Polymorphic Control of Glycine Crystals by LLIP Method under High Magnetic Field

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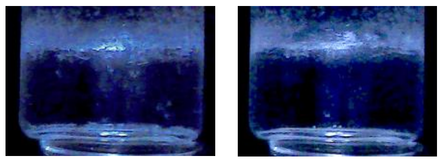
The glycine is an amino acid with the simplest structure, and has three crystalline polymorphs: two monoclinic α (space group, $P2_1$) and β (space group, $P2_1/n$) and the trigonal γ (space group. $P3_1/P3_2$). The control of crystal polymorphism is important to develop a new drug. We have reported that the glycine crystals were prepared by the liquid-liquid interfacial precipitation (LLIP) method, and discovered the change in the ratio among the polymorphs under the magnetic field. The magnetic field effects was considered that the magnetic force was influenced to the posture and the position of crystal in the reactor. When the crystals could be transported to the high or low concentration region by the magnetic force, a solvent mediated transformation (SMT) must suppress or promote. In order to confirm this consideration, *in situ* observation and the investigation of precipitation amount were carried out [1]. The purposes of our study are the polymorphic control using the magnetic field and its effect in the process of crystal growth and transformation of the polymorphism.

The glycine crystals were prepared by the LLIP method that is one of the crystallization techniques. The interface formed between good and poor solvents is a supersaturated region, where the crystal nuclei are generated and grown. The good solvent (glycine aqueous solution, 1 mL) and the poor solvent (1-propanol, 2 mL) were injected gently to make a layer in the reactor. The reactor was placed into the bore of the vertical magnet for a fixed time (4, 8, 16 h) at 10.0℃. After the reaction under the homogeneous and gradient magnetic fields, the liquid was removed from the reactor. The crystals were washed with methanol by the ultrasonic bath and dried by the vacuum desiccator. The each amount of polymorph was estimated by XRD data.

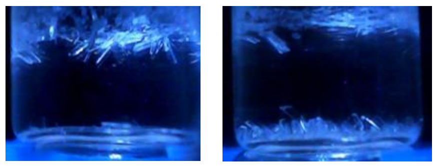
The magnetic orientation of crystals and the SMT were observed shown in Fig. 1. After 4 min from the start of reaction, the microcrystals precipitated from the interface to the bottom of the reactor (a). The microcrystals dissolved without growing after 10 min (b). While the crystals dissolved in this way, there were also the growing crystals observed in the bottom. From the viewpoint of solubility, the growing crystals are more stable than the dissolved crystals. These phenomena were the process of SMT. Standing crystals were observed in vertical magnetic field as shown in Fig. 2 (b). Assuming the orientation of crystals at the interface as the same as the bottom, the magnetic field effects are expected for the growth direction and the precipitation timing due to the posture of crystal.

Fig. 3 shows the amount of polymorph against the reaction time. The amounts of α and γ crystals were increased and decreased under the magnetic field, respectively, compared with the zero fields. In this *in situ* experimental system, it is understood that the crystal polymorphism was controlled by not only the magnetic force but also the magnetic orientation by using high magnetic fields.



(a) t = 4 min. (b) t = 10 min.

Fig. 1. Dissolution of crystals under zero MFs.



(a) Zero MFs. (b) Homogeneous MF.

Fig. 2 Crystals on the bottom appeared at 4.5 h.

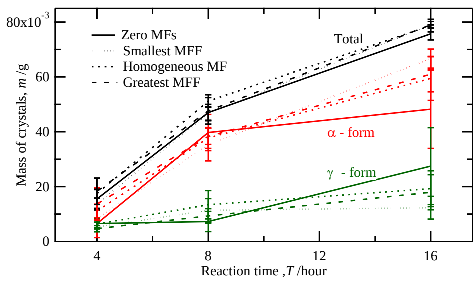


Fig.3 Changes in precipitation amount for each polymorph vs. time.

Acknowledgement: This study was supported partially by JPSJ (16K04946).

Reference: [1] N. Yokoyama *et al*, The76th JSAP Autumn Meeting, 14p-4B-5 (2015).