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Achiral amino acid glycine acts as an origin of homochirality in asymmetric autocatalysis†

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Chiral crystals of the only achiral proteinogenic α-amino acid, glycine induced the asymmetric autocatalysis with amplification of enantiomeric excess (ee). The $P3_1$ crystals of γ-glycine, which display positive Cotton effect (CD) at around 215 nm, mediate the asymmetric autocatalysis to yield (R)-pyrimidyl alkanol with high ee. In contrast, the enantiomorphic $P3_2$ crystals, which display negative Cotton effect, afford (S)-alkanol after the significant amplification of ee by asymmetric autocatalysis.
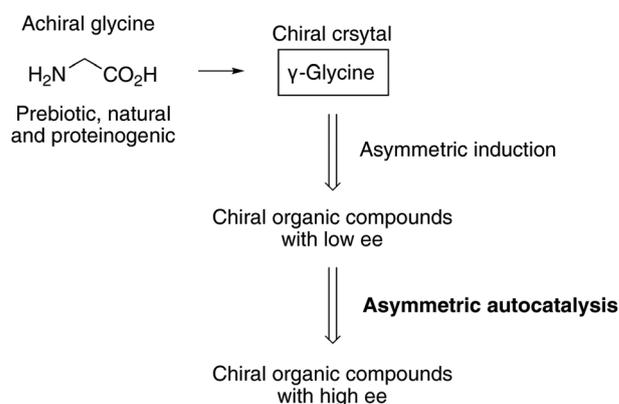
The origin of biological homochirality such as L-amino acids and D-sugars has been a long-standing subject of considerable interest.[1–16] Among the 20 natural amino acids, the only achiral glycine,[17–19] with no asymmetric carbon atom, stands as the simplest (Fig. S1, ESI†). Indeed, when the chirality of natural L-amino acids is mentioned, we often neglect the existence of achiral glycine. Therefore, except for the enantiomer-selective occlusion of the other amino acids,[20,21] it is believed that achiral glycine does not possess any role in the origin of chirality of organic compounds.

Nevertheless, the stable γ-glycine polymorph, which belongs to the Sohncke space group ($P3_1$ or $P3_2$), is known to have a chiral crystalline structure (Scheme 1).[22] However, a long-standing problem has been that the absolute crystal structure of γ-glycine could not be elucidated. We recently determined the absolute chiral crystalline structure of γ-glycine by single-crystal X-ray crystallography and optical rotatory dispersion.[23] Furthermore, the CD spectra of crystalline chiral γ-glycine was reported very recently by Guillemin.[24]

Asymmetric autocatalysis is a reaction in which a chiral product acts as a chiral catalyst for its own production.[25–42] We have been studying asymmetric autocatalysis of pyrimidyl alkanol in the enantioselective addition of diisopropylzinc (i-Pr$_2$Zn) to pyrimidine-5-carbaldehydes. The isopropylzinc alkoxide of 5-pyrimidyl alkanol[43–50] acts as a highly efficient asymmetric autocatalyst with amplification of enantiomeric excess (ee), wherein a very small enantiomeric imbalance can be significantly increased, leading to a nearly enantiopure state (>99.5% ee) during the consecutive reactions. Therefore, chiral factors[51–57] can act as a source of chirality to trigger the asymmetric autocatalytic amplification of ee.

Here we report the following findings: (1) the correlation between the absolute crystal structure of γ-glycine and the CD spectra, and (2) the chiral γ-polymorph of glycine acts as a chiral trigger of asymmetric autocatalysis to produce pyrimidyl alkanol with the absolute configuration corresponding to that of the γ-glycine crystal (Schemes 1 and 2).

The absolute structure of each enantiomorph of the γ-glycine has been determined by anomalous X-ray diffraction. The CD spectrum of each enantiomorph was determined by solid-state circular dichroism (CD) analysis in a KBr matrix

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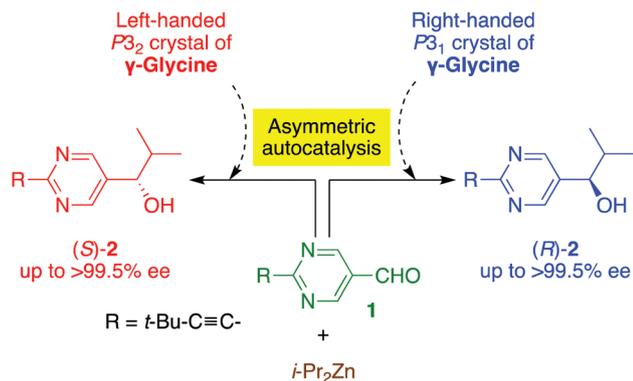*[b]Department of Advanced Science and Engineering, Graduate School of Advanced Science and Engineering, Waseda University, 3-4-1 Okubo, Shinjuku-ku, Tokyo 169-8555, Japan*
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Scheme 1 The concept of this work.

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Scheme 2 Asymmetric autocatalysis triggered by γ-glycine.

(Table S1, ESI†). In the crystal lattice, glycine molecules assume a twisted chiral configuration. The dihedral angle between the plane of the carboxylate and that containing the C–C–N atoms is *ca*. 15.4°. It has been confirmed that the glycine molecules in the crystal of space group $P3_1$, which are in right-handed twisted configuration, induce a positive Cotton effect at around 215 nm (Fig. 1); in contrast, crystals formed from glycine with left-handed configuration (space group: $P3_2$) induce a negative Cotton effect.

The enantiomorphic γ-glycine was then used as a heterogeneous chiral initiator for asymmetric autocatalysis of 5-pyrimidyl alkanol **2** (Scheme 2 and Table 1). In a typical procedure for asymmetric autocatalysis, an enantiomorphic crystal of γ-glycine was ground into a fine powder together with aldehyde **1**. To this powder, toluene solution of *i*-Pr₂Zn was slowly added and reacted for 12 h. Then, toluene solutions of *i*-Pr₂Zn and aldehyde **1** were slowly added. After finishing the reaction, the ee was determined by analysing purified 5-pyrimidyl alkanol **2** by chiral HPLC (for the experimental details, see ESI†).

As shown in entry 1, when pyrimidine-5-carbaldehyde **1** and *i*-Pr₂Zn reacted in the presence of $P3_1$ crystals, enantio-enriched (*R*)-pyrimidyl alkanol **2** was obtained with 73% ee after the subsequent asymmetric autocatalysis, through addition of aldehyde **1** and *i*-Pr₂Zn. On the other hand, $P3_2$ γ-glycine induced the production of enantioenriched (*S*)-alkanol **2** with 69% ee (entry 2). The reproducibility of the stereochemical relationships between the crystal chirality of γ-glycine and the resulting alkanol **2** is shown in entries 3–6 of Table 1. It should be noted that additional consecutive asymmetric autocatalysis afforded almost enantiopure (*R*)- or (*S*)-**2** with >99.5% ee (entries 7 and 8). Therefore, it was found that the crystalline chirality of the achiral glycine is responsible for the enantioselective addition of *i*-Pr₂Zn to aldehyde **1**; thus, the crystalline chirality, which comes from the solid-state chiral conformation of glycine molecules ($P3_1$ or $P3_2$), induces a tiny enantiomeric imbalance during the formation of the zinc alkoxide in the initial stage of the reaction. During the subsequent asymmetric autocatalysis, this tiny enantiomeric imbalance is significantly amplified to afford the near enantio-
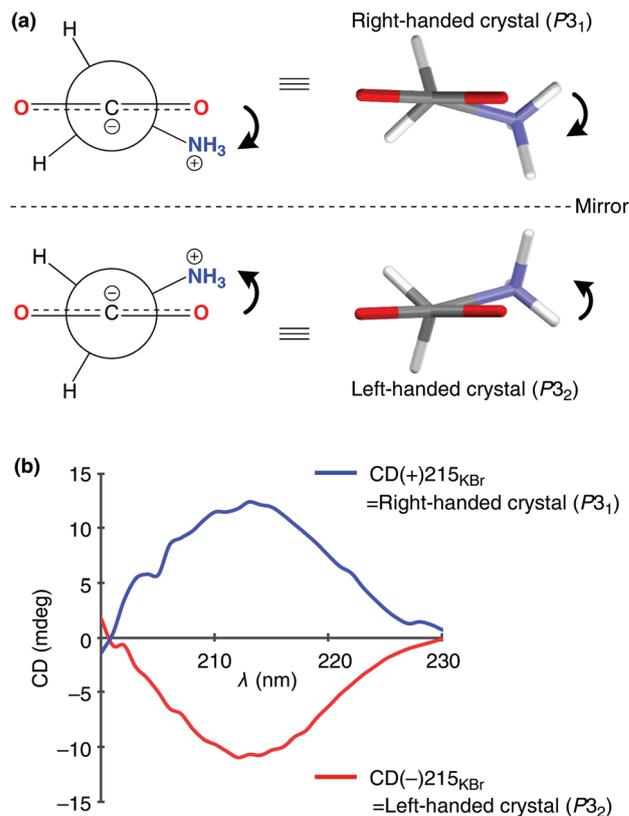
Fig. 1 Determination of the absolute structure of γ-glycine by the correlation between (a) twisted conformation of glycine molecule in the crystal structure (Newman projection and X-ray structure) and (b) Cotton effects of solid-state CD. [CD(+)215_{KBr}]-γ-Glycine with right-handed configuration, belong to the space group $P3_1$ and enantiomorphic [CD(−)215_{KBr}]-glycine with left-handed configuration belong to the space group: $P3_2$.

Table 1 Stereochemical relationships between γ-glycine and 5-pyrimidyl alkanol as a result of asymmetric autocatalysis with amplification of ee

	γ-Glycine		5-Pyrimidyl alkanol **2**		
Entry[a]	CD[b]	Helicity	Yield[c] (%)	ee[d] (%)	Config.
1	(+)	Right	68	73	R
2	(−)	Left	52	69	S
3	(+)	Right	59	43	R
4	(−)	Left	66	63	S
5	(+)	Right	69	35[e]	R
6	(−)	Left	66	52	S
7	(+)	Right	67 (94)[f]	57 (>99.5)[f]	R
8	(−)	Left	67 (89)[f]	72 (>99.5)[f]	S

[a] The molar ratio of γ-glycine/**1**/*i*-Pr₂Zn was 0.5 : 0.15 : 0.7 (mmol). [b] The Cotton effect of solid-state CD (KBr disk) at around 215 nm was indicated. [c] The yield of isolated product **2**. [d] The ee value was determined by HPLC on a chiral stationary phase. [e] Ee can be amplified by further asymmetric autocatalysis. See footnote f. [f] After the typical experimental method, additional rounds of consecutive asymmetric autocatalysis were performed after the isolation of **2**.[27]

pure alkanol **2** with the absolute configuration corresponding to handedness of γ-glycine.

This sequence of reactions represents one of the chemical processes in which the scenario for the evolution of enantio-enriched chiral organic compounds from the achiral natural amino acid glycine was achieved in real chemical reactions (Scheme 1). The process of asymmetric induction in the organic product with an asymmetric carbon atom and the amplification of chirality through asymmetric autocatalysis indicate the possibility of the simplest α-amino acid glycine being the origin of chirality.

The initial enantioimbalance of asymmetric autocatalyst **2** is likely generated on the chiral surface of γ-glycine,[58] because the dissolution of the crystal causes the disappearance of chirality. We postulated the possible mechanisms of asymmetric induction[59] are as follows: (1) enantioface-selective adsorption of aldehyde **1** followed by i-Pr$_2$Zn addition, and (2) enantio-selective adsorption of the initially formed alkanol **2** (as iso-propylzinc alkoxide), which can induce an enantiomerically imbalanced autocatalyst. Subsequent asymmetric autocatalysis then enhances the small ee of the asymmetric autocatalyst to a nearly enantiopure state.

In conclusion, we have established the correlation between the absolute crystal structure of γ-glycine and its CD spectra; we found that chiral γ-glycine crystal acts as a chiral trigger for asymmetric autocatalysis to afford a highly enantioenriched organic compound. The implication of the present results for the origin of homochirality is that achiral glycine, which has long been neglected as irrelevant to chirality, may play an important role as a chiral γ-glycine crystal as a chiral trigger for asymmetric autocatalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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