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Determination of the absolute structure of the chiral crystal consisting of achiral dibutylhydroxytoluene and asymmetric autocatalysis triggered by this chiral crystal

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ABSTRACT

Absolute structure is determined of chiral crystal composed of achiral dibutylhydroxytoluene (BHT, 2,6-di-*tert*-butyl-*p*-cresol) by single crystal X-ray diffraction and circular dichroism. Left-handed (*M*-) crystals exhibited a positive Cotton effect at a wavelength of approximately 288 nm observed using KBr disk [CD(+)288_{KBr}]. In contrast, right-handed (*P*-) crystals exhibited a negative Cotton effect at the same wavelength [CD(-)288_{KBr}]. Asymmetric autocatalysis is triggered by the chiral crystals of achiral BHT, *i.e.*, *M*-(+)-BHT afforded (*S*)-pyrimidyl alkanol and *P*-(-)-BHT afforded (*R*)-pyrimidyl alkanol.

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1. Introduction

Considerable interests have been focused on the origin of homochirality of biological compounds.¹ Several theories have been proposed as to the origins of chirality such as circularly polarized light, chiral inorganic crystals, spontaneous absolute asymmetric synthesis. The proposed theories on the origin of chirality usually induce only very low enantiomeric excesses. Thus, amplification mechanisms of low ee are necessary to reach high ee.

Chiral crystallization of achiral organic compounds to form enantiomorphs² has been one of the proposed origins of chirality. Stereospecific reactions using enantiomorphous crystals as reactants have been reported to form enantioenriched organic compounds.^{3,4} However, the process does not increase the molar amount of chirality. Thus, asymmetric reactions using chiral crystal of achiral compounds as a trigger or inducer remains as a challenge.

Asymmetric autocatalysis is the reaction in which the chiral product acts as a chiral catalyst for its own production. Asymmetric autocatalysis of pyrimidyl alkanol in the enantioselective addition of diisopropylzinc (*i*-Pr₂Zn) to pyrimidine-5-carbaldehyde provides a method of significant amplification of ee from extremely low to very high (>99.5%) ee.^{5–8} Although some chiral crystals composed of achiral compounds act as chiral triggers of asymmetric autocatalysis,⁹ chiral crystals of achiral phenolic compound have not been used.

Meanwhile, dibutylhydroxytoluene **1** (BHT, 2,6-di-*tert*-butyl-*p*-cresol) is an achiral phenolic compound, and has been widely used as an antioxidant of ether and tetrahydrofuran, etc. Although achiral BHT **1** is known to form chiral crystals,¹⁰ its absolute crystal chirality has not been established. Herein, we report the determination of the absolute crystal chirality of BHT and its solid-state circular dichroism. We also report the asymmetric autocatalysis triggered by chiral crystals of BHT (Fig. 1).

2. Results and discussion

2.1. Preparation and X-ray crystal structure analysis of a single crystal of BHT

The chiral single crystal of BHT was obtained by recrystallization from hexane. Single crystals of BHT **1** of the size of ca. 0.3 cm were obtained (Fig. 2a). We performed the X-ray single crystal structure analysis of the small piece of the obtained single crystal and confirmed that these crystals belong to the space group *P*2₁2₁2₁. According to the X-ray analysis, the recrystallization of BHT randomly afforded optically resolved chiral crystal and we could obtain the single crystals with both chiralities suitable for X-ray analysis. We assigned the crystal chirality as left (*M*) or right (*P*) according to the helical arrangements of supramolecular tilt-chirality¹¹ by choosing one of the six twofold screw axes existing in *P*2₁2₁2₁ space group. There are two types of twofold screw axes for each unit axis direction and a total of six types of screw axes. When looking down the *c*-axis, there are two types of twofold

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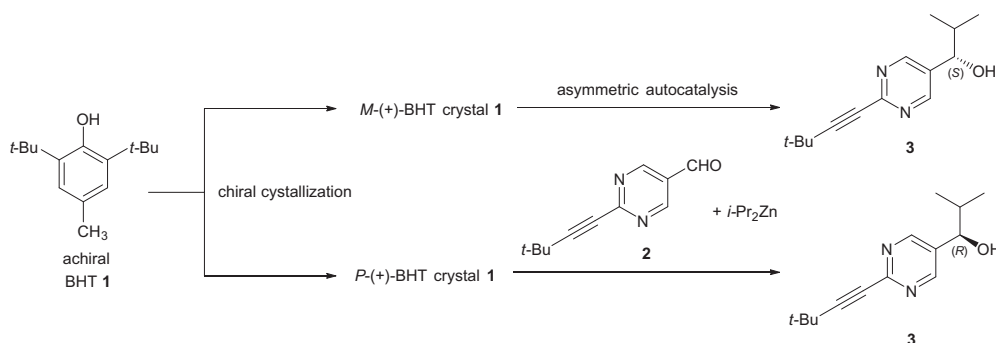


Figure 1. Asymmetric autocatalysis initiated by chiral crystal of achiral BHT 1.

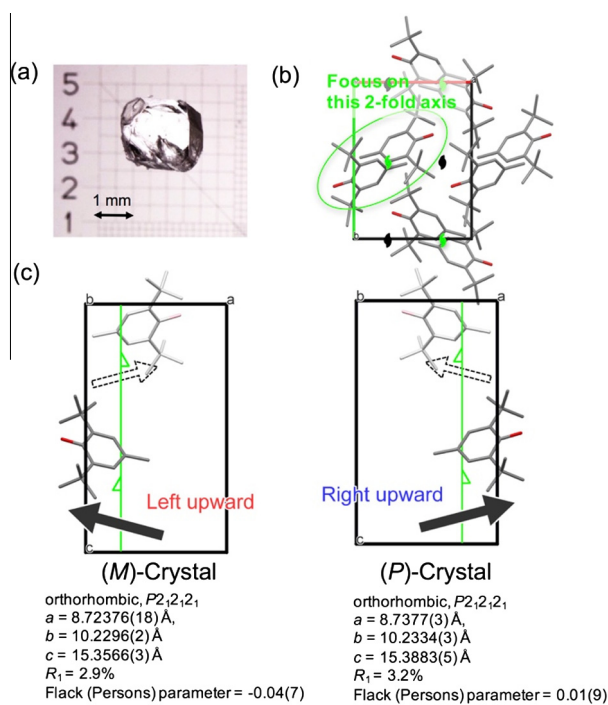


Figure 2. (a) Single crystal of BHT 1 (*M*-crystal). (b) Crystal packing of left handed crystal looking down from *c*-axis. (c) Crystalline packing from *b*-axis.

screw axes parallel to the *c*-axis (Fig. 2b). To define its chirality, we focus on the twofold screw axes near the aromatic rings. Figure 2c is the projection of the structure around this twofold axis to *ac*-plane. The green line shows the focused twofold screw axis. When the molecule in front of the screw axis inclines to the left upward, we assign this crystal as left-handed (*M*). On the other hand, we assign right-handed (*P*) when the molecule in front of the axis inclines to the right upward.

2.2. Solid-state CD spectra of a chiral crystal of BHT

Next, we measured the solid-state CD spectrum of the same single crystal 1 which had been analyzed by the X-ray crystal structure analysis (Fig. 3). In the solid-state CD analysis, the KBr disk was prepared from the fragment of the obtained single crystal (ca. 0.1 mg) and KBr (27 mg). As a result, left-handed *M*-crystal exhibited a positive Cotton effect at a wavelength of approximately 288 nm [$CD(+)288_{\text{KBr}}$], and right-handed *P*-crystal exhibited a negative Cotton effect at the same wavelength [$CD(-)288_{\text{KBr}}$]. We also prepared powder-like crystals of BHT by crystallization with stirring using chiral crystal seeds. Powder-like crystals exhibit the

same CD spectra with those of single crystals. Thus, the correlation between the absolute crystal chirality of BHT and its CD spectra has been established.

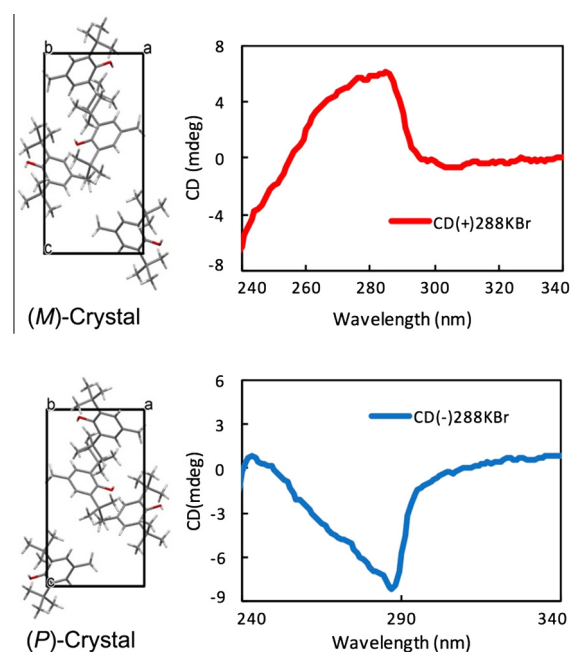


Figure 3. Solid-state CD spectrum of BHT crystal.

2.3. Asymmetric autocatalysis triggered by chiral crystals of BHT

Next, we used powder-like BHT crystals as the chiral trigger for asymmetric autocatalysis. After mixing pyrimidine-5-carbaldehyde 2 and BHT crystal, *i*-Pr₂Zn was dropped onto them. Pyrimidine-5-carbaldehyde 2 and *i*-Pr₂Zn were added to the flask again to amplify the ee of the product. After purification, the ee of the pyrimidyl alkanol 3 was determined by HPLC using a chiral column. The results are shown in Table 1. (*S*)-Pyrimidyl alkanol 3 with 68% ee was obtained in the presence of the left(*M*)-handed [$CD(+)288_{\text{KBr}}$] crystal of BHT (entry 1). In sharp contrast, (*R*)-pyrimidyl alkanol was obtained in the presence of the right(*P*)-handed [$CD(-)288_{\text{KBr}}$] crystal of BHT (entry 2). As shown in the other entries, the reproducibility of the stereocorrelation has been established. It should be emphasized that the obtained moderate (50–68%) ees of alkanol 3 can be amplified to >99.5% ee by further asymmetric autocatalysis.^{5c}

Table 1
Asymmetric autocatalysis initiated by chiral crystal of BHT

Entry ^a	BHT chiral crystal		Pyrimidylalkanol 3		
	Helicity	CD288 _{KBr}	Yield (%)	ee (%) ^b	Config.
1	M	(+)	75	68	(S)
2	P	(–)	69	62	(R)
3	M	(+)	77	50	(S)
4	P	(–)	80	66	(R)
5	M	(+)	75	54	(S)
6	P	(–)	79	66	(R)

^a Reaction conditions: **1**:*i*-Pr₂Zn = 2:1:4 in hexane at 0 °C, and additional **2**:*i*-Pr₂Zn = 2:6 were added stepwise.

^b The ee value was determined by HPLC fitted with chiral column. HPLC conditions: Chiralpak IB (4.6 mm φ × 250 mm), 5% IPA in hexane, 1.0 mL/min, 254 nm, rt, retention time (min) 11.0 for (S), 15.0 for (R).

3. Conclusion

We have assigned the absolute structure of chiral crystal composed of achiral dibutylhydroxytoluene (BHT) and have correlated the absolute structure to the solid-state circular dichroism (CD). We also demonstrated the asymmetric autocatalysis initiated by chiral crystal of achiral BHT. These results suggest that crystal chirality of achiral compounds such as achiral phenolic BHT can act as chiral initiator to induce the symmetry breaking of the molecular chirality.

4. Experimental

4.1. General

The CD spectra were recorded using a JASCO J-820 spectropolarimeter. The single-crystal X-ray diffraction analysis was performed using a Rigaku R-Axis RAPID II imaging plate system with Cu rotating anode X-ray source. Flack parameter × determined by using Parsons quotients method (Parsons, Flack and Wagner, *Acta Crystallogr.* **2013**, B69, 249–259).

The crystallographic data of BHT were deposited in Cambridge crystallographic data center as CCDC 1481198 for left handed crystal and CCDC 1481199 for right handed crystal.

4.2. Preparation of a chiral single crystal of 2,6-di-*tert*-butyl-*p*-cresol (BHT)

The chiral single crystal of BHT was obtained by recrystallization. BHT **1** (ca. 2.0 g) was dissolved in hexane (ca. 4.0 mL) at 75 °C under reflux conditions. Then, it was left at rt for about 18 h. A single crystal of BHT **1** of size ca. 0.3 cm was obtained (Fig. 2a).

4.3. Preparation of powder-like chiral crystal of BHT

BHT (3.5 g) was dissolved in ca. 3 mL of hexane under reflux conditions with stirring. While the solution was kept stirring, the heating oil-bath was removed. Then [CD(+)]288_{KBr} or [CD(–)]288_{KBr} seed crystal was added to the solution, and the mixture was kept stirring and cooled at room temperature. Powder-like chiral crystals of BHT, of which the chirality is the same as that of chiral seed, was obtained.

4.4. Typical experimental procedure of asymmetric autocatalysis using chiral BHT crystal as a chiral trigger

Powder-like crystals of BHT **1** (22.0 mg, 0.1 mmol) were mixed with pyrimidine-5-carbaldehyde **2** (9.4 mg, 0.05 mmol). Hexane solution (1 M) of *i*-Pr₂Zn (0.20 mL, 0.20 mmol) was added dropwise

at 0 °C with stirring. After stirring overnight at 0 °C, toluene (1.0 mL) was added to the mixture. Then, a toluene solution (1 M) of *i*-Pr₂Zn (0.30 mL, 0.30 mmol) and a toluene (0.4 mL) solution of pyrimidine-5-carbaldehyde **2** (19 mg, 0.10 mmol) were added dropwise alternately over a period of 2 h. The reaction mixture was stirred overnight, and then the reaction was quenched with a mixed solution of saturated aq ammonium chloride and aq ammonia (satd NH₄Cl:30% NH₄OH = 2:1 (v/v)). The resulting mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate. Purification of the residue by silica gel column chromatography gave 5-pyrimidylalkanol **3**.

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