Electronic Supplementary Information

pH-switchable vitamin B_9 gels for stoichiometry-controlled spherical co-crystallization

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EXPERIMENTAL SECTION

Materials. Isonicotinamide, nicotinamide, vitamins C, and B_9 were obtained from J&K Chemical Ltd, with greater than 99% purity. All analytical grade solvents were purchased from Sinopharm Chemical Reagent Co., Ltd and used without further purification.

Gel formation (Vial inversion test). Method A: 4 mg of vitamin B_9 was dissolved in 1 mL methanol and heated up until it resulted in a clear solution. After cooling down to room temperature the gel was formed within minutes. Method B: 6 mg of vitamin B_9 was dissolved in 1 mL dimethyl sulfoxide / nitromethane (2:8) and heated up until it resulted in a clear solution. After cooling down to room temperature the gel was formed within minutes.

Preparation of (VC)·(INA). 176 mg (1 mmol) VC and 122 mg (1 mmol) INA were dissolved in 1 mL methanol by heating, respectively. The addition of 4 mg of VB_9 and cooling down to room temperature resulted in the immediate formation of gels, and then kept in 4 °C. Crystals grew within a few days. The gels are then dissolved by addition of 10 uL Et_3N. The orange needle-like crystals recovered by filtration. Yield: 95 mg, 32%. Anal. (%) Calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 4.73; N, 9.39. Found: C, 48.36; H, 4.71; N, 9.37.

Preparation of (VC)·(INA)$_2$. 176 mg (1 mmol) VC and 244 mg (2 mmol) INA were dissolved in 1 mL methanol by heating, respectively. The addition of 4 mg of VB_9 and cooling down to room temperature resulted in the immediate formation of gels, and then kept in 4 °C. Crystals grew within a few days. The gels are then dissolved by addition of 10 uL Et_3N. The pale blue plate-like crystals recovered by filtration. Yield: 193 mg, 46%. Anal. Anal. (%) Calcd for $C_{18}H_{20}N_4O_8$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.41; H, 4.78; N, 13.35.

Preparation of (VC)·(NA). 176 mg (1 mmol) VC and 122 mg (1 mmol) NA were dissolved in 1 mL methanol by heating, respectively. The addition of 4 mg of VB_9 and cooling down to room temperature resulted in the immediate formation of gels,

and then kept in 4 °C. Crystals grew within a few days. The gels are then dissolved by addition of 10 uL Et_3N. The colorless column-like crystals recovered by filtration. Yield: 98 mg, 33%. Anal. (%) Calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 4.73; N, 9.39. Found: C, 48.30; H, 4.73; N, 9.35.

Preparation of (VC)·(NA)$_3$. 141 mg (0.8 mmol) VC and 293 mg (2.4 mmol) NA were dissolved in 1 mL methanol by heating, respectively. The addition of 4 mg of VB_9 and cooling down to room temperature resulted in the immediate formation of gels, and then kept in 4 °C. Crystals grew within a few days. The gels are then dissolved by addition of 10 uL Et_3N. The orange needle-like crystals recovered by filtration. Yield: 226 mg, 52%. Anal. Anal. (%) Calcd for $C_{24}H_{26}N_6O_9$: C, 53.14; H, 4.83; N, 15.49. Found: C, 53.13; H, 4.80; N, 15.50.

Synthesis of VB_9 diester derivatives. To a solution of 805 mg (8.38 mmol) methanesulfonic acid in 50 mL methanol (ethanol, propanol, or butanol) 400 mg (0.838 mmol) folic acid dihydrate were added. The mixture was stirred at room temperature overnight, the precipitate was sucked off, added Et_3N (1.16 mL, 846 mg, 8.38 mmol) to neutralize methanesulfonic acid, washed with methanol and dried at 40 ^oC and 20 mbar vacuum to give diester as a bright yellow powder; yield: 343 mg (0.732 mmol, 87%) for dimethyl ester, 394 mg (0.792 mmol, 95%) for diethyl ester, 392 mg (0.747 mmol, 89%) for dipropyl ester, and 429 mg (0.775 mmol, 92%) for dibutyl ester. ^1H NMR (DMSO-d_6, 400 MHz) spectra see Fig. S2.

Thermogravimetric analysis (TGA). Thermogravimetric analysis was carried out in Netzsch TG 209 F3 equipment, using dry air with a nitrogen gas flow of 20 mL/min and a scan rate of 10 °C/min.

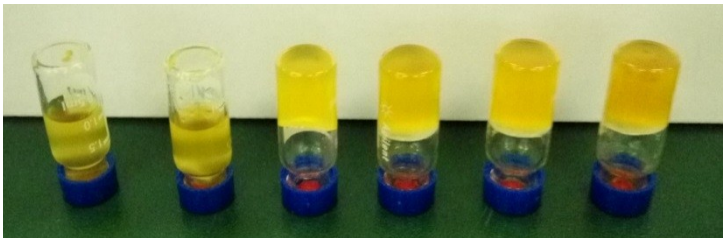
Differential scanning calorimetry (DSC). Differential scanning calorimetry (DSC) was performed with a PerkinElmer DSC 8500 instrument under nitrogen gas flow of 20 mL/min purge. Samples weighting 3−5 mg were heated in standard aluminium pans at scan rates from 5 to 10 °C/min. Two-point calibration using indium and tin was carried out to check the temperature axis and heat flow of the equipment.

Powder X-ray diffraction (PXRD). PXRD patterns were obtained using a Bruker D8 Advance X-ray diffractometer (Cu Kα radiation). The voltage and current applied were 40 kV and 40 mA respectively. Samples were measured in reflection mode in the 2θ range 3–40° with a scan speed of 1.2 °/min (step size 0.025°, step time 1.0 s) using a LynxEye detector. Data were imaged and integrated with RINT Rapid, and the peaks are analysed with Jade 6.0 software from Rigaku. Calibration of the instrument was performed using Corindon (Bruker AXS Korundprobe) standard.

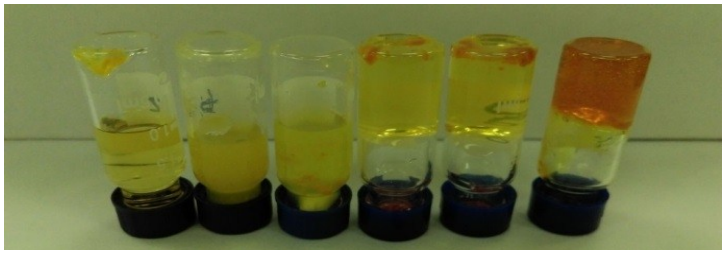
Single crystal X-ray diffraction. Single crystals were performed on a Bruker Apex II CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å) at 100(2) K. The structures were solved by direct methods and refined with full-matrix least-squares difference Fourier analysis using SHELX-97 software. All non-hydrogen atoms were refined with anisotropic displacement parameters, and all hydrogen atoms were placed in calculated positions and refined with a riding model. Data were corrected for the effects of absorption using SADABS.

Fourier-transform Infrared (FTIR). Fourier-transform Infrared (FTIR) spectra were collected by a Nicolet-Magna FT-IR 750 spectrometer in the range of 4000 to 350 cm^{-1} with a resolution of 4 cm^{-1} at ambient conditions.

Scanning Electron Microscopy (SEM). The surface morphology of all of the samples was viewed using scanning electron microscopy (Agilent 8500) operated at a beam voltage of 1 kV. The samples were mounted onto a steel stage using double-sided adhesive tape before the analysis.

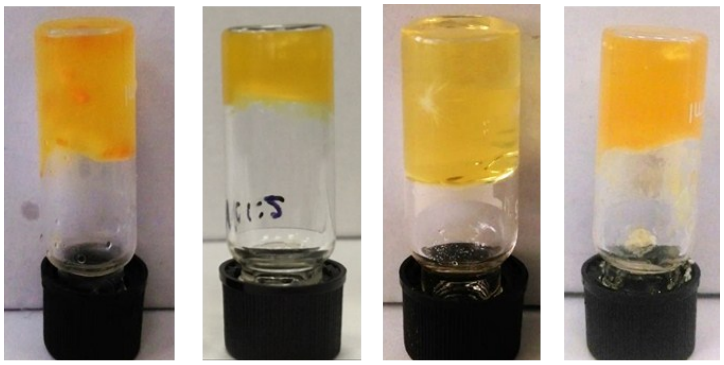


(a) 2, 3, **4**, 5, 6, and 7 mg/mL in methanol



(b) 2, 4, 5, **6**, 8, and 9 mg/mL in dimethyl sulfoxide / nitromethane (2:8)

Fig. S1 VB_9 organogels undergoing the inversion test.



(VC)·(INA) (VC)·$(INA)_2$ (VC)·(NA) (VC)·$(NA)_3$

Fig. S2 Single crystals from VB_9 gels.

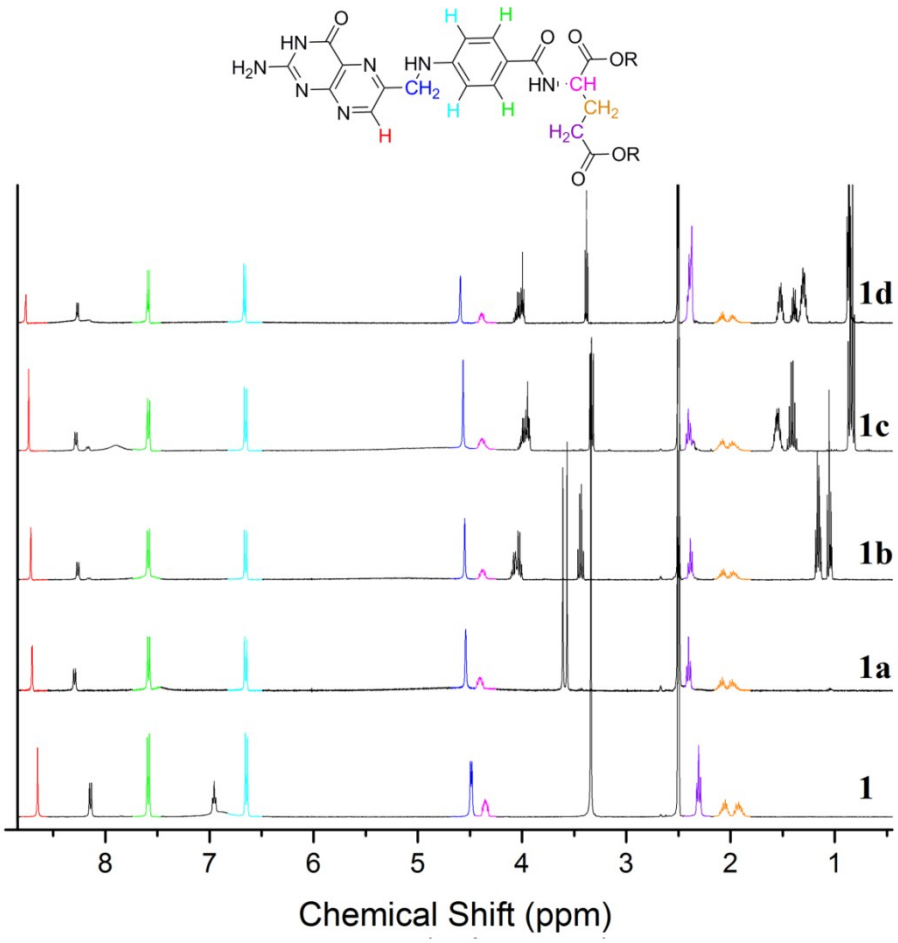


Fig. S3 Comparison of ^{1}H NMR spectra of VB_9 (**1**), dimethyl ester (**1a**), diethyl ester (**1b**), dipropyl ester (**1c**) and dibutyl ester (**1d**).

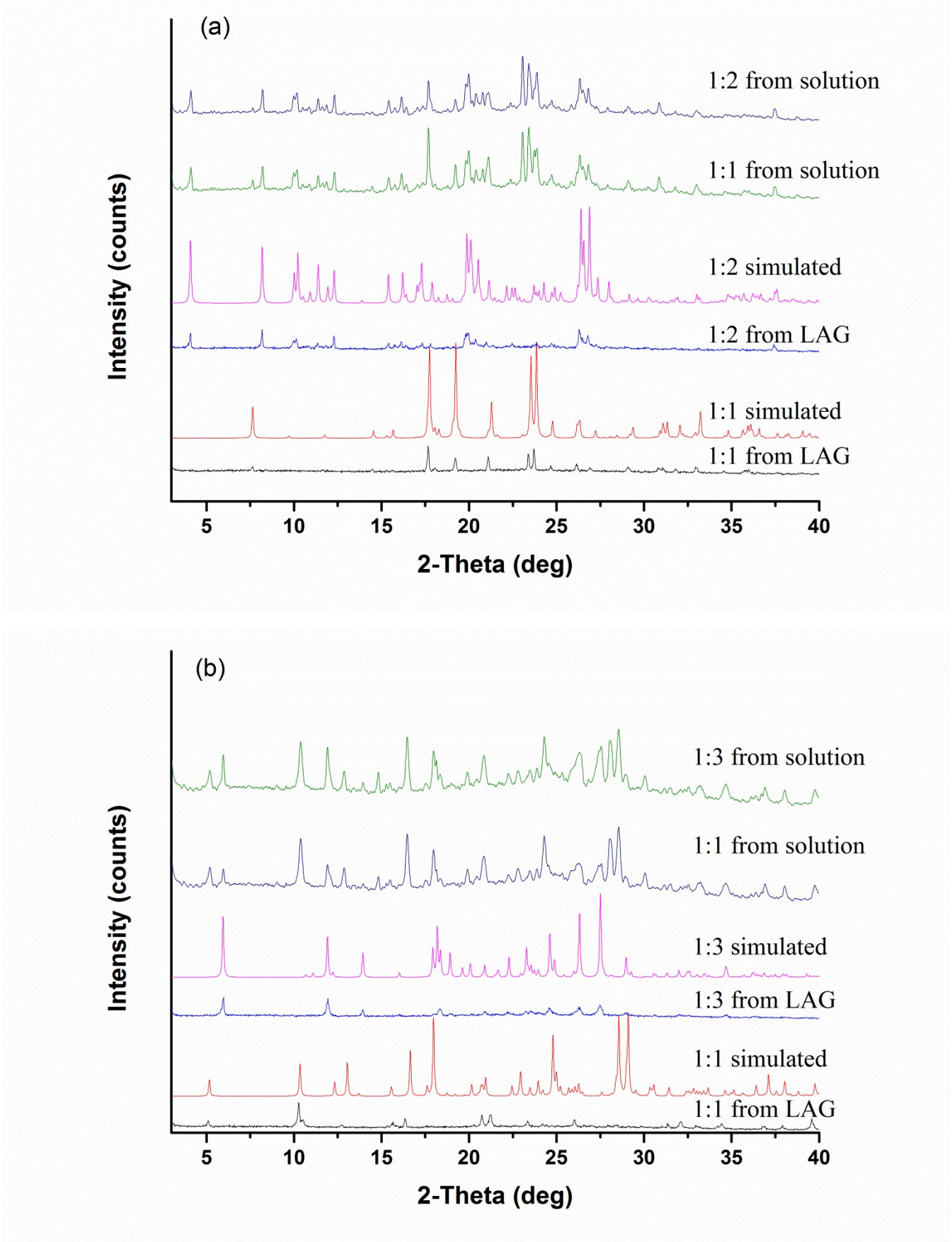


Fig. S4 PXRD patterns of co-crystals (a) VC / INA and (b) VC / NA from LAG.

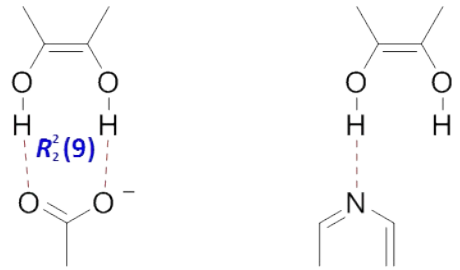


Fig. S5 Hydrogen-bonding interactions: **I** for reported co-crystals, **II** for co-crystals in this paper.

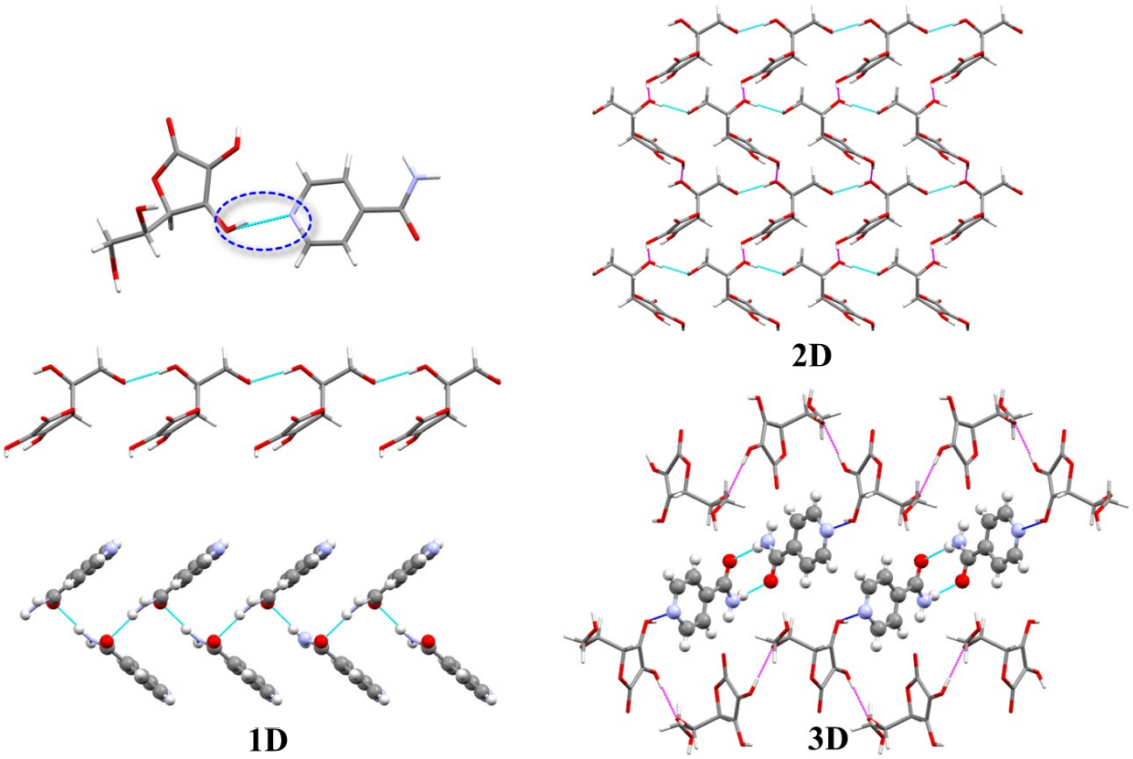


Fig. S6 Crystal structure of (VC)·(INA)

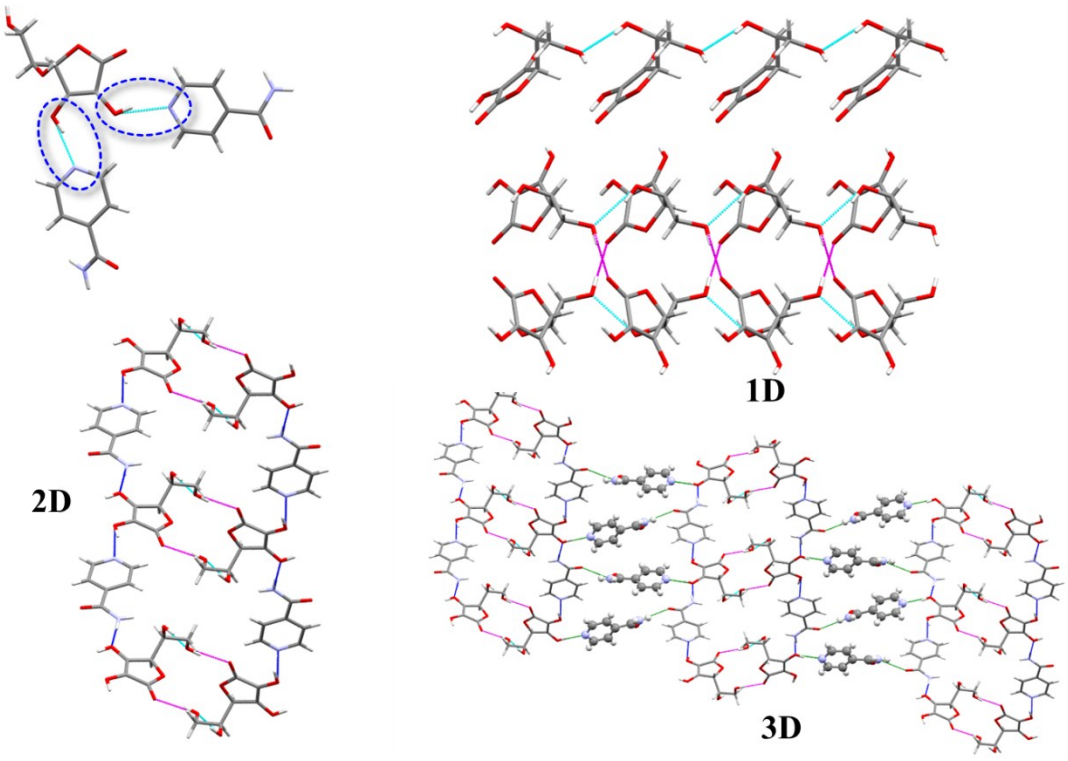


Fig. S7 Crystal structure of (VC)·$(INA)_2$.

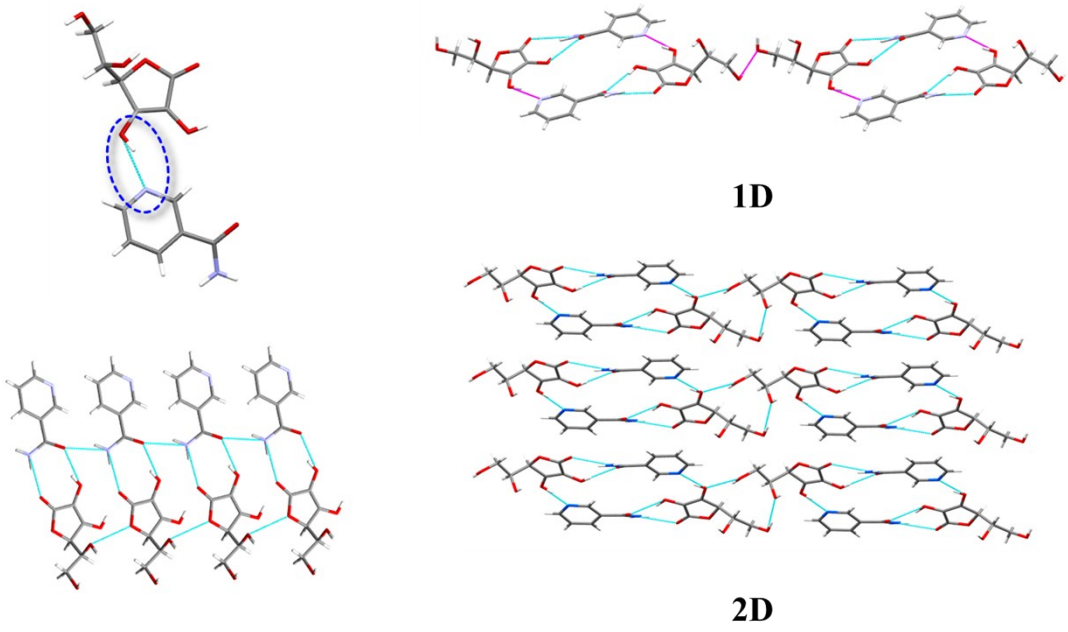


Fig. S8 Crystal structure of (VC)·(NA).

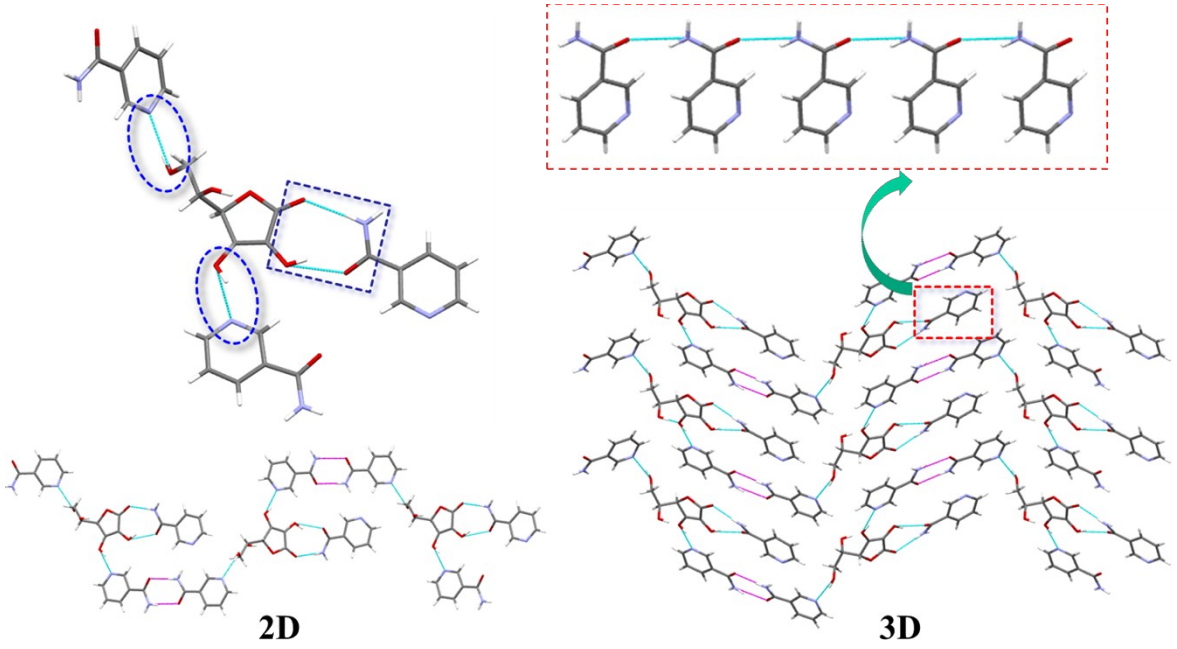


Fig. S9 Crystal structure of (VC)·$(NA)_3$.

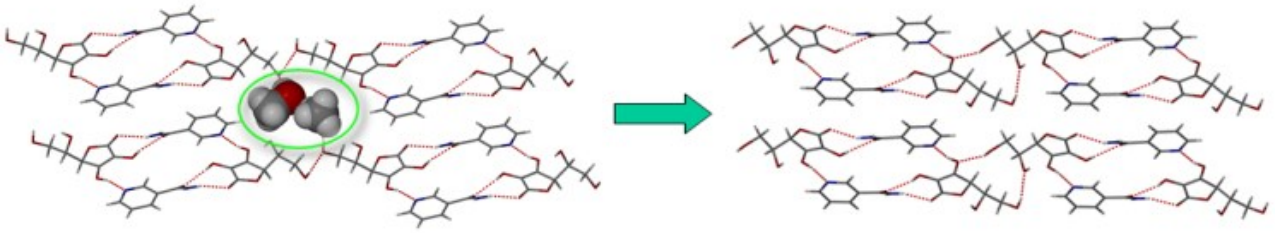


Fig. S10 Single-crystal to single-crystal transformation from solvate to (VC)·(NA).

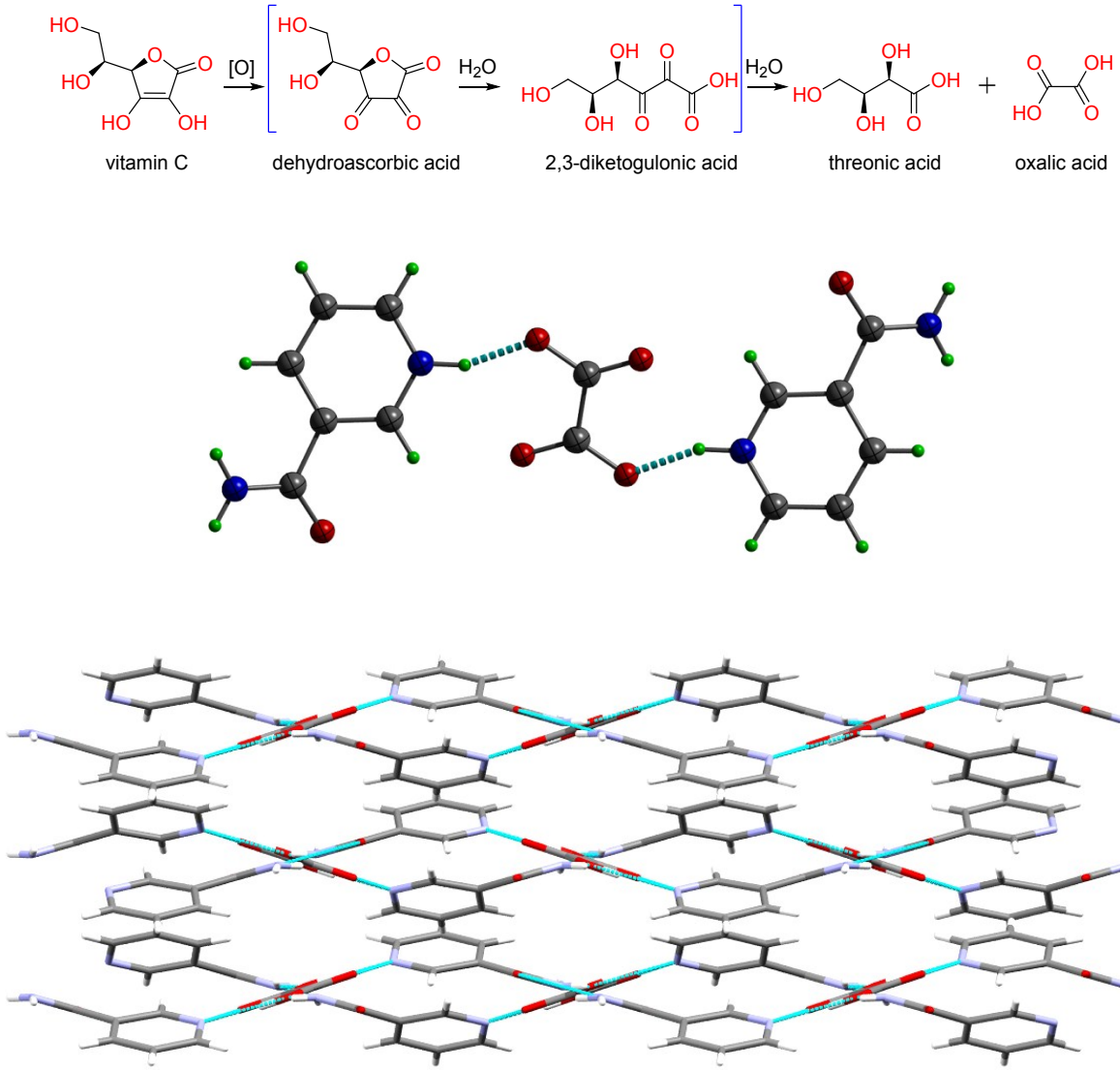
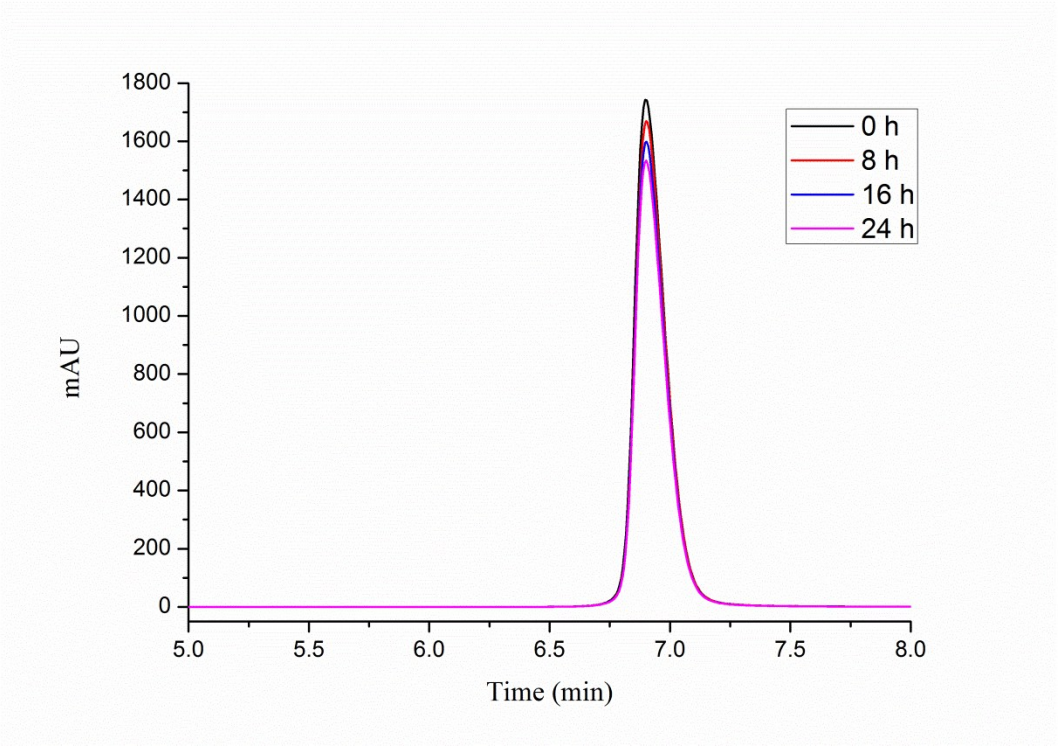
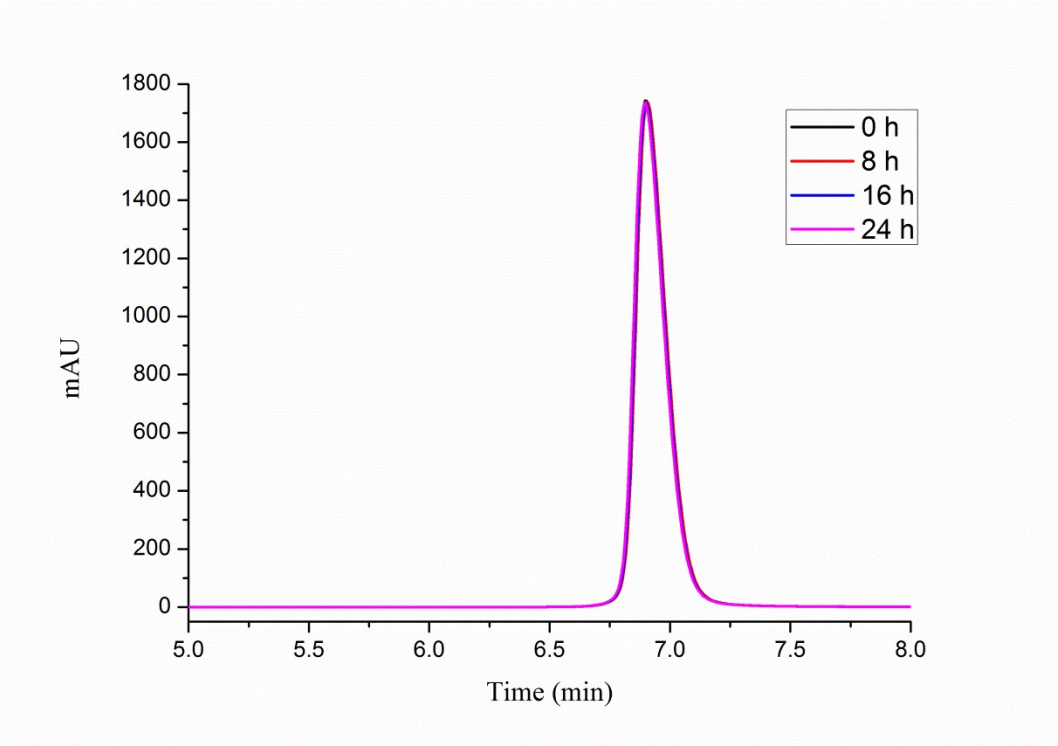


Fig. S11 Oxidative decomposition of VC and NA oxalate (2:1).



(a)



(b)

Fig. S12 HPLC chromatograms of VC 50 mg/mL in (a) MeOH solution and (b) VB_9 gels.

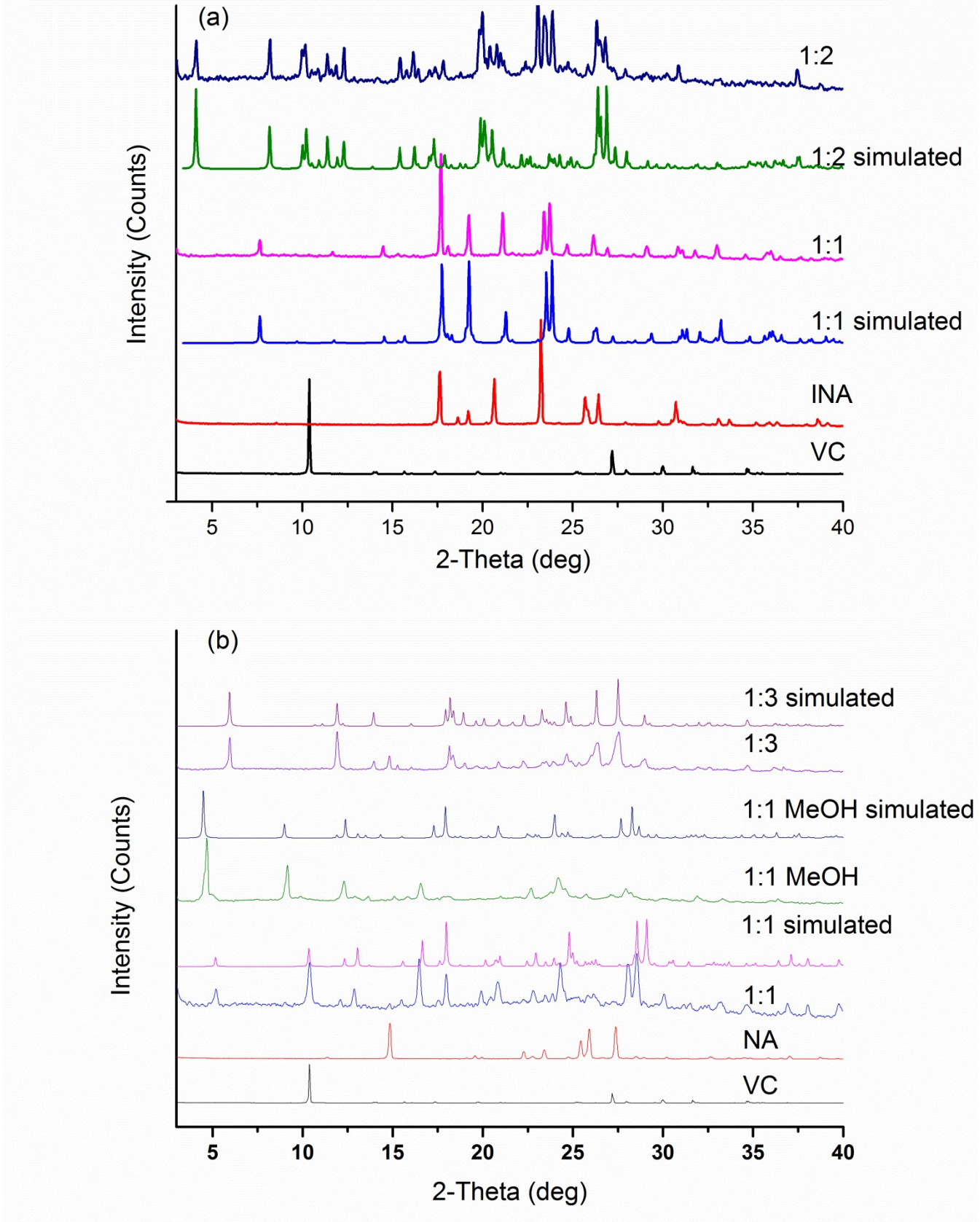


Fig. S13 PXRD patterns of co-crystals (a) VC / INA and (b) VC / NA from gels.

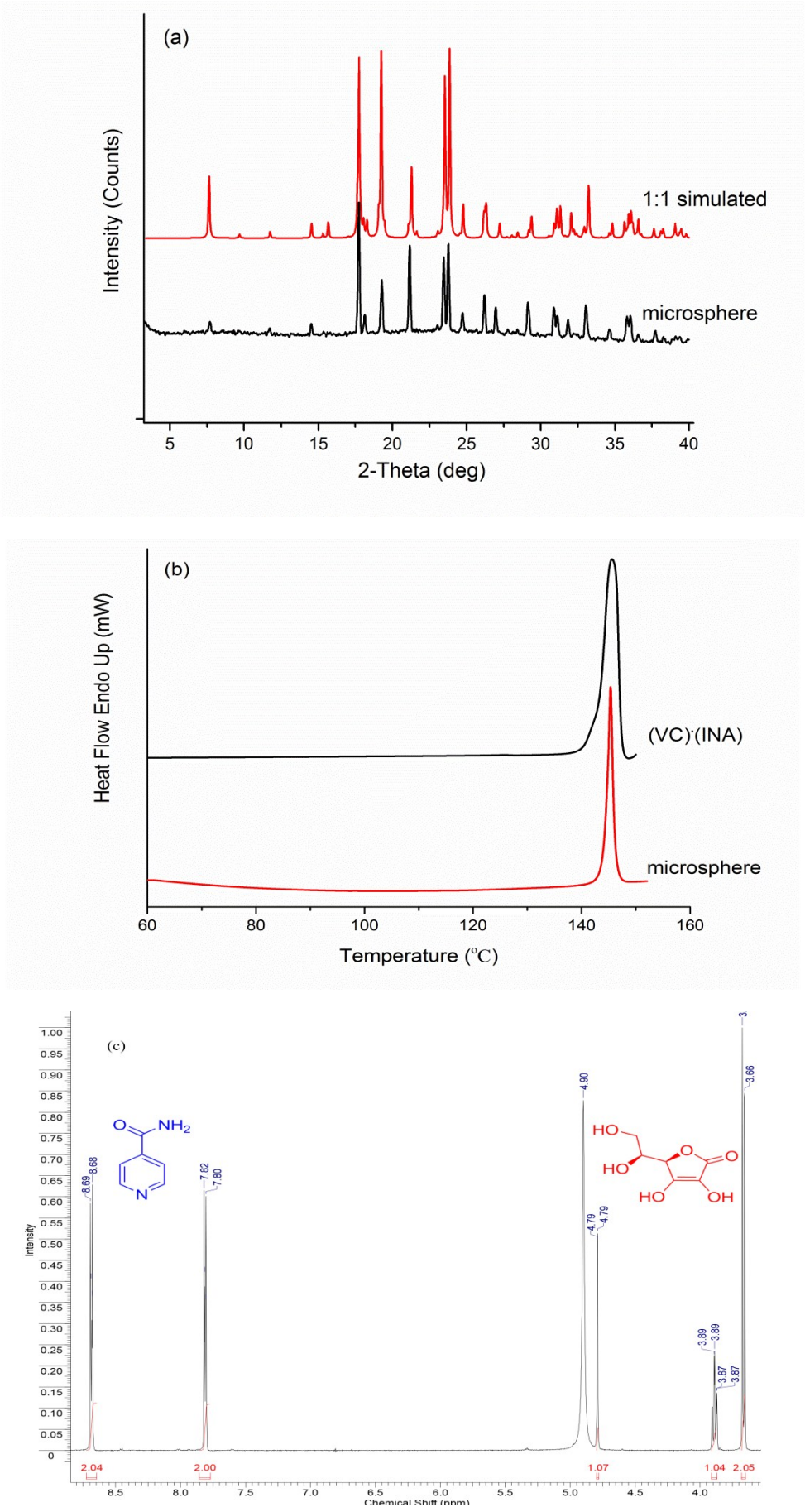
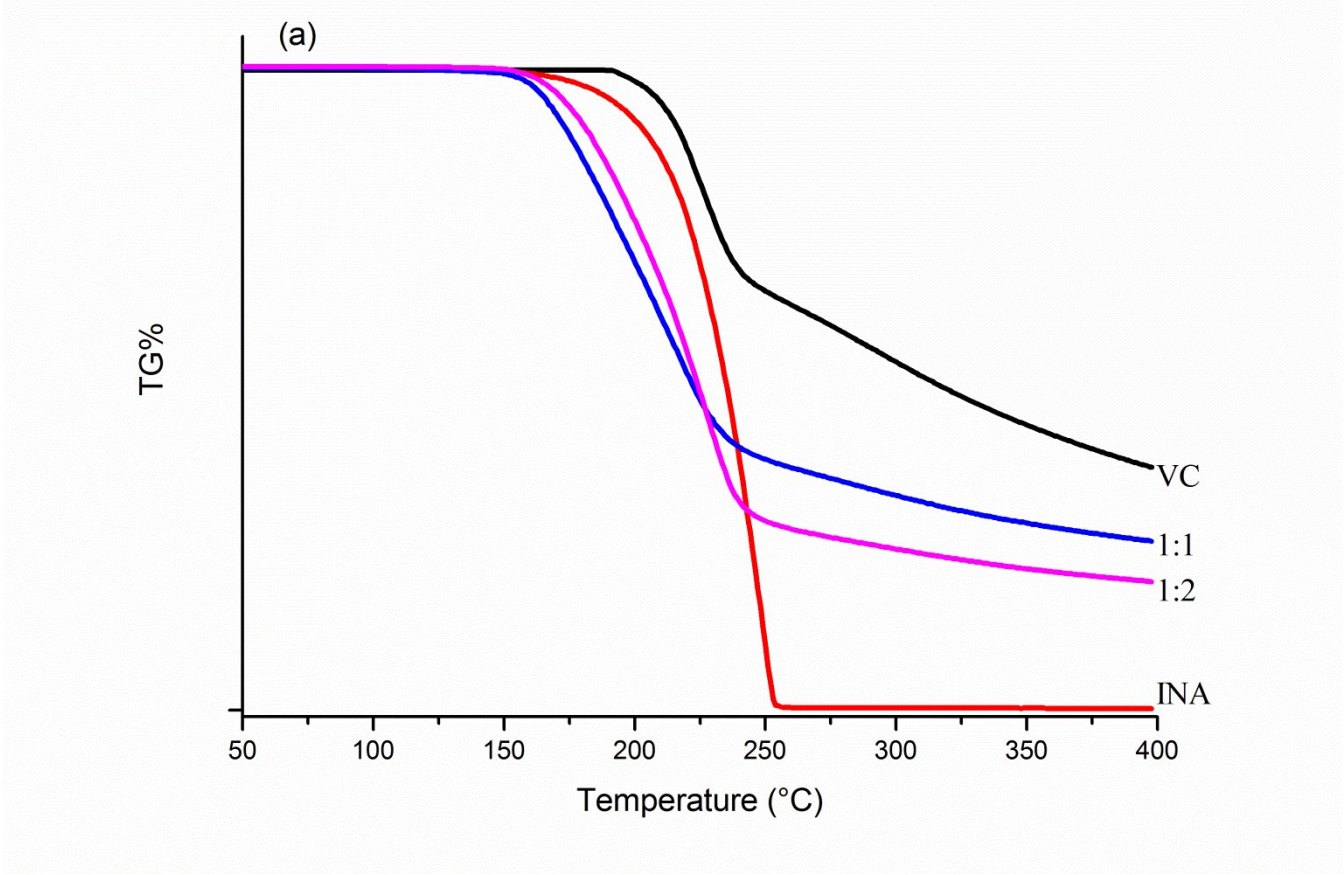


Fig. S14 PXRD patterns (a), DSC curves (b) and NMR spectrum (c) of (VC)·(INA) microsphere.


(a)
TG%
VC
1:1
1:2
INA
50
100
150
200
250
300
350
400
Temperature (°C)

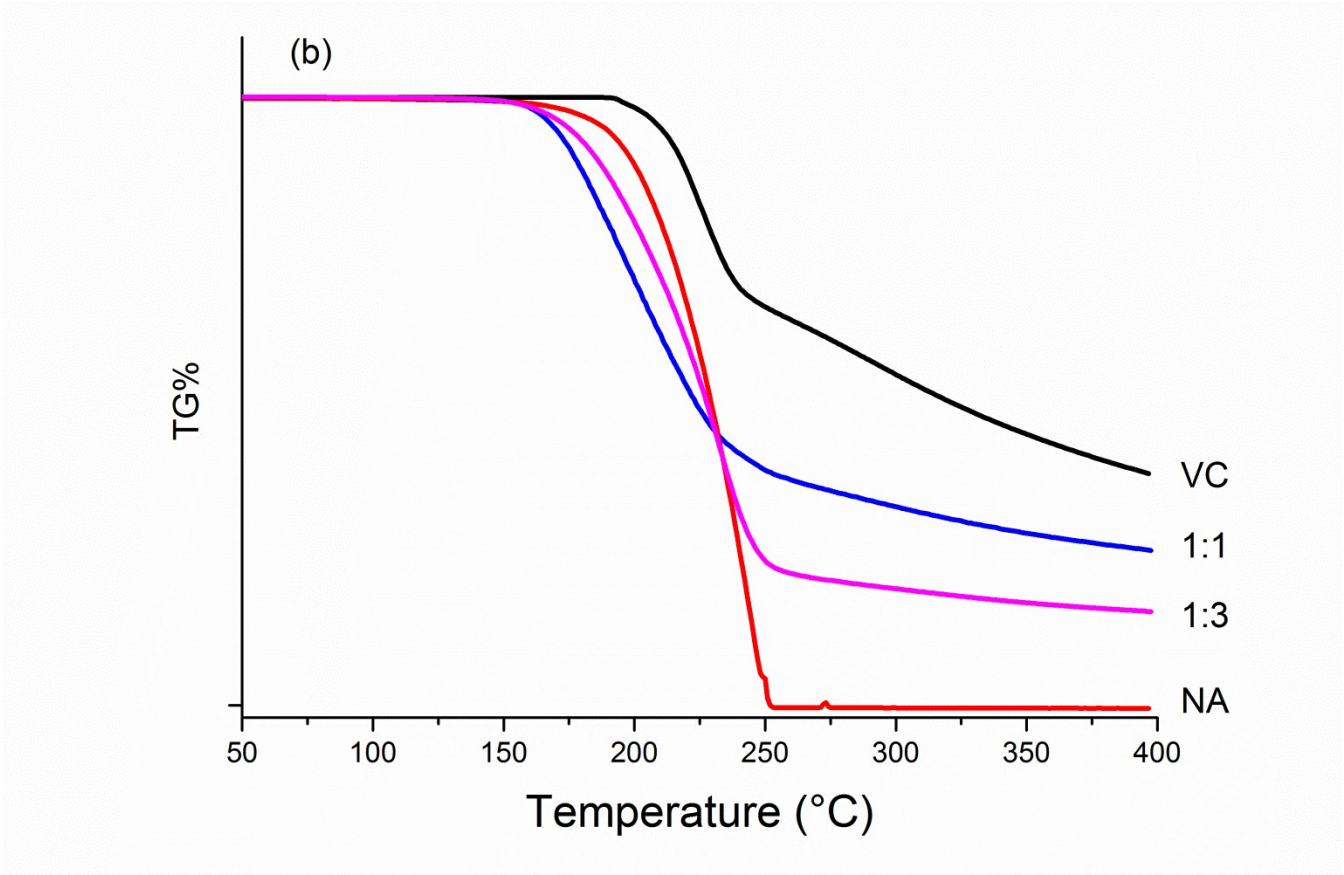
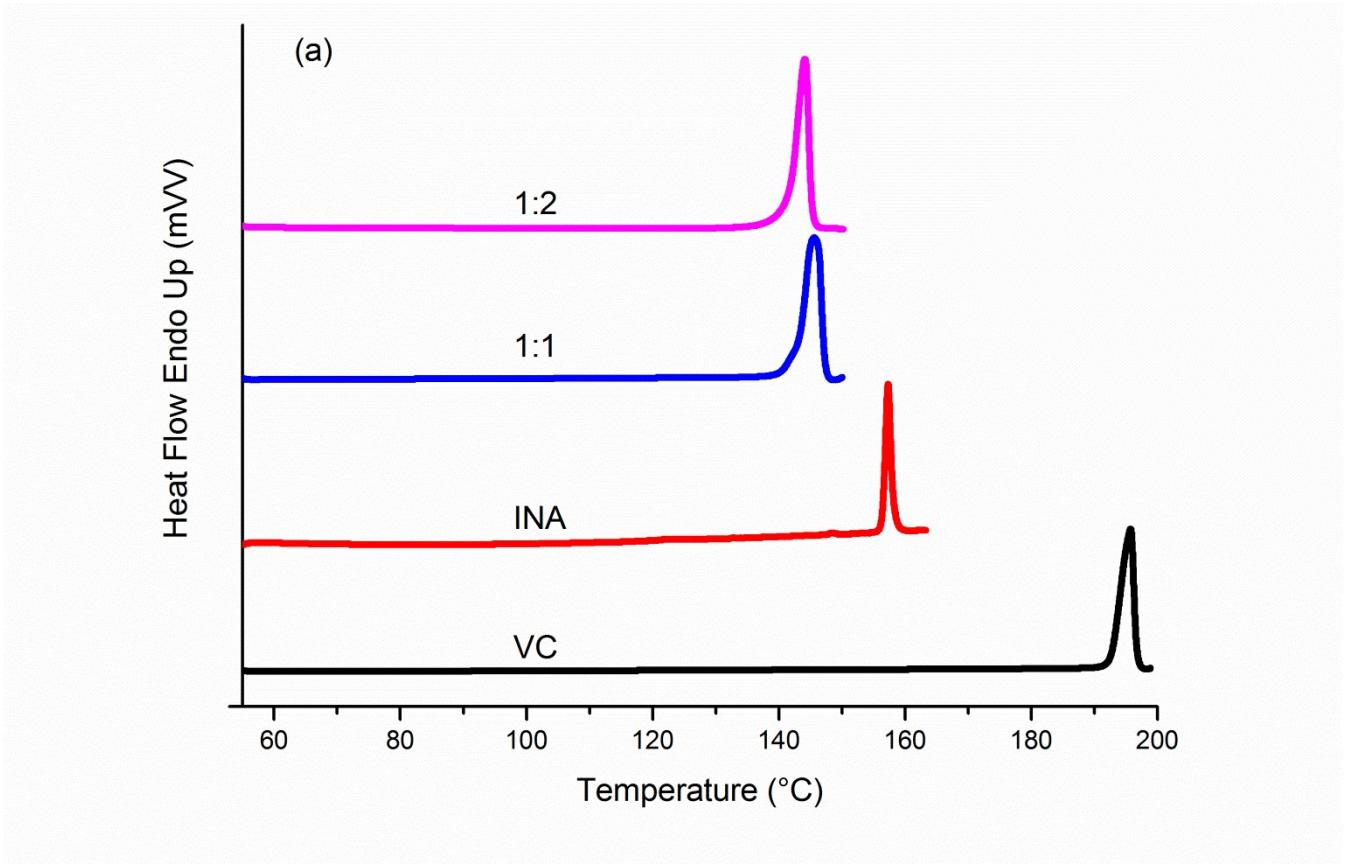

(b)
TG%
VC
1:1
1:3
NA
50
100
150
200
250
300
350
400
Temperature (°C)

Fig. S11 TGA thermograms of co-crystals (a) VC / INA and (b) VC / NA from gels.



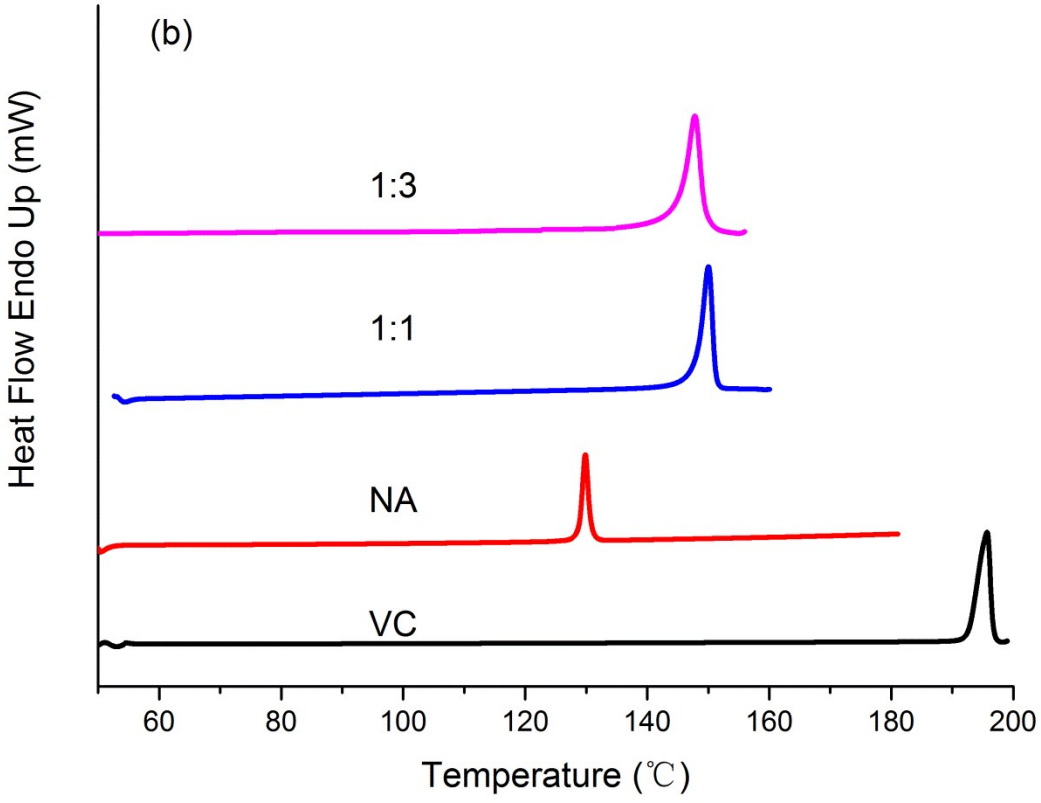


Fig. S12 DSC thermograms of co-crystals (a) VC / INA and (b) VC / NA from gels.

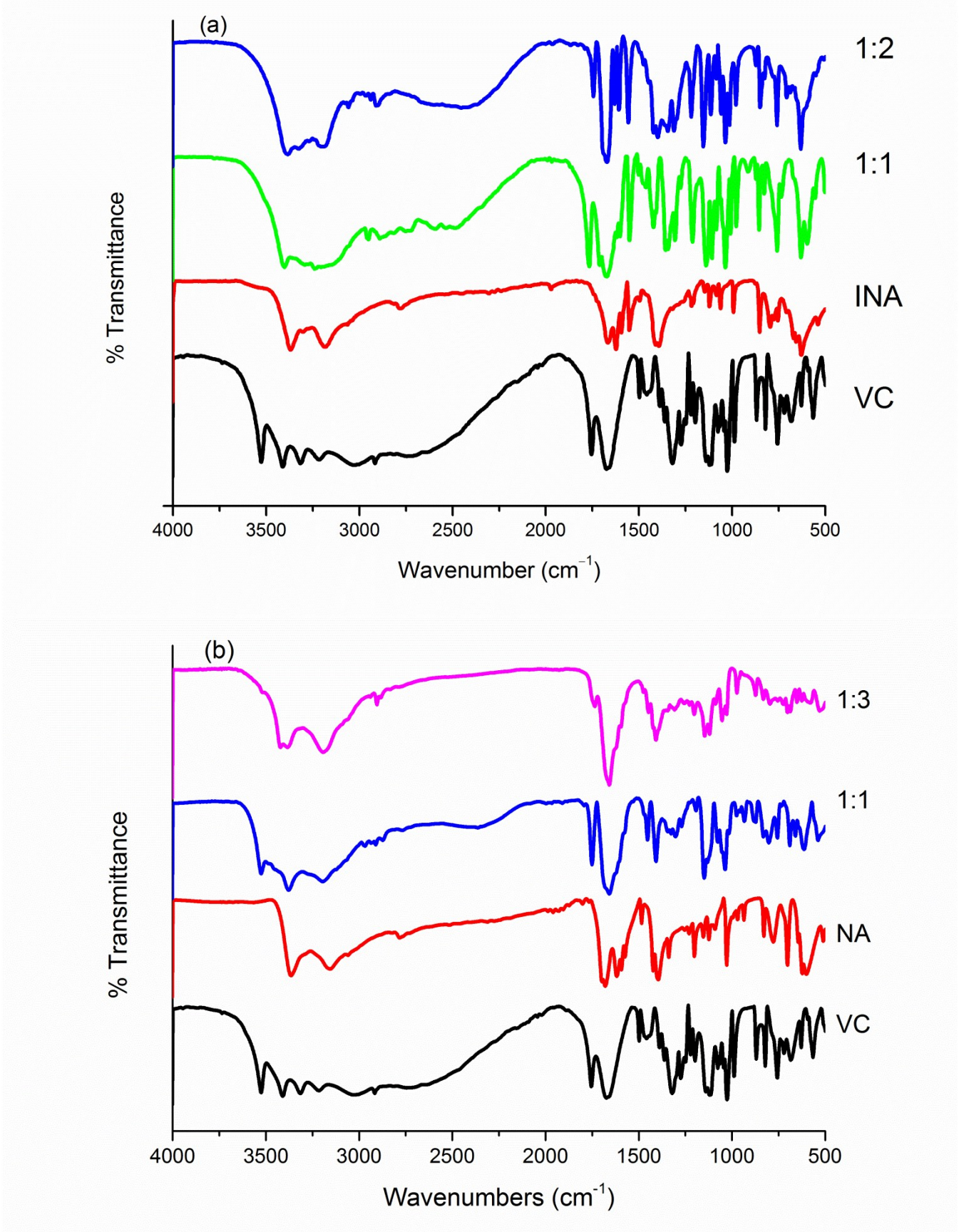


Fig. S13 FT-IR spectra of co-crystals (a) VC / INA and (b) VC / NA from gels.

Table S1 Crystallographic Data for co-crystals and NA oxalate.

	(VC)·(INA)	(VC)·$(INA)_2$	(VC)·(NA)·MeOH	(VC)·(NA)	(VC)·$(NA)_3$	$(NA)_2$·(OA)
Formula	$C_{12}H_{14}N_2O_7$	$C_{18}H_{20}N_4O_8$	$C_{13}H_{18}N_2O_8$	$C_{12}H_{14}N_2O_7$	$C_{24}H_{26}N_6O_9$	$C_7H_7N_2O_3$
Mr.	298.25	420.38	330.29	298.25	542.51	167.15
Crystal system	Orthorhombic	Monoclinic	Triclinic	Triclinic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2$	$P1$	$P1$	$P2_1$	Pbca
Temperature (K)	100(2)	100(2)	100(2)	100(2)	100(2)	100(2)
a (Å)	5.8274(2)	8.9340(9)	5.0892(3)	5.0886(2)	5.074(2)	7.2149(4)
b (Å)	9.9168(3)	5.1587(5)	7.5329(5)	7.2518(3)	29.696(14)	12.4451(7)
c (Å)	23.1227(8)	43.225(4)	19.7851(12)	17.1681(7)	8.498(4)	15.6775(8)
α (°)	90	90	84.757(4)	93.324(3)	90	90
β (°)	90	93.000(7)	85.752(4)	93.952(3)	103.16(3)	90
γ (°)	90	90	81.727(4)	97.338(3)	90	90
Cell volume ($Å^3$)	1336.24(8)	1989.4(3)	746.03(8)	625.42(4)	1246.9(11)	1407.69(13)
Calc. density (g/cm^3)	1.483	1.404	1.470	1.584	1.445	1.577
Z	4	4	2	2	2	8
λ	0.71073	0.71073	0.71073	0.71073	0.71073	0.71073
S	1.021	1.022	1.078	1.039	0.992	1.018
R_1	0.034	0.049	0.108	0.073	0.083	0.040
R_{int}	0.065	0.058	0.037	0.040	0.114	0.086
wR_2	0.073	0.082	0.304	0.193	0.202	0.098