Tuning Organic Crystal Chirality by Enantiomer-Specific Oriented Attachment

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Chemicals

N-benzoylglycine (CAS no. 495-69-2, purity ≥ 99.0 %) and maleic acid (CAS no. 110-16-7, purity ≥ 99.0 %) were purchased from Tianjin Heowns Biochemistry Technology Co. LTD of China. L-isoleucine (CAS no. 73-32-5, purity ≥ 99.0 %), L-leucine (CAS no. 61-90-5, purity ≥ 99.0 %), L-valine (CAS no. 72-18-4, purity ≥ 99.0 %), and pyridine (CAS no. 110-86-1, purity ≥ 99.0 %) were purchased from Shanghai Aladdin Biological Co. LTD of China. All of the chemicals were used without further purification. Ultrapure water (resistivity = 18.2 MΩ cm) was prepared in our laboratory using the NANOPURE system from BARNSTEAD (Thermo Scientific Co., China).

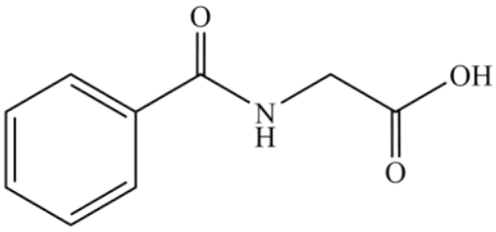


Fig. S1 Chemical structure of N-benzoylglycine.

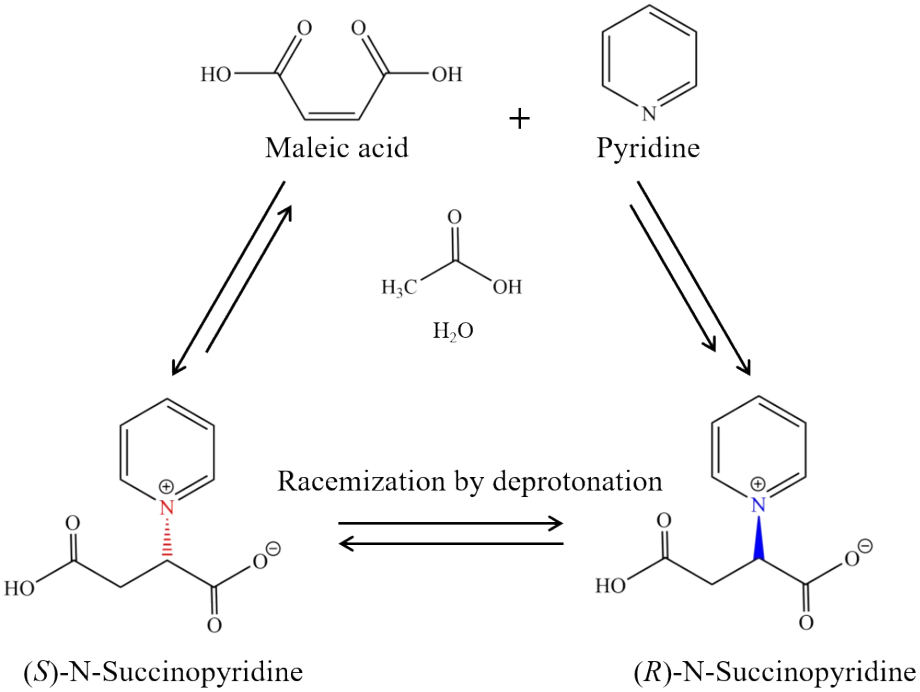
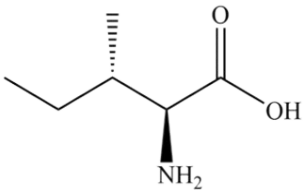
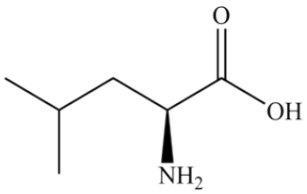


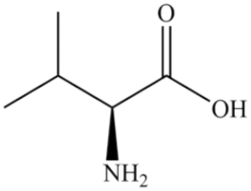
Fig. S2 Aza-Michael addition of pyridine to maleic acid.



L-Isoleucine



L-Leucine



L-Valine

Fig. S3 Chemical structure of L-Isoleucine, L-Leucine and L-Valine.

Detailed Experimental Procedures

1. Viedma Ripening: The sample of commercially available N-benzoylglycine powder (0.25 g) was suspended in a saturated solution of 1 mL distilled water using a sealed round-bottom flask (5 mL). Grinding medium (3.0 g of 0.8 mm YTZ zirconia ceramic beads) was added and the sample was stirred at 1500 rpm with a magnetic stirring bar (10 mm×4 mm, oval). Slurry samples (ca. 100 μL) were collected at regular intervals using an automatic pipet and deposited on filter paper to dry, and then analyzed through CD. After each sample, an equal volume of saturated solution was replenished to the round-bottomed flask.

2. Synthesis of N-succinopyridine: A solution of maleic acid (11.9 g, 10.24 mol) and 1.0 equiv. of liquid pyridine (8.1 g, 10.24 mol) and water (8 mL) was stirred in a sealed crystallizer using an oval magnetic stir bar at 90 ℃. After a large number of white crystals appeared in the clarified solution, acetic acid (12 mL) was added. The solution was then stirred and kept in suspension at the same temperature for several days and finally filtered to obtain white N-succinopyridine crystals.

3. Crystallization through Slow Evaporation: Single crystals of N-succinopyridine were grown by slow evaporation of water from a Petri dish (10 cm diameter). N-succinopyridine (ca. 10 g) was dissolved in distilled water (50 mL) at room temperature with stirring and subsequently covered with perforated aluminum foil to slow evaporation. Slow crystallization of large single crystals occurred over several days. Crystals typically measured 1 x 0.5 x 0.25 cm.

4. Boiling Experiments: Boiling experiments were performed using a round bottomed flask (100 mL). Ground N-benzoylglycine (ca. 30 g) was dissolved in water (20 mL) in a round bottom flask. The mixture was refluxed at 180 ℃ for about 6-24 h until aggregate formation was observed. The size of the aggregates ranged from 0.2 cm to 1 cm in diameter (20 mg to 1.5 g in mass). For N-succinopyridine, the formation of large aggregates was clearly observed by refluxing approximately 15 g dissolved in 10 mL of water at 160 ℃ for 15-24 h.

For the three amino acids of the racemic compounds, mainly isoleucine as an

example, ZnO (ca. 3 g) and DL-isoleucine (ca. 3 g) dissolved in the volume ratio of 60% ethanol aqueous solution (ca. 15 mL) were added to a round-bottomed flask (100 mL), and refluxed for 6-12 h at a temperature of 120 ℃. Formation of large aggregates of the conglomerate containing ZnO was clearly observed.

5. Circular Dichroism:

N-benzoylglycine: Solid-state circular dichroism was used to quantify the crystal enantiomeric excess (CEE) of N-benzoylglycine aggregates obtained during the Viedma ripening process as well as in boiling experiments. CD spectra were recorded from 240 to 350 nm using a MOS-500 circular dichroism spectrometer. The resolution of 5 points/nm was used and each curve generated was the average of 3 or 5 accumulations collected at a scan rate of 50 nm/min. Solid samples of N-benzoylglycine were prepared as KBr pellets. N-benzoylglycine was ground with a mortar and pestle, KBr pellets were prepared by adding 50 mg of potassium bromide crystals (concentration 2.0% wt/wt) to the mortar, mixing the sample until a homogeneous mixture was obtained, and then this mixture was vacuum-pressed at ca. 8 tons for ca. 20 s to form a translucent and homogeneous pellet. The sample assembly is mounted using a standard circle cell holder with the sample placed as close to the detector as possible.

N-succinopyridine: As we tested the circular dichroism chromatogram of synthesized N-succinopyridine, we did not find any significant characteristic peaks in the region of 200-800 nm, whereas there was a significant signal in the near-infrared band at 800-900 nm. Therefore, for the circular dichroism chromatogram of N-succinopyridine, we tested it using a Jasco J-1700 circular dichroism spectrometer in the near-infrared band. Pure chiral samples of the standards were obtained by cultivating single crystals with a bandwidth of 20 nm for testing, sample and potassium bromide concentrations of 3.0% wt/wt, and other conditions were the same as those for benzoylglycine.

6. Calibration Curves: The crystal enantiomeric excess (CEE) of viedma ripening and N-benzoylglycine aggregates was determined using a calibration curve. The enantiomeric excess (% ee) of the crystalline samples was calculated using Equation 1,

where $x_{(+)}$ and $x_{(-)}$ are the weights of CD-positive and CD-negative crystals, respectively.

$$\text{enantiomeric excess}(\%) = \frac{x_{(+)} - x_{(-)}}{x_{(+)} + x_{(-)}} \times 100\% \quad (1)$$

Samples with varying enantiomeric excess are prepared by mixing appropriate proportions of levo- and dextro-crystallized powders while maintaining a constant total weight. The calibration curve is generated by plotting the CD signal at a specified wavelength (260 nm) against the enantiomeric excess of the standard. For each standard, multiple pellets are prepared and measured to determine the average CD signal and standard deviation (typically n = 3). The calibration curve was then used to determine the enantiomeric excess of the samples in the boiling experiment. Pure chiral samples used as standards for the construction of calibration curves were obtained by viedma ripening, and the chiral purity of the Vviedma ripening samples was continuously determined by circular dichroism until the peak spectral signals determined by sampling two adjacent time intervals were essentially unchanged, such that we considered the viedma ripening to have proceeded completely and pure enantiomers of a single chirality were obtained.

7. Scanning electron microscopy: SEM images were obtained using an Field Emission Scanning Electron Microscopy (Apreo S LoVac, Thermo Fisher Scientific) operating at 15 keV acceleration voltage. The samples were fixed on glass slides (7.5 cm x 2.5 cm) using double-sided conductive tape. An MSP-1S Magnetron Sputter was used to apply a gold layer (ca. 10 nm) on the samples prior to imaging.

8. Powder x-ray diffraction (PXRD): Powder XRD of the milled crystals was determined using a powder X-ray diffractometer (Rigaku MiniFlex 600, Rigaku, Japan) by Cu. Kα radiation (1.54046 Å) at 40 kV and 100 mA, with diffraction angles (2θ) in the range of 2-40°, and scanning rate of 8°/min.

9. High performance liquid chromatography (HPLC) assay: The enantiomeric excesses in the amino acid aggregates were determined by a Waters 2695 series high

performance liquid chromatograph (HPLC). The chromatographic analysis was performed on a MCI GEL CRS10W column (50 × 4.6 mm, 3 μm) at 25 ℃ with a UV detection wavelength of 256 nm, and the mobile phase was a 1% (by mass concentration) copper sulfate salt solution at a flow rate of 1.0 mL/min.

10. Thermal analysis: Simultaneous thermogravimetric analysis (TGA) was performed on a TGA/DSC 3+/1100 SF thermal balance (Mettler-Toledo) and differential scanning calorimetry (DSC) on a DSC 1 differential scanning calorimeter (Mettler-Toledo) with sample volumes ranging from 4 mg to 8 mg. All measurements were carried out under dynamic nitrogen protection (airflow 25 mL/min) and heated at a constant rate of 10 ℃/min to 400 ℃ or 600 ℃.

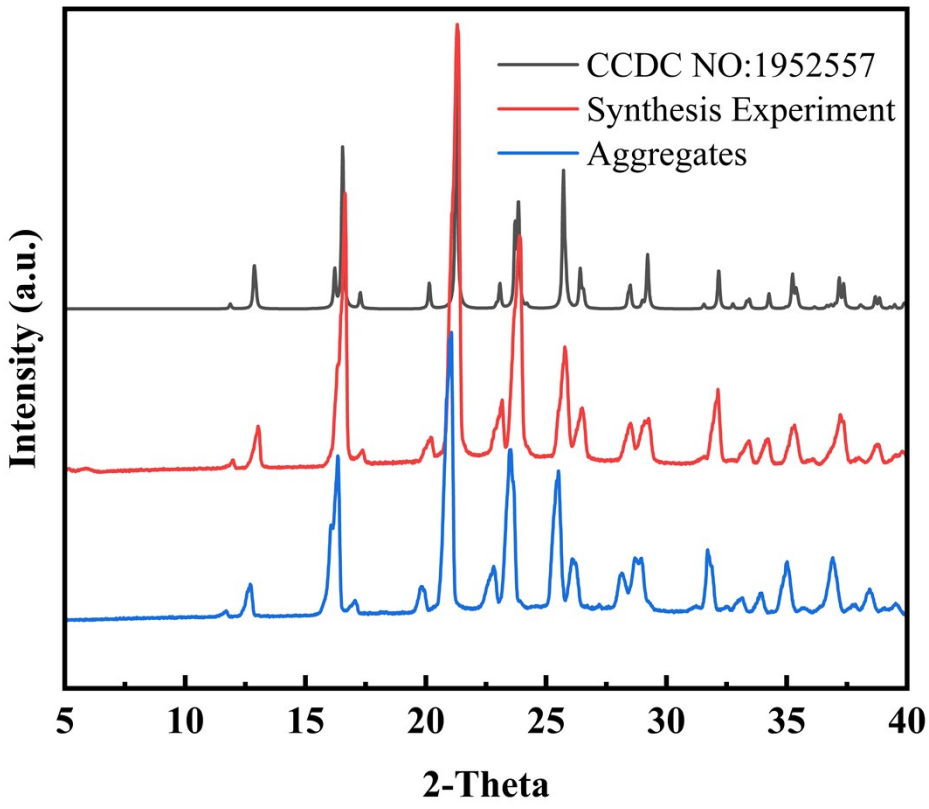


Figure S4. The X-ray powder diffraction patterns of the N-Succinopyridine crystals and aggregates we prepared, and the simulated X-ray crystallographic diffraction pattern of N-Succinopyridine from its single crystal structure (CCDC: 1952557).

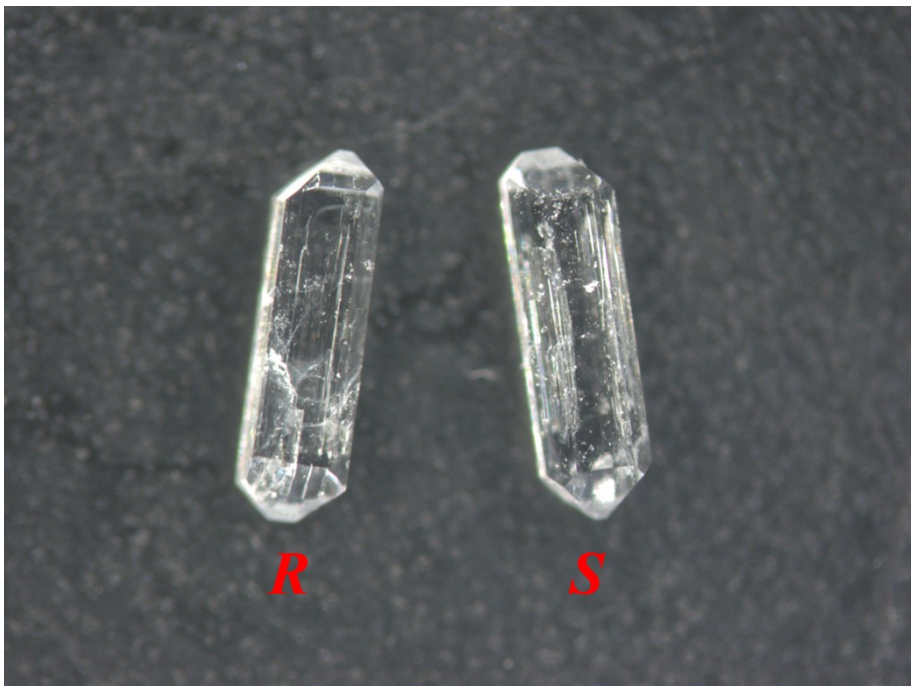


Fig. S5 Microphotographs of the single crystals of (*R*)-N-Succinopyridine and (*S*)-N-Succinopyridine.

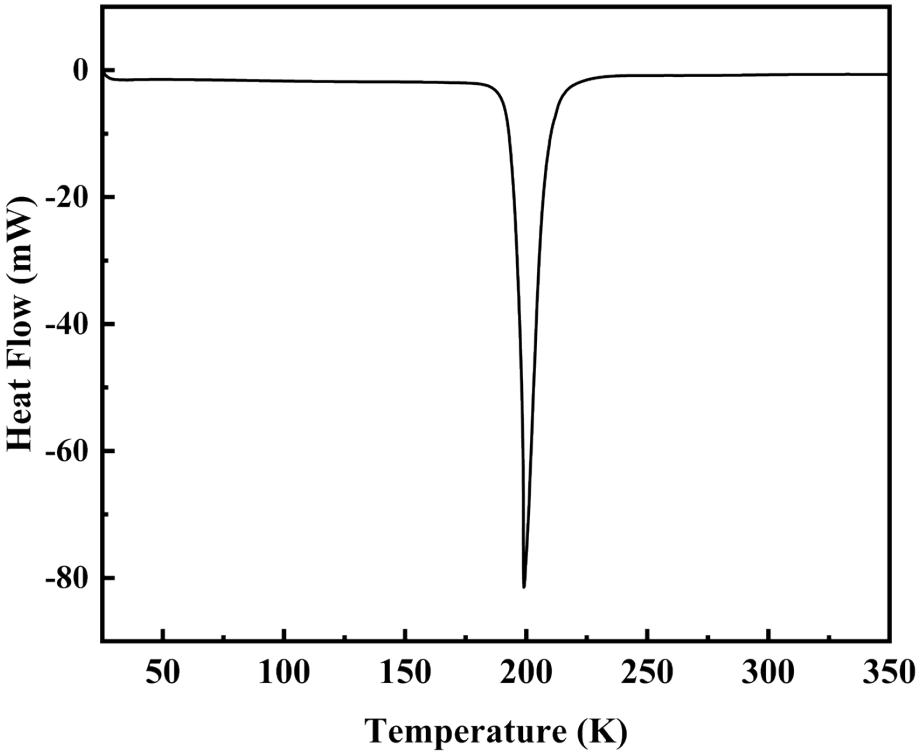


Fig. S6 DSC shows heat flow response of N-succinopyridine.

Notes: After synthesizing N-succinopyridine, we obtained by DSC test that it starts melting at a temperature of about 180 ℃, so in the case of water as a solvent, we need

to preferably 160 ℃ while maintaining the ability to boil.

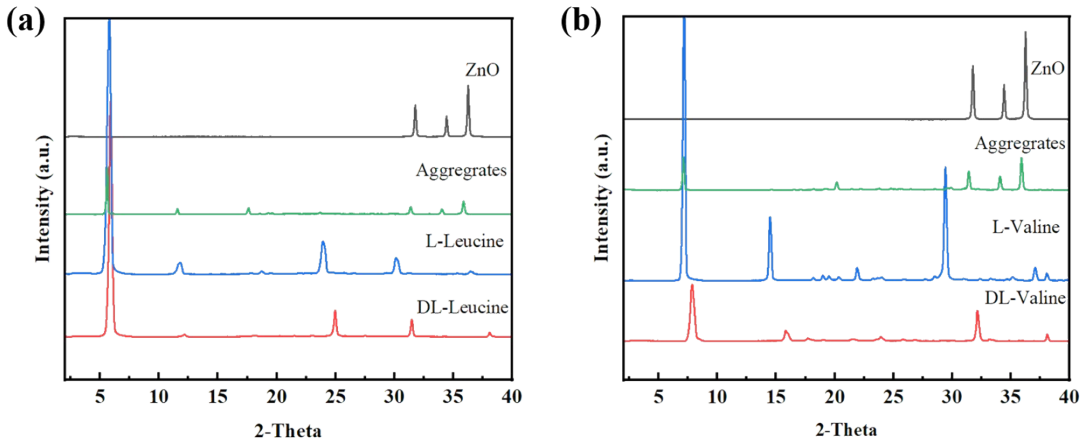


Fig. S7 (a) XRD pattern of the pure DL-leucine, L-leucine, ZnO and the aggregates. (b) XRD pattern of the pure DL-valine, L-valine, ZnO and the aggregates.

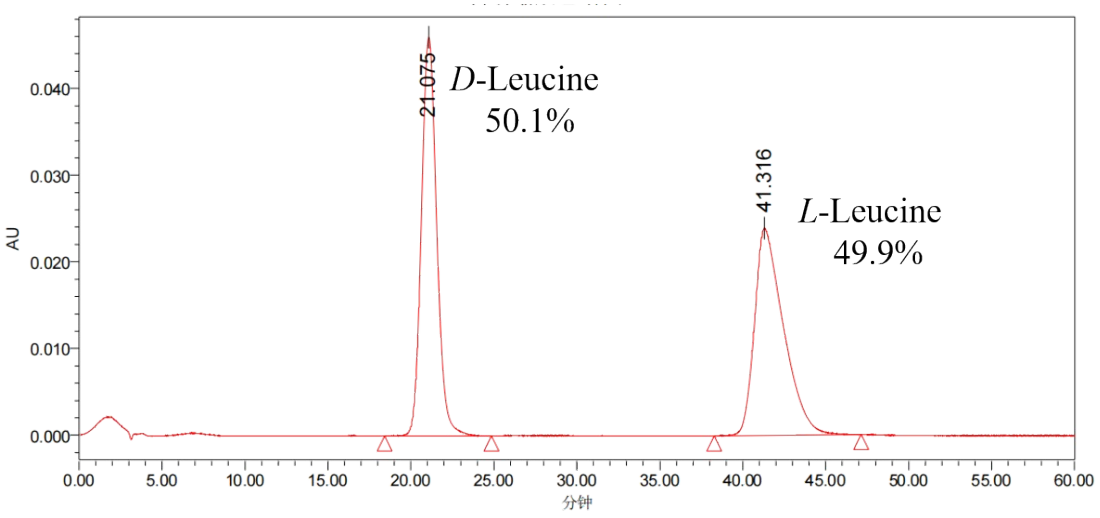


Fig. S8 Liquid chromatographic detection of DL-leucine crystal aggregates formed in the presence of zinc oxide.

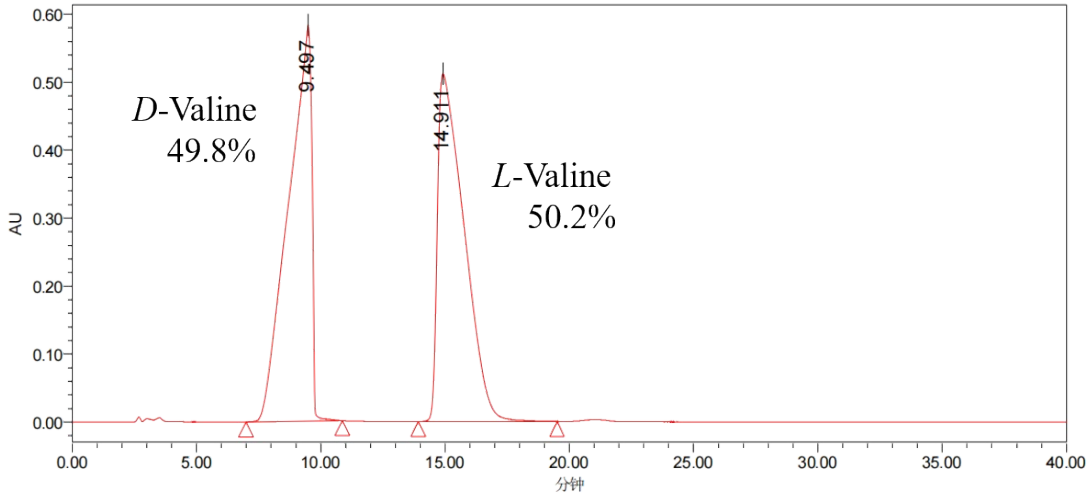


Fig. S9 Liquid chromatographic detection of DL-valine crystal aggregates formed in the presence of zinc oxide.

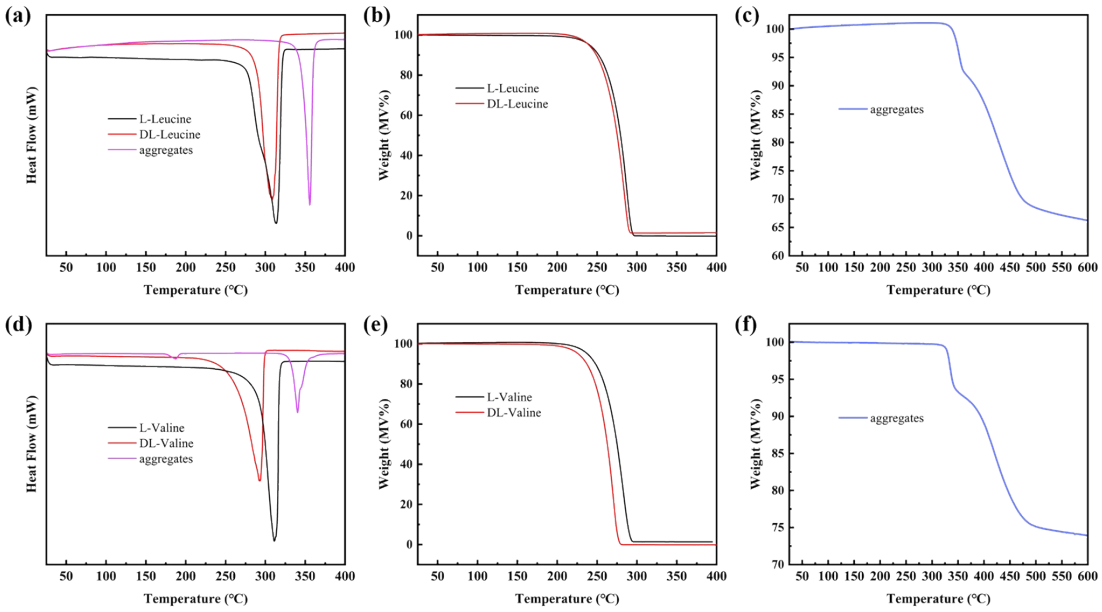


Fig. S10 (a) TGA showing thermal response of DL-leucine, L-leucine and the aggregates. (b) (c) DSC shows heat flow response of DL-leucine, L-leucine and the aggregates. (d) TGA showing thermal response of DL-valine, L-valine and the aggregates. (e) (f) DSC shows heat flow response of DL-valine, L-valine and the aggregates.