Supporting Information

Solubility Behavior and Polymorphism of *N*-Acetyl-DL-methionine in 16 Individual Solvents from 283.15 to 323.15 K

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1. Detailed Process for Solubility Measurement

The static gravimetric method was used to determine the solubility of *N*-Acetyl-DL-methionine (NAM) in sixteen pure solvents. The detailed processes of the experiments are listed as follows:

(1) Charging. The masses of NAM and solvents were weighed by an analytical balance, then the weighed solute and solvents were added into a jacketed crystallizer kept at a constant temperature (from 283.15 to 323.15 K with an interval of 10 K) monitored by a mercury thermometer and controlled by a thermostatic water bath.

(2) Stirring. The solution system was stirred by a magnetic stirrer continuously for about 1 h (according to our exploration, 1 h is enough for establishing the solid-liquid equilibrium).

(3) Settling. The whole solution system was settled for about 30 minutes at a fixed temperature to ensure that no large particles could be seen in the supernatant.

(4) Sampling. About 3 ml supernatant was withdrawn and transferred into a Petri dish by using a syringe with an organic membrane filter (removing the fine particles that could not be separated by settling). After sampling, the temperature of the system was elevated to the next one. More solute can be added to the crystallizer to rebuild the solid-liquid equilibrium if it

was dissolved during the heating.

(5) Evaporating. The Petri dish with saturated solution was weighed quickly and then put into a drying oven for about 24 h at 333.15 K to evaporate all the solvents.

(6) Weighing. The Petri dish with the residual solid after evaporating was taken out from the drying oven and then weighed after cooling to the room temperature. The weighing process was ended until there was no obvious weight loss for the Petri dish with the residual solid.

The above experimental processes were carried out continuously for the temperatures from 283.15 to 323.15 K with an interval of 10 K. The detailed information of the apparatus used in this work was tabulated in Table S1, and the flow-diagram for the process of solubility determination was shown in Figure S1. In addition, each experimental point was repeated at least three times to acquire the final solubility value. The relative standard uncertainties of solubility ($u_r(x_1)$) were evaluated by dividing the orders of magnitude into five cases, i.e., 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}. After analyzing, it was found that 0.15 is suitable for assessing the overall uncertainty for solubility determined by the static gravimetric method in this work when $x_1 \geq 1.000 \times 10^{-4}$, while for the case of $x_1 < 1.000 \times 10^{-4}$, 0.95 is appropriate for evaluating the relative uncertainty.

2. Representative XRPD Samples

To optimize the preparation process and minimize the number of samples for testing, XRPD samples were taken at representative temperature to characterize the polymorphic transformation of a solute throughout the solubility determination. In general, the state of suspension or the solubility curve would change when the crystal form of a solute is varied with temperatures.[1] So, if there is no change observed during the temperature rising process, the representative XRPD sample of each experimental system could be prepared at the final temperature ($T = 323.15$ K) of the continuously operated static gravimetric method described above for convenience.

3. Preparation Process of XRPD Samples

The detailed procedures for preparing the XRPD samples of a solute are as follows:

(1) At the end of the continuous solubility determination process, the residue suspended solution was stirred for extra 2 h at the final temperature $T = 323.15$ K.
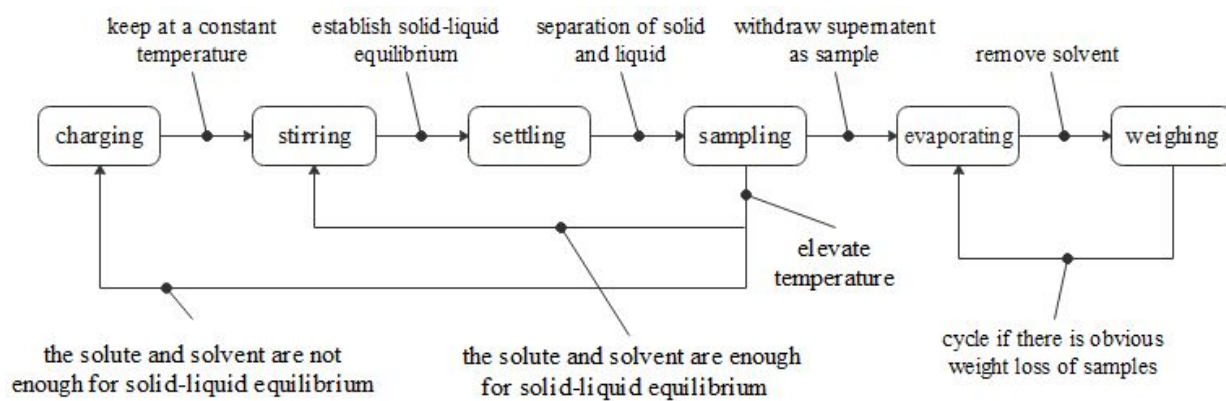
(2) The above suspension was filtered by using a Buchner funnel at negative pressure to

remove most of the solvent.

(3) The filter cake was dried in a drying oven at 333.15 K for about 72 h to evaporate the residual solvents. The obtained solids were tested by the XRPD device.

Table S1. Detailed Information for the Apparatus Used in the Solubility Measurement

apparatus name	model	manufacturer	accuracy
thermostatic water bath	DC-0506	Jiangsu Tenlin Instrument Co., Ltd.	± 0.01 K
analytical balance	SI-224	Sartorius Scientific Instruments (Beijing) Co., Ltd.	± 0.0001 g
aneroid barometer	DYM3	Shanghai Yipin Instruments & Meters Co., Ltd.	± 0.1 kPa

Figure S1. Flow-diagram of the solubility determination process.

References

(1)   Blanco, L. H.; Sanabria, N. R.; Dávila, M. T. Solubility of 1,3,5,7-Tetra Azatricyclo[3.3.1.13,7]Decane (HMT) in Water from 275.15K to 313.15K. *Thermochim. Acta* **2006**, *450*, 73–75.