Tuning Crystallization and Stability of Metastable Polymorph of DL-methionine by a Structurally Similar Additive

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Contents of Supporting Information

■ The detailed simulation method

DL-leu, as the additive, was built on crystal faces during the simulation. The detailed simulation method was summarized below

(1) AE model was used to simulate the morphology of DL-met α form under vacuum conditions by Materials Studio. And the important crystal faces were obtained.

(2) For each face, the periodic superstructure was constructed and cleaved parallel to the face with a deep of 3 d_{hkl} along the main stable surfaces according to vacuum conditions. Afterwards the face was built to become a vacuum slab.

(3) The solvent molecules and additive molecules (DL-leu) were constructed in an amorphous box with proportion by Amorphous Cell module. In this work, three different additive concentrations were investigated, so we build three amorphous boxes. The size of amorphous box was set to fit the lattice parameter of surface face.

(4) The amorphous box was adsorbed as solvent layer on every crystal face along c axis. To avoid the impact of additional free boundaries, a vacuum with a thickness of 30 Å was set to be the third layer above the

solvent layer.

(5) Geometry and dynamic optimization of structure were performed in the Forcite module. NVT (a system of a fixed number of particles (N), in a fixed volume (V), and with a fixed temperature (T)) ensemble method was carried out and the time step for the MD simulation is 1 fs with a period of 500 ps, controlled by Andersen thermostat.

(6) For the non-bonding interactions, both the electrostatic interactions and the van der Waals forces were calculated by Atom based methods. In addition, the calculation accuracy of electrostatic interactions is 0.0001 kcal•mol^{-1}, and the cutoff radius of van der Waals is 12.5 Å.

■ Solubility Measurement Experiment

To investigate the dissolve property of DL-met after adding DL-leu, solubility was experimentally measured by a gravimetric method[1-4]. First, about 30 ml aqueous solution with known concentration of an additive was prepared in a 50 ml conical flask under stirring. The temperature of the solution was kept constant using a thermostatic water bath, then excess α or β form DL-met solids were added into the thermostatic solution. The supersaturated solution was kept agitating for enough time to achieve equilibrium. After that, a few milliliters of upper clear solution with certain mass was withdrawn by a membrane filter (pore size = 0.2 μm) and moved into capacity bottle to dilute. Then the solubility of the supernatant after dilution was determined by high-performance liquid chromatography (HPLC). The undissolved substance and raw solute in beakers were tested by a Powder X-Ray Diffraction (PXRD) device to ensure no polymorphic transformation during the solubility measurement. Each experiment was repeated three times.

■ Solubility of DL-met in the presence of DL-leu

The effect of DL-leu on solubility data α of and β polymorphs of DL-met in water are shown in Fig.S1. It can be seen that the solubility of both α and β form increase with increasing temperature. Besides, the α-form is more soluble than β-form at room temperature, which indicates that β-form is the stable form. When adding concentration 0.002, 0.01, 0.02 mol/L DL-leu in aqueous solution, respectively. The solubility of α and β form was

measured. Relative error (RE) are listed in Table S1, which defined as:

$$RE\% = \frac{x_{ad} - x_1}{x_{ad}}$$

Where x_{ad} is solubility of DL-met in pure aqueous solution and x_1 is the solubility of DL-met in the presence of DL-leu. From Table S1 and Fig.S1, it can be shown there is no obvious impaction of DL-leu on solubility of DL-met, thus the solubility data change of DL-met after adding additives could be ignored in the following work. And the supersaturation of DL-met could still be calculated as in aqueous solution. Actually, Jin et al. found that over one kind of L- amino acid additives which the concentration in solution is more than 1.5 mol/L could enlarge some amino acids solubility[5], the reason was that electrolysis condition of amino acid was changed caused by pH changed by additives. But in this research, concentration of additives would far less than 1.5 mol/L. So effect of DL-leu on DL-met solubility could be ignored in this work.

Table S1. Solubility of DL-met and RE values (Form α and β) in pure and different DL-leu concentration aqueous solutions.

Additives Concentration (mol/L)	β-form				α-form			
Temperature (℃)	30		40		50		60	
	x_{ad}/x_1	RE/%	x_{ad}/x_1	RE/%	x_{ad}/x_1	RE/%	x_{ad}/x_1	RE/%
0	4.565	0	5.417	0	7.263	0	9.239	0
0.002	4.334	5.06	5.494	1.42	7.422	2.19	9.021	2.35
0.004	4.356	4.58	5.543	2.34	7.164	1.36	9.171	0.74
0.008	4.415	3.29	5.756	6.27	7.065	2.72	9.459	2.39
0.016	4.407	3.46	5.299	2.17	7.255	0.10	9.333	1.02
0.024	4.438	2.77	5.487	1.31	7.272	0.13	9.459	2.39
0.032	4.421	3.15	5.684	4.93	7.262	0.01	9.172	0.72
0.036	4.674	2.39	5.565	2.73	7.191	0.99	9.237	0.02

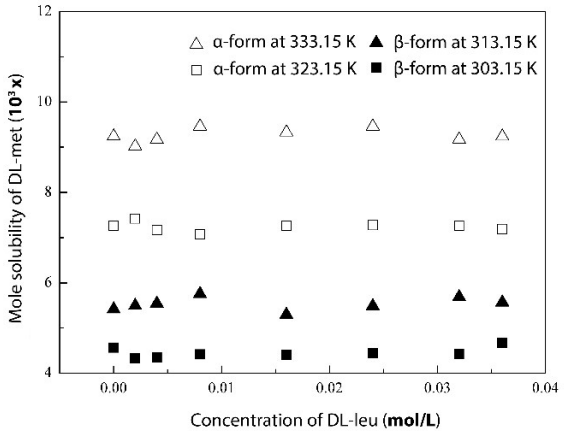


Figure S1. Mole solubility of DL-met with concentration of DL-leu.

■ The binding energy between DL-leu and the polymorphs of DL-met

Table S2. The binding energy between DL-leu and the polymorphs of DL-met.

Crystal facets		Binding energy (kcal/mol)	
α-form	*β*-form	*α*-form	*β*-form
(110)	(110)	-49.888	-82.903
(100)	(100)	-56.299	-61.403
(011)	(11-1)	-87.951	-135.582
(10-2)	(10-1)	-56.312	-147.560
(002)	(002)	-79.844	-67.054

■ Single crystal experiments of DL-met *α*-form

Single crystal experiments under T= 293.15 K and S=1.2 in a sealed environment were conducted with no additive, 0.002 mol/L, 0.01 mol/L and 0.02 mol/L DL-leu, respectively. After over 15 days, single crystals appear gradually. The higher the additive concentration, the longer the induction time, which shows the inhibition of additive. The form of samples has been identified by PXRD. The morphologies of crystals in difference conditions are shown below. We found that the results accord with the previous conclusions of this work basically. In order to ensure further that the morphologies of single crystals are corresponding to the simulation results, the Miller indices of crystal facets are measured and analyzed. Firstly, the single crystals were tiled on the sample holder with the largest facet placed face up, which is shown in Figure S2. According to the principle of X-ray powder diffraction, the majority of peaks in PXRD pattern are expected to disappear thanks to the “preferred orientation”.

Then the Miller indice of the upwards lattice facet can be determined by comparing the remaining diffraction peak(s) and the simulated pattern (by using Mercury). The result is shown in Figure S3. Obviously, there are only two primary peaks which represent (100) and (400) planes. And (400) is parallel to (100). Thus it is in line with the simulated morphologies, and based on the dihedral angles and the relatively positions, the conformity between experimental and simulated results are confirmed (Table S3).

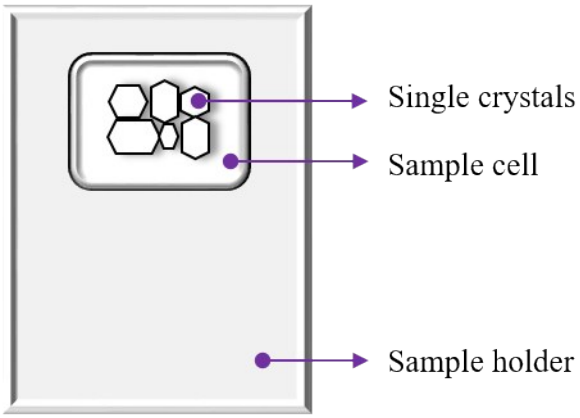


Figure S2. Sketch map of measurement of Miller indices of crystal facets.

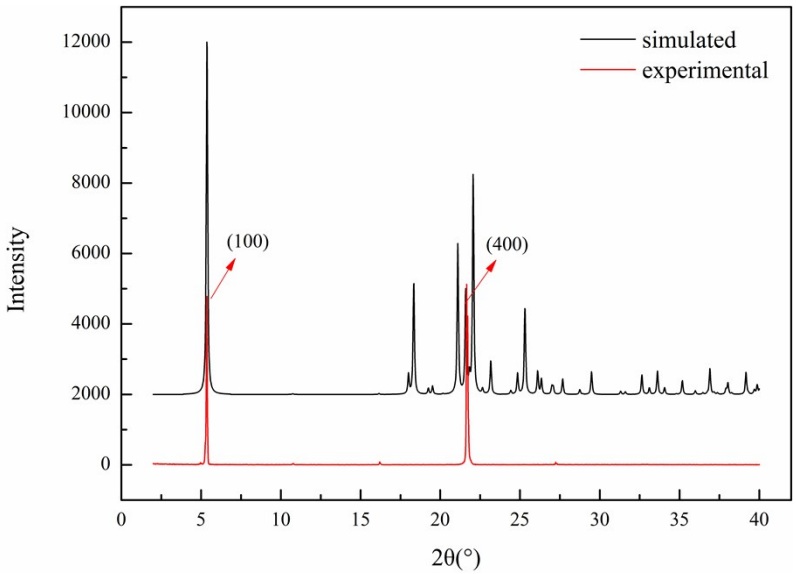
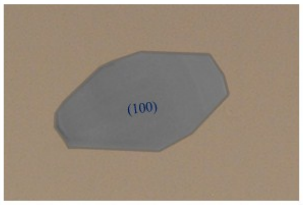
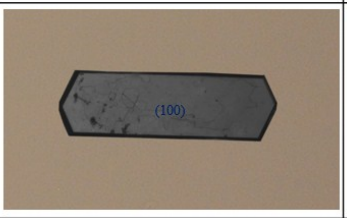
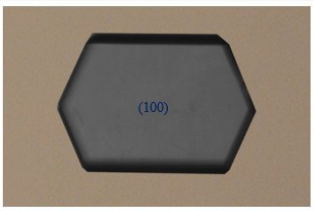
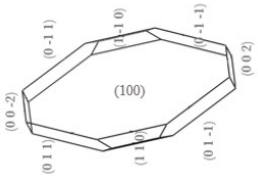
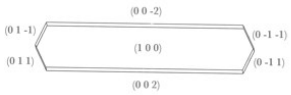
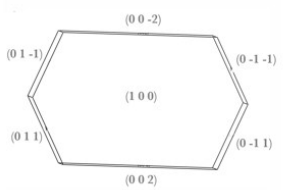


Figure S3. The comparison between the experimental and simulated PXRD patterns.

Table S3. The single crystal experimental and simulation results of α-form DL-met morphology in solutions with different concentration of DL-leu (0.002, 0.01 and 0.02 mol/L, respectively).

concentration of DL-leu / comparation of morphology	0.002mol/L	0.01mol/L	0.02mol/L
single crystal experiments results of α-form DL-met morphology			
simulation results of α-form DL-met morphology			

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