Multicomponent crystal forms of a biologically active hydrazone with some dicarboxylic acids: Salts or cocrystals?

Liliana Mazur,[a]* Ilona Materek,[a] Andrew D. Bond[b] and William Jones[b]

[a] Faculty of Chemistry, Maria Curie-Skłodowska University, Maria Curie-Skłodowska Square 2, 20-031 Lublin, Poland

[b] Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

* Corresponding author: Liliana Mazur (l.mazur@poczta.umcs.lublin.pl)

1. Cocrystal screening

Table 1S. Physicochemical characteristics (T_m – melting point, T_{fus} – temperature of fusion) of the studied adducts.

Form	T_m (acid) / °C	T_m (adduct) / °C (HSM)	T_{fus} (adduct)/ °C		IR (ν_{max}, cm^{-1})
			(*onset*)	(*peak*)	
BZH·H$_2$O	–	128 – 130	121	125	See Ref. 42.
1	132 –135	100 – 119	108	113	3249, 3224, 3047, 2970, 2937, 1725, 1694, 1617, 1603, 1578, 1544, 1489, 1470, 1450, 1422, 1375, 1351, 1259, 1183, 1153, 1092, 1034, 1023, 1001, 957, 933, 921
2	184 –186	118 –139	137	140	3205, 3116, 3082, 3065, 3032, 2970, 2943, 1718, 1688, 1636, 1602, 1556, 1494, 1467, 1417, 1352, 1318, 1264, 1252, 1182, 1141, 1096, 1076, 1029, 938, 917
3	95 – 98	103 – 111	101	105	3268, 3084, 2933, 2658, 2593, 1716, 1642, 1602, 1581, 1557, 1474, 1458, 1437, 1421, 1386, 1363, 1326, 1308, 1290, 1249, 1220, 1184, 1170, 1147, 1103, 1080, 1054, 1042, 1030, 1004, 941, 926
4a	200 –202	115 –133	124	128 132	3261, 3065, 2799, 2720, 2440, 1687, 1637, 1602, 1591, 1578, 1557, 1498, 1470, 1448, 1436, 1362, 1346, 1331, 1312, 1287, 1266, 1208, 1150, 1126, 1105, 1080, 1008, 967, 943, 922
4b		112 – 138	132	136	3299, 3064, 2918, 2848, 2567, 1719, 1698, 1681, 1644, 1605, 1591, 1580, 1551, 1493, 1475, 1493, 1386, 1370, 1343, 1309, 1257, 1214, 1192, 1147, 1127, 1097, 1077, 1026, 1014, 1001, 941, 919, 908
4a·CH$_3$OH		60 – 90 119 – 133	124	127 131	3326, 3114, 3082, 3034, 2942, 2720, 2502, 1717, 1689, 1642, 1601, 1580, 1556, 1494, 1467, 1446, 1418, 1374, 1320, 1252, 1182, 1141, 1143, 1096, 1076, 1028, 1000, 938, 917

2. X-ray crystallography

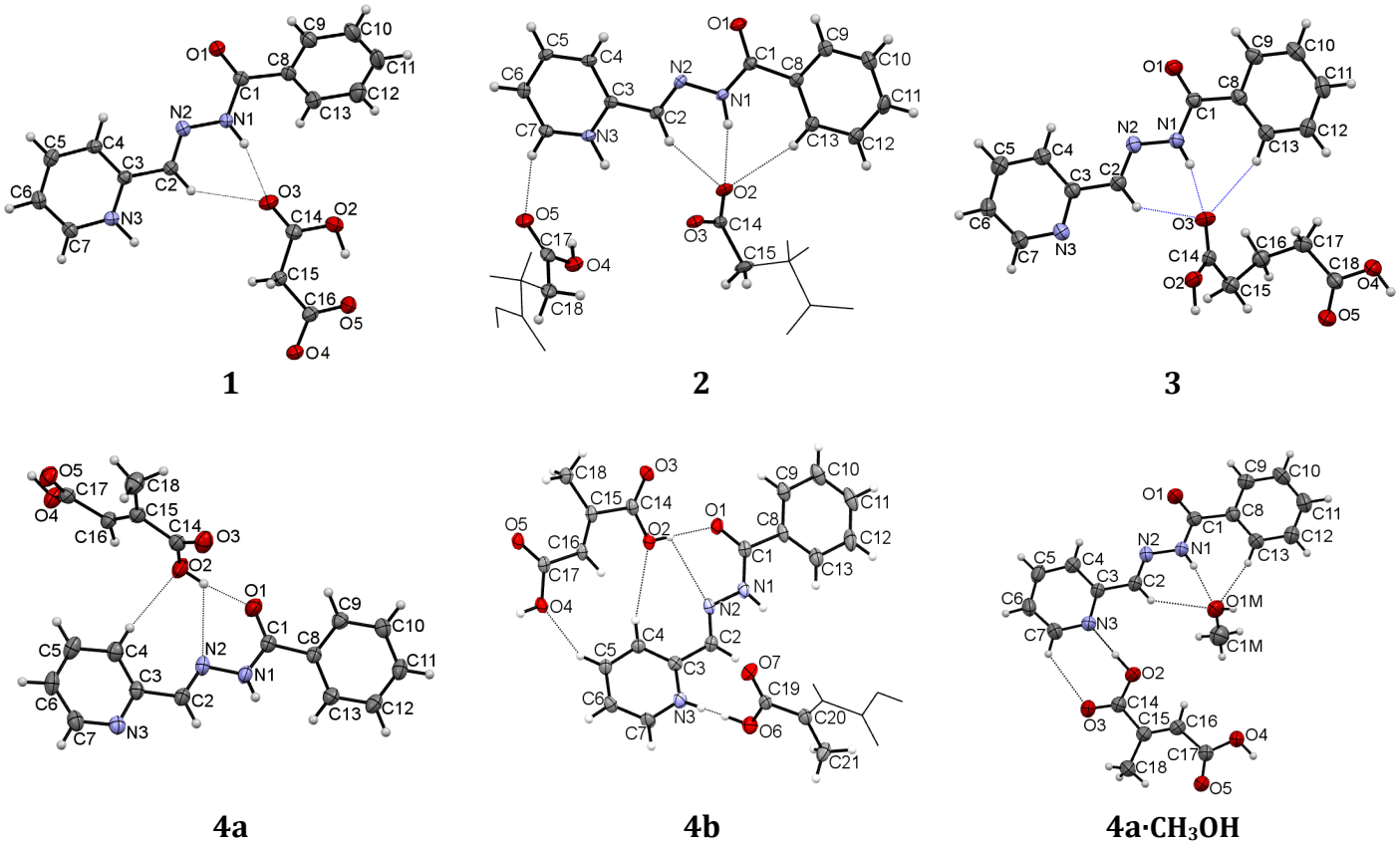


Figure 1S. Labelling of atoms and estimation of their thermal motion parameters as ADPs (50% probability level) for studied forms. Dashed lines indicate hydrogen bonds.

Table 2S. Selected geometric parameters (d - bond distance, θ – bond angle, τ - torsion angle).

d/ Å	**BZH·H_2O** CIZRAE02[42]	**1**	**2**	**3**	**4a**	**4b**	**4a·CH_3OH**
C1–O1	1.229(1)	1.223(2)	1.224(3)	1.235(2)	1.229(3)	1.224(3)	1.220(2)
C1–N1	1.362(1)	1.378(2)	1.372(3)	1.354(2)	1.345(3)	1.356(3)	1.358(2)
N1–N2	1.368(1)	1.360(2)	1.368(3)	1.375(2)	1.379(3)	1.375(3)	1.375(2)
N2–C2	1.283(1)	1.283(2)	1.281(3)	1.278(2)	1.281(3)	1.281(3)	1.271(2)
C3–N3	1.344(1)	1.348(2)	1.352(3)	1.343(2)	1.351(3)	1.345(3)	1.347(2)
N3–C7	1.339(1)	1.340(2)	1.345(3)	1.343(2)	1.345(3)	1.338(3)	1.338(2)
C14–O2		1.311(2)	**1.289(3)**	1.322(2)	1.316(3)	1.324(3)	1.308(2)
C14–O3		1.216(2)	**1.236(3)**	1.216(2)	1.218(3)	1.206(3)	1.205(2)
C16/C17–O4		**1.269(2)**	1.329(3)	1.325(2)	1.331(3)	1.318(3)	1.314(2)
C16/C17–O5		**1.243(2)**	1.223(3)	1.206(2)	1.203(3)	1.230(3)	1.217(2)
C19–O6						**1.300(3)**	
C19–O7						**1.217(3)**	
θ / °							
C3–N3–C7	118.1(1)	121.6(2)	122.5(2)	117.4(1)	117.6(2)	118.9(2)	118.0(2)
O1–C1–N1	123.0(1)	122.1(2)	122.4(2)	122.2(1)	122.3(2)	122.1(2)	121.9(2)
N1–N2–C2	115.3(1)	117.1(1)	115.4(2)	116.2(1)	115.3(2)	116.6(2)	117.0(2)
τ / °							
O1–C1–N1–N2	-1.7(1)	2.1(2)	1.5(4)	-5.8(2)	2.1(4)	2.7(4)	-0.3(3)
C1–N1–N2–C2	-176.9(1)	-177.6(2)	177.9(2)	-177.7(1)	179.0(2)	-169.8(2)	177.9(2)
N1–N2–C2–C3	178.9(1)	179.5(1)	179.2(2)	178.0(1)	-179.1(2)	-177.2(2)	178.6(2)
N2–C2–C3–N3	-175.1(1)	174.1(1)	178.5(2)	168.1(1)	178.6(2)	-171.8(2)	168.2(2)
O1–C1–C8–C13	-158.2(1)	-153.0(2)	-179.4(3)	-166.6(2)	-170.4(2)	175.4(2)	-165.6(2)

Table 3S. Geometries of hydrogen bonds and selected short contacts for studied structures.

Form	Interaction	$d_{D...H}$ /Å	$d_{H...A}$ / Å	$d_{D...A}$ / Å	<D-H...A /°	Symmetry code
1	N1–H1n···O3	0.91(2)	1.99(2)	2.878(2)	165(2)	x, y, z
	C2–H2···O3	0.95	2.44	3.235(2)	141	
	N3–H3n···O4	1.04(3)	1.53(3)	2.564(2)	179(3)	
	N3–H3n···O5	1.04(3)	2.61(3)	3.275(2)	122(2)	-x, -y+1, -z+1
	C7–H7···O5	0.95	2.59	3.240(2)	125	
	O2–H2o···O4	0.98(3)	1.58(3)	2.530(2)	163(3)	x, y, z
	C11–H11···O5	0.95	2.65	3.500(2)	149	-x, -y+2, -z+1
	C5–H5···O1	0.95	2.45	3.197(2)	135	-x+2, -y+1, -z
	C15–H15a···O4	0.99	2.67	3.448(2)	136	-x, -y+1, -z+1
	C15–H15b···O4	0.99	2.62	3.498(2)	149	-x-1, -y+1, -z+1
2	N1–H1n···O3	0.89(3)	1.93(3)	2.801(3)	166(2)	
	C2–H2···O3	0.93	2.44	3.176(3)	137	x, y, z
	C13–H13···O3	0.93	2.45	3.331(4)	157	
	N3–H3n···O2	0.99(3)	1.61(3)	2.599(3)	176(2)	x, y-1, z
	O4–H4o···O2	0.87(4)	1.73(4)	2.594(3)	177(2)	x, y-2, z
	C5–H5···O1	0.93	2.58	3.012(4)	109	-x+1/2, y-1/2, -z+3/2

	C5–H5···N2	0.93	2.67	3.456(4)	142	
	C7–H7···O5	0.93	2.22	3.107(3)	159	x, y, z
	C15–H15a···O4	0.97	2.66	3.414(3)	135	x, y+2, z
	C17–H17b···O5	0.97	2.58	3.336(4)	135	-x, -y-2, -z+1
3	O2–H2o···O1	0.95(3)	1.69(3)	2.619(2)	163(2)	
	O2–H2o···N2	0.95(3)	2.58(3)	3.194(2)	122(2)	x, y, z
	C4–H4···O2	0.95	2.69	3.598(2)	161	
	N1–H1n···O3	0.91(2)	2.03(2)	2.926(2)	167(2)	
	C2–H2···O3	0.95	2.66	3.395(2)	135	x, -y+1/2, z-1/2
	C13–H13···O3	0.95	2.54	3.314(2)	138	
	O4–H4o···N3	0.92(2)	1.84(2)	2.761(2)	179(2)	-x+1, -y, -z+1
	C7–H7···O5	0.95	2.40	3.109(2)	131	
	C6–H6···O2	0.95	2.53	3.247(2)	132	-x+2, y-1/2, -z+3/2
	C11–H11···O5	0.95	2.30	3.211(2)	161	-x+1, -y+1, -z+1
4a	O2–H2o···O1	0.86(4)	1.78(4)	2.600(3)	158(2)	
	O2–H2o···N2	0.86(4)	2.64(4)	3.188(3)	123(2)	x, y, z
	C4–H4o···O2	0.95	2.67	3.610(3)	172	
	O4–H4o···N3	1.00	1.71	2.699(3)	169	x, y+1, z
	N1–H1n···O3	0.83(2)	2.10(2)	2.897(3)	162(2)	
	C2–H2···O3	0.95	2.69	3.404(3)	133	-x+1, -y+1, -z+1
	C13–H13···O3	0.95	2.64	3.372(3)	134	
	C6–H6···O5	0.95	2.71	3.210(4)	113	-x+1, -y+2, -z
	C7–H7···O5	0.95	2.74	3.240(3)	114	
	C9–H9···O5	0.95	2.37	3.298(3)	166	-x+1, -y+2, -z+1
4b	O2–H2o···O1	0.81(4)	1.87(4)	2.684(3)	179(2)	
	O2–H2o···N2	0.81(4)	2.66(4)	3.028(3)	110(2)	x, y, z
	C4–H4···O2	0.93	2.64	3.415(4)	141	
	C5–H5···O4	0.93	2.71	3.367(4)	128	
	N1–H1n···O7	0.87(3)	2.02(3)	2.878(3)	170(2)	
	C2–H2···O7	0.93	2.50	3.259(4)	139	x+1, y, z
	C13–H13···O7	0.93	2.42	3.338(4)	168	
	O4–H4o···O5	0.84(4)	1.78(4)	2.628(4)	179(2)	-x-1, -y+1, -z+1
	O6–H6o···N3	0.93(5)	1.67(5)	2.601(5)	179(3)	x, y, z
	N3–H3n···O6	0.79(8)	1.81(8)	2.601(8)	179(4)	
	C6–H6···O3	0.93	2.39	3.085(3)	131	x-1, y+1, z
	C5–H5···O5	0.93	2.71	3.534(3)	148	-x, 1-y, 1-z
	C4–H4···O4	0.93	2.59	3.336(3)	137	x+1, y, z
4a·CH$_3$OH	N1-H1n···O1m	0.86(2)	2.05(2)	2.908(2)	172(1)	
	C2–H2···O1m	0.93	2.57	3.350(2)	141	x, y, z
	C13–H13···O1m	0.93	2.49	3.360(3)	156	
	C6–H6···O3	0.93	2.60	3.372(3)	141	
	O1m–H1m···O1	0.91(3)	1.97(3)	2.817(3)	154(2)	
	O1m–H1m···N2	0.91(3)	2.60(3)	3.213(3)	125(2)	x-1, y, z
	C1m–H1m···N2	0.96	2.74	3.362(3)	123(1)	
	O2–H2o···N3	1.03(2)	1.61(2)	2.643(2)	178(1)	-x, -y+1, -z
	C7–H7···O3	0.93	2.64	3.294(2)	128	
	O4–H4o···O5	0.92(3)	1.73(3)	2.648(3)	175(2)	-x+2, -y+2, -z
	C5–H5···O1	0.93	2.67	3.439(3)	140	-x+1, -y, -z+1
	C10–H10···O5	0.93	2.67	3.575(3)	166	

3. Powder X-ray diffraction

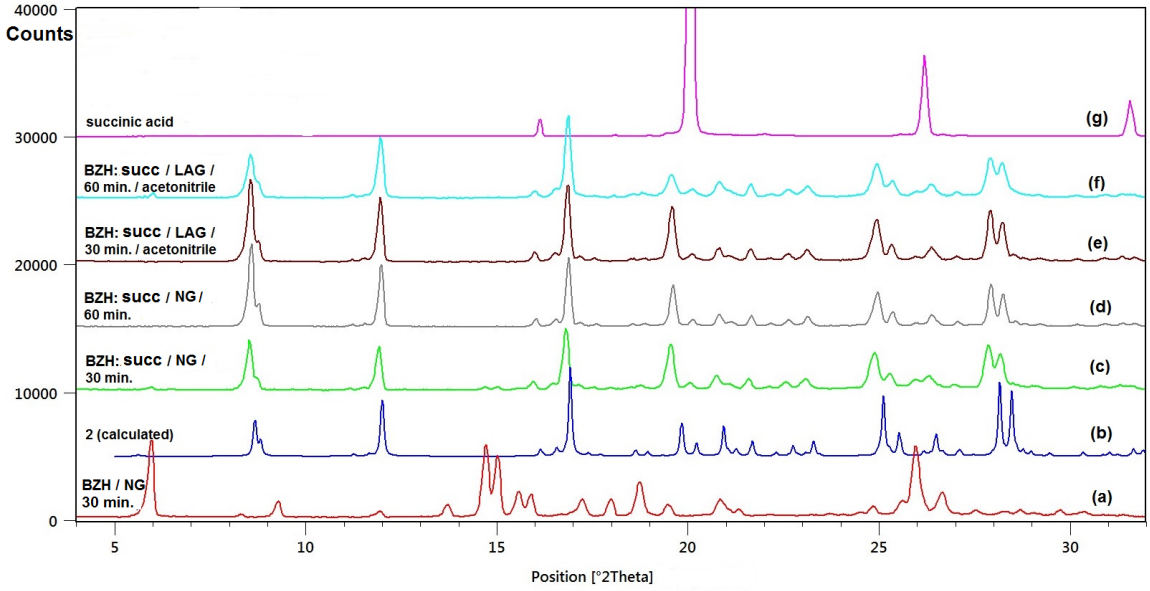


Figure 2S. PXRD patterns of: (*a*) pure **BZH·H$_2$O** after NG; (b) calculated BZH-succ (**2**); (c), (d) BZH-succ prepared by NG after 30 and 60 minutes of milling; (e), (f) BZH-succ prepared by LAG using acetonitrile after 30 and 60 minutes of milling, respectively; (g) pure succinic acid.

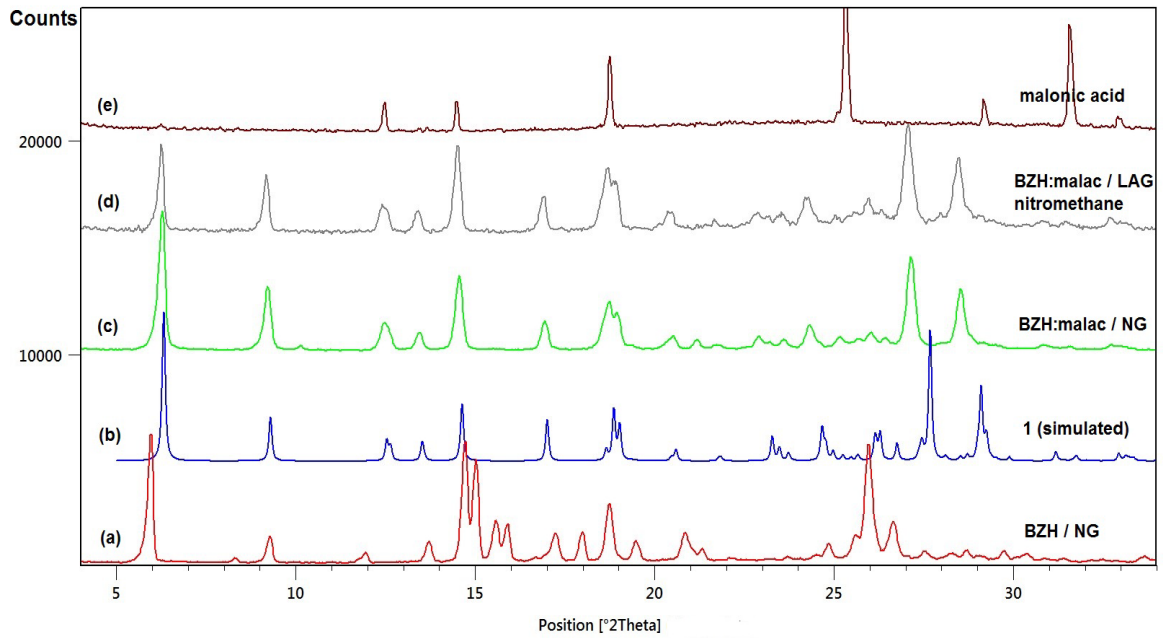


Figure 3S. PXRD patterns of: (*a*) pure **BZH·H$_2$O** after neat grinding; (b) calculated BZH-malac (**1**); (c) BZH-malac prepared by NG; (d) BZH-malac prepared by LAG using nitromethane; (e) pure malonic acid.

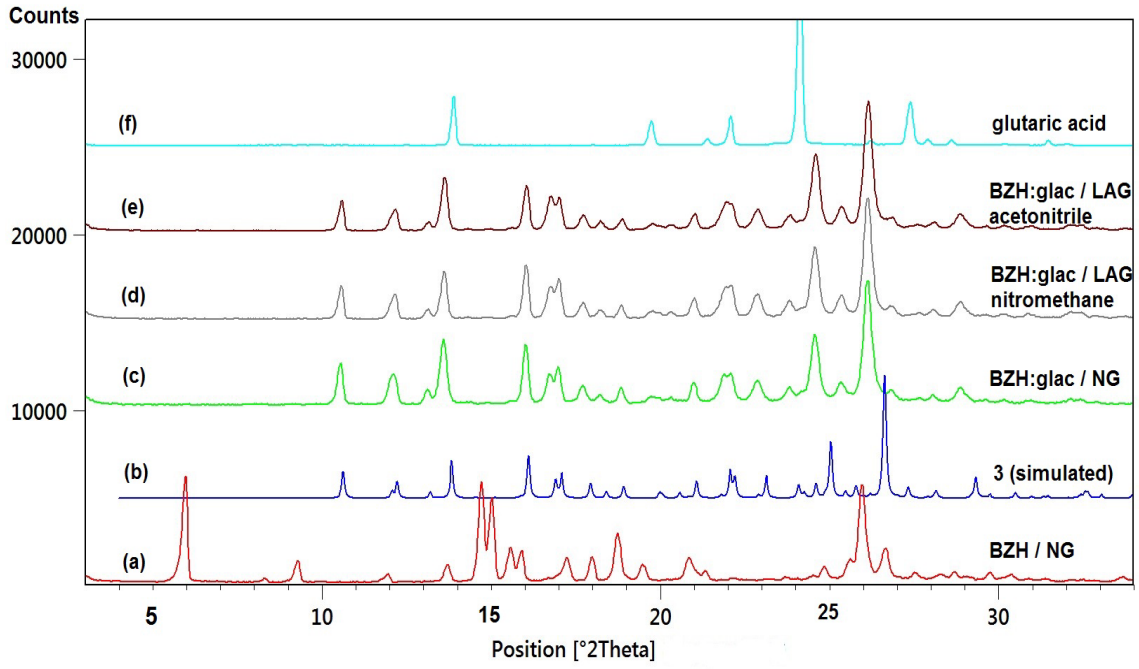


Figure 4S. PXRD patterns of: (*a*) pure **BZH·H$_2$O** after NG; (b) calculated BZH-glac (**3**); (c) BZH-glac prepared by NG; (d), (e) BZH-glac prepared by LAG using nitromethane or acetonitrile; (f) pure glutaric acid. All PXRD patterns were recorded at room temperature.

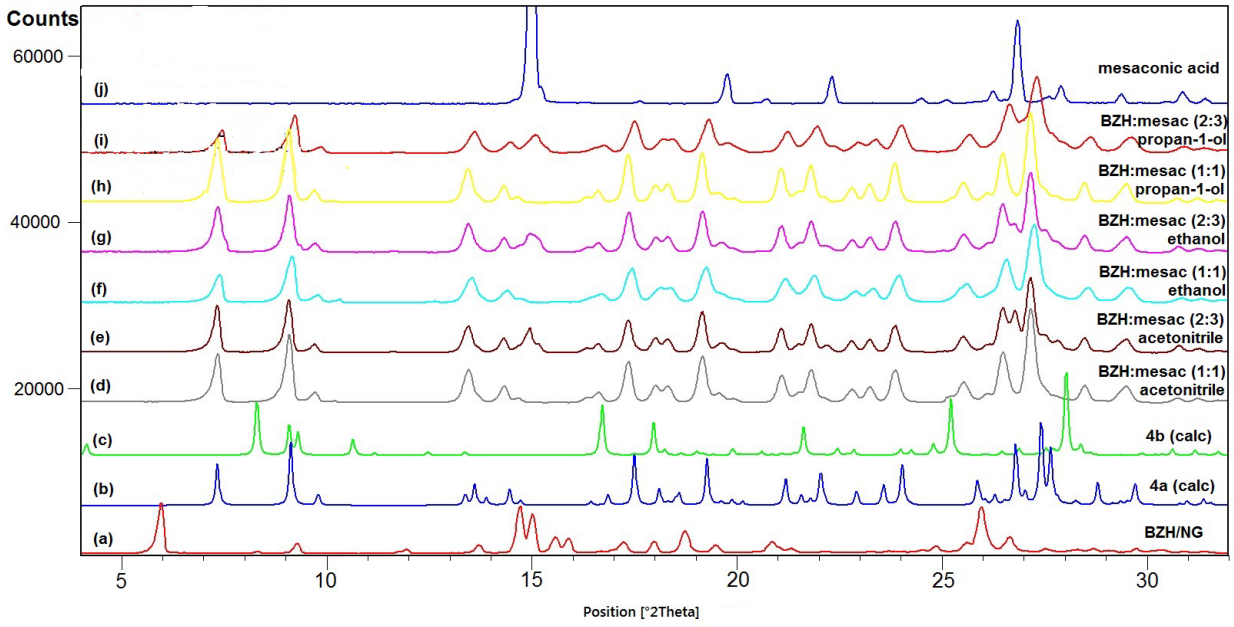


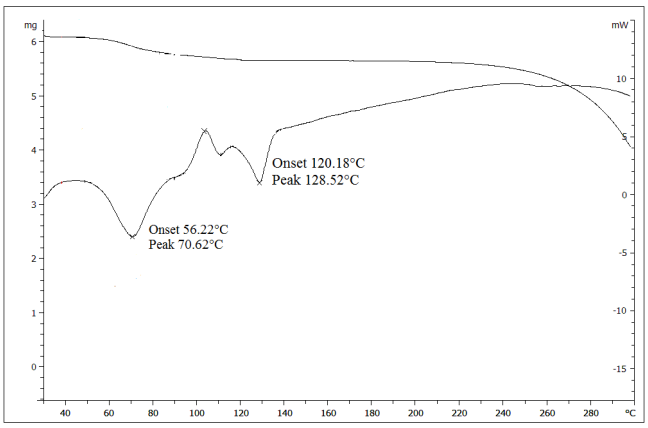
Figure 5S. PXRD patterns of: (*a*) pure **BZH·H$_2$O** after NG; (b) calculated BZH-mesac (**4a**); (c) calculated BZH-mesac (**4b**); (d), (f), (h) BZH-mesac (1:1) and (e), (g), (i) BZH-mesac (2:3) after LAG using acetonitrile; ethanol or propan-1-ol; (j) pure mesaconic acid.

4. Synthon occurrences (CSD searches)

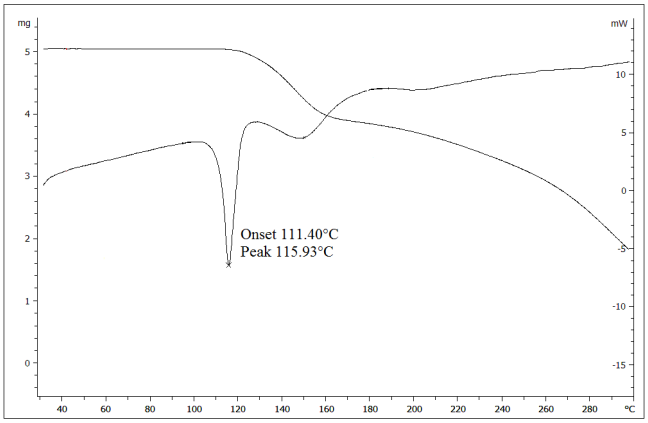
Table 4S. Modes of binding of 2-pyridinecarboxaldehyde N^1-acylhydrazones - carboxylic acid solids (CSD survey).

Entry	CSD reference code	Hydrate	Hydrogen-bond donor group	Hydrogen-bond acceptor group	Synthon	Ref.
N'-(pyridin-2-ylmethylene)isonicotinohydrazide / 2-Pyridylcarboxaldehyde isonicotinoyl hydrazone						
1.	LATCIU	√	carboxyl	4-pyridyl	B	4
2.	LATCOA	√	carboxyl	4-pyridyl	B	4
3.	LATCUG	√	carboxyl	4-pyridyl	B	4
4.	LATDAN	√	carboxyl	4-pyridyl	B	4
5.	LATDER	√	carboxyl	4-pyridyl	B	4
6.	LATDIV	√	carboxyl	4-pyridyl	A	4
7.	LATDOB	√	carboxyl	4-pyridyl	B	4
8.	LATDUH	√	carboxyl	4-pyridyl	A	4
N'-(pyridin-3-ylmethylene)pyridine-2-carbohydrazide						
9.	KECKEL		carboxyl, amide	3-pyridyl, amide, carboxyl	B, D C	51
10.	KECKIP		carboxyl, amide	3-pyridyl, amide, carboxyl	B, D C	51
11.	KECLOW		carboxyl	3-pyridyl, amide	A, D	51
12.	KECMAJ		carboxyl	3-pyridyl, amide	A, D	51
13.	KECSUJ		carboxyl	3-pyridyl	B	51
N'-(pyridin-3-ylmethylene)nicotinohydrazide						
14.	KECKOV	√	carboxyl	3-pyridyl	A, B	51
N'-(pyridin-4-ylmethylene)nicotinohydrazide						
15.	KECKUB	√	carboxyl	3-pyridyl	A	51
16.	KECSOD		carboxyl	4-pyridyl, amide	A, D	51
17.	KECTAQ	√	carboxyl	3-pyridyl, 4-pyridyl	A, B	51
4-Pyridylcarboxaldehyde isonicotinoylhydrazone						
18.	LATFET	√	carboxyl	4-pyridyl		4
19.	LATFIX	√	carboxyl	4-pyridyl	A, B	4
20.	LATFOD	√	carboxyl	4-pyridyl	A, B	4
4-(2-((2-hydroxyphenyl)methylidene)hydrazinecarbonyl)pyridin-1-ium						
21.	OKAVED		4-pyridyl, amide	carboxyl, carboxylate carboxylate	B, B' C	50
22.	OKAVIH		4-pyridyl, amide	carboxylate	A', C	50
23.	OKAVON		4-pyridyl, amide	carboxylate	B', C	50
24.	OKAWAA	√	4-pyridyl, amide	carboxylate	B', C	50
N'-(4-methylbenzylidene)isonicotinohydrazide						
25.	SAYQEQ	√	carboxyl	4-pyridyl	A	S1
26.	ZAQMIP	√	carboxyl	4-pyridyl	A	S1
N'-(2-methoxybenzylidene)isonicotinohydrazide						
27.	LEFQUK		carboxyl	4-pyridyl	A	S2
N'-(4-methoxybenzylidene)isonicotinohydrazide						
28.	CEFZEU		carboxyl	4-pyridyl, amide	B, D	S3
(E)-N'-(5-Chloro-3-methoxy-2-(4-methylphenylsulfonyloxy)benzylidene)isonicotinohydrazide						
29.	JIRWOX		carboxyl amide	amide, carboxyl	D C	S4
(E)-N'-(2-(4-Chloro-3-nitrophenylsulfonyloxy)-3-methoxybenzylidene)isonicotinohydrazide						
30.	IGABEY		carboxyl, amide	4-pyridyl, amide, carboxyl	A, D C	S5
(N'-furfurylidene)isonicotinoylhydrazide						
31.	NOSZAW	√	carboxyl	4-pyridyl	A	S6

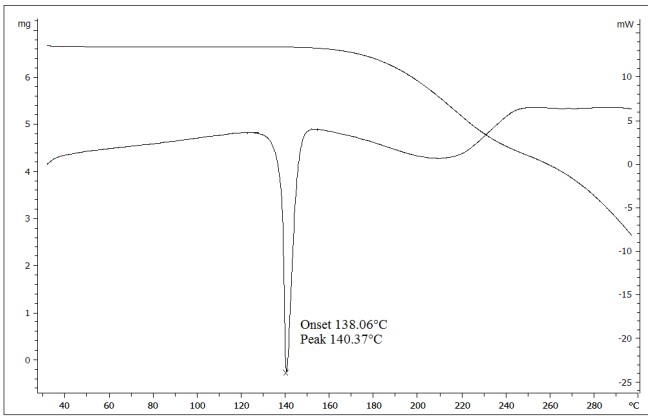
5. Thermal stability studies



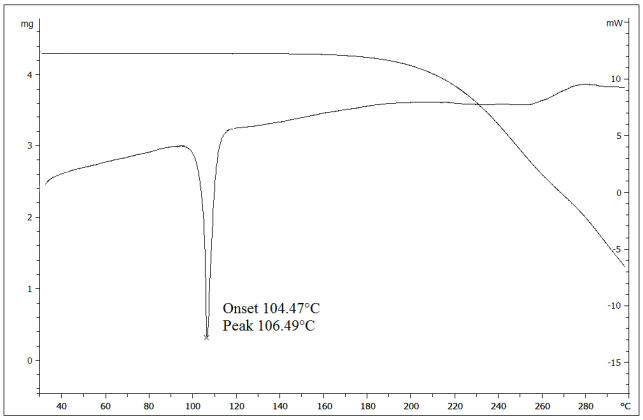
(*a*)



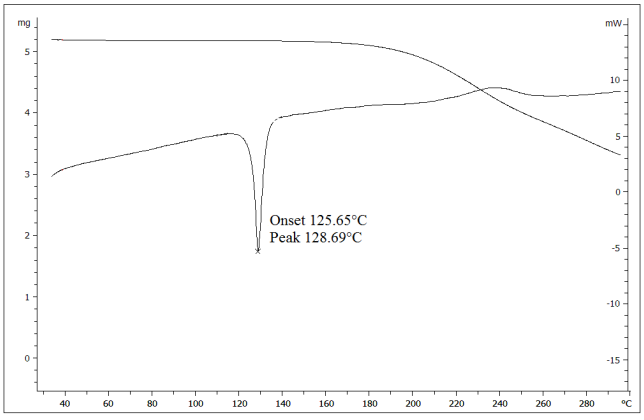
(*b*)



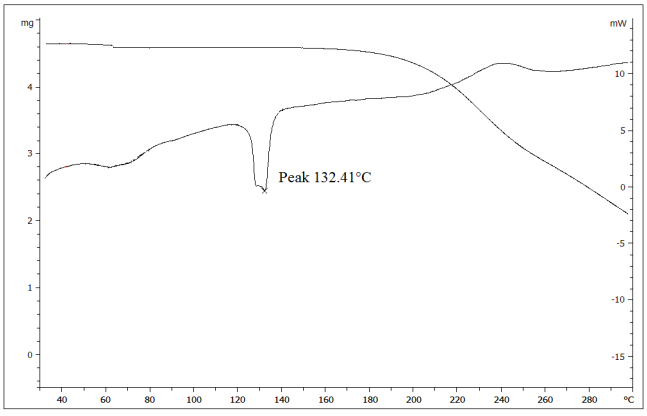
(*c*)



(*d*)



(*e*)



(*f*)

Figure 6S. TG/DSC plots for: (*a*) **BZH·H$_2$O**, (*b*) **1**, (*c*) **2**, (*d*) **3**, (*e*) **4a**, (*f*) **4b** recorded in the N_2 atmosphere with a heating rate of 10 °C min^{-1}.

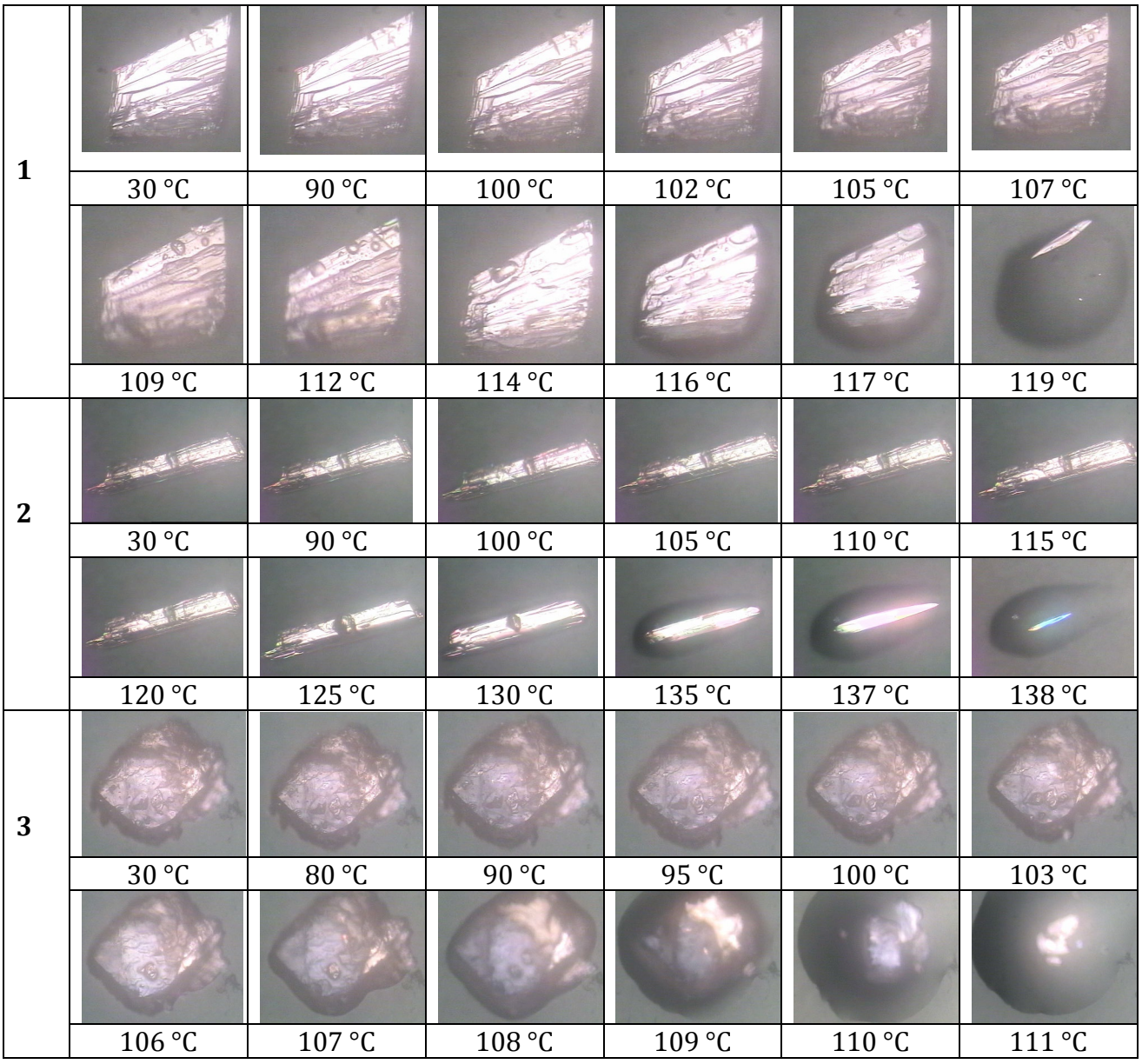


Figure 7S. Hot-stage micrographs of salts BZH-malac (**1**), BZH-succ (**2**) and cocrystal BZH-glac (**3**). The micrographs were recorded in the air with the heating rate of 2 °C min^{-1}.

References

S1. Lemmerer, A.; Bernstein, J.; Kahlenberg, V. Covalent assistance in supramolecular synthesis: *in situ* modification and masking of the hydrogen bonding functionality of the supramolecular reagent isoniazid in co-crystals. *CrystEngComm* **2011**, *13*, 5692-5708.

S2. Mohamed, S. K.; Farrukh, M. A.; Akkurt, M.; Albayati, M. R.; Abdelhamid, A. A. 2-(1,3-Dioxoisoindolin-2-yl)acetic acid-*N*'-[(E)-2-methoxybenzylidene]pyridine-4-carbohydrazide (1/1). *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2012**, *68*, o2442.

S3. Novakovic, S. B.; Bogdanovic, G. A.; Mohamed, S. K.; Albayati, M. R.; Hameed, A. S. 2-(1,3-Dioxoisoindolin-2-yl)acetic acid–N′-[(E)-4-methoxybenzylidene]pyridine-4-carbohydrazide (2/1). *Acta Crystallogr.*, *Sect. E: Struct. Rep. Online* **2012**, *68*, o2897-o2898.
S4. Diao, Ch.-H.; Fan, Z.; Chen, X. (*E*)-*N*′-[5-Chloro-3-methoxy-2-(4-methylphenylsulfonyloxy)benzylidene]isonicotinohydrazide acetic acid solvate: hydrogen-bonded network of alternating $R^4_4(42)$, $R^5_5(33)$ and $R^6_6(40)$ rings. *Acta Crystallogr*., *Sect. C: Cryst. Struct. Commun.* **2007**, *63*, o717-o719.
S5. Zhen, X.-L.; Li, X.-L. (E)-N'-[2-(4-Chloro-3-nitro-phenyl-sulfon-yloxy)-3-methoxy-benzylidene]isonicotinohydrazide acetic acid tetra-solvate. *Acta Crystallogr*., *Sect. E: Struct. Rep. Online* **2008**, *64*, o2170.
S6. Chuev, I. I.; Nikonova, L. A.; Atovmyan, E. G.; Utenyshev, A. N.; Aldoshin, S. M. Molecular and Crystal Structure of the Products of Crystallization of (*N*'-Furfurylidene)isonicotinoylhydrazide from Aquaeous Solutions of hydrochloric and Acetic Acids. *Kristallografiya* **2001**, *46*, 444-447.