Supporting Information

Solubility Behavior and Synergistic Solvation Effects of *N*-Benzylglycine in Nine Neat and One Binary Solvent Systems 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*-benzylglycine in eleven pure solvents and one binary mixed solvent. The detailed processes of the experiments are listed as follows:

(1) An analytical balance was used to weigh the mass of solute and solvents and the weighed solute and solvents were added into the jacketed crystallizer kept at a constant temperature which was monitored by a mercury thermometer and controlled by using a thermostatic water bath;

(2) The mixed solution was continuously stirred by a magnetic stirrer for about 2 h (according to our exploration, 2 h is sufficient to establish the dissolution equilibrium for *N*-benzylglycine);

(3) The whole solution system was settled for about 30 minutes at a constant temperature to ensure that there were no obvious fine particles in the supernatant;

(4) About 3 - 15 ml (the amount could be adjusted in this range according to the solubility magnitudes) supernatant was withdrawn and transferred into a Petri dish by utilizing a syringe with an organic membrane filter;

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

(6) 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 information of the apparatus used in this work was tabulated in Table S1 in detail. In addition, each experimental point was repeated at least three times to obtain 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^{-6}, 10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}. After analyzing, it was found that 0.15 can be used to assess the overall uncertainty for solubility determined by the static gravimetric method in our 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 proper for evaluating the uncertainty.

2. Representative PXRD Samples

To optimize the preparation process and minimize the number of samples for testing, representative PXRD samples were taken from different experimental systems and temperatures to characterize the polymorphic transformation of a solute throughout the

solubility determination. Two basic rules for selecting representative PXRD samples are as follows:

(1) Selection of representative solvent composition for preparing samples.

For binary solvent system, the representative PXRD sample was prepared at positive solvent composition x_2 = 0.500. If the crystal form of a solute was the same in the two pure solvents of the binary system, sampling at x_2 = 0.500 was enough for the verification purpose as there was no polymorphic transformation reported by the literatures or found by our works in this case. If the crystal forms were different in the two pure solvents, a "critical point"[1,2] for polymorphic transformation should exist at a certain solvent composition. Thus, the PXRD test of sample at x_2 = 0.500 could help searching the "critical point" in this case without testing all the solvent compositions.

(2) Selection of representative temperatures for preparing samples.

In general, the state of suspension or the solubility curve would change when the crystal form of a solute is varied with temperatures.[3] So, if there is no change observed during the temperature rising process, the representative PXRD 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 PXRD Samples

The detailed procedures for preparing the PXRD 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 PXRD device.

Table S1. Meanings and Units of the Symbols in Formulas

symbol	meaning	unit
m_1	the mass of solute	g
m_2	the mass of positive solvent	g
m_3	the mass of anti-solvent	g
M_1	the molar mass of solute	g/mol
M_2	the molar mass of positive solvent	g/mol
M_3	the molar mass of anti-solvent	g/mol
x_1^{cal}	the calculated mole fraction solubility	mol/mol
x_1^{exp}	the experimental mole fraction solubility	mol/mol
n	the number of data points	none
T	the absolute temperature	K
A_0	the model parameter[a]	none
B_0	the model parameter[a]	none
C_0	the model parameter[a]	none
x_1	the mole fraction solubility	mol/mol
x_2	the mole fraction of positive solvent in the binary solvent	mol/mol
x_3	the mole fraction of anti-solvent in the binary solvent	mol/mol
N	the number of "curve fit" parameters ($N = 2$)[b]	none
A_1	the model parameter[b]	none
B_1	the model parameter[b]	none
C_1	the model parameter[b]	none
A_2	the model parameter[b]	none
B_2	the model parameter[b]	none
C_2	the model parameter[b]	none
J_i	the model parameter[b]	none
α	the hydrogen bond donation ability of solvent[c]	none
β	the hydrogen bond acceptance ability of solvent[c]	none
π^*	the dipolarity–polarizability parameter[c]	none
δ_H	the Hildebrand solubility parameter[c]	$(J/cm^3)^{1/2}$
C_0	the model coefficient[c]	none
C_1	the model coefficient[c]	none
C_2	the model coefficient[c]	none
C_3	the model coefficient[c]	none
C_4	the model coefficient[c]	none
V_S	the molar volume of solute[c]	cm^3/mol
ρ	the density of solute	g/cm^3
R^2	the correlation coefficient[c]	none

F	the F-statistic[c]	none

[a]Modified Apelblat model; [b]Apelblat-Jouyban-Acree model; [c]The KAT-LSER model.

Table S2. Solvent Property Parameters of Eleven Neat Solvents

solvent	π^*[a]	$\sum\alpha$[b]	$\sum\beta$[c]	cohesive energy density[d]
		polar protic solvents		
water	1.09	1.17	0.47	2095.93
methanol	0.60	0.43	0.47	808.26
ethanol	0.54	0.37	0.48	618.87
n-propyl alcohol	0.52	0.37	0.48	520.37
isopropyl alcohol	0.48	0.33	0.56	489.11
n-butyl alcohol	0.47	0.37	0.48	446.01
		polar aprotic solvents		
acetone	0.71	0.04	0.49	362.07
acetonitrile	0.75	0.07	0.32	522.95
ethyl acetate	0.55	0.00	0.45	300.64
DCM	0.82	0.10	0.05	400.22
1,4-dioxane	0.51	0.00	0.64	372.17

[a]Dipolarity/polarizability of the solvent. [b]Summation of the hydrogen bond donor propensities of the solvent. [c]Summation of the hydrogen bond acceptor propensities of the solvent. [d]Cohesive energy density in the unit of $J \cdot mol^{-1}$, taken from ref 4–6.

Table S3. 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

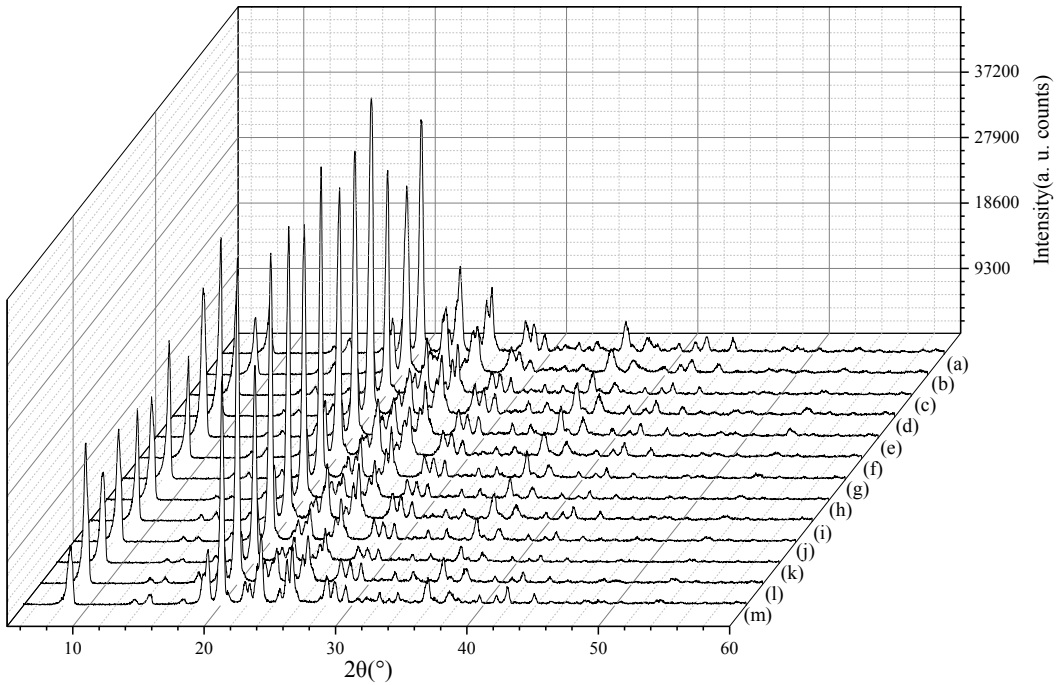

Figure S1. Powder X-ray diffraction patterns of *N*-benzylglycine in equilibration with different solvent systems: (a) raw material; (b) water; (c) methanol; (d) ethanol; (e) *n*-propyl alcohol; (f) isopropyl alcohol; (g) *n*-butyl alcohol; (h) acetone; (i) acetonitrile; (j) ethyl acetate; (k) DCM; (l) 1,4-dioxane; (m) water + ethanol (x_2 = 0.500)

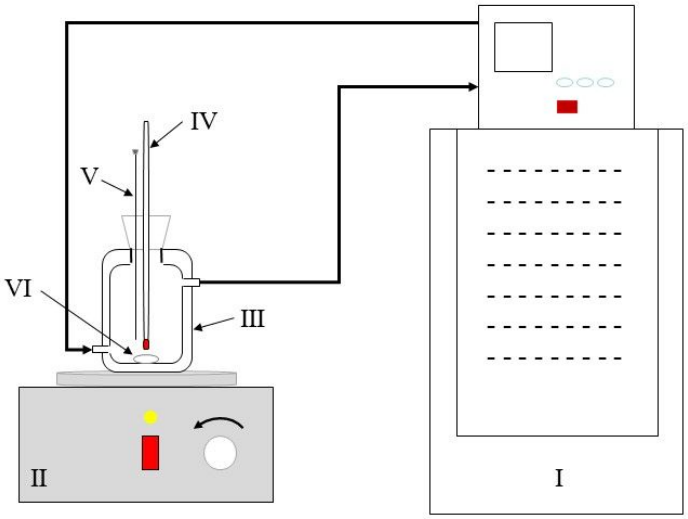

Figure S2. Schematic diagram of experimental apparatus: I, thermostatic water bath; II, magnetic stirrer; III, jacketed crystallizer; IV, mercury thermometer; V, sampling needle; VI, rotor of magnetic stirrer.

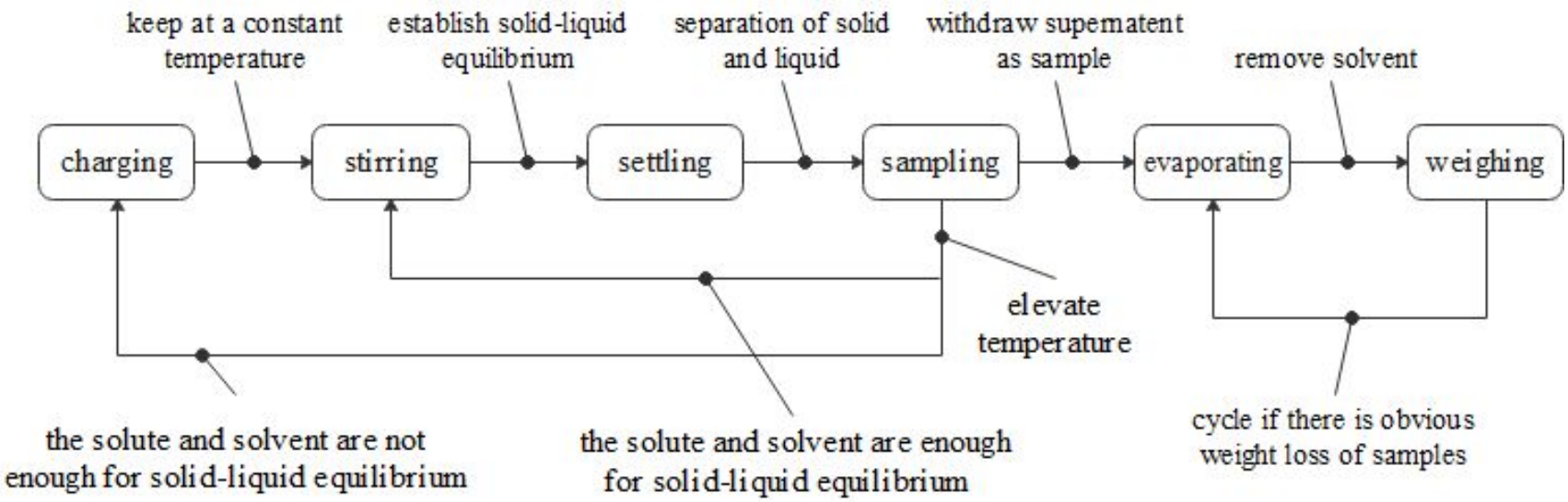

Figure S3. Flow-diagram of the solubility determination process.

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