Supporting Information

Authors: XingchenHu[1]; YuntianXiao[1]; LuguangQi[1]; YunheBai[1]; YingSun[1]; YangYe[1]; Chuang Xie[123]

Affiliates:

1 School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, PR China

2 National Engineering Research Center of Industrial Crystallization Technology, Tianjin University, Tianjin 300072, P.R. China

3 State Key Laboratory of Chemical Engineering, Tianjin University, Tianjin 300072, China

Preparation of Multicomponent Crystal

Preparation of TMP-SYA-0.16H: 0.0002 mol of TMP and 0.0002 mol of SYA were added to the glass bottle, and then 2.0 mL of methanol and 0.5 mL of water were added to the glass bottle. Filter the suspension using a 0.45μm syringe filter into another clean glass vial. The single crystal of TMP-SYA-0.16H can be obtained by placing the vial in a ventilated place at room temperature for 7-10 days.

TMP-2,5HBA and **TMP-2,6HBA** are prepared in a similar way to TMP-SYA-0.16H. The difference is that the solvent used by TMP-2,5HBA is 3mL methanol, and the solvent used by TMP-2,6HBA is 3mL acetonitrile.

Preparation of TMP-OA: Add 0.01molTMP and 0.01molOA into a 100mL glass bottle, and add 40mL methanol and 20mL water into the glass bottle. Heat the glass bottle in water at 70°C to dissolve the solid. Filter the solution into a clean glass bottle with a 0.45μm syringe filter, and cool down to 2°C at a cooling rate of 0.1°C/min. The single crystal of TMP-OA was obtained. **Preparation of TMP-GA-2M**: Add 0.009 mol TMP and 0.009 mol GA into a glass bottle, and then add 2.0 mL of methanol into the glass bottle. Heat the glass bottle in water at 60°C to dissolve the solid. Filter the solution into a clean glass bottle with a 0.45μm syringe filter, and cool down to 2°C at a cooling rate of 0.1°C/min. The single crystal of TMP-GA-2M was obtained.

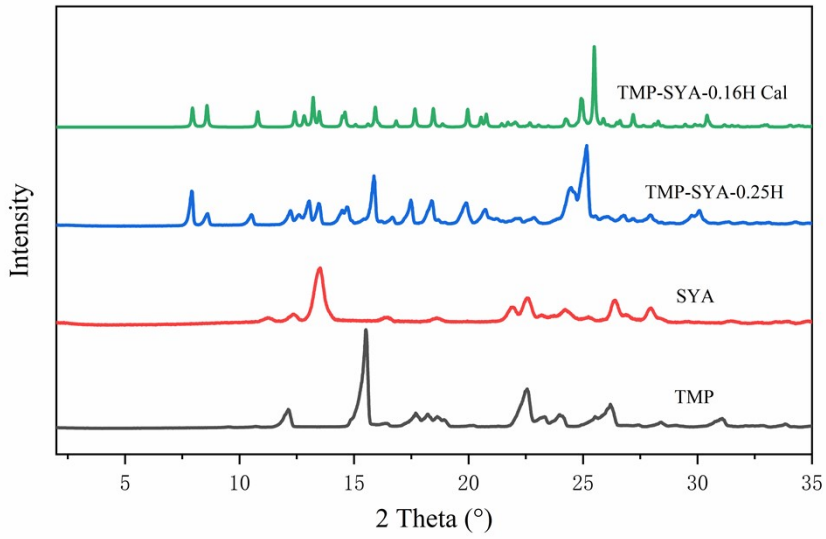

Figure S1. PXRD patterns of TMP, SYA, TMP-SYA-0.16H and calculated from the single crystal data: Cal.

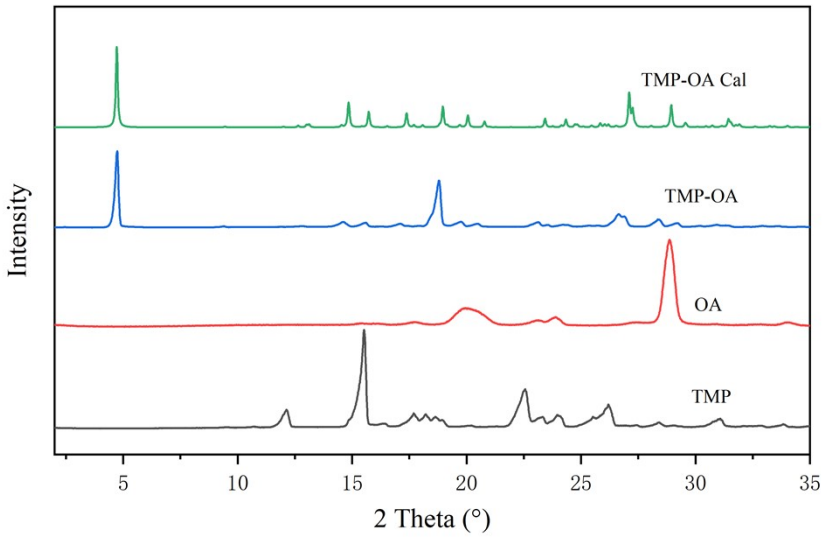

Figure S2. PXRD patterns of TMP, OA, TMP-OA and calculated from the single crystal data: Cal.

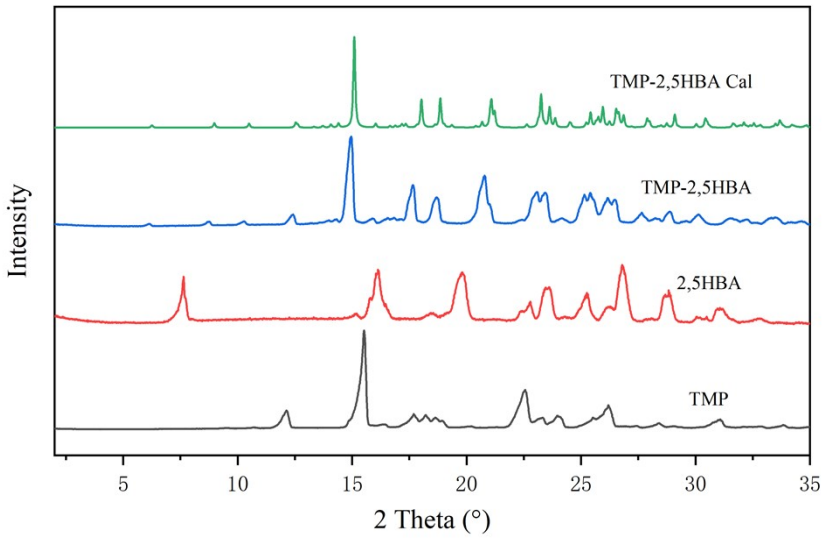

Figure S3. PXRD patterns of TMP, 2,5HBA, TMP-2,5HBA and calculated from the single crystal data: Cal.

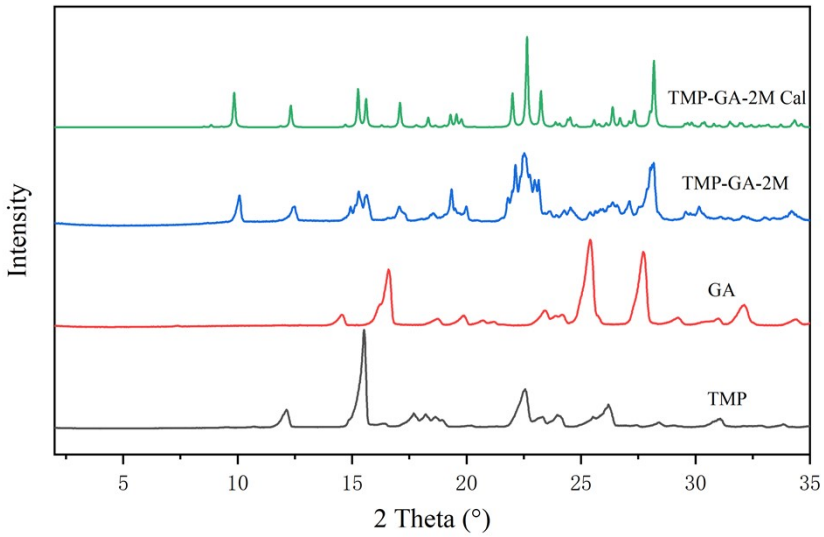

Figure S4. PXRD patterns of TMP, GA, TMP-GA-2M and calculated from the single crystal data: Cal.

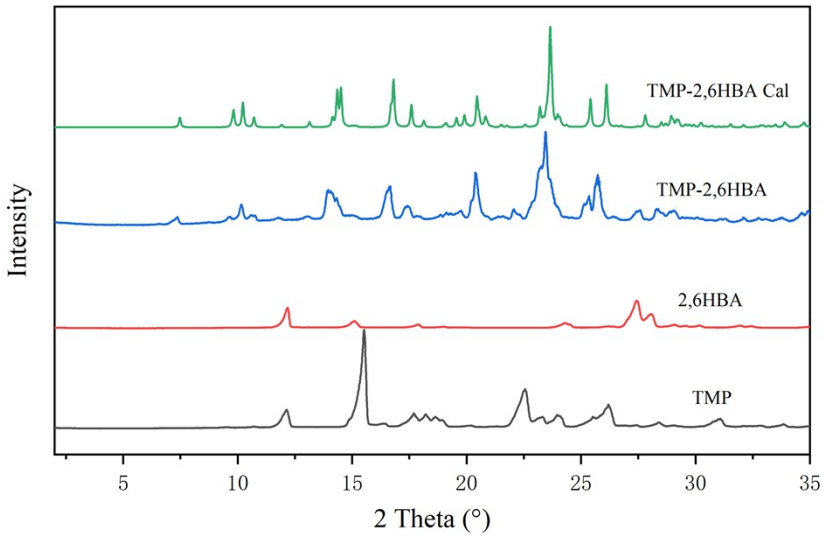

Figure S5. PXRD patterns of TMP, 2,6HBA, TMP-2,6HBA and calculated from the single crystal data: Cal.

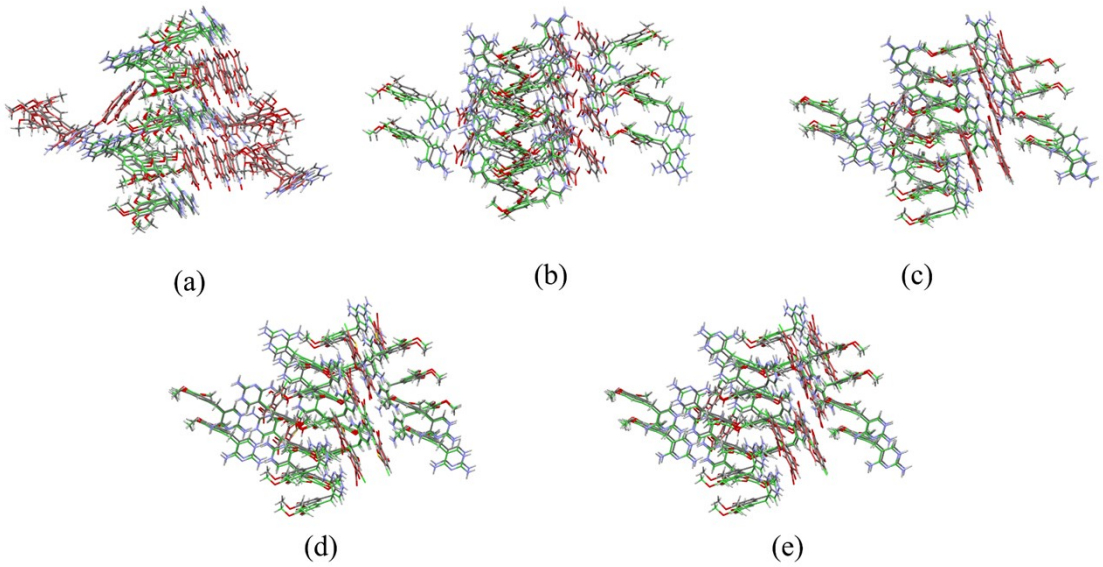

Figure S6. Analysis results of packing similarity of TMP-2,5HBA. The gray structure is TMP-2,5HBA, and the green structure is CSD Refcodes PARWOV (a), PARWUB (b), CESRUN (c), VADVOM (d) and HURMOW (e) respectively.

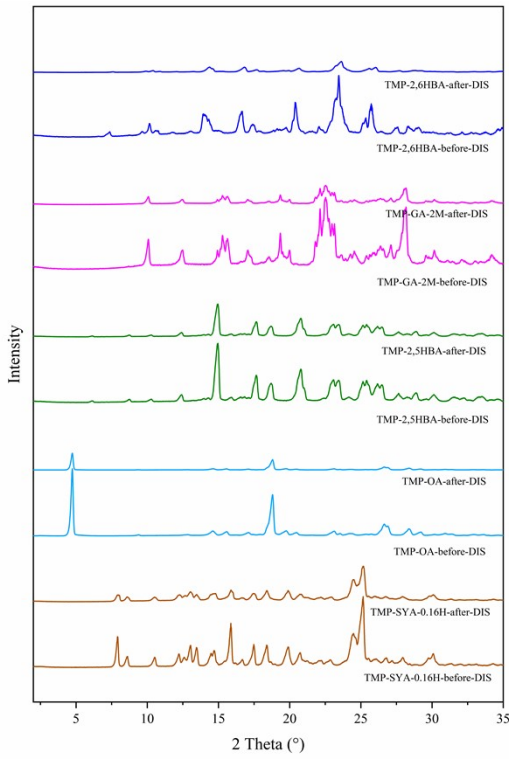

Figure S7. PXRD comparison of five salts before and after dissolution in buffer of pH=1.2.

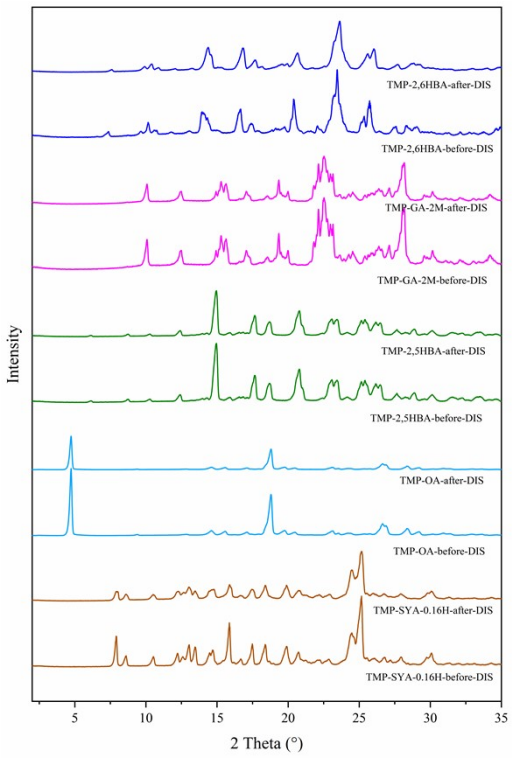

Figure S8. PXRD comparison of five salts before and after dissolution in buffer of pH=6.8.

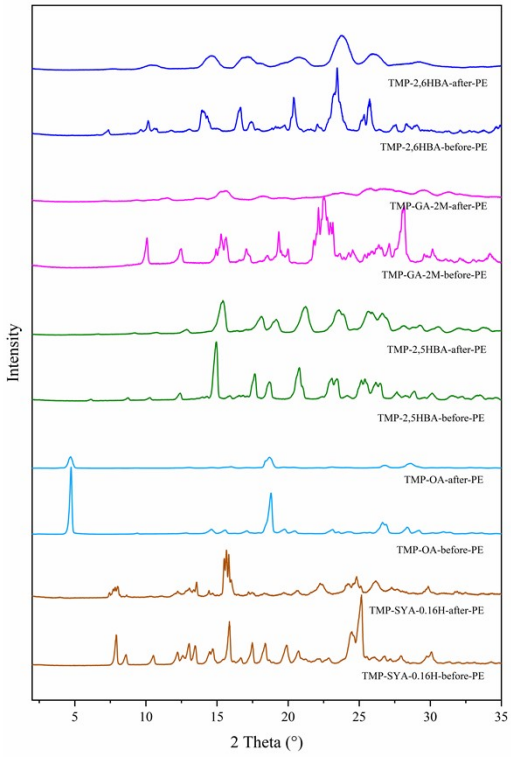

Figure S9. PXRD comparison of five salts before and after 48 hours phase equilibration in buffer of pH=1.2.

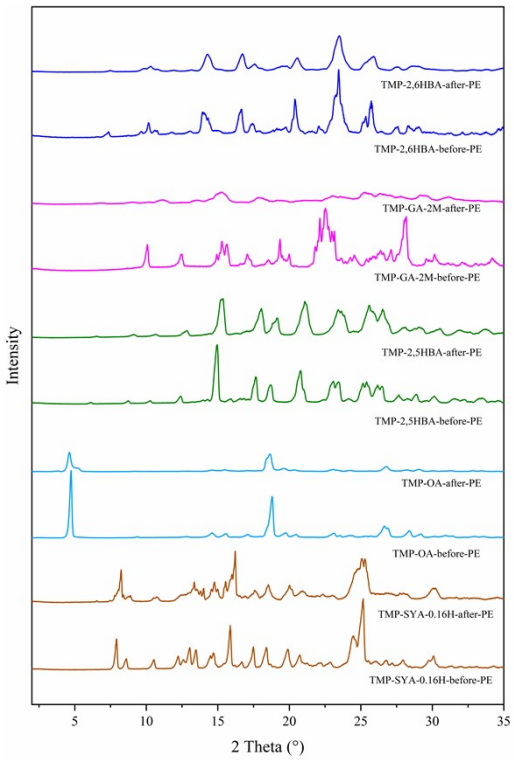

Figure S10. PXRD comparison of five salts before and after 48 hours phase equilibration in buffer of pH=6.8.

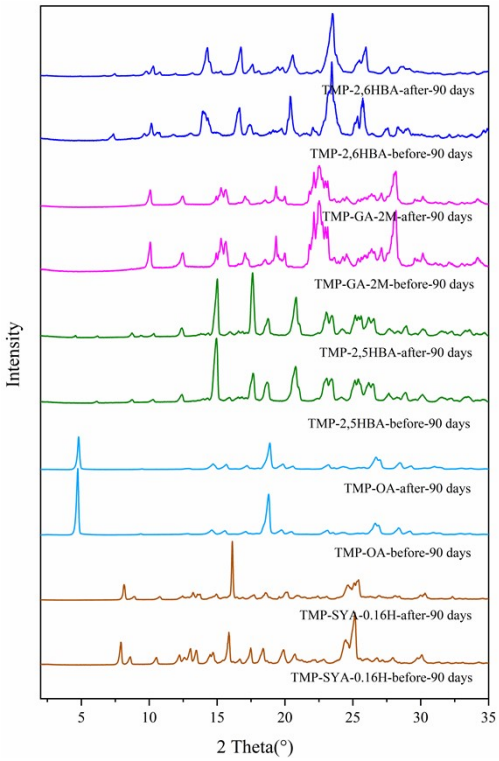

Figure S11. XRD comparison of samples before and after storage (40℃, RH=75%) for 90 days.

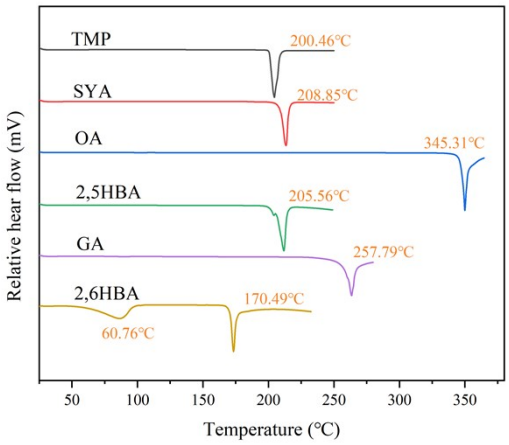

Figure S12. DSC thermograms of TMP and CCFs.

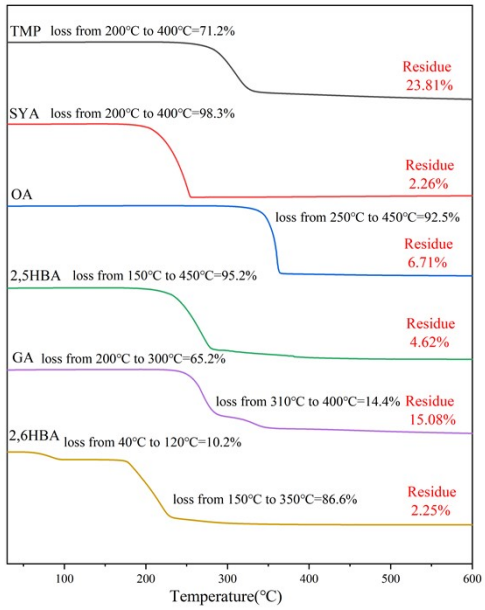

Figure S13. TGA profiles of TMP and CCFs.

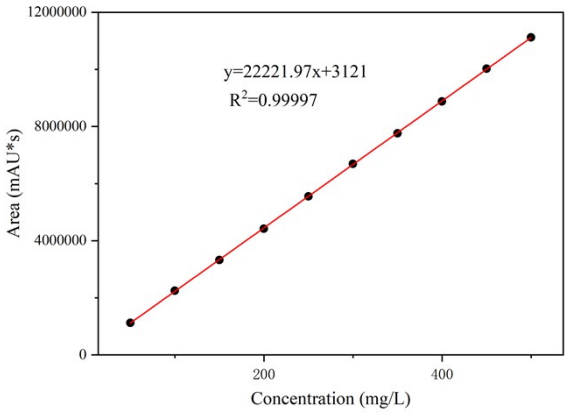

Figure S14. Standard curve of Trimethoprim content (concentration-peak area) determined by

HPLC-UV.

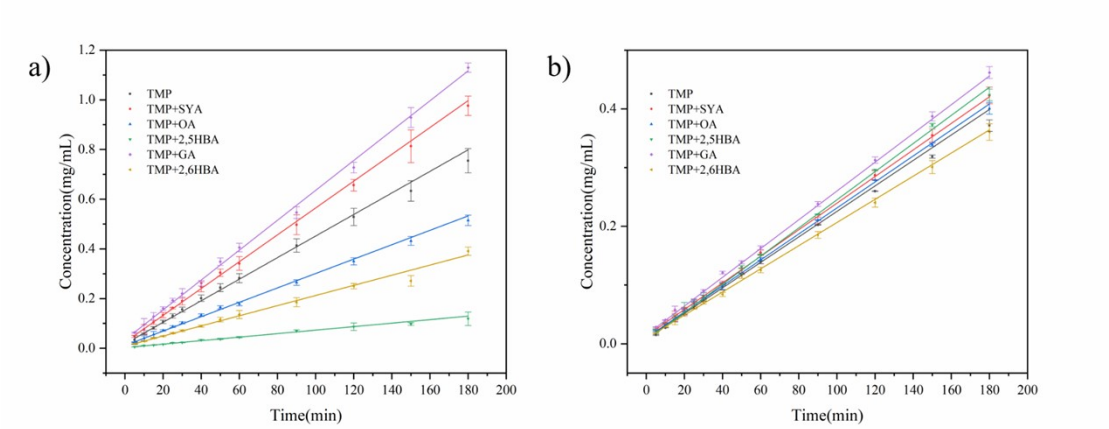

Figure S15. (a) IDR profiles of TMP and mixtures in pH 1.2 buffer at 37 °C; (b) IDR profiles of TMP and mixtures in pH 6.8 buffer at 37 °C.

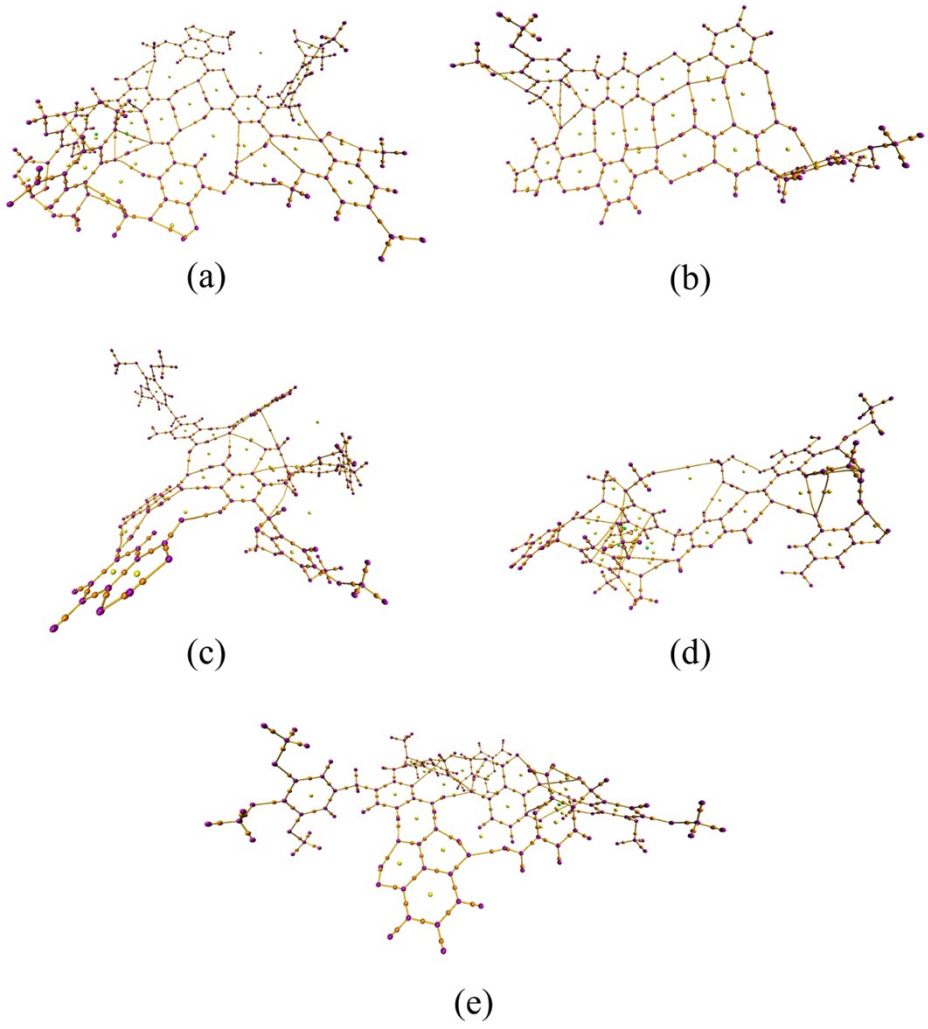

Figure S16. The topological geometrical structures of five salts, the purple, orange, yellow and

green spheres correspond to (3, -3), (3, -1), (3, +1) and (3, +3) critical points of electron density (nuclear critical point, bond critical point, ring critical point, cage critical point), respectively. The orange curve corresponds to the bond diameter. (a)TMP-SYA-0.16H, (b)TMP-OA, (c)TMP-2,5HBA, (d)TMP-GA-2M, (e)TMP-2,6HBA.

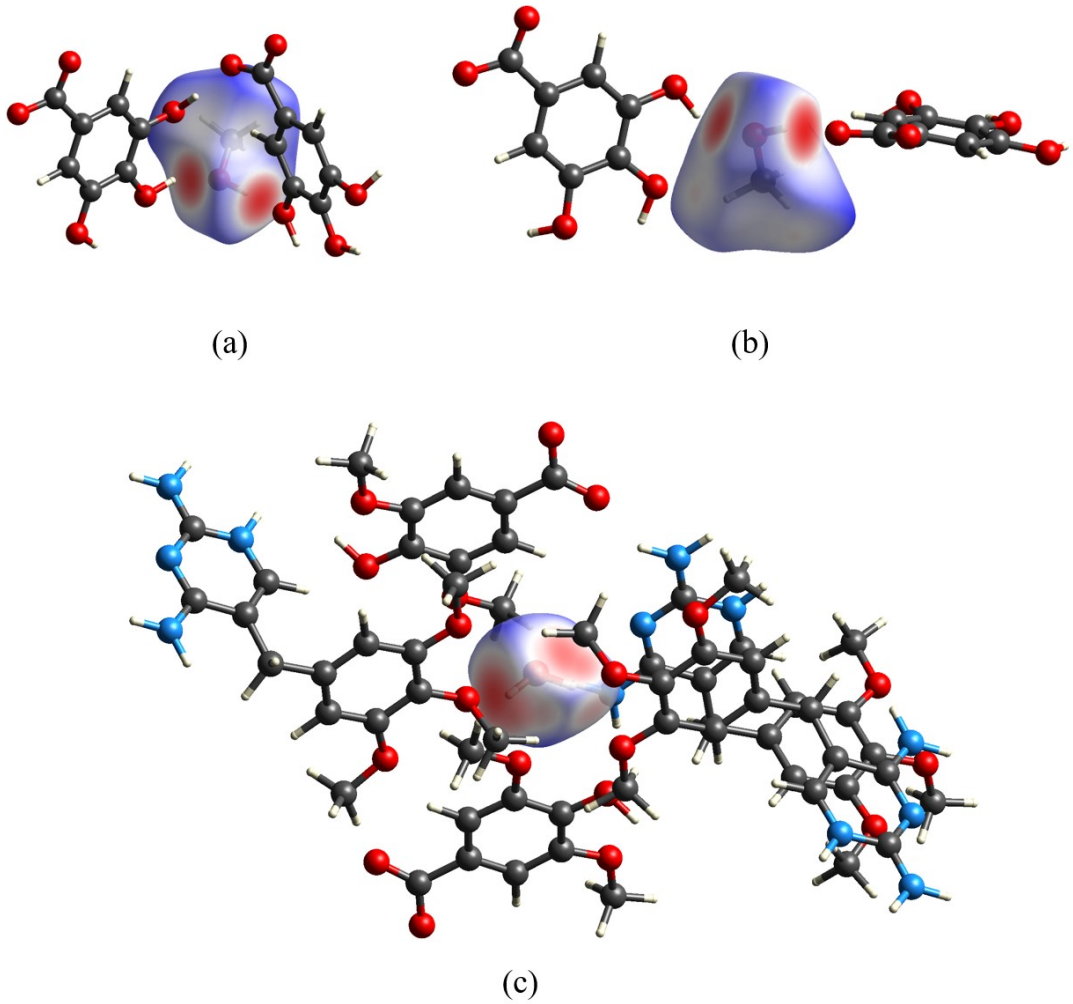

Figure S 17. (a)(b) The Hirshfeld Surface of two methanol molecules in TMP-GA-2M. (c) Hirshfeld Surface of water molecules in TMP-SYA-0.16 H.

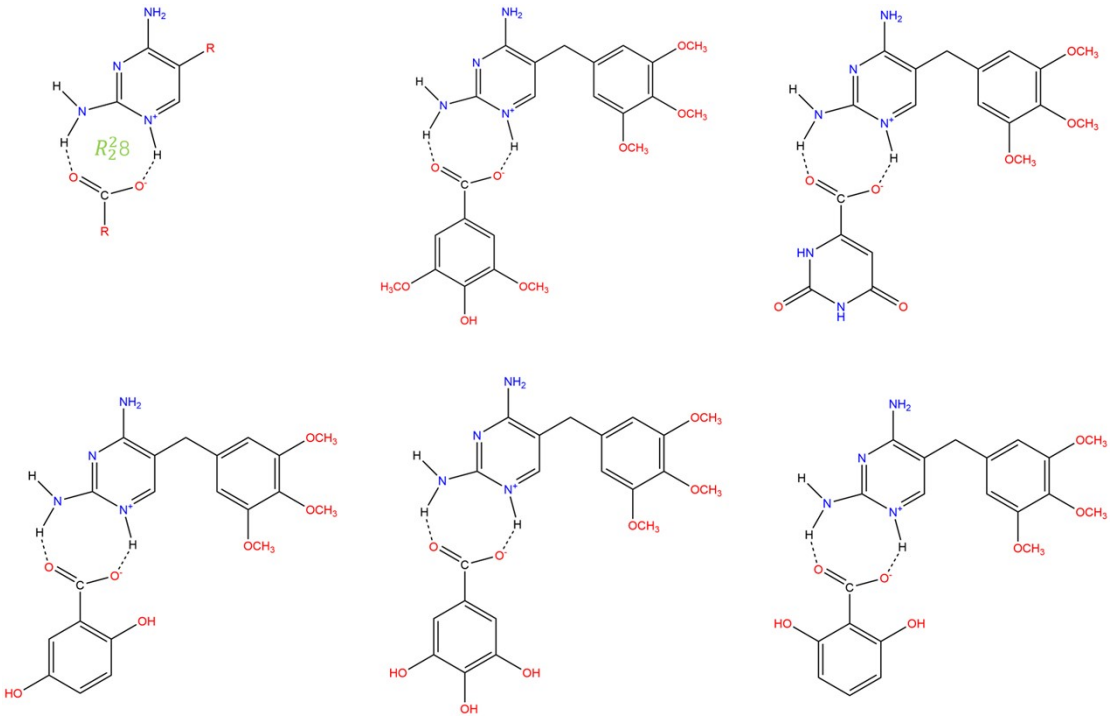

Figure S18. $R_2^2(8)$ motif in five salts.

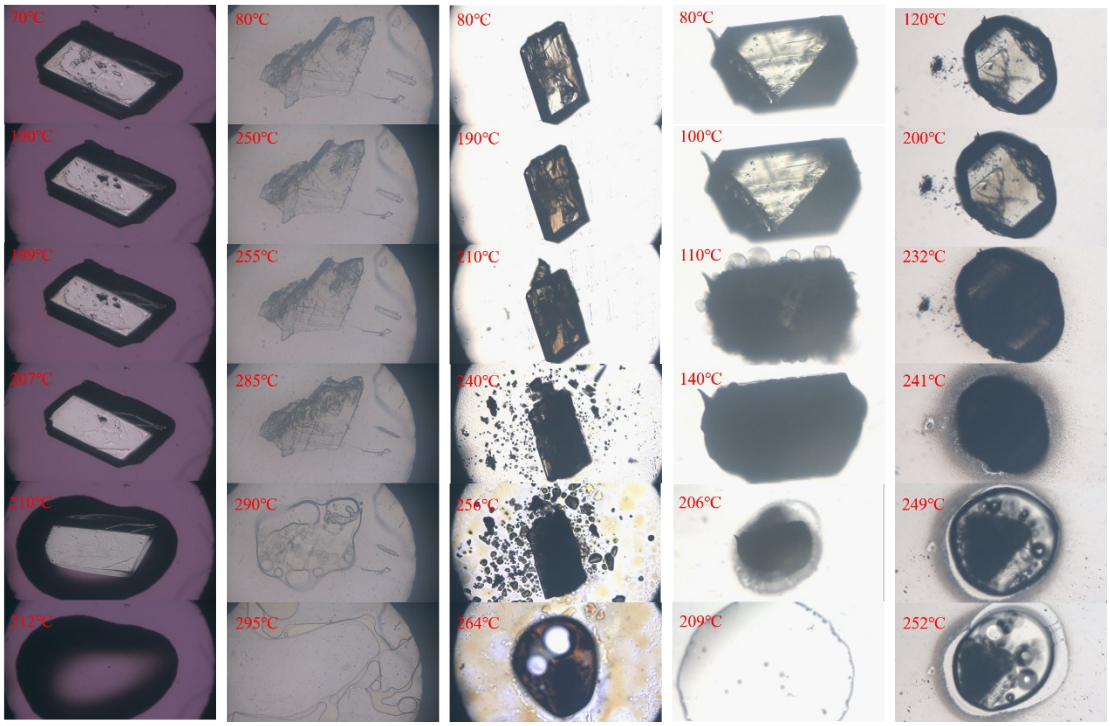

Figure S 19. The pictures of hot stage microscope. (From left to right are TMP-SYA-0.16H; TMP-OA; TMP-2,5HBA; TMP-GA-2M; TMP-2,6HBA.)

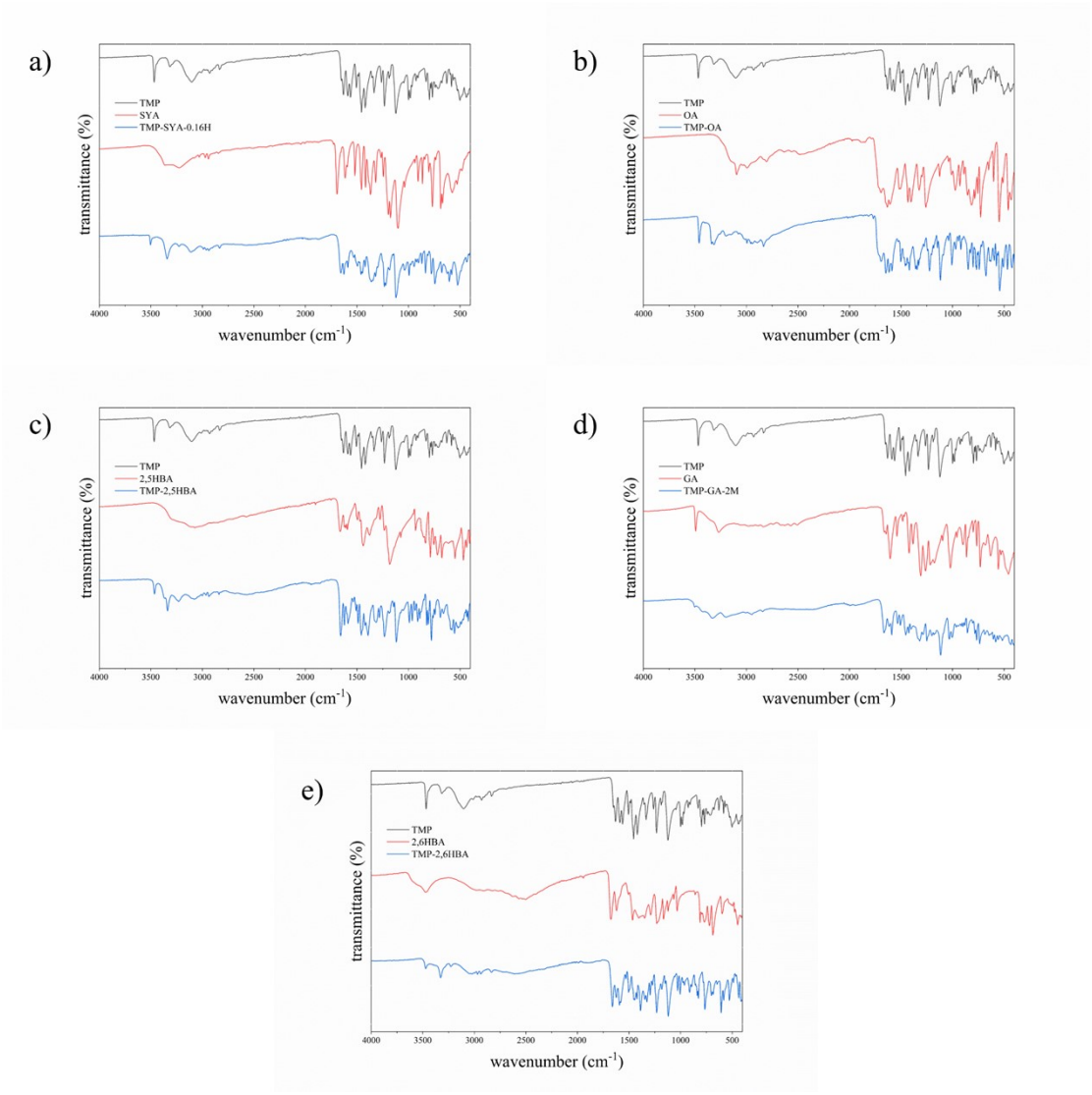

Figure S20. FTIR spectrogram of TMP, CCFs and salts. (a)TMP-SYA-0.16H (b)TMP-OA (c)TMP-2,5HBA (d)TMP-GA-2M (e)TMP-2,6HBA.

Table S1. Screening Experiment Results Overview. (✘ Indicates that there is no new phase detected by PXRD; ✔Indicates the presence of a new phase detected by PXRD; ✔✔Indicates the presence of a new phase detected by PXRD and the crystal structure determined by SCXRD)

API	CCF	Result
Trimethoprim	L-glutamic acid	✔
Trimethoprim	L-aspartic acid	✔
Trimethoprim	L-glutamine	✔
Trimethoprim	L-threonine	✘
Trimethoprim	L-asparagine	✘
Trimethoprim	DL-serine	✔
Trimethoprim	L-cysteine	✘
Trimethoprim	Syringic acid	✔✔
Trimethoprim	Coumalic acid	✔
Trimethoprim	DL-proline	✘
Trimethoprim	Orotic acid	✔✔
Trimethoprim	Diflunisal	✔
Trimethoprim	2,5-dihydroxybenzoic acid	✔✔
Trimethoprim	2,6-dihydroxybenzoic acid	✔✔
Trimethoprim	3,4- dihydroxybenzoic acid	✘
Trimethoprim	3,5- dihydroxybenzoic acid	✔
Trimethoprim	Gallic acid	✔✔
Trimethoprim	Ellagic acid	✔
Trimethoprim	Caffeic acid	✘
Trimethoprim	Cinnamic acid	✘
Trimethoprim	DL-mandelic acid	✘
Trimethoprim	Metformin hydrochloride	✘

Table S2. Crystallographic Parameters of three unsolvated salts and two solvated salts.

Compound	TMP-SYA-0.16H	TMP-OA	TMP-2,5HBA	TMP-GA-2M	TMP-2,6HBA
Empirical formula	$C_{23}H_{28.33}N_4O_{8.16}$	$C_{19}H_{22}N_6O_7$	$C_{21}H_{24}N_4O_7$	$C_{23}H_{32}N_4O_{10}$	$C_{21}H_{24}N_4O_7$
Formula weight	491.42	446.42	444.44	524.52	444.44
Temperature (K)	113.15	113.15	113.15	113.15	113.15
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic

Space group	P 2_1/n	P-1	P 2_1/n	P 2_1/c	C 2/c
a (Å)	12.1553(5)	7.0878(6)	7.0172(3)	11.2636(10)	25.4626(13)
b (Å)	8.8076(3)	7.5969(7)	28.2186(13)	20.7045(13)	9.2831(4)
c (Å)	22.3040(7)	18.9464(14)	10.7877(5)	12.0759(11)	19.5540(11)
α (°)	90	91.152(7)	90	90	90
β (°)	94.608(3)	98.566(7)	103.469(5)	117.535(11)	111.922(6)
γ (°)	90	103.763(8)	90	90	90
Volume (Å^3)	2380.13(15)	978.19(15)	2077.38(17)	2497.2(4)	4287.8(4)
Z	4	2	4	4	8
P_{calc} (g/cm^3)	1.376	1.516	1.421	1.395	1.377
F (000)	1038	468	936	1112	1873
Reflections collected	18662	14852	26572	19767	23814
Goodness-of-fit on F^2	1.023	1.0461	1.0391	1.054	1.0264
R_{int}	0.0412	0.0606	0.0853	0.0944	0.0573
R_1 indexes [$I > 2\sigma(I)$]	0.0425	0.0757	0.0650	0.0551	0.0597
wR_2 indexes [all data]	0.1115	0.2203	0.1586	0.1415	0.1504
CCDC	2221414	2221420	2221421	2221425	2221430

Table S3. Hydrogen bond geometrical parameters of salts

Compound	D–H···A	d(D–H)/Å	d(H···A)/Å	d(D···A)/Å	θ(D–H···A)/°	Symmetry code
TMP-SYA-0.16H	O_5-H_5···O_1	0.841(9)	1.836(10)	2.6799(14)	171.5(19)	-x+1/2, y+1/2, -z+1/2
	C_9-H_{9A}···O_6	0.98	2.42	2.773(8)	153	-x+1, -y+1, -z+1
	C_9-H_{9A}···O_{9A}	0.98	2.14	2.789(8)	122	-x+1, -y+1, -z+1
	C_9-H_{9C}···O_6	0.98	1.91	2.773(8)	145	
	O_6-H_{6A}···O_9	0.85	1.51	2.299(7)	153	
	O_6-H_{6A}···O_{7A}	0.85	2.62	3.152(10)	122	
	O_6-H_{6A}···O_{9A}	0.85	2.11	2.903(10)	156	
	O_6-H_{6B}···O_7	0.85	2.42	3.130(8)	142	-x+1, -y, -z+1
	O_6-H_{6B}···O_{7^a}	0.85	2.48	3.206(10)	147	-x+1, -y, -z+1
	N_1-H_{1A}···O_6	0.870(9)	2.427(14)	3.145(7)	140.1(15)	x+1/2, -y+1/2, z-1/2
	N_1-H_{1B}···O_5	0.877(9)	2.091(10)	2.9523(16)	167.1(16)	-x+3/2, y-1/2, -z+1/2
	N_2-H_{2A}···O_2	0.872(9)	2.060(12)	2.8550(16)	151.0(14)	x+1/2, -y+1/2, z-1/2
	N_2-H_{2B}···O_2	0.874(9)	2.040(9)	2.9066(16)	171.1(15)	-x+1/2, y+1/2, -z+1/2
	N_4-H_4···O_1	0.881(9)	1.789(10)	2.6586(15)	169.2(16)	-x+1/2, y+1/2, -z+1/2
TMP-OA	N_1-H_1···O_2	0.88	1.90	2.775(2)	174	-x, -y-1, -z+1
	N_3-H_3···O_3	0.88	2.04	2.919(2)	174	
	N_5-H_{5A}···O_4	0.88	1.81	2.680(3)	162	-x+1, -y+1, -z+1
	N_5-H_{5B}···O_4	0.88	1.94	2.797(3)	172	
	N_6-H_{6A}···O_2	0.88	2.00	2.874(3)	174	-x+1, -y+1, -z+1

TMP-2,5HBA	N_1-H_{1B}···O_1	0.88	2.27	3.006(2)	142	-1/2+x, 3/2-y, 1/2+z
	N_1-H_{1B}···O_2	0.88	2.39	3.151(2)	145	-1/2+x, 3/2-y, 1/2+z
	N_3-H_3···O_6	0.88	1.79	2.667(2)	170	1-x, 1-y, 1-z
	N_4-H_{4A}···O_7	0.88	2.16	2.921(2)	153	-1+x, y, 1+z
	N_4-H_{4B}···O_7	0.88	2.06	2.900(2)	177	1-x, 1-y, 1-z
	O_4-H_4···O_5	0.84	1.86	2.696(2)	171	1+x, y, z
	O_5-H_{5A}···O_6	0.84	1.74	2.493(2)	152	
TMP-GA-2M	N_1-H_1···O_5	0.88	1.92	2.794(3)	177	
	N_2-H_{2B}···O_4	0.88	1.85	2.724(3)	177	
	N_2-H_{2A}···O_2	0.88	2.25	2.994(3)	140	x+1, y, z+1
	N_4-H_{4B}···N_3	0.88	2.25	3.103(2)	163	-x+1, -y+1, -z+2
	N_4-H_{4A}···O_1	0.88	2.23	3.030(3)	152	-x, -y+1, -z+1
	O_6-H_{6A}···O_4	0.84	1.78	2.615(2)	170	x, -y+1/2, z-1/2
	O_7-H_7···O_{10}	0.84	1.89	2.663(2)	152	
	O_8-H_{8A}···O_9	0.84	1.91	2.685(2)	152	
	O_9-H_9···O_5	0.84	1.87	2.689(2)	166	x+1, -y+1/2, z+1/2
	C_{22}-H_{22A}···O_7	0.98	2.56	3.193(3)	123	
	O_{10}-H_{10}···O_8	0.84	1.97	2.784(2)	164	x, -y+1/2, z-1/2
TMP-2,6HBA	N_1-H_1···O_7	0.88	1.84	2.7208(19)	175	
	N_2-H_{2B}···O_6	0.88	1.93	2.778(2)	162	
	N_2-H_{2A}···O_4	0.88	2.08	2.8736(19)	149	-x+3/2, y+1/2, -z+1/2
	N_4-H_{4A}···O_1	0.88	2.20	3.0620(18)	165	x, -y+2, z-1/2
	N_4-H_{4A}···O_2	0.88	2.51	3.0825(18)	123	x, -y+2, z-1/2
	O_4-H_4···O_6	0.84	1.72	2.4793(19)	149	
	O_5-H_5···O_7	0.84	1.82	2.5667(18)	147	

Table S4. HPLC-UV method parameters for TMP.

Parameter	Details
Column	Agilent Extend C18 column (5μm,4.6mm x 250mm)
Mobile phase	Acetic acid-methanol -water (3.75: 25: 71.25)
Flow rate	1 mL/min
Inject volume	20μL
Column temperature	37℃
Sample temperature	37℃
λ_{max}	275nm
Retention time	4.5min
Equation	y=22221.97x+3121
Regression coefficient (R^2)	0.99997
Calibration range	50-500mg/L

Table S5. Parameters of the Hydrogen Bonds for five salts in AIM Analysis.

Compound	Bond Type	ρ (a.u.)	$\nabla^2\rho$ (a.u.)	G (a.u.)	V (a.u.)	H (a.u.)	E_H (kJ·mol^{-1})
TMP-SYA-0.16H	$N_4H_4\cdots O_1$	6.07E^{-02}	1.47E^{-01}	4.27E^{-02}	-4.89E^{-02}	-6.11E^{-03}	-5.35E^{+01}
	$N_2H_{2B}\cdots O_2$	3.09E^{-02}	8.13E^{-02}	2.13E^{-02}	-2.24E^{-02}	-1.02E^{-03}	-2.57E^{+01}
	$N_2H_{2A}\cdots O_2$	2.58E^{-02}	8.14E^{-02}	2.01E^{-02}	-1.98E^{-02}	2.49E^{-04}	-2.10E^{+01}
	$C_1O_1\cdots O_8$	1.08E^{-02}	3.67E^{-02}	8.87E^{-03}	-8.56E^{-03}	3.08E^{-04}	-6.95E^{+00}
	$O_5H_5\cdots O_1$	3.60E^{-02}	1.18E^{-01}	2.82E^{-02}	-2.69E^{-02}	1.27E^{-03}	-3.05E^{+01}
	$O_6H_{6A}\cdots O_9$	4.85E^{-02}	2.00E^{-01}	4.88E^{-02}	-4.77E^{-02}	1.13E^{-03}	-4.22E^{+01}
	$N_1H_{1B}\cdots O_5$	2.54E^{-02}	7.22E^{-02}	1.86E^{-02}	-1.91E^{-02}	-5.21E^{-04}	-2.06E^{+01}
TMP-OA	$N_1H_{1A}\cdots O_4$	7.88E^{-03}	3.39E^{-02}	7.05E^{-03}	-5.62E^{-03}	1.43E^{-03}	-4.25E^{+00}
	$N_3H_3\cdots O_3$	3.17E^{-02}	7.60E^{-02}	2.03E^{-02}	-2.16E^{-02}	1.28E^{-03}	-2.64E^{+01}
	$N_5H_{5B}\cdots O_4$	5.33E^{-02}	1.51E^{-01}	4.03E^{-02}	-4.29E^{-02}	-2.54E^{-03}	-4.67E^{+01}
	$N_5H_{5A}\cdots O_4$	3.22E^{-02}	1.10E^{-01}	2.64E^{-02}	-2.52E^{-02}	1.14E^{-03}	-2.69E^{+01}
	$N_6H_{6A}\cdots O_2$	2.97E^{-02}	9.28E^{-02}	2.27E^{-02}	-2.23E^{-02}	4.64E^{-04}	-2.46E^{+01}
	$N_1H_1\cdots O_2$	3.94E^{-02}	1.21E^{-01}	2.99E^{-02}	-2.94E^{-02}	4.67E^{-04}	-3.37E^{+01}
TMP-2,5HBA	$N_3H_3\cdots O_6$	5.87E^{-02}	1.48E^{-01}	4.19E^{-02}	-4.69E^{-02}	-4.93E^{-03}	-5.17E^{+01}
	$N_4H_{4B}\cdots O_7$	3.16E^{-02}	8.10E^{-02}	2.15E^{-02}	-2.27E^{-02}	-1.24E^{-03}	-2.64E^{+01}
	$N_4H_{4A}\cdots O_7$	2.16E^{-02}	6.67E^{-02}	1.67E^{-02}	-1.68E^{-02}	-6.24E^{-05}	-1.71E^{+01}
	$O_4H_4\cdots O_5$	4.08E^{-02}	1.28E^{-01}	3.16E^{-02}	-3.12E^{-02}	3.47E^{-04}	-3.49E^{+01}
	$N_1H_{1A}\cdots O_1$	1.46E^{-02}	4.95E^{-02}	1.20E^{-02}	-1.16E^{-02}	4.02E^{-04}	-1.06E^{+01}
TMP-GA-2M	$N_1H_1\cdots O_5$	4.39E^{-02}	1.08E^{-01}	2.87E^{-02}	-3.05E^{-02}	-1.78E^{-03}	-3.79E^{+01}
	$N_2H_{2B}\cdots O_4$	4.80E^{-02}	1.33E^{-01}	3.47E^{-02}	-3.61E^{-02}	-1.39E^{-03}	-4.17E^{+01}
	$O_6H_{6A}\cdots O_4$	4.99E^{-02}	1.60E^{-01}	4.04E^{-02}	-4.09E^{-02}	-4.60E^{-04}	-4.35E^{+01}
	$O_9H_9\cdots O_5$	4.00E^{-02}	1.29E^{-01}	3.18E^{-02}	-3.12E^{-02}	5.22E^{-04}	-3.43E^{+01}
	$O_8H_{8A}\cdots O_9$	3.81E^{-02}	1.15E^{-01}	2.88E^{-02}	-2.89E^{-02}	-3.48E^{-05}	-3.25E^{+01}
	$O_{10}H_{10}\cdots O_8$	3.28E^{-02}	1.00E^{-01}	2.49E^{-02}	-2.47E^{-02}	1.75E^{-04}	-2.75E^{+01}
	$O_7H_7\cdots O_{10}$	4.00E^{-02}	1.22E^{-01}	3.07E^{-02}	-3.09E^{-02}	-2.56E^{-04}	-3.43E^{+01}
	$N_4H_{4B}\cdots O_1$	1.93E^{-02}	5.46E^{-02}	1.43E^{-02}	-1.50E^{-02}	-6.75E^{-04}	-1.49E^{+01}
TMP-2,6HBA	$N_1H_1\cdots O_7$	5.09E^{-02}	1.32E^{-01}	3.55E^{-02}	-3.80E^{-02}	-2.48E^{-03}	-4.44E^{+01}
	$N_2H_{2B}\cdots O_6$	4.02E^{-02}	1.18E^{-01}	2.97E^{-02}	-3.00E^{-02}	-3.32E^{-04}	-3.44E^{+01}
	$N_2H_{2A}\cdots O_4$	2.52E^{-02}	7.60E^{-02}	1.93E^{-02}	-1.95E^{-02}	-2.74E^{-04}	-2.04E^{+01}
	$N_4H_{4A}\cdots O_1$	1.98E^{-02}	5.43E^{-02}	1.44E^{-02}	-1.52E^{-02}	-8.13E^{-04}	-1.54E^{+01}
	$O_4H_4\cdots O_6$	7.43E^{-02}	1.71E^{-01}	5.68E^{-02}	-7.08E^{-02}	-1.40E^{-02}	-6.62E^{+01}
	$O_5H_5\cdots O_7$	5.30E^{-02}	1.50E^{-01}	4.06E^{-02}	-4.37E^{-02}	-3.10E^{-03}	-4.64E^{+01}

Table S6. FTIR stretching vibration frequencies of TMP, CCF and salts.

Compound	C=O (cm^{-1})	N-H (cm^{-1})
TMP	N/A	3471.0; 3319.5
SYA	1694.5	N/A
OA	1694.5	N/A
2,5HBA	1663.6	N/A

GA	1665.6	N/A
2,6HBA	1675.9	N/A
TMP-SYA-0.16H	1657.4	3502.3; 3343.6
TMP-OA	1694.5	3459.0; 3341.6
TMP-2,5HBA	1659.4	3465.2; 3337.4
TMP-GA-2M	1663.6	3432.2; 3331.2
TMP-2,6HBA	1661.5	3471.4; 3327.1

Table S7. pKa and ΔpKa values of TMP and the coformers.

$pK_a(pK_{a1})$	Coformer	$pK_a(pK_{a2})$	$\Delta pK_a(pK_{a1}\text{-}pK_{a2})$	forms
	SYA	4.33	2.71	salt
	OA	2.78	4.26	salt
TMP (7.04)	2,5HBA	3.01	4.03	salt
	GA	4.21	2.83	salt
	2,6HBA	1.30	5.74	salt

Table S8. Test results of water content in sample TMP-SYA-0.16H.

Sample	Water content (Mass ratio)	Corresponding molecular formula
1st	0.5762%	**TMP-SYA-0.157H**
2nd	0.6120%	**TMP-SYA-0.170H**
3rd	0.5831%	**TMP-SYA-0.159H**
4th	0.6019%	**TMP-SYA-0.164H**
5th	0.5976%	**TMP-SYA-0.162H**
6th	0.6002%	**TMP-SYA-0.164H**
Average	0.5952%	**TMP-SYA-0.162H**