Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl20

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Version of record first published: 31 Aug 2006

To cite this article: Hideko Koshima (2005): Absolute Asymmetric Photoreactions of Acridines with Diphenylacetic Acid in their Cocrystals, Molecular Crystals and Liquid Crystals, 440:1, 207-214

To link to this article: http://dx.doi.org/10.1080/15421400590958520

Mol. Cryst. Liq. Cryst., Vol. 440, pp. 207–214, 2005

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/15421400590958520

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Absolute Asymmetric Photoreactions of Acridines with Diphenylacetic Acid in their Cocrystals

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Solid-state photodecarboxylation occurs in a chiral cocrystal of acridine and diphenylacetic acid to afford a chiral condensation product in modest enantiomeric excess. A chiral cocrystal of 9-methylbenz[c]acridine and diphenylacetic acid also undergoes similar photodecarboxylation but gives an almost racemic product. The different enantioselectivities between the two chiral cocrystals can be understood on the basis of the molecular arrangements in the lattice.

Keywords: absolute asymmetric photoreactions; acridine; cocrystals; diphenylacetic acid; 9-methylbenz[*c*]acridine; photodecarboxylation

INTRODUCTION

Absolute asymmetric synthesis by solid-state reaction of a chiral crystal spontaneously formed from achiral molecules is a promising methodology for asymmetric synthesis [1–3]. Since our success in absolute asymmetric photodecarboxylative condensation of acridine (**1**) with diphenylacetic acid (**a**) in the chiral cocrystal (**1**·**a**) [4], we would like to design new cases of absolute asymmetric synthesis with high reliability. However, spontaneous chiral crystallization cannot be predicted at the present time [5,6]. Hence, we have prepared several series of chiral cocrystals by combining two different achiral molecules, based on the working hypothesis that chiral crystallization can occur by freezing two molecules into chiral conformations through hydrogen

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Kurata Memorial Hitachi Science and Technology Foundation.

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bonding [7–10]. Recently we found a chiral cocrystal (**2·a**) of 9-methylbenz[*c*]acridine (**2**) with diphenylacetic acid (**a**), but the solid-state photoreaction afforded an almost racemic condensation product, rather than achieving absolute asymmetric synthesis [11]. Herein the solid-state photoreactions in the chiral cocrystals **1·a** and **2·a** are reviewed, and the difference of enantioselectivities is discussed based on their molecular arrangements.

RESULTS AND DISCUSSION

The cocrystals incorporate acridine **1** or 9-methylbenz[*c*]acridine **2** as electron acceptors and diphenylacetic acid **a** as an electron donor in the photoreactions (Chart 1). Recrystallization of equimolar solutions of the two components in acetonitrile gave the chiral cocrystals **1·a** or **2·a**. Their melting points are 101 and 138°C, respectively. Seed crystals of both enantiomorphous crystals of **1·a** and **2·a** were initially obtained by spontaneous crystallization from slightly supersaturated solutions in several vessels, and were easily discriminated by the measurement of their solid-state circular dichroism (CD) spectra as Nujol mulls (Fig. 1). Then the left and right handed crystals could be separately prepared by seeding on a large scale. X-Ray crystallographic analysis of **1·a** and **2·a** confirmed the chiral nature of these products whose space groups are $P2_12_12_1$ and $P1$, respectively. Their crystal data are summarized in Table 1. The absolute structure of *M*-**1·a** was satisfactorily determined by the Bijvoet method based on anomalous dispersion of the oxygen atom with Cu Kα radiation. The CD spectrum of *M*-**1·a** corresponds to the curve M in Figure 1a. The absolute structure of **2·a** is not yet determined. Figure 2 shows

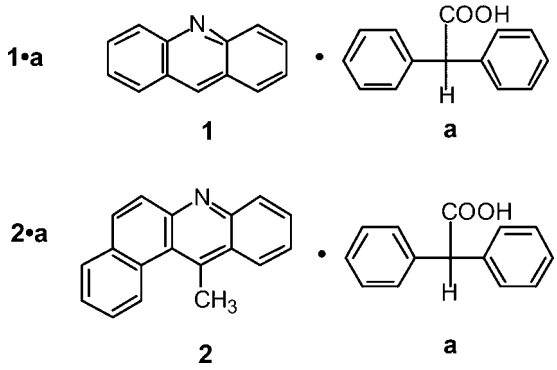


CHART 1 Chiral cocrystals.

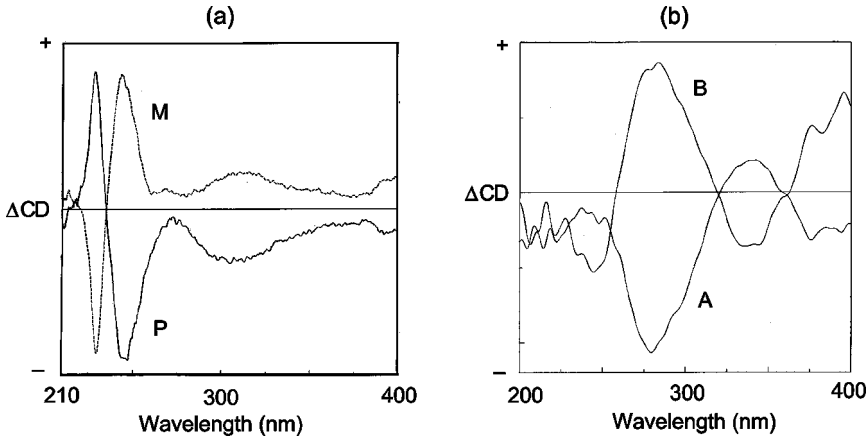


FIGURE 1 Solid-state CD spectra of the enantiomorphous cocrystals (a) **1·a** and (b) **2·a**.

the molecular arrangements in *M*-**1·a** and **2·a**. Hydrogen bond pairs between **1** or **2** and **a** are formed with H···N distances of 1.79 or 1.46 Å. In both cocrystals, the diphenylacetic acid molecule has a propeller-like conformation. The common feature of enantiomorphous **1·a** and **2·a** is that only one type of molecular pair of the absolute configuration forms noncentrosymmetrically in a unit cell (Z = 4 and 1), thereby inducing the crystal chirality (Fig. 3). Namely, the molecules in themselves are achiral but the molecular shapes are frozen in chiral forms within the lattice.

TABLE 1 Crystal Data of the Chiral Cocrystals

	M-**1·a**	**1·b**	((*S*)-**3**)$_2$·MeOH	**7**·MeOH
Formula	$C_{27}H_{21}NO_2$	$C_{32}H_{25}NO_2$	$C_{53}H_{46}N_2O$	$C_{32}H_{29}NO$
Space group	$P2_12_12_1$	$P1$	$P1$	*Pbca*
a, Å	14.908(4)	5.683(1)	9.871(1)	18.995(1)
b, Å	25.367(6)	9.110(2)	17.6408(9)	12.2607(6)
c, Å	5.457(3)	12.111(2)	6.1787(9)	21.294(1)
α, deg	90.0	101.443(6)	90.280(7)	90.0
β, deg	90.0	98.399(6)	107.31(1)	90.0
γ, deg	90.0	103.08(1)	101.002(6)	90.0
V, Å^3	2063(1)	586.5(2)	1006.1(2)	4959.3(4)
Z	4	1	1	8
R	0.043	0.061	0.033	0.073
R_w	0.058	0.144	0.050	0.228

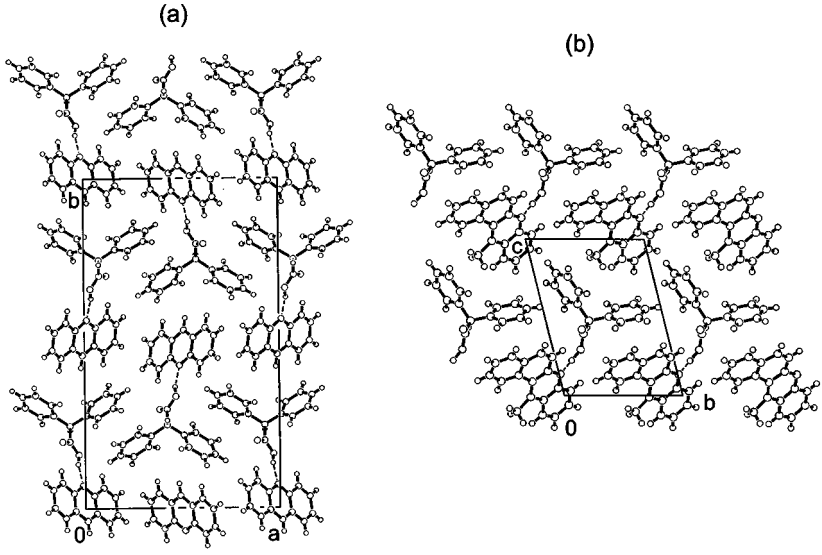


FIGURE 2 Molecular arrangements in the chiral cocrystals (a) **1·a** and (b) **2·a**.

Crystals of *M*-**1·a** were pulverized, placed between two Pyrex plates and irradiated with a 400 W high-pressure mercury lamp under argon for 3 h at 15°C on a preparative scale. Solid-state photodecarboxylation occurred to give three products (Scheme 1). The main product was a chiral condensation product ((*S*)-(–)-**3**) in 35% ee and 37% chemical yield, achieving absolute asymmetric synthesis. Minor products were the achiral condensation product (**4**) and diphenylmethane (**5**). The

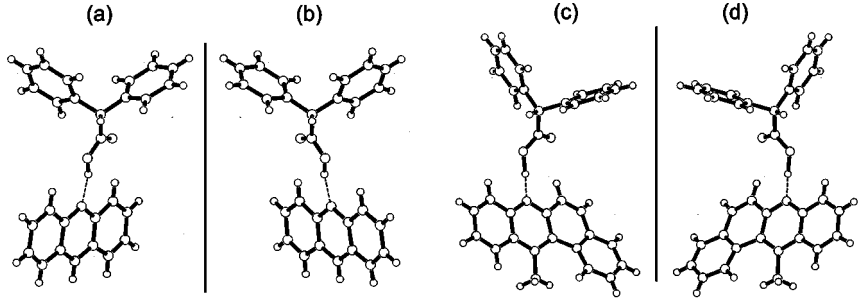
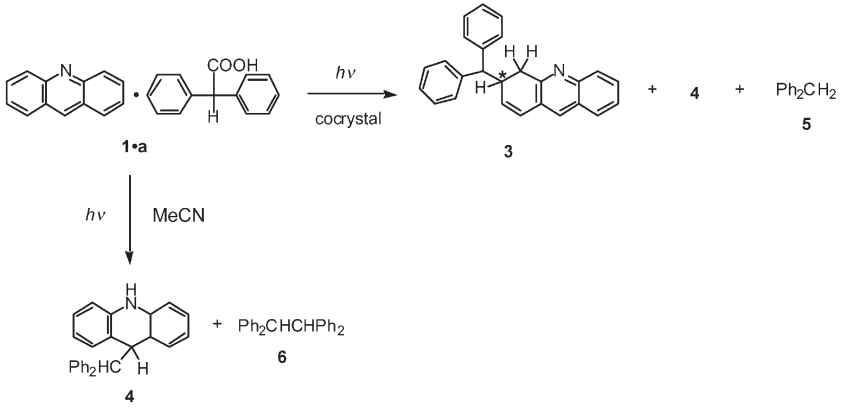


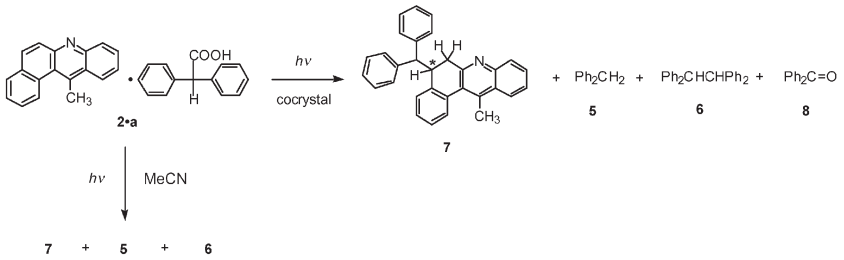
FIGURE 3 Molecular pairs in the chiral cocrystals (a) *M*-**1·a**, (b) *P*-**1·a**, (c) enantiomorphous **2·a** and (d) opposite handed **2·a** to (c).



SCHEME 1 Photoreaction of **1** with **a** in the chiral cocrystals and in the solution.

absolute configuration of **3** was successfully determined as *S* by X-ray anomalous dispersion of the sulfur atom of the trifluoromethanesulfonate salt of methylated (–)-**3**. Irradiation of the opposite crystals, *P*-**1•a**, gave (*R*)-(+)-**3** in 33% ee and in 38% yield. In contrast, solution photolysis of **1** with **a** in acetonitrile did not produce the chiral product **3** but gave the achiral product **4** and 1,1,2,2-tetraphenylethane (**6**) in 74% and 24% yield, respectively. Namely, the production of **3** is specific to the solid-state photoreaction.

Enantiomorphous cocrystals of **2•a** prepared by seeding (CD curve A in Figure 1b) were also irradiated with a 400 W high-pressure mercury lamp under argon for 4 h at 15°C on a preparative scale (Scheme 2). Similar photodecarboxylation to **1•a** occurred and afforded four products. Chiral condensation product (**7**) was obtained in 13% chemical yield



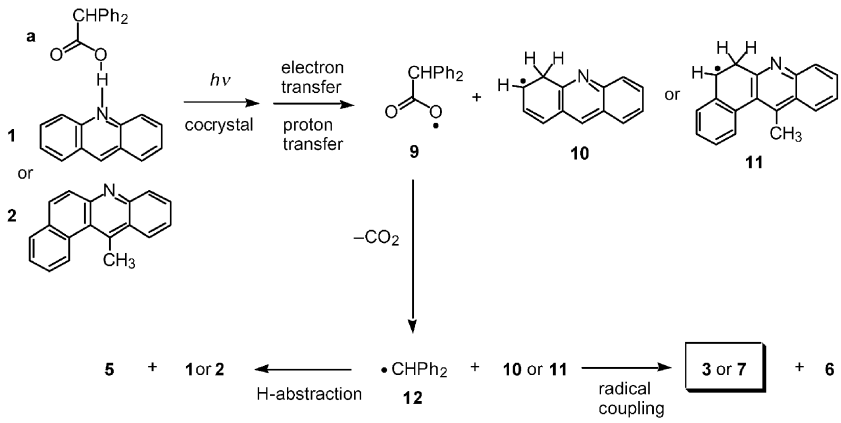
SCHEME 2 Photoreaction of **2** with **a** in the chiral cocrystals and in the solution.

but the enantiomeric excess was almost 0% ee. The main product was diphenylmethane **5** in 34% yield, and the other minor products were tetraphenylethane **6** and benzophenone (**8**) in 3% and 13%, respectively. Irradiation of the opposite handed crystals of **2·a** also afforded almost racemic **7**. Therefore we conclude that absolute asymmetric synthesis was not achieved in the enantiomophous cocrystals of **2·a**.

On the other hand, solution photolysis of **2** and **a** in acetonitrile afforded racemic **7** as the main product in 53% yield, and **4** and **5** in 2% and 12% yields, showing different reactivity and product selectivity from the solid-state photoreaction. The molecular structure of **7** was confirmed by X-ray crystallographic analysis using a single crystal of the 1:1 inclusion complex of racemic **7** with MeOH.

The reasons for successful and unsuccessful absolute asymmetric reactions in the chiral crystals **1·a** and **2·a** can be discussed based on the possible reaction mechanism (Scheme 3) and the coupling paths (Fig. 4). Irradiation of **1·a** or **2·a** can cause electron transfer from **a** to **1** or **2** followed by proton transfer to afford a carboxylate radical (**9**) and hydroacridine radical (**10**) or (**11**) [4,11]. Then decarboxylation of the carboxylate radical yields a $\cdot CHPh_2$ diphenylmethyl radical (**12**). Next, radical coupling between the $\cdot CHPh_2$ radical **12** and the hydroacridine radical **10** or **11** produces **3** or **7**.

In the crystal *M*-**1·a**, two directions for the radical coupling are possible, which are shown by thick and thin arrows in Figure 4a. The absolute configuration of **3** obtained by front attack with the shorter distance (5.1 Å) gives the (*S*)-form in higher priority than



SCHEME 3 Possible reaction mechanism in the chiral cocrystals **1·a** and (b) **2·a**.

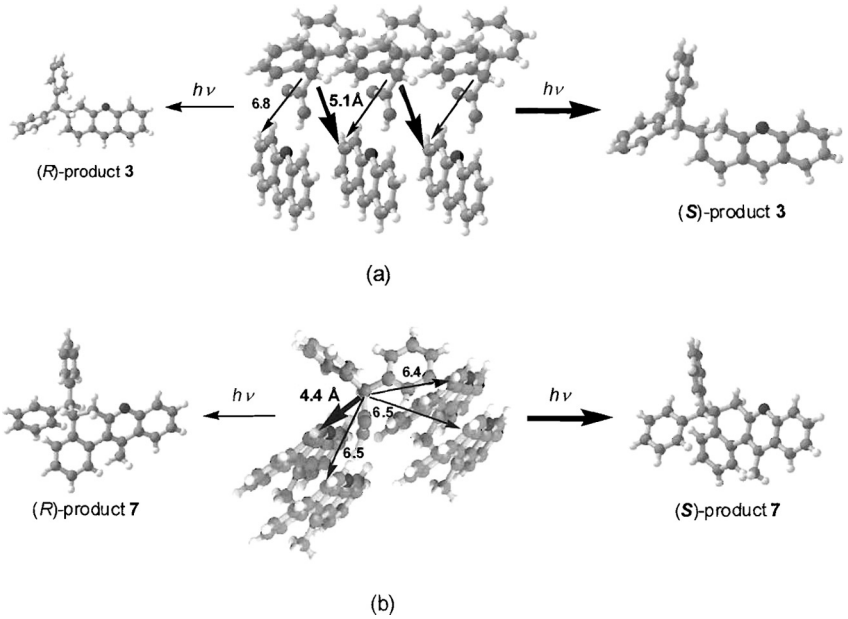


FIGURE 4 Possible reaction paths in the chiral cocrystals (a) *M*-**1·a** and (b) **2·a**.

the (*R*)-form by back attack involving the longer distance (6.8 Å). The *S*:*R* ratio is calculated as around 2:1 based on the experimental ee value of 35% ee. On the other hand, in the enantiomorphous crystal **2·a**, four radical coupling paths are possible (Fig. 4b). The absolute configuration of **7** obtained by frontal attack (thick arrow) with the shortest distance (4.4 Å) is opposite to that obtained by the three back attacks (thin arrows) involving longer distances (6.4, 6.5 and 6.5 Å). This results in the formation of an almost 1:1 racemic mixture of (*S*)- and (*R*)-**7**. In conclusion, enantioselectivities in chiral crystals are very much controlled by the precise molecular arrangements present.

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