

# **Insight into Solvent-Dependent Conformational Polymorph Selectivity: The Case of Undecanedioic Acid**

*PengShi<sup>1,2</sup>; Shijie Xu<sup>1,2</sup>; Shichao Du<sup>1,2</sup>; Sohrab Rohani<sup>3</sup>; Shiyuan Liu<sup>1,2</sup>; Weiwei Tang<sup>1,2</sup>; Lina Jia<sup>1,2</sup>; Jingkang Wang<sup>1,2</sup>; JunboGong<sup>1,2\*</sup>*

<sup>1</sup>School of Chemical Engineering and Technology, State Key Laboratory of Chemical Engineering, Tianjin University, Tianjin300072, China;

<sup>2</sup>The Co-Innovation Center of Chemistry and Chemical Engineering of Tianjin, Tianjin300072, China

<sup>3</sup>Department of Chemical and Biochemical Engineering, the University of Western Ontario, London, Ontario N6A 5B9, Canada

Supporting information:

## **Solubility Measurements**

A gravimetric method was employed to determine the solubility of the stable form I of UDA in 16 mono-solvents (ethanol, n-propanol, n-butanol, isobutanol, acetone, butanone, methyl isobutyl ketone, cyclohexanone, ethyl acetate, isopropyl acetate, ethyl propionate, acetic acid, propionic acid, isobutyl ether, n-butyl ether, 1,4-dioxane) at 318.15 K and in ethanol+1, 4-dioxane binary mixtures at 303.15 K. In this process, excess solid UDA and corresponding single or binary solvents (with deterministic mole fraction of solvents), were added to 50 mL flasks so that to obtain the suspensions. Then the suspensions were shaken by a thermostatic bath shaker (CHY1015, Shanghai Sunny Hengping Scientific Instrument Co. Ltd., China) at a

certain temperature under uncertainty of 0.1 K. And this process would last for 12 h which had been proved to be long enough to achieve solid-liquid equilibrium in preliminary experiment. After turning off the bath shaker, 5 mL of the supernatant liquor was filtered by the pre-cooled/heated syringes filters (0.22  $\mu\text{m}$ ) and moved into pre-weighted glass dishes as quickly as possible. Immediately, the total weight was determined. After that, the dishes were dried in a vacuum oven (DZ-2BC, Tianjin Taisite Instrument Co. Ltd., China) at  $T=343.15$  K and their mass was periodically measured until the data remained constant, which meant that the solvent had been completely evaporated. In all above experiments, the masses were determined by an electronic balance (AB204-N, Mettler-Toledo, Switzerland) with an accuracy of  $\pm 0.0001$  g. The experiment was repeated three times for error reduction, and the result was from the average value.

The mole fraction solubility of UDA( $x_1$ ) was calculated by using Eq. (S1), and the initial mole fraction of 1, 4-dioxane of the binary solvent mixtures ( $x_2$ ) is expressed by Eq. (S2):

$$x_1 = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2 + m_3/M_3} \quad (\text{S} \quad 1)$$

$$x_2 = \frac{m_2/M_2}{m_2/M_2 + m_3/M_3} \quad (\text{S} \quad 2)$$

In binary solvents where  $m_1$  represents the mass of solute UDA,  $m_2$  and  $m_3$  mean the masses of 1,4-dioxane and ethanol, respectively.  $M_1$ ,  $M_2$  and  $M_3$  are the corresponding molecule mass of them. In single solvents where  $m_3 = 0$ ,  $x_1$  and  $x_2$

represents the mole fraction of solute and solvent, respectively.

The solubility of UDA (form I) in 16 pure solvents and ethanol/1,4-dioxane mixture solvents was shown in **Table S1** and **Figure S1**, respectively.

### **Establishment of PXRD calibration curve of form I and form II of UDA for quantitative analysis**

The generation of authentic and validated calibration curve is the most critical factor in developing any assay for solid-state form<sup>1</sup>. The reference mixture samples were prepared by mixing the pure form I and II powders. Form I and II, obtained from the cooling crystallization experiments in 1, 4-dioxane and ethanol, respectively, were ground individually using an agate mortar and pestle for 1 min. There is no occurring of phase change. (In fact, we have proven that phase transformation of form II, as the metastable one in normal conditions, would not occur during mechanically ball milling at 30 Hz until ground after about 30 min). Before mixed, two pure forms have passed through 400 mesh sieve to reduce the effect of particle size on preferred orientation. Different ratios of form I and form II were weighed out to a total mass of 0.1 g. Six standard samples containing corresponding amounts of UDA form I and II powders were mixed as listed in **Table S2**. The mixed samples at the ratios were ground gently for 10 min using an agate mortar and pestle.

Two forms can be kept unchanged for a long time under normal storage conditions (e.g., 25 °C, 75% RH) and are chemically stable. Thus, both sieving and mixing of samples were performed under normal conditions.

Every studied sample was manually loaded in a glass holder (20 mm × 20 mm ×

0.2 mm) and pressed by a clean glass slide to ensure co-planarity of the powder surface with the surface of the holder. All the X-ray diffraction experiments were performed for three times, and the average values were used to construct the calibration curve.

Each test sample was ground for 30 s by using an agate mortar and pestle before PXRD measures. And each experiment was repeated three times for the accuracy and repeatability.

### **Computational methods**

The molecular conformation energy in each form was calculated by Accelrys Material Studio DMol<sup>3</sup> program. The geometry optimization of the single molecule, picked from two crystal structures, was performed at first. The proton balance equation (PBE) functional and the double numerical plus polarization (DNP) basic set were used for simulations. Integration accuracy was fine. Then molecular electronic energy was calculated using the PBE functional and the DNP basic set.

The calculations of the strength of the hydrogen bonds were also carried out in Accelrys Material Studio Dmol<sup>3</sup> programme at the DFT level. In form I, all the hydrogen bonds formed between UDA dimers are the same due to the molecular symmetry. However, the hydrogen bonds in alternating carboxyl dimers in form II show the different bond lengths and angles. So, the geometries of three types of dimers, listed in **Table S3**, were picked from two crystal structures and optimized by using the double numerical plus polarization (DNP) basic set and the PBE functional with the distances between two oxygen atoms fixed. The binding energy ( $\Delta E_{bind}$ ) was

quantified by

$$\Delta E_{bind} = E_{UDA-UDA} - 2E_{UDA} + BSSE \quad (S3)$$

where  $E_{dimer}$  is the energy of the solute dimer, and  $E_{UDA}$  is the energy of the isolated monomer UDA.  $BSSE$  is the basic set superposition error (BSSE) term and calculated for the correction of overestimation in binding energies due to the overlapping of basic functions<sup>2</sup>.

The calculations were carried out using the Accelrys Materials Studio package. The ab initio condensed-phase optimized molecular potentials for atomistic simulation studies (COMPASS) was chosen throughout the whole simulation. The COMPASS force field was proved to be suitable for study of condensed-phase materials with accurately structure and property predictions<sup>3, 4</sup>. Before calculation, geometry optimization was performed on UDA and solvent molecules. Then an amorphous cubic cell was constructed with 300 solvent molecules and two isolated UDA molecules or one UDA dimer which was built and optimized in advance. The eight atoms in a carboxyl acid  $R_2^2(8)$  dimer synthon were in constraint during the solvation energy calculations of the dimer, and other atoms were relaxed. A group based summation method was utilized to handle the dispersion and electrostatic interactions with a cutoff distance of 15.5 Å. Molecular dynamic calculation was performed by using the NVT ensemble method and NHL thermostat and the total simulation time is 500 ps at 298.15 K. On that basis, solvation free energies were calculated over three runs, that is, the sum of ideal contribution, van der Waals contribution and electrostatic contribution. All calculations were conducted for two

times to obtain the average value.

The conformations of UDA after MD simulations in solvents are shown in **Figure S4**. The messages and comparison about hydrogen bonds in two forms were listed in **Table S3**. Torsions of two conformers in form I and II were shown in **Table S4**. The connection modes of lateral molecules in two forms were shown in **Figure S3**. Lateral molecules are linked by carboxyl acid  $R_2^2(8)$  dimer synthons to generate infinite hydrogen-bonded chains in an end-to-end manner. The carboxyl dimers in both forms turn out of plane relative to the methylene chains.

PXRD patterns of samples collected after nucleation in cooling experiments in ethanol are shown in **Figure S2**. It suggests that polymorphism nucleation results are reliable. Meanwhile, form I is the stable form at normal temperature.

**Table S1.** Molar solubility of UDA (form I) in solvents.

Solvent	$x_1$ (form I at 318.15 K)
ethanol	0.0811
n-propanol	0.0823
n-butanol	0.0856
isobutanol	0.0795
acetic acid	0.0385
propionic acid	0.0519
acetone	0.0306
butanone	0.0244
methyl isobutyl ketone	0.0152
cyclohexanone	0.0516
ethyl acetate	0.0189
isopropyl acetate	0.0124
ethyl propionate	0.0148
isopropyl ether	0.0354
n-butyl ether	0.0024
1,4-dioxane	0.0770

**Table S2.** The standard mixture samples prepared by mixing the pure form I and II powders

Samples (%)	Composition
10.0	10.0wt.% form II + 90.0wt.% form I
20.0	20.0wt.% form II + 80.0wt.% form I
40.0	40.0wt.% form II + 60.0wt.% form I
50.0	50.0wt.% form II + 50.0wt.% form I
70.0	70.0wt.% form II + 30.0wt.% form I
80.0	80.0wt.% form II + 20.0wt.% form I



**Table S3.** The hydrogen bonds of two forms.

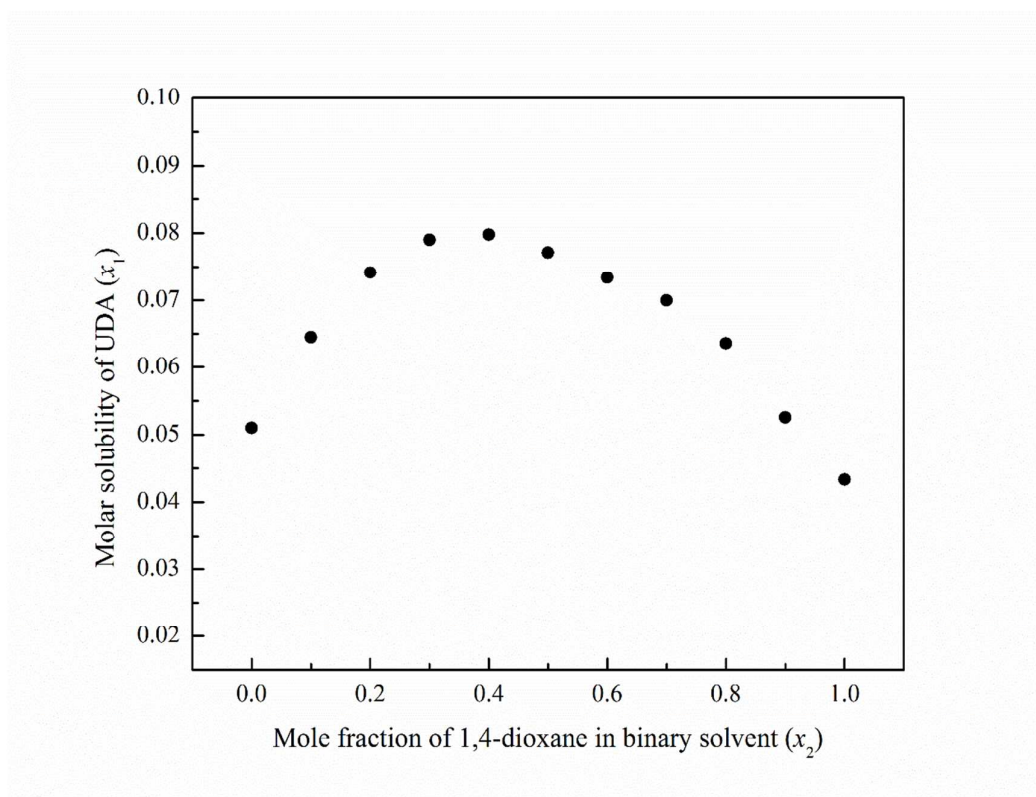
Form I	d (D–H) (Å)	d (H···A) (Å)	d (D···A) (Å)	$\theta(\text{DHA})$ (°)	$\Delta E_{\text{bind}}$ (kJ·mol <sup>-1</sup> )
O <sub>1</sub> –H···O <sub>2</sub>	0.84	1.820	2.657	174.32	-33.65
O <sub>3</sub> –H···O <sub>4</sub>	0.84	1.820	2.657	174.32	-33.65

Form II	d (D–H) (Å)	d (H···A) (Å)	d (D···A) (Å)	$\theta(\text{DHA})$ (°)	$\Delta E_{\text{bind}}$ (kJ·mol <sup>-1</sup> )
O <sub>1</sub> –H···O <sub>2</sub>	0.84	1.821	2.660	175.57	-33.08
O <sub>3</sub> –H···O <sub>4</sub>	0.84	1.836	2.670	171.96	-32.09

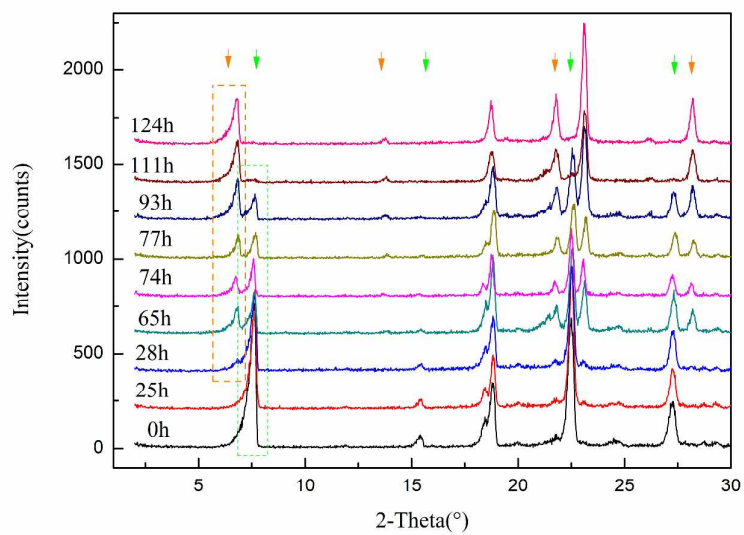
**Table S4.** Torsions of two conformations in form I and II.

Torsion (°)	O <sub>1</sub> -C <sub>1</sub> -C <sub>2</sub> -C <sub>3</sub>	C <sub>1</sub> -C <sub>2</sub> -C <sub>3</sub> -C <sub>4</sub>	C <sub>2</sub> -C <sub>3</sub> -C <sub>4</sub> -C <sub>5</sub>	C <sub>3</sub> -C <sub>4</sub> -C <sub>5</sub> -C <sub>6</sub>	C <sub>4</sub> -C <sub>5</sub> -C <sub>6</sub> -C <sub>7</sub>
I	163.14	170.76	175.69	177.73	178.60
II	178.94	174.39	179.78	176.78	179.79

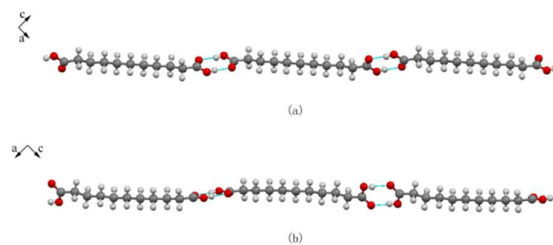
Torsion (°)	C <sub>5</sub> -C <sub>6</sub> -C <sub>7</sub> -C <sub>8</sub>	C <sub>6</sub> -C <sub>7</sub> -C <sub>8</sub> -C <sub>9</sub>	C <sub>7</sub> -C <sub>8</sub> -C <sub>9</sub> -C <sub>10</sub>	C <sub>8</sub> -C <sub>9</sub> -C <sub>10</sub> -C <sub>11</sub>	C <sub>9</sub> -C <sub>10</sub> -C <sub>11</sub> -O <sub>3</sub>
I	178.60	177.73	175.69	170.76	163.14
II	176.13	179.09	170.73	177.91	-36.71



**Figure S1.** Molar solubility of UDA (form I) in ethanol/1, 4-dioxane mixture solvents at 303.15K.



**Figure S2.** PXRD patterns of samples collected after nucleation in cooling experiment in ethanol. Pure form II was formed at first and form I appeared up to 28h. Then the whole polymorph transformation lasted about 96 hours. It suggests that polymorphism nucleation results are reliable. Meanwhile, form I is the stable form at normal temperature.



**Figure S3.** Lateral molecules are linked by carboxyl acid  $R_2^2(8)$  dimer synthons to generate infinite hydrogen-bonded chains in an end-to-end manner (a) in form I; (b) in form II. The carboxyl dimers in both forms turn out of plane relative to the methylene chains.

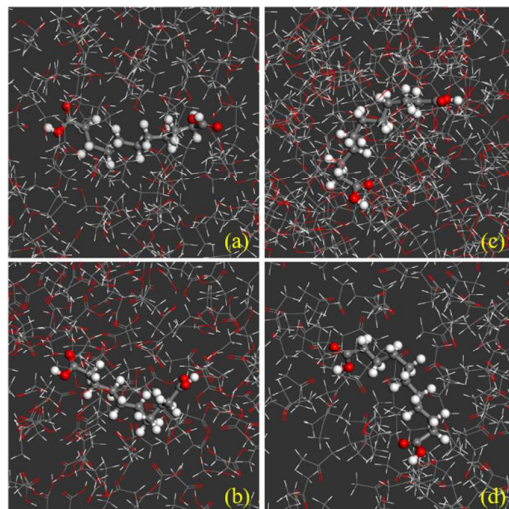


Figure S4. The conformations of UDA after MD simulations in solvents (a) ethanol; (b) acetic acid; (c) 1, 4-dioxane; (d) acetone.

#### REFERENCES

- (1) Qiu, J.; Li, G.; Sheng, Y.; Zhu, M., Quantification of febuxostat polymorphs using powder X-ray diffraction technique. *Journal of pharmaceutical and biomedical analysis* **2015**, 107, 298-303.
- (2) Boys, S. F.; Bernardi, F., The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors. *Molecular Physics* **2006**, 19, (4), 553-566.
- (3) Sun, H., COMPASS: An ab Initio Force-Field Optimized for Condensed-Phase Applications-Overview with Details on Alkane and Benzene Compounds. *The Journal of Physical Chemistry B* **1998**, 102, 7338-7364.
- (4) Tang, W.; Dai, H.; Feng, Y.; Wu, S.; Bao, Y.; Wang, J.; Gong, J., Solubility of tridecanedioic acid in pure solvent systems: An experimental and computational study. *The Journal of Chemical Thermodynamics* **2015**, 90, 28-38.