

# Combined virtual and experimental screening multicomponent crystals of 2,4- Dichlorophenoxyacetic acid

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## Contents

- Table S1** The preparation conditions for multicomponent crystals
- Table S2** HPLC method parameters for 2,4-D.
- Table S3** COSMO-RS calculation and MC analysis results of 2,4-D with coformers.
- Table S4** Parameters (Å, Degree) of the hydrogen bonds.
- Table S5** Equilibrium solubility of pure 2,4-D and its multicomponent crystals in the water at 25°C.
- Table S6** The water solubilities of the coformers of all salts.
- Table S7** The pH of a saturated solution at 25°C.
- Figure S1** PXRD patterns of LAG experiment product with new phases.
- Figure S2** PXRD patterns of LAG experiment product without new phases.
- Figure S3** PXRD patterns of multicomponent crystals (black and blue represent the results of slurry suspension experiments and software calculations, respectively).
- Figure S4** DSC curves of 2,4-D, (2,4-D)<sup>-</sup>(PZ)<sup>+</sup>, (2,4-D)<sup>-</sup>(BZ)<sup>+</sup>, (2,4-D)<sup>-</sup>(ABA)<sup>+</sup>, (2,4-D)<sup>-</sup>(PPD)<sup>+</sup>, (2,4-D)<sup>-</sup>(OPD)<sup>+</sup>, and 2,4-D-EB.
- Figure S5** DSC curves of coformers in all multicomponent crystals.
- Figure S6** TGA and DSC curves of (2,4-D)<sup>-</sup>(ABA)<sup>+</sup>.
- Figure S7** FTIR spectra of the starting materials and multicomponent crystals.
- Figure S8** The PXRD patterns of 2,4-D and multicomponent crystals before (black) and after (blue) equilibrium solubility experiment.
- Figure S9** The standard curve of pure 2,4-D solubility.
- Figure S10** The PXRD patterns of 2,4-D and multicomponent crystals before (black) and after (blue) accelerated stability experiment.
- Figure S11** The MEPs of multicomponent crystals.
- Figure S12** Hirshfeld 2D fingerprint plots of 2,4-D and multicomponent crystals.

**Table S1** The preparation conditions for multicomponent crystals

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Compound	Detail
	slurry suspension method

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(2,4-D) <sup>-</sup> (PZ) <sup>+</sup>	2,4-D (884 mg, 4 mmol), PZ (172 mg 2 mmol), methanol (10 ml)
(2,4-D) <sup>-</sup> (BZ) <sup>+</sup>	2,4-D (884 mg, 4 mmol), BZ (472 mg 4 mmol), acetonitrile (10 ml)
(2,4-D) <sup>-</sup> (ABA) <sup>+</sup>	2,4-D (884 mg, 4 mmol), ABA (548 mg 4 mmol), acetonitrile (10 ml)
(2,4-D) <sup>-</sup> (PPD) <sup>+</sup>	2,4-D (884 mg, 4 mmol), PPD (432 mg 4 mmol), ethanol (10 ml)
(2,4-D) <sup>-</sup> (OPD) <sup>+</sup>	2,4-D (884 mg, 4 mmol), OPD (432 mg 4 mmol), methanol (10 ml)
2,4-D-EB	2,4-D (884 mg, 4 mmol), EB (660 mg 4 mmol), methanol (10 ml)
	slow solvent evaporation method
(2,4-D) <sup>-</sup> (PZ) <sup>+</sup>	2,4-D (88.4 mg, 0.4 mmol), PZ (34.4 mg 0.4 mmol), methanol (4 ml)
(2,4-D) <sup>-</sup> (BZ) <sup>+</sup>	2,4-D (88.4 mg, 0.4 mmol), BZ (47.2 mg 0.4 mmol), acetonitrile (4 ml)
(2,4-D) <sup>-</sup> (ABA) <sup>+</sup>	2,4-D (88.4 mg, 0.4 mmol), ABA (54.8 mg 0.4 mmol), acetonitrile (4 ml)
(2,4-D) <sup>-</sup> (PPD) <sup>+</sup>	2,4-D (88.4 mg, 0.4 mmol), PPD (43.2 mg 0.4 mmol), ethanol (4 ml)
(2,4-D) <sup>-</sup> (OPD) <sup>+</sup>	2,4-D (88.4 mg, 0.4 mmol), OPD (43.2 mg 0.4 mmol), methanol (4 ml)
2,4-D-EB	2,4-D (88.4 mg, 0.4 mmol), EB (66.0 mg 0.4 mmol), methanol (4 ml)

**Table S2** HPLC method parameters for 2,4-D.

Parameter	Details
Column	C18 reverse phase column (4.6 mm × 250 mm, 5 μm)
Mobile phase	acetonitrile, water and acetic acid (v/v/v, 50:50:1)
Flow rate	1 mL/min
Inject volume	20 μL
Column temperature	25 °C
Sample temperature	25 °C
$\lambda_{\max}$	283 nm
Retention time	8.4 min
Calibration range	0.1 – 0.6 g/L

**Table S3** COSMO-RS calculation and MC analysis results of 2,4-D with cofomers.

	Cofomer	CAS No.	$\Delta H_{ex}$ (kcal·mol <sup>-1</sup> )	Hit Rate (%)	New form
1	piperazine	110-85-0	-5.502	100	yes
2	L-proline	147-85-3	-4.882	100	yes
3	6-aminocaproic acid	60-32-2	-4.762	100	yes
4	gabapentin	60142-96-3	-4.470	0	
5	L-glutamine	56-85-9	-4.103	0	
6	4,4'-bipyridine <sup>1</sup>	553-26-4	-3.920	100	yes
7	L-alanine	56-41-7	-3.570	0	
8	L-valine	72-18-4	-3.480	0	
9	L-histidine	71-00-1	-3.455	0	
10	L-asparagine	70-47-3	-3.396	0	
11	glycine	56-40-6	-3.226	0	
12	creatine	57-00-1	-3.198	0	
13	pyrazine <sup>2</sup>	290-37-9	-2.662	100	yes
14	L-threonine	6028-28-0	-2.624	0	
15	imidazole <sup>3</sup>	288-32-4	-2.560	100	yes
16	2-ethoxybenzamide	938-73-8	-2.513	100	yes
17	3-aminobenzoic acid	99-05-8	-2.484	100	yes
18	1,2,4-triazole	288-88-0	-2.470	0	
19	2-aminopyrimidine <sup>4</sup>	109-12-6	-2.409	100	yes
20	methylurea	598-50-5	-2.322	0	
21	<i>p</i> -phenylenediamine	106-50-3	-2.279	100	yes
22	L-serine	56-45-1	-2.164	0	
23	2-aminopyridine <sup>3</sup>	504-29-0	-2.129	100	yes
24	benzimidazole	51-17-2	-2.082	100	yes

25	isonicotinamide <sup>3</sup>	1453-82-3	-2.068	100	yes
26	urea	57-13-6	-2.012	0	
27	L-aspartic acid	56-84-8	-2.005	0	
28	pyrazinamide <sup>3</sup>	98-96-4	-1.851	100	yes
29	picolinamide	1452-77-3	-1.772	100	yes
30	sulfanilic acid	121-57-3	-1.586	100	no
31	<i>o</i> -phenylenediamine	95-54-5	-1.556	100	yes
32	theophylline	58-55-9	-1.525	100	yes
33	taurine	107-35-7	-1.492	0	
34	mannitol	87-78-5	-1.196	0	
35	6-hydroxypurine	68-94-0	-1.038	100	no
36	2,2'-bipyridine <sup>2</sup>	366-18-7	-0.969	100	yes
37	2-hydroxynicotinic acid	609-71-2	-0.840	100	no
38	2-hydroxybenzylamine	932-30-9	-0.620	100	yes
39	oxalic acid	144-62-7	-0.516	0	
40	3-hydroxyisonicotinic acid	10128-71-9	-0.253	100	no
41	3,5-dinitrobenzoic acid	99-34-3	-0.235	0	
42	2-aminonicotinic acid	5345-47-1	-0.202	100	no
43	malic acid	6915-15-7	-0.176	0	
44	malonic acid	141-82-2	-0.137	0	
45	3-aminopyridine <sup>3</sup>	462-08-8	-0.085	100	yes
46	2-nitrobenzoic acid	552-16-9	-0.033	0	
47	3-methoxyphenol	150-19-6	0.006		
48	3,4-dihydroxybenzoic acid	99-50-3	0.015		
49	caffeic acid	331-39-5	0.017		
50	2-nitrophenol	88-75-5	0.048		
51	tartaric acid	147-71-7	0.060		

52	saccharin	81-07-2	0.105
53	barbituric acid	67-52-7	0.222

**Table S4** Parameters (Å, Degree) of the hydrogen bonds.

Compound	D-H...A	D-H	H...A	D...A	D-H...A	symmetry
(2,4-D)-(PZ) <sup>+</sup>	N <sub>1</sub> -H <sub>1A</sub> ...O <sub>1</sub>	1.01(2)	1.68(2)	2.681(2)	174(2)	
	N <sub>1</sub> -H <sub>1B</sub> ...O <sub>5</sub>	0.84(2)	1.94(2)	2.784(19)	179(2)	1-x,-y,1-z
	N <sub>1</sub> -H <sub>2A</sub> ...O <sub>4</sub>	0.97(2)	1.75(2)	2.715(2)	173(2)	
	N <sub>2</sub> -H <sub>2B</sub> ...O <sub>2</sub>	0.91(2)	1.80(2)	2.706(19)	172(2)	1-x,1-y,1-z
	C <sub>4</sub> -H <sub>4A</sub> ...O <sub>2</sub>	0.97	2.37	3.267(2)	153	-x,1-y,1-z
	C <sub>2</sub> -H <sub>6B</sub> ...O <sub>5</sub>	0.97	2.41	3.289(2)	151	2-x,-y,1-z
(2,4-D)-(BZ) <sup>+</sup>	N <sub>1</sub> -H <sub>1</sub> ...O <sub>1</sub>	0.95(2)	1.70(2)	2.650(16)	177.0(19)	
	N <sub>1</sub> -H <sub>1</sub> ...O <sub>2</sub>	0.95(2)	2.51(2)	3.069(17)	117.2(16)	3/2-x,-y,-1/2+z
	N <sub>2</sub> -H <sub>2</sub> ...O <sub>2</sub>	0.89(2)	1.89(2)	2.683(17)	147(2)	-1/2+x,1/2-y,1-z
	C <sub>9</sub> -H <sub>7</sub> ...O <sub>2</sub>	0.93	2.56	3.087(2)	117	
(2,4-D)-(ABA) <sup>+</sup>	N <sub>1</sub> -H <sub>1A</sub> ...O <sub>1</sub>	0.91(3)	1.86(3)	2.7713(19)	175(2)	
	N <sub>1</sub> -H <sub>1B</sub> ...O <sub>5</sub>	0.86(3)	2.12(3)	2.690(2)	124(2)	-1/2+x,5/2-y,-1/2+z
	N <sub>1</sub> -H <sub>1C</sub> ...O <sub>1</sub>	0.90(3)	1.90(3)	2.7762(19)	166(2)	3/2-x,1/2+y,1/2-z
	N <sub>1</sub> -H <sub>1C</sub> ...O <sub>2</sub>	0.90(3)	2.52(3)	3.132(2)	126.4(19)	3/2-x,1/2+y,1/2-z
	O <sub>4</sub> -H <sub>2</sub> ...O <sub>2</sub>	0.80(3)	1.84(3)	2.633(2)	169(4)	1/2+x,3/2-y,1/2+z
	C <sub>14</sub> -H <sub>9</sub> ...O <sub>4</sub>	0.93	2.53	3.369(2)	149	x,1+y,z
	C <sub>15</sub> -H <sub>10</sub> ...O <sub>1</sub>	0.93	2.48	3.361(2)	159	x,1+y,z
(2,4-D)-(PPD) <sup>+</sup>	N <sub>1</sub> -H <sub>1A</sub> ...O <sub>2</sub>	0.89	1.87	2.724(2)	160	
	N <sub>1</sub> -H <sub>1B</sub> ...O <sub>1</sub>	0.89	1.86	2.7476(19)	174	2-x,1-y,-z

	$N_1-H_{1C} \cdots O_1$	0.89	1.98	2.748(2)	144	1+x,y,z
	$C_9-H_6 \cdots O_2$	0.93	2.53	3.265(2)	136	2-x,1-y,-z
(2,4-D)-(OPD) <sup>+</sup>	$N_1-H_{1A} \cdots O_1$	0.911(18)	0.911(18)	2.7378(13)	156.1(16)	
	$N_1-H_{1B} \cdots O_2$	0.922(16)	1.957(16)	2.8448(13)	161.1(14)	1-x,-1/2+y,1/2-z
	$N_1-H_{1C} \cdots O_2$	0.929(15)	1.929(15)	2.8220(14)	160.7(13)	x,3/2-y,1/2+z
	$N_2-H_{2A} \cdots O_1$	0.870(18)	2.068(18)	2.9301(15)	170.6(14)	x,3/2-y,1/2+z
2,4-D-EB	$O_1-H_1 \cdots O_4$	0.94(3)	1.64(3)	2.578(2)	175(4)	
	$N_1-H_{2A} \cdots O_2$	0.90(3)	2.01(3)	2.887(3)	166(3)	
	$N_1-H_{2B} \cdots O_5$	0.94(4)	1.87(3)	2.633(3)	137(4)	
	$C_8-H_6 \cdots O_4$	0.93	2.57	3.478(4)	164	1/2-x,-1/2+y,3/2-z
	$C_{15}-H_{10} \cdots O_4$	0.93	2.37	2.719(3)	102	
	$C_{17}-H_{12A} \cdots O_2$	0.96	2.56	3.417(4)	149	1/2-x,3/2-y,1-z

**Table S5** Equilibrium solubility of pure 2,4-D and its multicomponent crystals in the water at 25°C.

Component	Solubility (g/L)
2,4-D	0.6914 ± 0.0039
(2,4-D)-(PZ) <sup>+</sup>	2.7417 ± 0.0118
(2,4-D)-(BZ) <sup>+</sup>	2.4590 ± 0.0094
(2,4-D)-(ABA) <sup>+</sup>	1.0464 ± 0.0062
(2,4-D)-(PPD) <sup>+</sup>	0.6350 ± 0.0031
(2,4-D)-(OPD) <sup>+</sup>	1.6883 ± 0.0088
2,4-D-EB	0.3828 ± 0.0008

**Table S6** The water solubilities of the cofomers of all salts.

Compounds	solubility (g/L)
PZ <sup>5</sup>	190.7 (25°C)
BZ <sup>6</sup>	7.6 (25°C)
ABA <sup>7</sup>	5.9 (25°C)
PPD <sup>8</sup>	47.2 (25°C)
OPD <sup>9</sup>	40.4 (35°C)

**Table S7** The pH of a saturated solution at 25°C.

Solution	Final pH
pure water	7.18
2,4-D	3.00
(2,4-D)-(PZ) <sup>+</sup>	4.86
(2,4-D)-(BZ) <sup>+</sup>	4.76
(2,4-D)-(ABA) <sup>+</sup>	3.51
(2,4-D)-(PPD) <sup>+</sup>	3.53
(2,4-D)-(OPD) <sup>+</sup>	4.37
2,4-D-EB	3.20



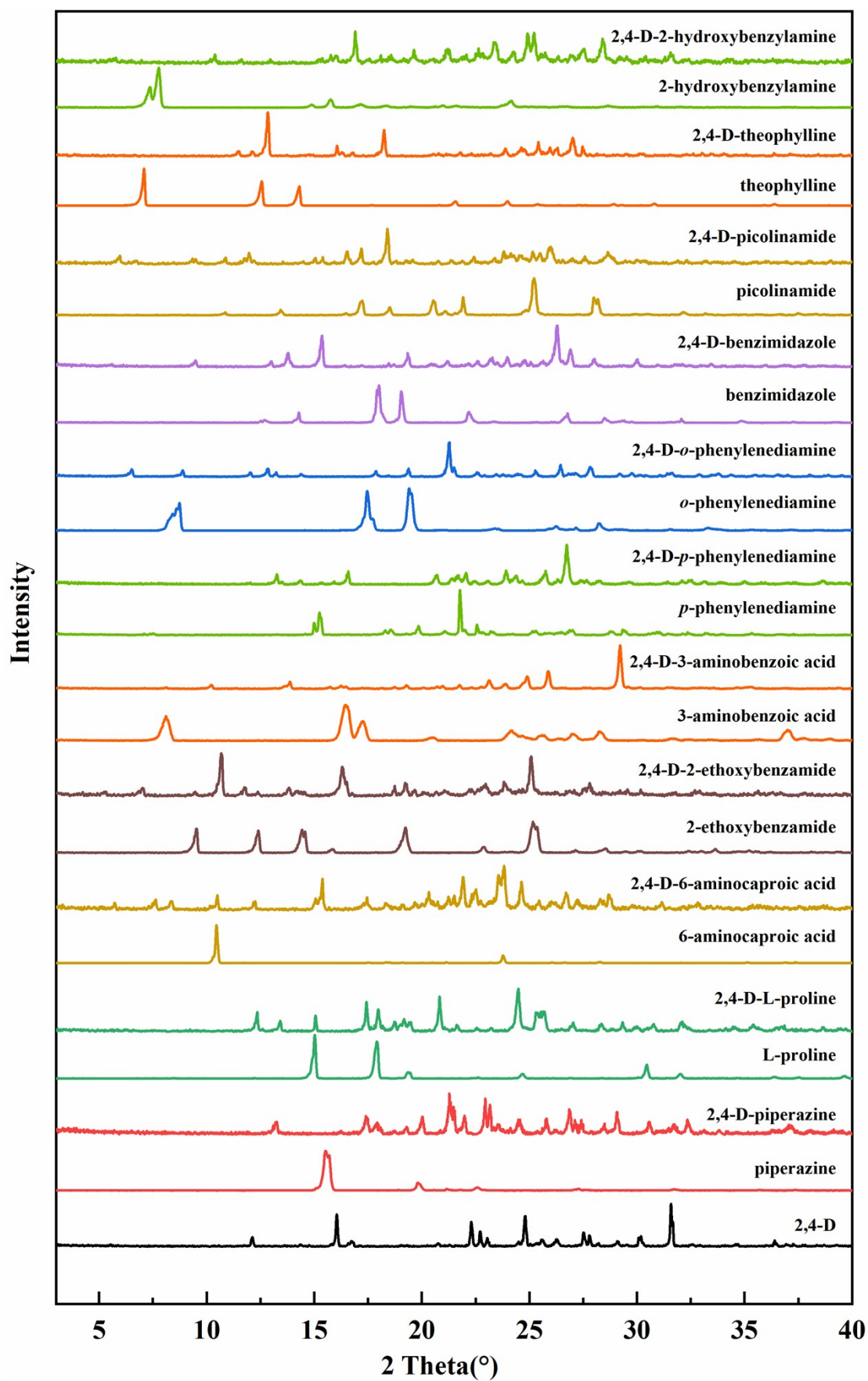


Figure S1 PXRD patterns of LAG experiment product with new phases.

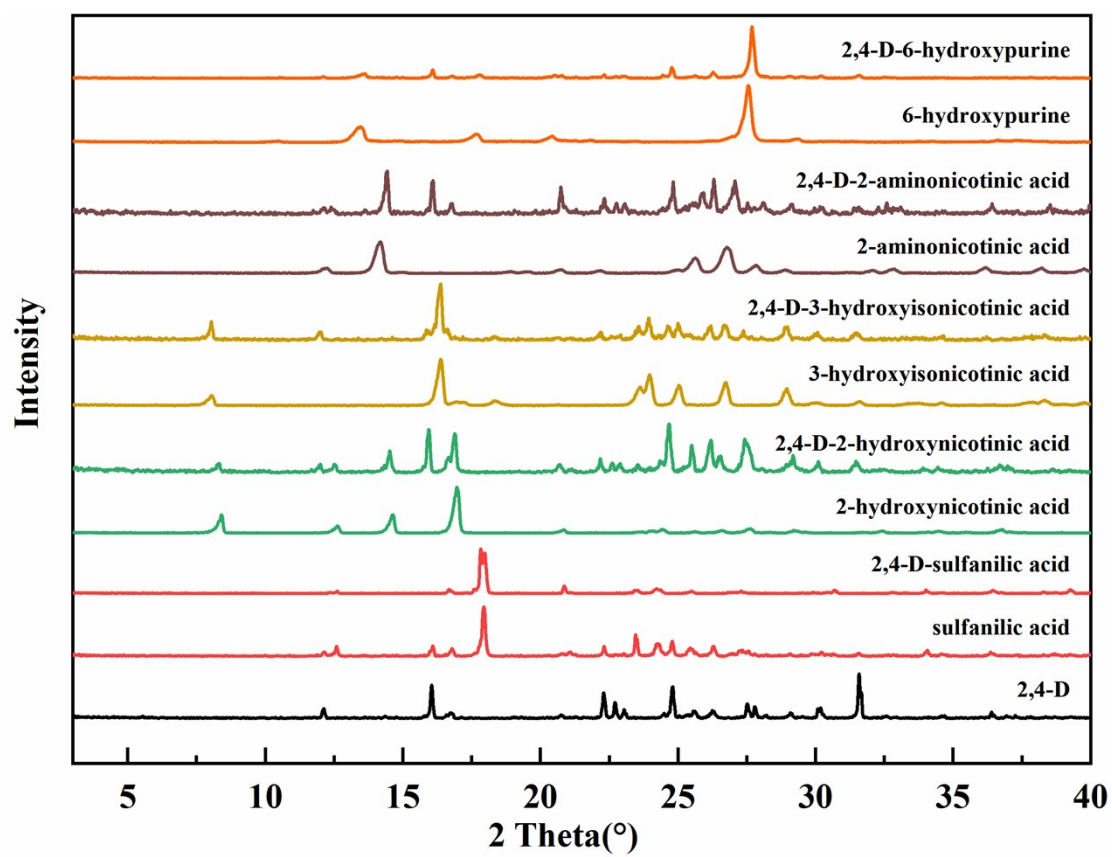
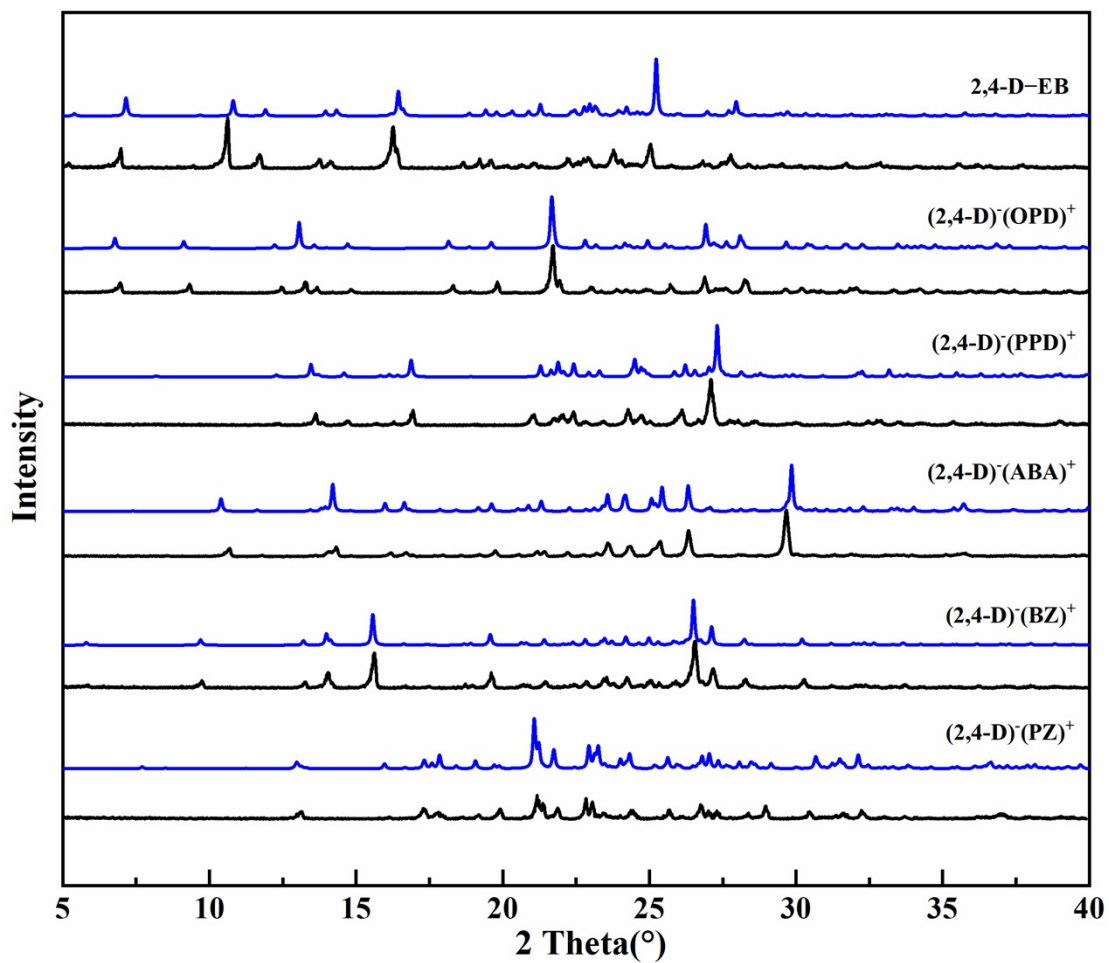
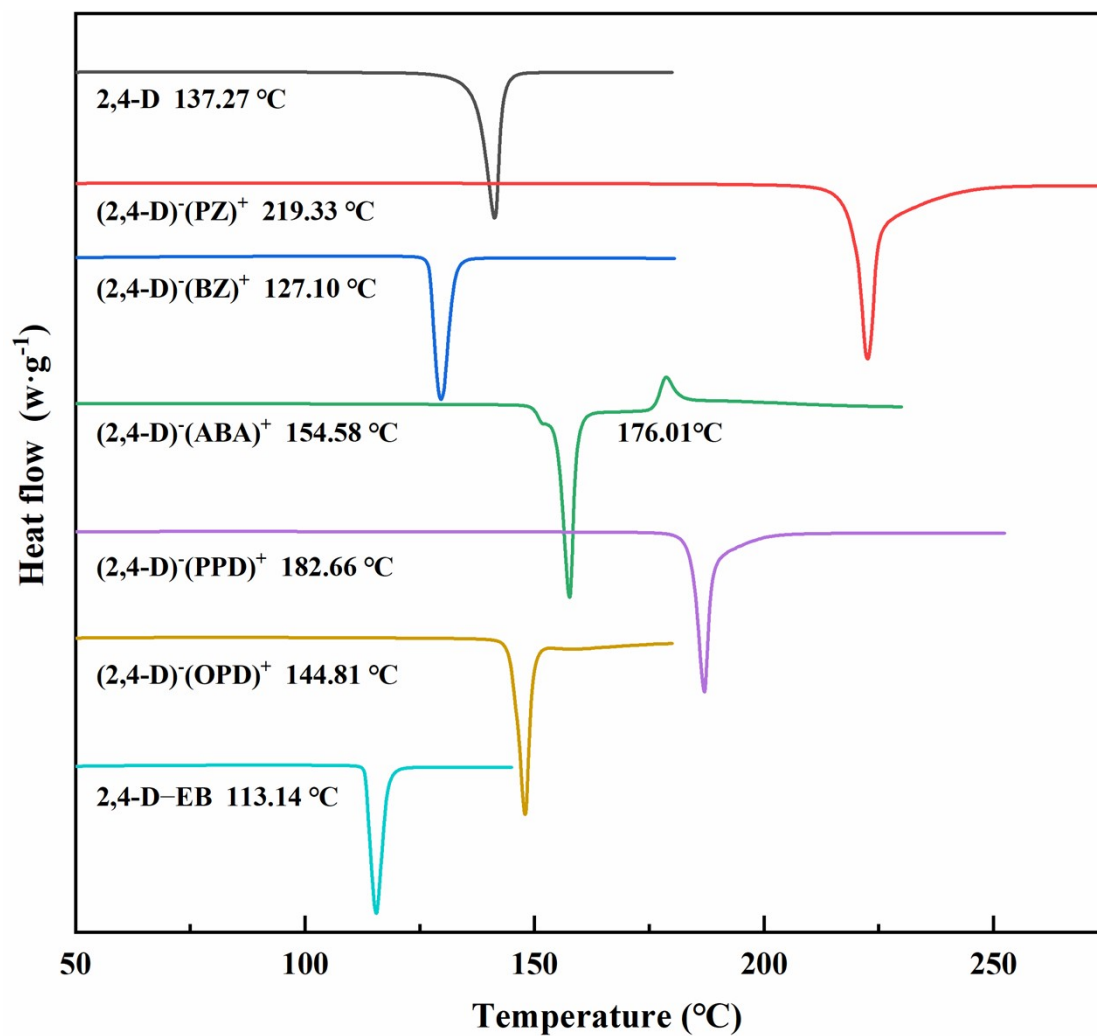


Figure S2 PXRD patterns of LAG experiment product without new phases.



**Figure S3** PXR D patterns of multicomponent crystals (black and blue represent the results of slurry suspension experiments and software calculations, respectively).



**Figure S4** DSC curves of 2,4-D, (2,4-D) $^{-}$ (PZ) $^{+}$ , (2,4-D) $^{-}$ (BZ) $^{+}$ , (2,4-D) $^{-}$ (ABA) $^{+}$ , (2,4-D) $^{-}$ (PPD) $^{+}$ , (2,4-D) $^{-}$ (OPD) $^{+}$ , and 2,4-D-EB.

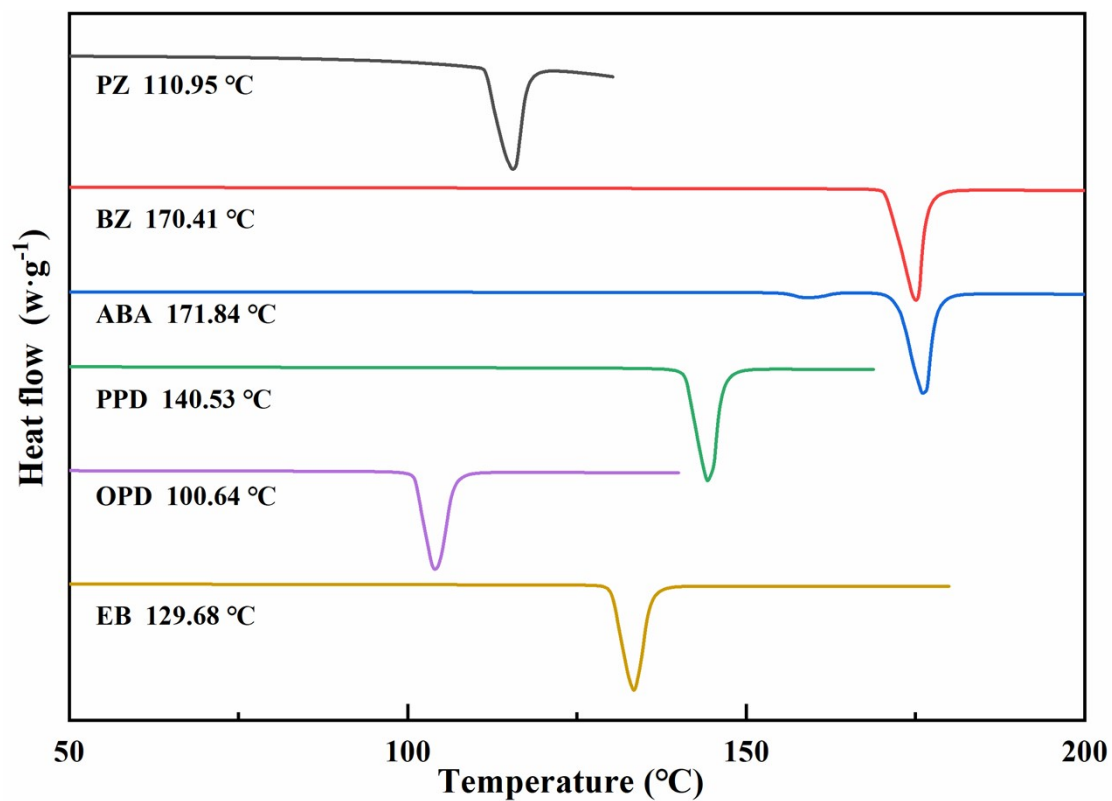


Figure S5 DSC curves of coformers in all multicomponent crystals.

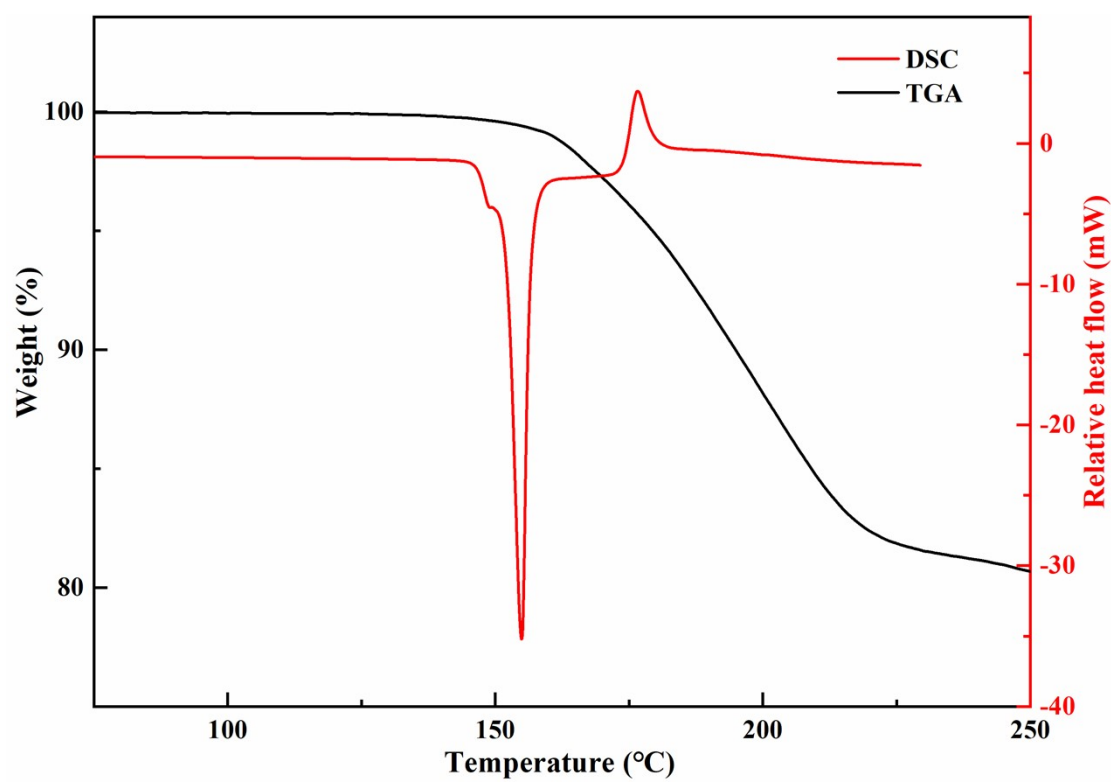
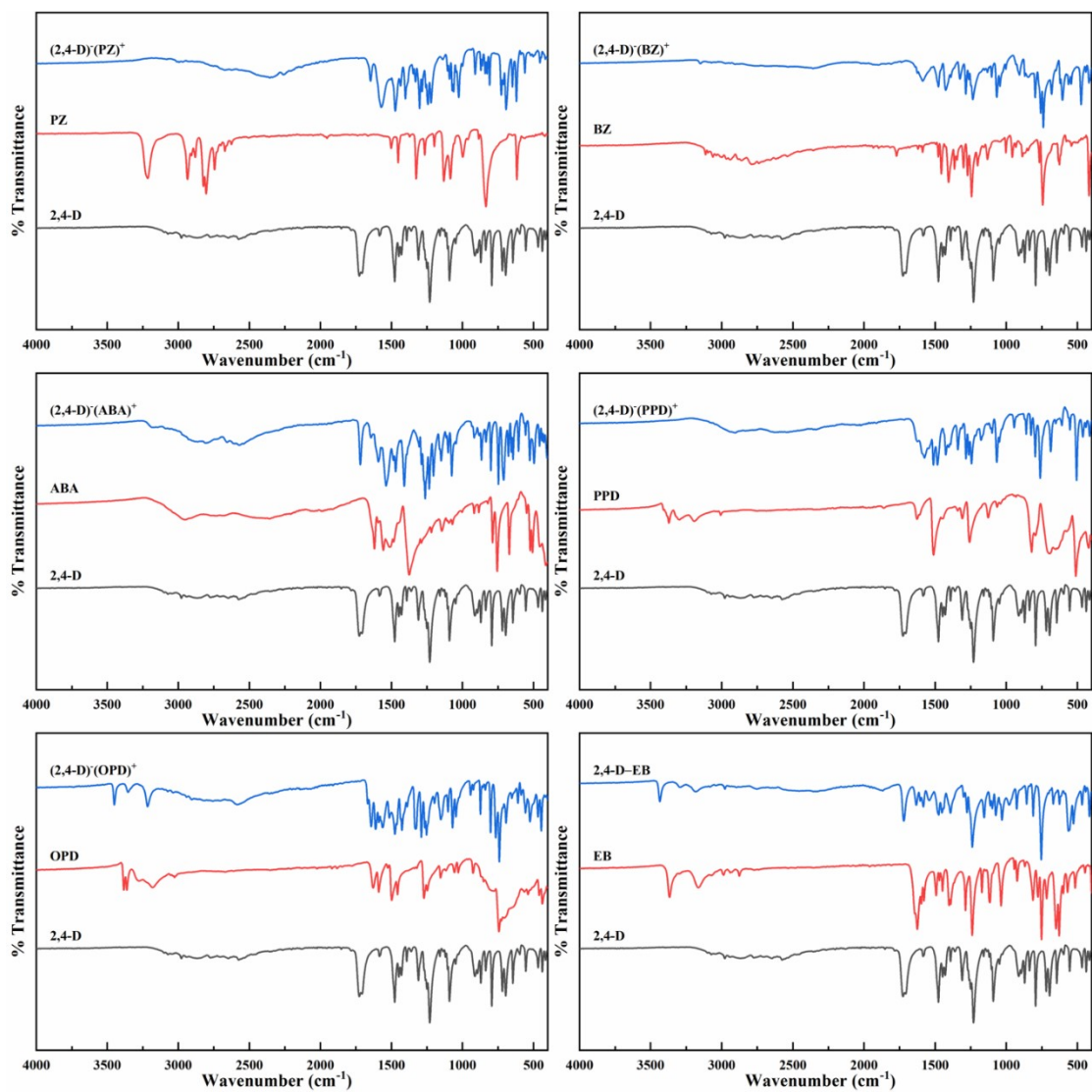
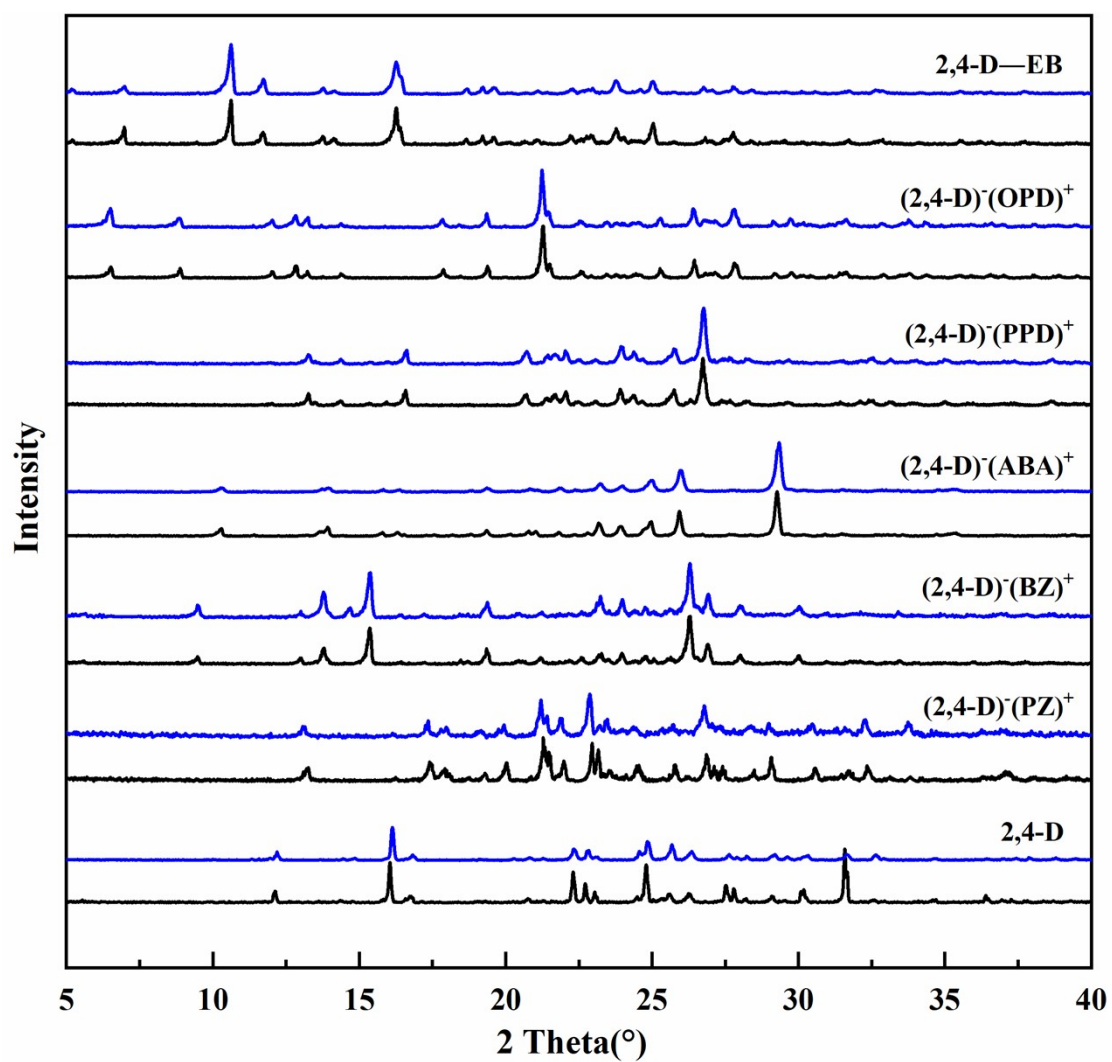


Figure S6 TGA and DSC curves of  $(2,4\text{-D})\text{-}(\text{ABA})^+$ .

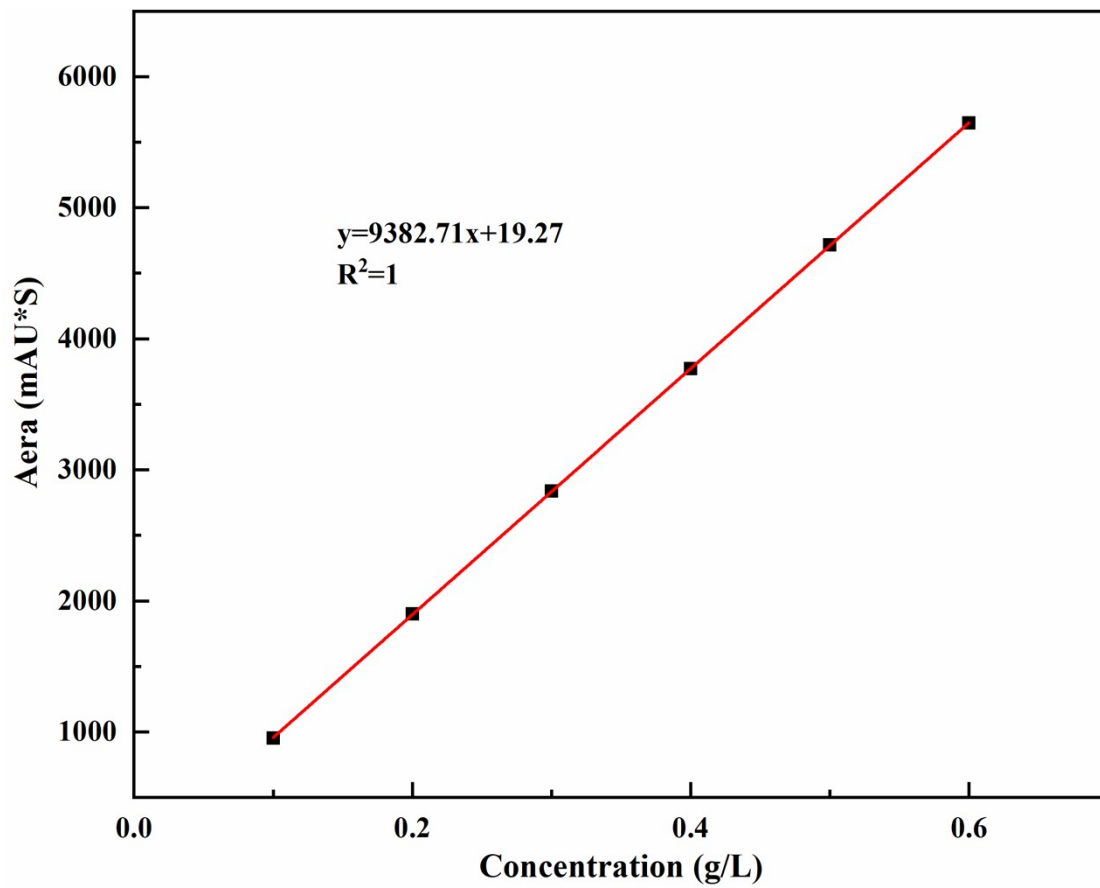


**Figure S7** FTIR spectra of the starting materials and multicomponent crystals.



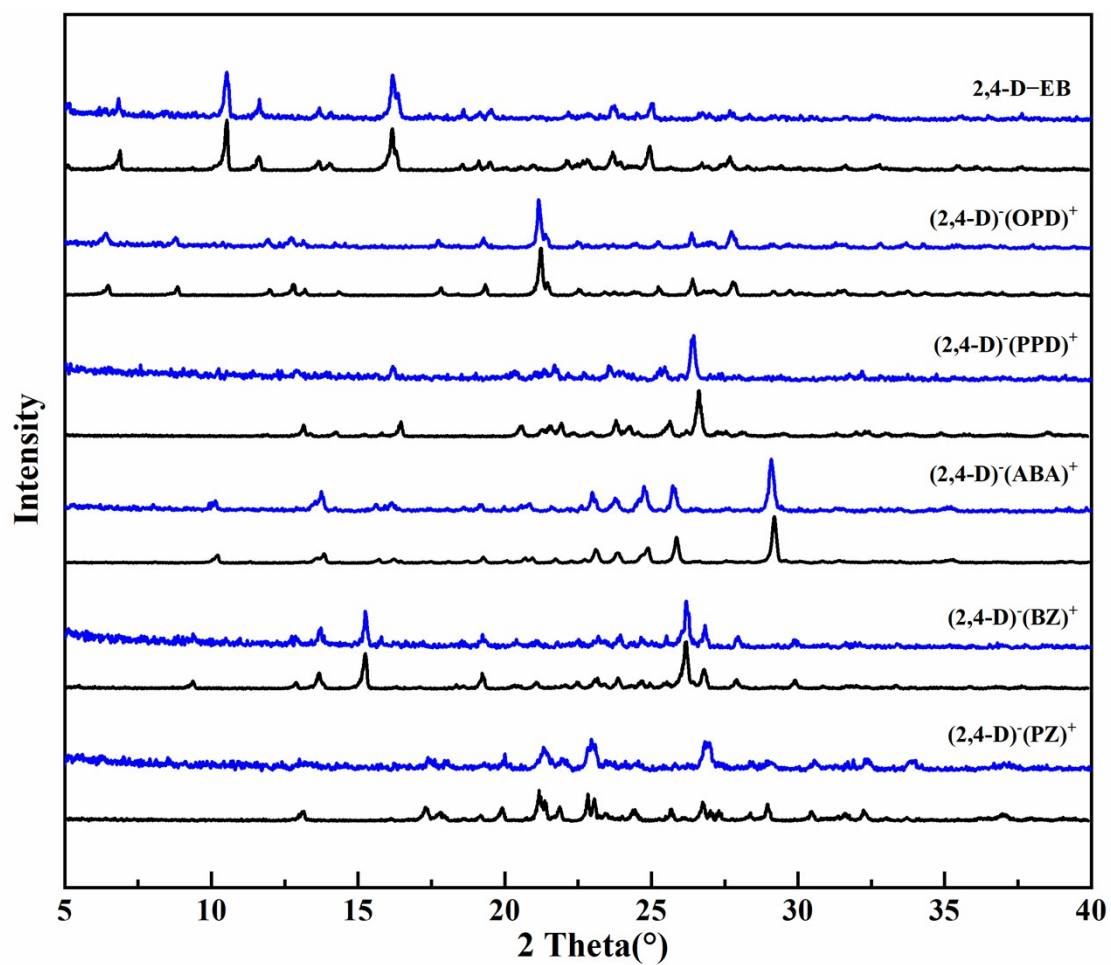


**Figure S8** The PXR D patterns of 2,4-D and multicomponent crystals before (black) and after (blue) equilibrium solubility experiment.



**Figure S9** The standard curve of pure 2,4-D solubility.





**Figure S10** The PXR D patterns of 2,4-D and multicomponent crystals before (black) and after (blue) accelerated stability experiment.

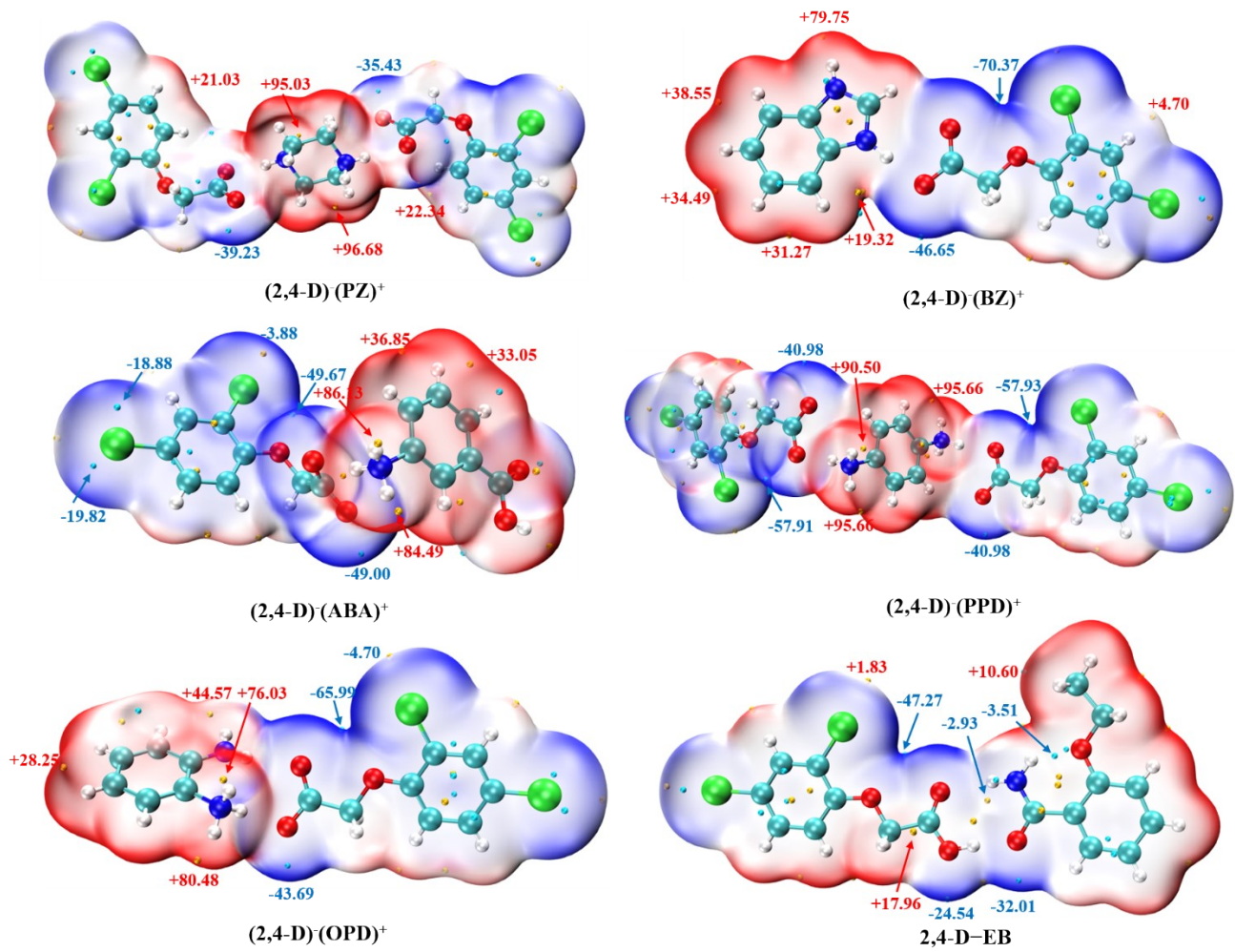
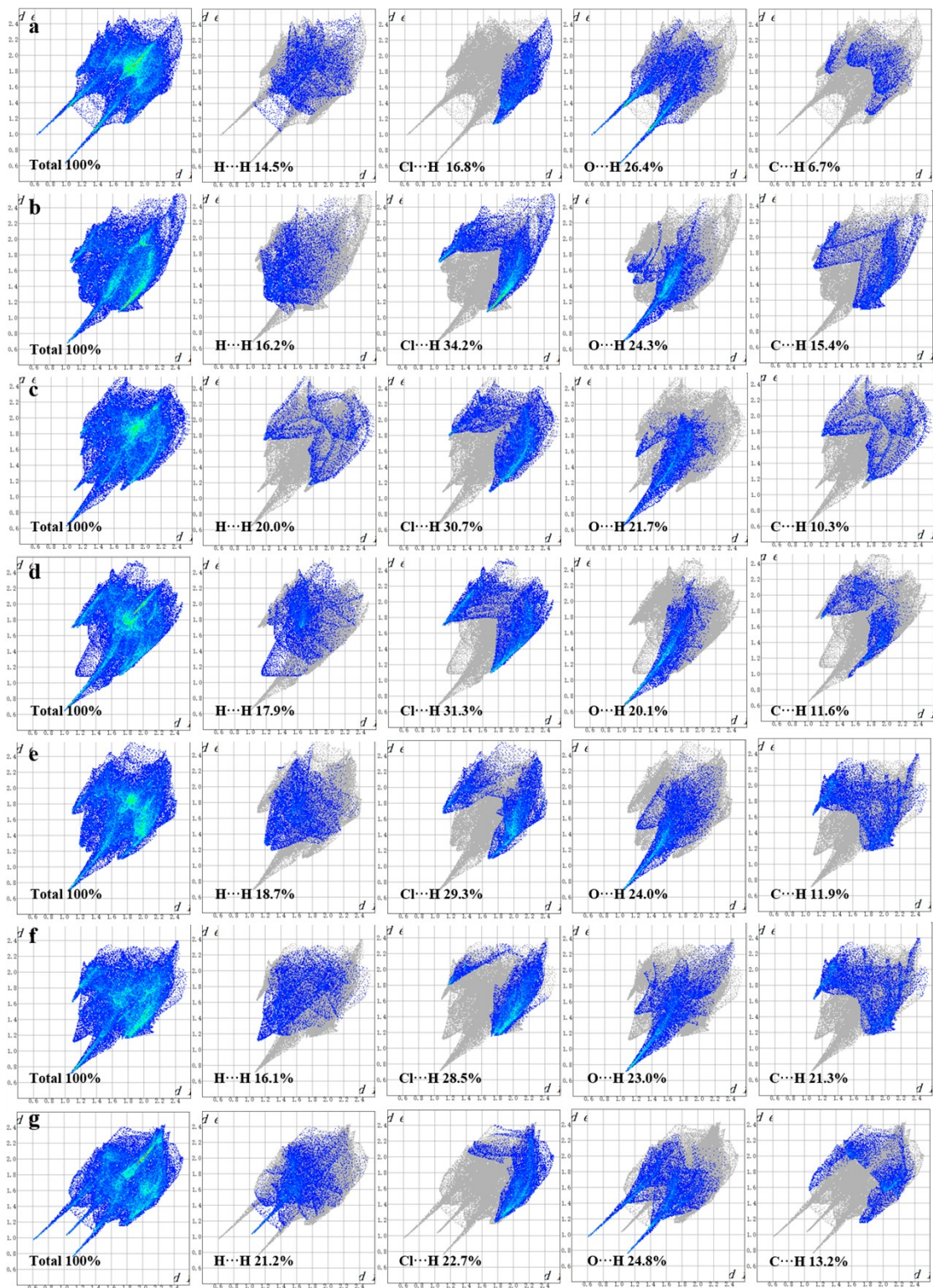


Figure S11 The MEPs of multicomponent crystals.



**Figure S12** Hirshfeld 2D fingerprint plots of 2,4-D and multicomponent crystals.

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