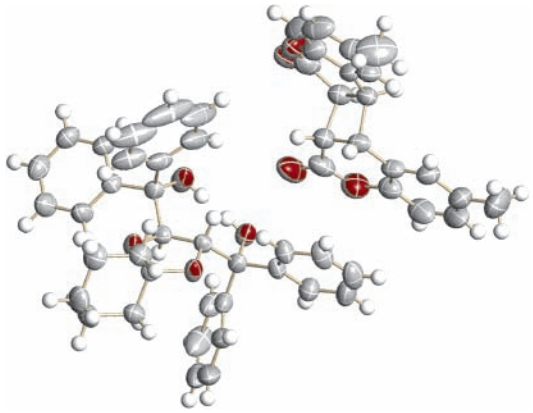


Figure 1. X-ray structure of the 2:1 inclusion complex of (*R*,*R*)-(−)-**2** and (*S*,*S*,*S*,*S*)-(+)-**4b**.

In summary, a highly enantioselective [2 + 2]photodimerization reaction of coumarins in solution has been described. Enantioselective photoreactions in solution in the presence of chiral host compounds have been studied less extensively. Recent successful work (up to 98% ee) in this area has been based on a chiral lactam as a host compound.[5] Contrary to the limited work conducted in solution, many examples of enantioselective photoreactions in the solid-state have been reported so far.[6] Further studies on the application to other asymmetric photoreactions are in progress.

Acknowledgment. K.T. acknowledges the X-ray analysis of the inclusion complex of (−)-**2** and (+)-**4** by Bruker AXS K.K. Japan.

Supporting Information Available: X-ray crystallographic file (CIF) on the structure determination of the inclusion complex of (−)-**2** and (+)-**4** and some experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) Data for the 2:1 inclusion complex of (*R*,*R*)-(−)-**2** and (*S*,*S*,*S*,*S*)-(+)-**4b**: colorless prisms; monoclinic, *C*2, $a = 35.019(5)$ Å, $b = 9.7404(13)$ Å, $c = 10.6220(14)$ Å; $Z = 4$.

(5) (a) Brandes, S.; Selig, P.; Bach, T. *Synlett* **2004**, 2588. (b) Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc*. **2002**, *124*, 7982. (c) Bach, T.; Bergmann, H.; Harms, K. *Org. Lett.* **2001**, *3*, 601. (d) Bach, T.; Bergmann, H.; Harms, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2302. (e) Bach, T.; Bergmann, H. *J. Am. Chem. Soc*. **2000**, *122*, 11525.

(6) (a) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025. (b) Toda, F. *Organic Solid-State Reactions*; Kluwer Academic Publishers: Norwell, MA, 2000.