Electronic Supplementary Information

Are gamma amino acids promising tools of crystal engineering? – Multicomponent crystals of baclofen

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Crystal growth

All chemicals were purchased from Sigma Aldrich and used without further purification.

BAC•BA: Single crystals of baclofen (BAC) with benzoic acid (BA) were obtained by slow evaporation of 1:1 ethanol/water solution containing 50 mg baclofen (0.23 mmol) and 30 mg benzoic acid (0.25 mmol). Colourless crystals were obtained after ca. 8 weeks.

BAC•PTA: Baclofen (33 mg, 0.15 mmol) and p-toluic acid, PTA (34 mg, 0.25 mmol) were dissolved in a minimum amount of 1:1 ethanol/water and colourless crystals of BAC•PTA were obtained by slow evaporation of the solvent after several weeks.

(BAC^+)(HNA^-): Baclofen (20 mg, 0.10 mmol) and 1-hydroxy-2-naphthoic acid, HNA (20 mg, 0.10 mmol) were mixed together and dissolved in 1:1 of ethanol/water. The solution was allowed to slowly evaporate at room temperature to yield brown block shapes crystals after 4 weeks.

($2BAC^+$)(OA^{2-}): Crystals of baclofen and oxalic acid (OA) were prepared by dissolving 49 mg (0.23 mmol) of BAC and 10 mg (0.11 mmol) of OA in a minimal amount of 1:1 methanol/water. Colourless blocked shape crystals were obtained after 4 weeks.

(BAC^+)(MA^-): Crystals of baclofen and maleic acid (MA) were prepared by dissolving 35 mg (0.16 mmol) of BAC with 18 mg (0.16 mmol) of MA in 1:1 ethanol/water. Colourless blocked shape crystals were obtained after several weeks.

(BAC^+)($PTSA^-$)•IPA: The crystal of baclofen and p-toluene sulfonic acid (PTSA) was prepared by dissolving 45mg (0.21 mmol) of BAC with 36mg (0.21 mmol) of PTSA in a minimal amount of isopropanol (IPA) until the solution became clear and left to crystallize at room temperature. Colourless crystals were obtained after several weeks.

Table S1 Crystallographic data and refinement details for crystals.

	BAC•BA	**BAC•PTA**	**(BAC$^+$)(HNA$^-$)**	**(2BAC$^+$)(OA^{2-})**	**(BAC$^+$)(MA$^-$)**	**(BAC$^+$)(PTSA$^-$)•IPA**
Molecular formula	$C_{41}H_{42}Cl_2N_2O_{10}$	$C_{18}H_{20}ClNO_4$	$C_{21}H_{20}ClNO_5$	$C_{11}H_{13}ClNO_4$	$C_{14}H_{16}ClNO_6$	$C_{20}H_{28}ClNO_6S$
Formula weight (g.mol^{-1})	793.67	349.80	401.83	258.67	329.73	445.94
Crystal system	monoclinic	triclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/c$ (No.14)	P-1 (No.2)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)	$P2_1$ (No. 4)	$P2_1/c$ (No. 14)
a(Å)	14.910(3)	6.1768(12)	6.6251(13)	15.035(3)	5.7206(11)	5.4900(11)
b(Å)	35.478(7)	7.5101(15)	34.490(7)	7.2113(14)	13.677(3)	13.400(3)
c(Å)	7.4293(15)	19.092(4)	8.4698(17)	11.025(2)	9.6377(19)	28.910(6)
α(°)	90.00	79.43(3)	90.00	90.00	90.00	90.00
β(°)	99.21(3)	82.90(3)	95.75(3)	106.86(3)	106.78(3)	90.90(3)
γ(°)	90.00	84.25(3)	90.00	90.00	90.00	90.00
V(Å)	3879.3(14)	861.2(3)	1925.6(7)	1143.9(4)	722.00(2)	2126.5(7)
Z	4	2	4	4	2	4
ρ_{calc} / g.cm^{-3}	1.359	1.349	1.386	1.502	1.517	1.393
μ (MoKα)/mm^{-1}	0.229	0.243	0.231	0.336	0.295	0.315
F(000)	1664	368	840	540	344	944
Crystal size (mm)	0.05 ×0.23 ×0.30	0.02×0.07 ×0.80	0.11×0.16×0.45	0.09×0.17×0.24	0.16×0.18×0.28	0.05×0.06×0.54
Temperature (K)	173(2)	173(2)	173(2)	173(2)	173(2)	173(2)
Radiation [Å]	MoKα, 0.71073	MoKα, 0.71073	MoKα, 0.71073	MoKα, 0.71073	MoKα, 0.71073	MoKα, 0.71073
Theta min-max[°]	1.80, 26.38	2.18, 27.94	2.36, 27.12	2.83, 27.48	2.21,28.37	1.41, 28.83
Dataset	-18:18; -44: 0; 0: 9	-8: 8; -9:9; -25: 25	-6:8;-44:44;-10:10	-19:19; -9:9; -14:14	-7:7;-18:18;-8:12	-7:7;-17:17;-37:39
Final R indices [I>2σ (I)]	R_1= 0.0430, wR_2= 0.0966	R_1= 0.0385, wR_2=0.0985	R_1= 0.0424, wR_2=0.0955	R_1=0.0353, wR_2=0.0886	R_1=0.0330, wR_2=0.0783	R_1= 0.0680, wR_2=0.1291
R indices (all data)	R_1= 0.0610, wR_2= 0.1068	R_1=0.0484, wR_2=0.1045	R_1= 0.0655, wR2=0.1065	R_1=0.0508, wR_2=0.0979	R_1=0.0369, wR2=0.0807	R_1=0.1152, wR_2=0.1444
Tot., uniq.data, R(int)	7879, 6254, 0.0243	4103, 3392, 0.0304	4260, 3098, 0.0343	2618, 2054, 0.0161	3605, 3345, 0.0210	5211, 3301, 0.0573
N_{ref}, N_{par}	7879, 533	4103, 223	4260,274	2618,171	3605,220	5211, 284
S	1.029	1.044	1.022	1.046	1.047	1.059
Max. and av. Shift/error	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00
Min. and max. res. dens.	0.550, -0.383	0.275, -0.285	0.296, -0.450	0.214, -0.279	0.218, -0.179	-0.396, 0.340

Table S2 Hydrogen bond metrics.

	D-H/Å	*H...A/Å*	*D...A/Å*	*D-H...A/°*	Symmetry operators
BAC•BA					
O4C-H7C···O1B	0.88	1.72	2.60	176	1-x, -y, 2-z
O4D-H7D···O1A	1.05	1.59	2.63	172	1-x, -y,1-z
O4E-H7E···O2B	0.89	1.69	2.57	174	-x, -y, 1-z
N1-H11A···O2A	0.93	1.85	2.72	154	1-x, -y,- z
N1-H11B···O3C	0.88	2.15	2.70	120	x, y,-1+ z
N1-H11C···O1A	1.00	1.78	2.77	171	x, y,-1+ z
N2-H11D···O3D	0.89	2.57	3.03	113	
N2-H11D···O3E	0.89	2.12	2.76	128	
N2-H11E···O1A	0.91	2.08	2.99	175	1-x, -y,1- z
N2-H11F···O1B	0.91	1.79	2.73	170	x, y,-1+ z
C10A-H10A···O2B	0.99	2.53	3.46	157	1-x, -y,1- z
C10A-H10B···O2A	0.99	2.44	3.05	120	
C10B-H10C···O2B	0.99	2.35	3.01	124	
C10A-H10B···O2A	0.99	2.44	3.05	120	
C10B-H10C···O2B	0.99	2.35	3.01	124	
BAC•PTA					
N1-H11A···O1	0.94	1.88	2.81	169	-x, -y, 1-z
N1-H11B···O2	0.92	1.88	2.77	163	1-x, -y,1- z
N1-H11C···O2	0.95	1.83	2.77	169	x, 1+y, z
O3-H18···O1	0.91	1.73	2.64	175	1+x, 1+y, z
C7-H7···O2	1.00	2.55	3.49	156	-x, -y,1- z
C8-H8B···N1	0.99	2.48	2.98	111	
(BAC$^+$)(HNA$^-$)					
O2-H9···O4	0.93	1.69	2.61	173	1-x, -y, 2-z
N1-H11A···O5	0.95	1.99	2.93	172	1-x, -y,1-z
N1-H11B···O4	0.92	1.94	2.85	169	1+x, y, z
N1-H11C···O5	0.92	2.00	2.89	162	
O3-H18···O5	0.89	1.70	2.54	157	
C8-H8B···O3	0.99	2.54	3.18	122	x, y,1+z
C10-H10A···O1	0.99	2.32	2.99	124	2-x, -y, 2-z
C10-H10B···O2	0.99	2.54	3.17	121	1-x, -y,2-z
(2BAC$^+$)(OA^{2-})					
O2-H9···O3	0.97	1.53	2.50	179	x, 3/2-y, ½+z
N1-H11A···O1	0.94	1.95	2.88	175	x, -1+y, z
N1-H11B···O4	0.89	2.01	2.85	157	-x, 1/2+y, ½-z
N1-H11B···O3	0.89	2.26	2.82	120	x, ½-y,1/2+z
N1-H11C···O4	0.90	2.47	2.94	113	
N1-H11C···O2	0.90	2.54	3.22	133	x, 3/2-y, -1/2+z
C7-H7···O2	1.00	2.53	2.92	103	
C7-H7···O4	1.00	2.59	3.37	134	-x, ½+y, ½-z
(BAC$^+$)(MA$^-$)					
O2-H9···O4	0.88	1.77	2.65	170	1-x,-1/2+ y,-z
O2-H9···O5	0.88	2.57	3.20	130	1-x, -½+y,-z
N1-H11A···O3	0.96	1.93	2.82	155	
N1-H11B···O3	0.94	2.56	3.45	160	-1+x, y, z
N1-H11B···O6	0.94	2.28	2.93	126	-1+x, y, z
N1-H11C···O4	0.91	2.04	2.86	149	x, y, 1+z
O5-H14···O6	1.20[#]	1.21	2.41	176	
C3-H3···O1	0.95	2.42	3.36	169	1+x, y, z
C10-H10A···O1	0.99	2.59	3.48	149	1+x, y, z
(BAC$^+$)(PTSA$^-$)•IPA					
O2-H1···O6	0.98	1.63	2.60	172	-1+x, y, z
O6-H6A···O3	0.79	1.96	2.74	167	1-x, ½+y,1/2-z
N1-H11A···O4	0.91	2.44	2.78	102	1-x, -1/2+y,1/2- z
N1-H11A···O5	0.91	2.18	2.89	135	-x, -1/2+y,1/2- z
N1-H11B···O4	0.91	2.40	2.78	105	1-x,-1/2+ y,-1/2- z
N1-H11B···O5	0.91	1.99	2.85	157	1+x, ½-y, -1/2+z
N1-H11C···O3	0.91	1.87	2.76	164	x,1/2-y, -1/2+z
C3-H3···O1	0.95	2.39	3.33	171	1+x, y, z
C8-H8A···O1	0.99	2.43	3.36	156	1+x, y, z
C12-H12···O4	0.95	2.55	2.89	101	

[#] The H14 hydroxyl proton of the MA forms an intramolecular hydrogen bond and it is positioned at an equal distance from O5 and O6.

Powder X-ray diffraction results

The crystallisation from solution yielded very few crystals thus the PXRD patterns of the bulk materials were not recorded. Several attempts were made to reproduce more cocrystals/salts via solution crystallisation but these were unsuccessful. Thus grinding experiments were carried out to produce more of the multicomponent crystals.

1:1 ratio of BAC and BA, PTA or HNA with the addition of several drops of 1:1 ethanol/water were ground for 60 minutes and the XRD patterns were collected (**Figure S1 for** BAC•BA, **Figure S2** for BAC•PTA and **Figure S3** for (BAC$^+$)(HNA$^-$)). The XRD of the ground material (blue) were compared to the single crystal structures (green). For BAC•BA and BAC•PTA the obtained patterns from the ground material did not show good agreement with the generated pattern of the single crystal data. The 60 mins grinding resulted in a physical mixture of the starting materials and it may be concluded that the grinding experiment was unsuccessful. In case of (BAC$^+$)(HNA$^-$), after 60 mins grinding a pattern emerged that shows similarities with the pattern derived from the single crystal structure. However, several peaks appear on the pattern which may be related to residual of BAC in the ground material. Thus the solvent drop grinding is a promising method to form a salt pair of BAC and HNA but clearly not an efficient way because 60 mins grinding did not result in a good conversion of the starting materials.

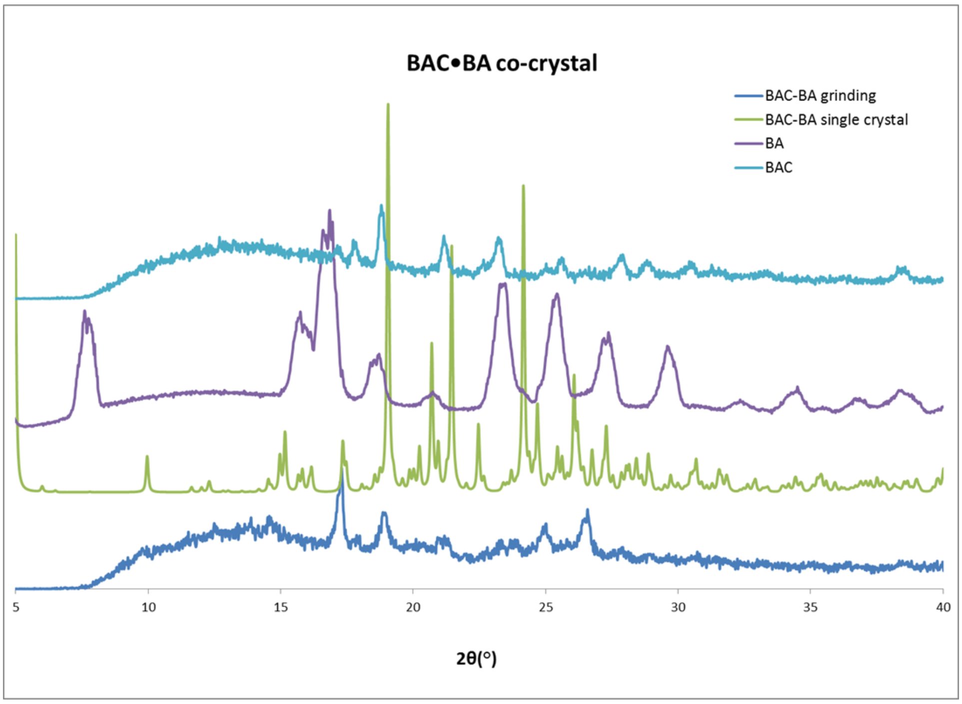

Figure S1 PXRD pattern of BAC (light blue), BA (purple), BAC•BA single crystal (green), BAC•BA grinding (blue).

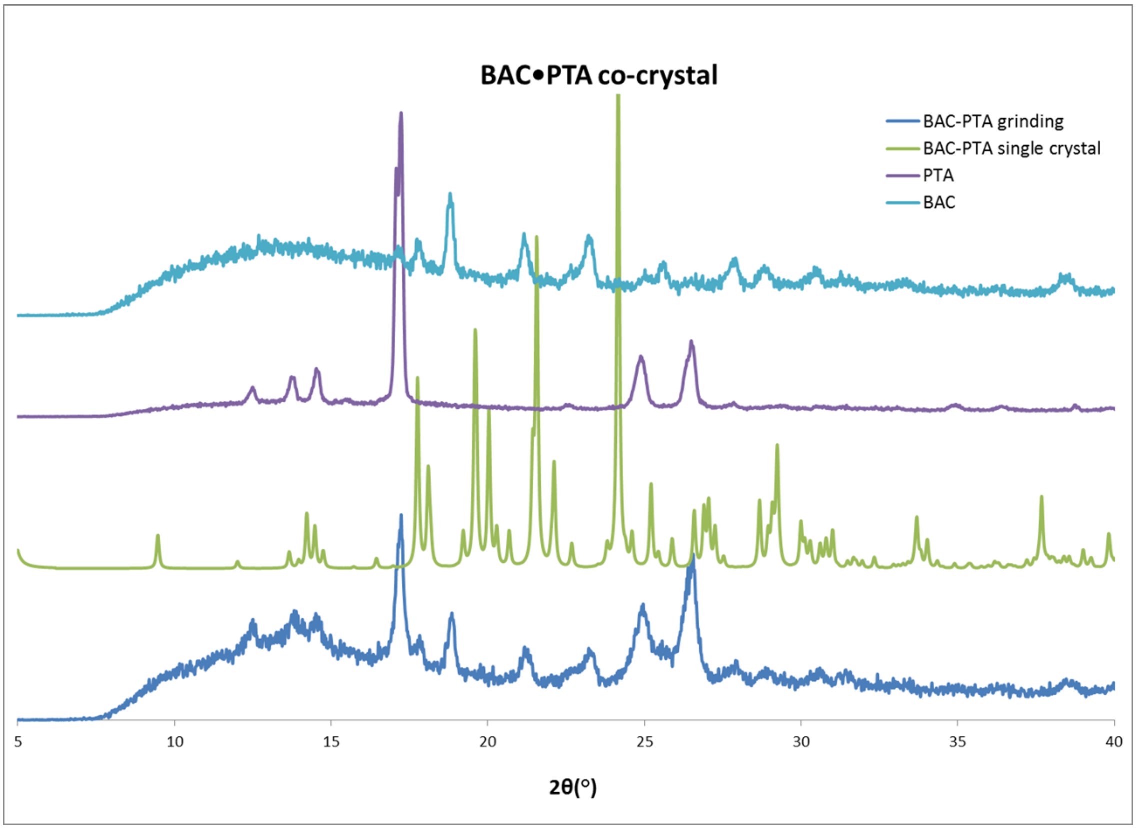

Figure S2 PXRD pattern of BAC (light blue), PTA (purple), BAC•PTA single crystal (green), BAC•PTA grinding (blue).

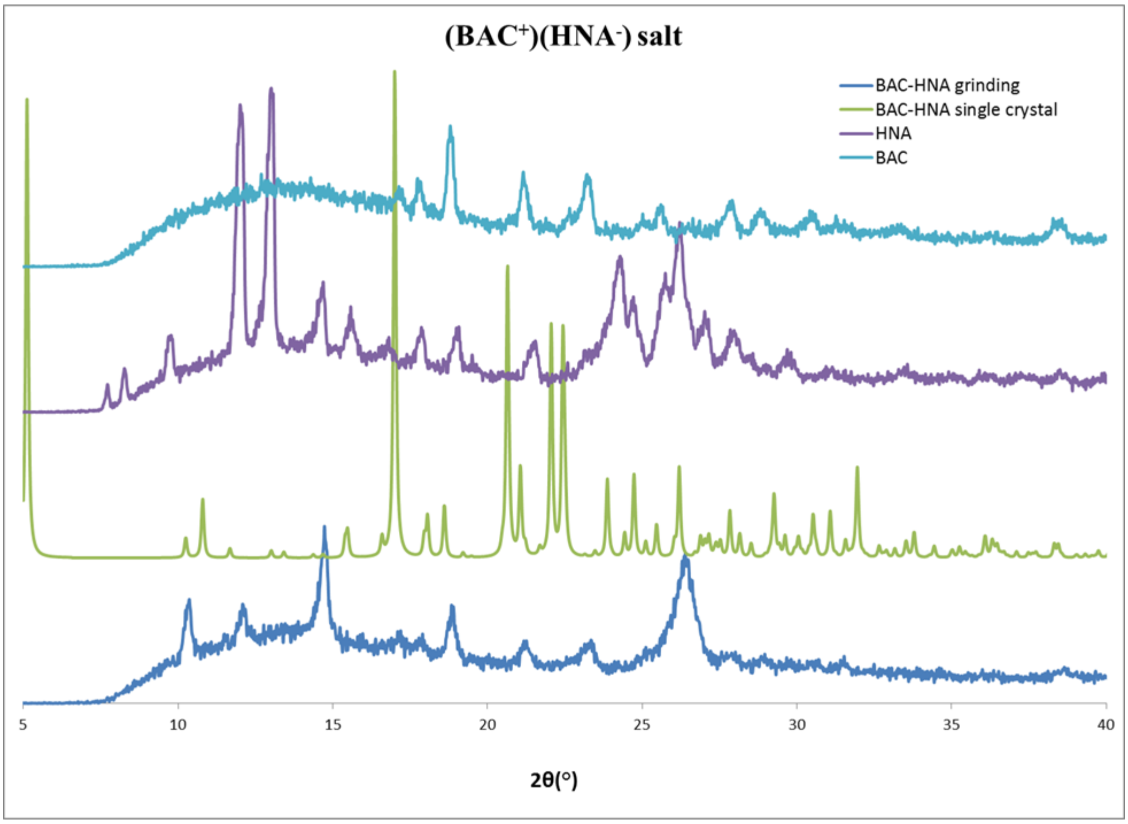

Figure S3 PXRD pattern of BAC (light blue), HNA (purple), $(BAC^+)(HNA^-)$ single crystal (green), $(BAC^+)(HNA^-)$ grinding (blue).

Grinding experiments with BAC and dicarboxylic acids, oxalic acid (OA) and maleic acid (MA), resulted very similar results. ($2BAC^+$)(OA^{2-}) salt was aimed to prepare by grinding the staring materials in a 2:1 ratio with several drops of methanol for 60 mins (**Figure S4** blue). The XRD pattern was compared to the starting pattern of the pure BAC and OA (**Figure S4**, light blue-BAC, purple- OA). The patterns for the single crystal and the ground material are not similar but clearly differ from the starting compounds, thus the solvent drop grinding initiated reaction between the starting materials and produced an unidentified complex.

Pure BAC and MA were ground together in a 1:1 ratio with a minimal amount of methanol. (The ratio was selected hence it is a well-known that MA acid is likely to be mono deprotonated and one of the carboxylic proton will be positioned half way between the two carboxylic groups.) After 60 mins grinding, the PXRD pattern was collected (**Figure S5** blue) and was concluded as unsuccessful.

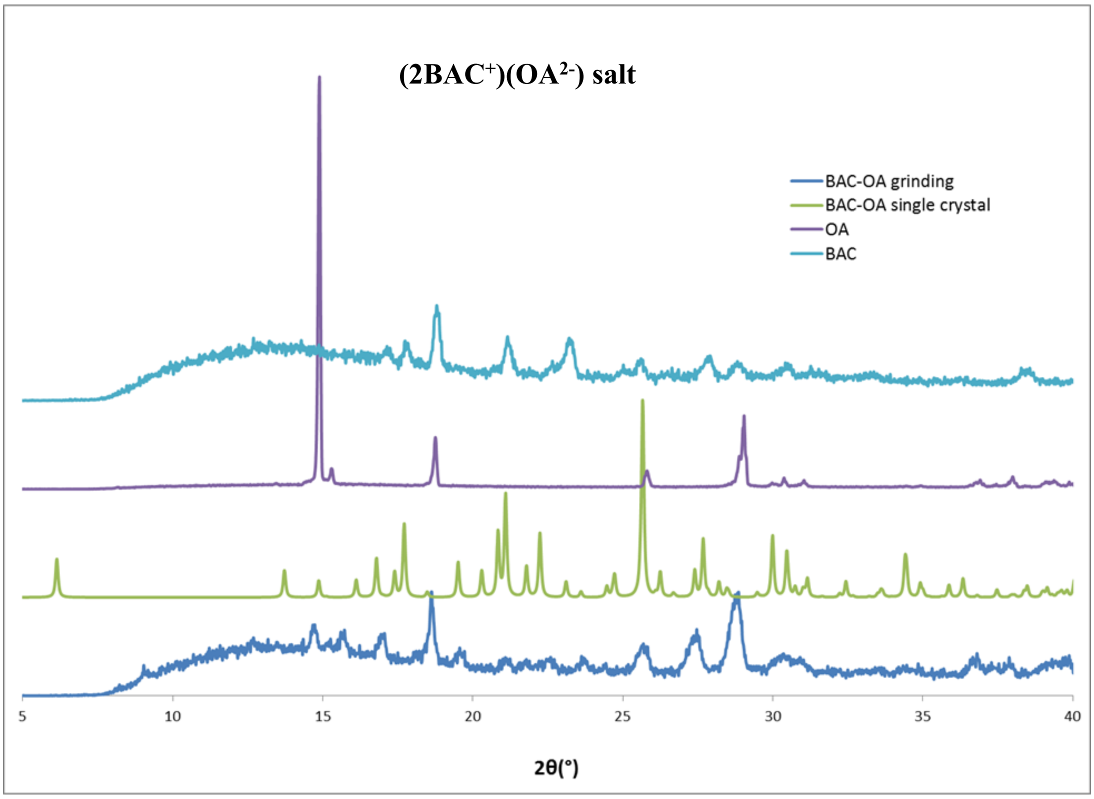

Figure S4 PXRD patterns of BAC (light blue), OA (purple), ($2BAC^+$)(OA^{2-}) pattern generated from single crystal structure (green) and ($2BAC^+$)(OA^{2-}) grinding (blue).

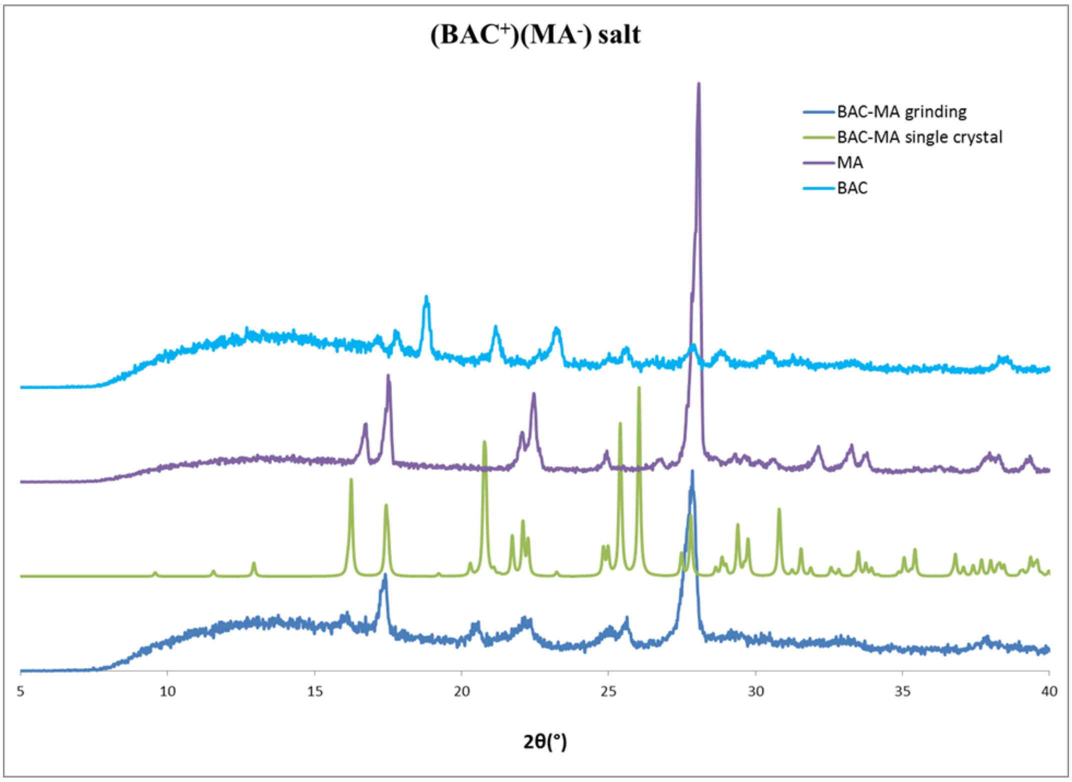

Figure S5 PXRD patterns of BAC (light blue), MA (purple), BAC•MA pattern generated from single crystal structure (green) and BAC•MA grinding (blue).

Powder X-ray analysis was carried out to show that the structure detected by using one single crystal only (**Figure S6**, green- BAC•PTSA single crystal) is representative to the material obtained via grinding (**Figure S6**, blue-BAC•PTSA grinding). Pure BAC and PTSA were ground with several drops of isopropanol and after 60 mins the PXRD patter was collected (**Figure S6**, blue- BAC•MA grinding). This was compared to the pattern of the starting materials, pure BAC and PTSA (**Figure S6,** light blue-BAC, purple- PTSA). The patterns for the single crystal and the ground material are quite similar and clearly differ from the starting compounds. However, the match is not perfect and several peaks related to BAC and PTSA are still noticeable, therefore the reaction occurs only partially.

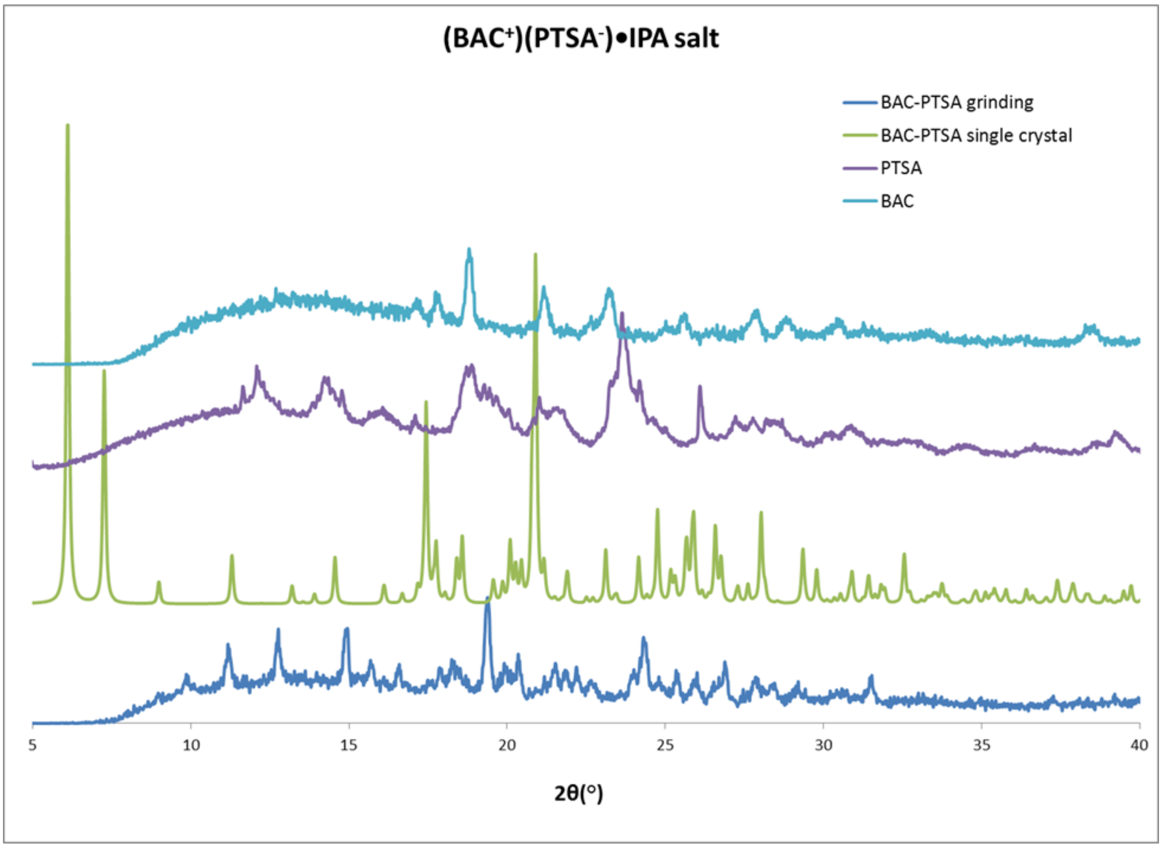

Figure S6 PXRD patterns of BAC (light blue), PTSA (purple), (BAC^{+})(PTSA^{-})•IPA pattern generated from single crystal structure (green) and (BAC^{+})(PTSA^{-})•IPA grinding (blue).

Thermal analysis

The DSC curve of BAC•BA crystals (**Figure S7**) is inconclusive. A possible explanation of the thermal events is that the minor endotherm corresponding to the melting point of the crystal (T_{1on}= 98.1°C, T_{1peak}= 98.7°C). Thus the melting point of the co-crystal is lower than the melting points of the two starting material, BAC (T_{on}= 205.5°C, T_{peak}= 210.4°C) and BA (T_{on}= 121.6°C, T_{peak}= 125.5°C). The other two endotherms between ca. 150 and 160°C are likely to be associated with the unreacted starting material.

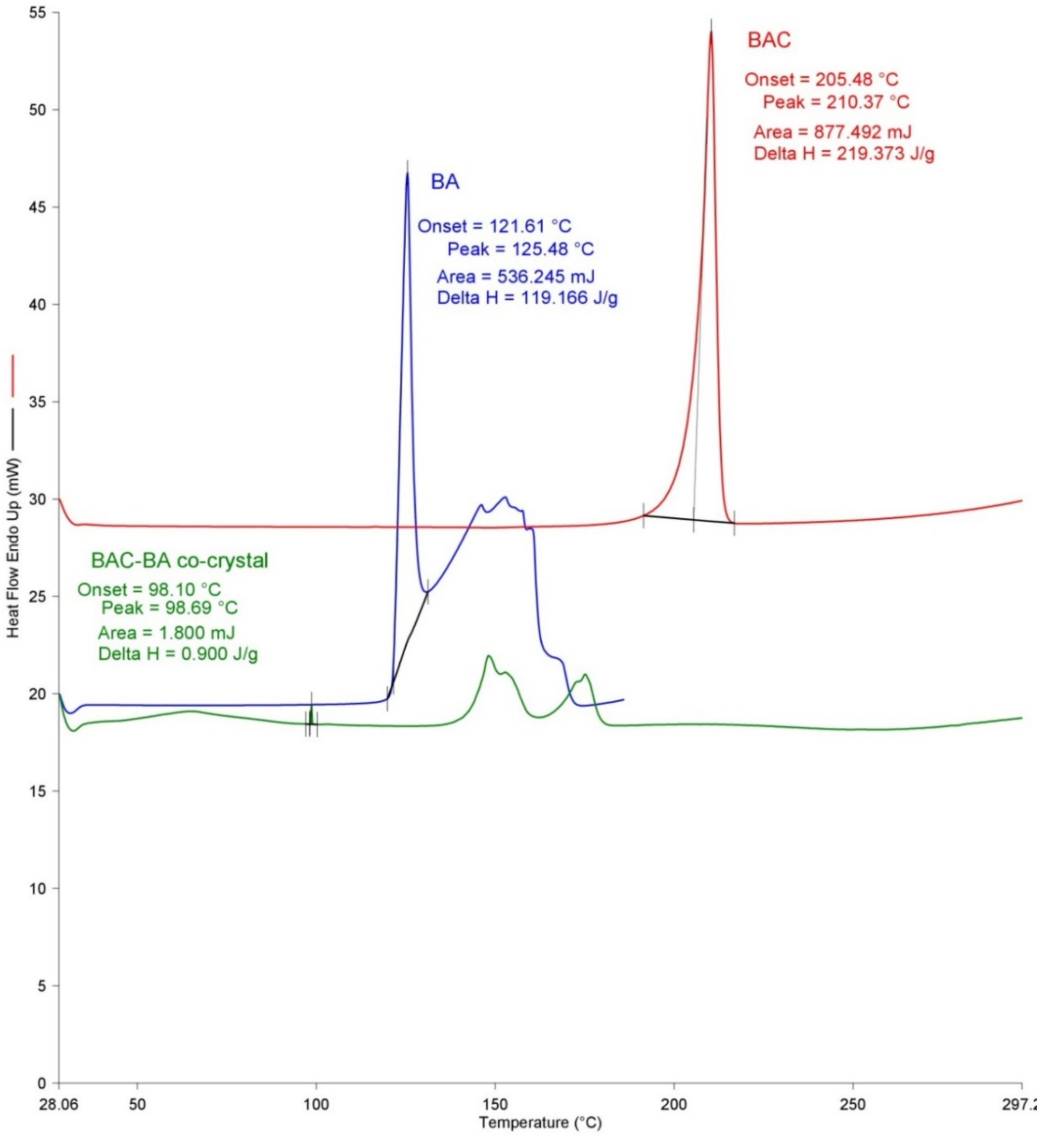

Figure S7 *DSC curve of BAC•BA and the starting materials.*

The DSC curve of BAC•PTA crystal (**Figure S8**) shows one endotherm corresponding to the melting of the co-crystal (T_{on}= 166.7°C, T_{peak}= 171.4°C). The melting point of the co-crystal is lower than the melting points of the two starting material, BAC (T_{on}= 205.5°C, T_{peak}= 210.4°C) and PTA (T_{on}= 178.0°C, T_{peak}= 181.9°C).

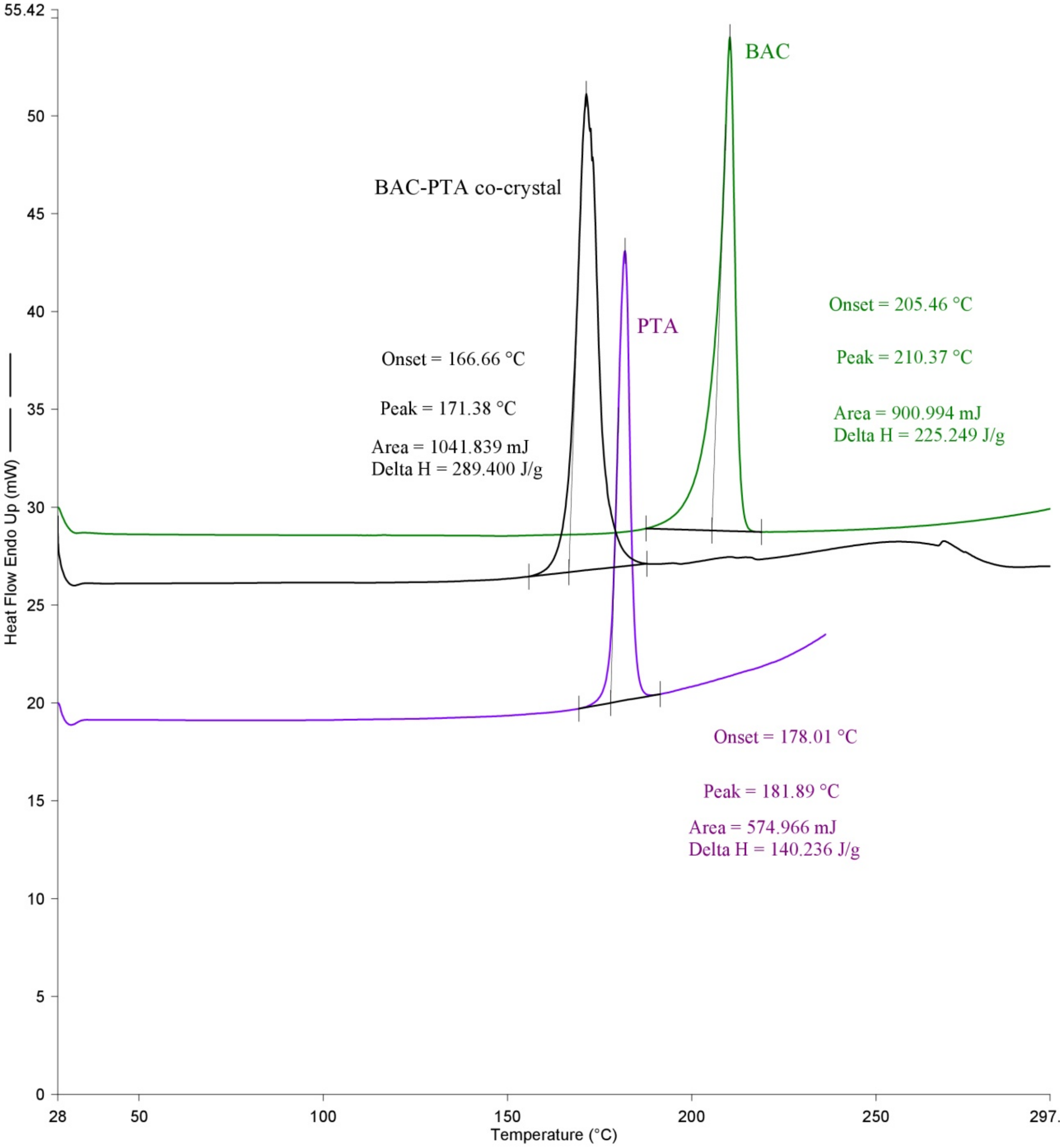

Figure S8 *DSC curve of BAC•PTA and the starting materials*

The DSC curve of (BAC^+)(HNA^-) crystals (**Figure S9**) shows one endotherm corresponding to the melting point of the crystal (T_{on}= 166.4°C, T_{peak}= 170.3°C). The melting point of the salt is lower than the melting points of the two starting material, BAC (T_{on}= 205.5°C, T_{peak}= 210.4°C) and HNA (T_{on}= 195.6°C, T_{peak}= 200.8°C).

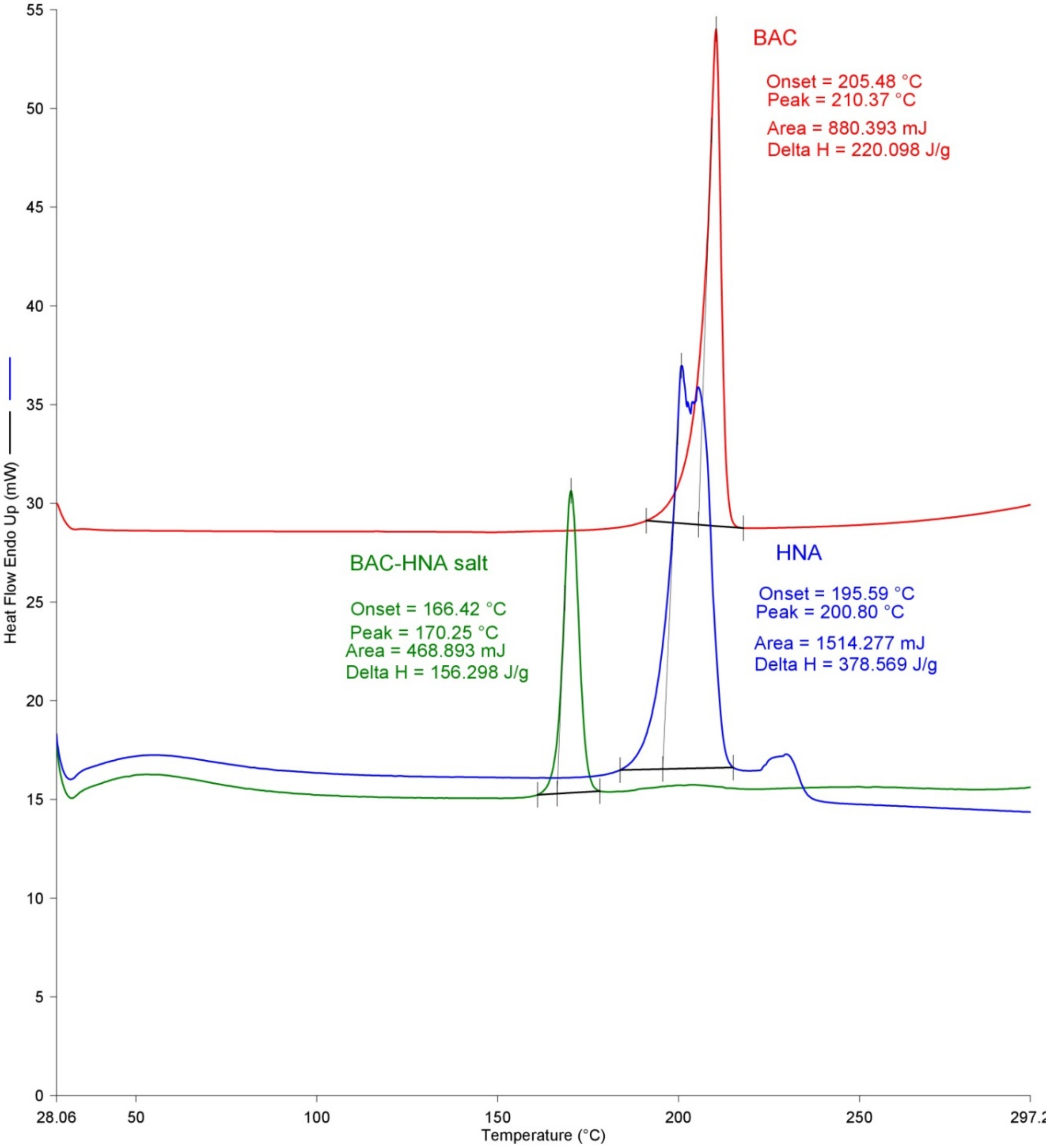

Figure S9 *DSC curve of (BAC⁺)(HNA⁻) and its starting materials*

The DSC curve of $(2BAC^{+})(OA^{2-})$ salt (**Figure S10**) shows one endotherm corresponding to the melting point of the salt (T_{on}= 165.4°C, T_{peak}= 169.5°C). The melting point of the salt is located between the melting points of the two starting material, BAC (T_{on}= 205.5°C, T_{peak}= 210.4°C) and OA (T_{on}= 103.4°C, T_{peak}= 105.4°C).

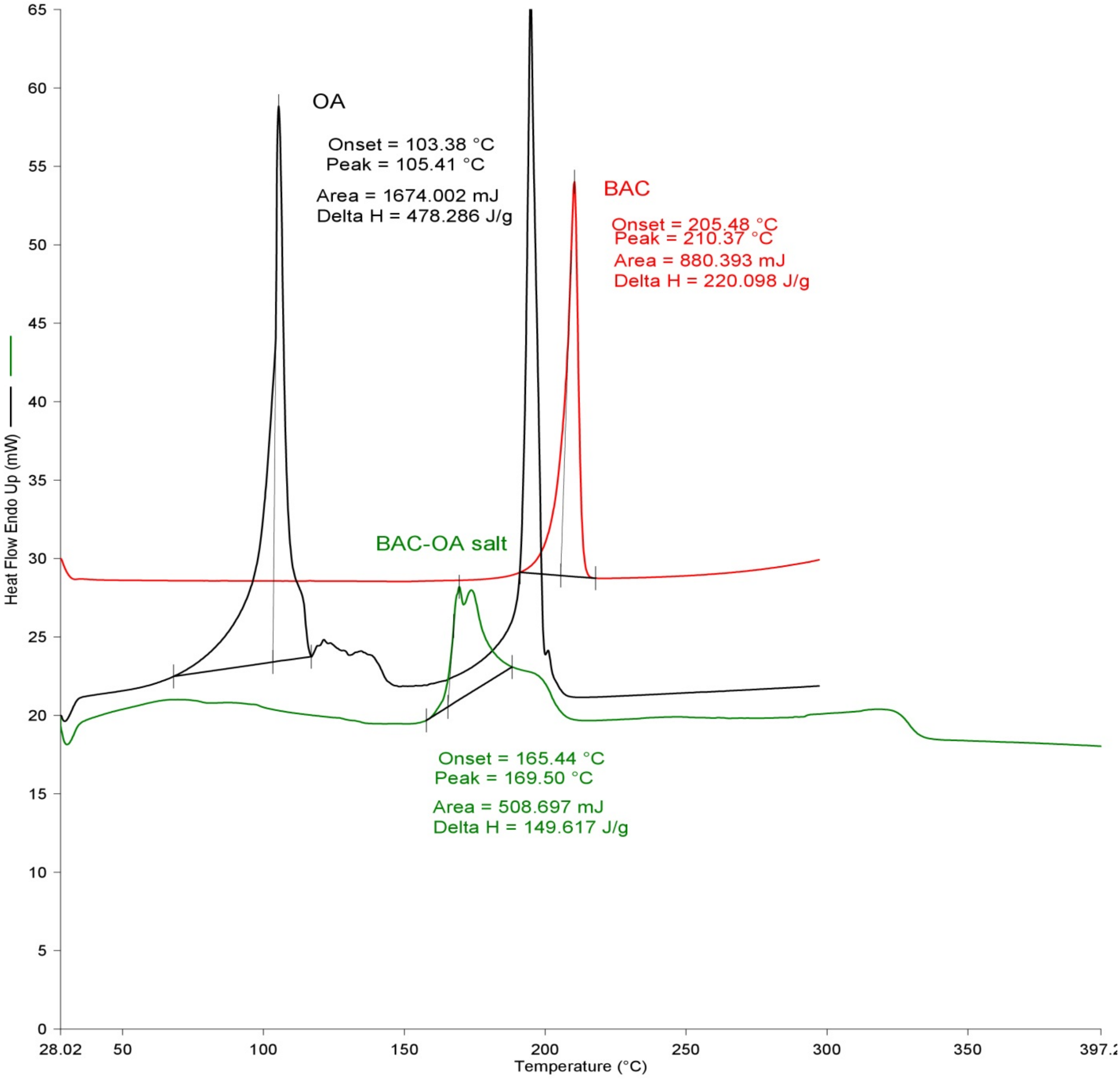

Figure S10 *DSC curves of (2BAC⁺)(OA²⁻) and its starting materials.*

The DSC curve of (BAC^+)(MA^-) salt (**Figure S11**) shows one endotherm corresponding to the melting point of the salt (T_{on}= 180.1°C, T_{peak}= 186.5°C). The melting point of the salt is located before the melting points of the two starting material, BAC (T_{on}= 205.5°C, T_{peak}= 210.4°C) and MA (T_{on}= 151.5°C, T_{peak}= 153.3°C).

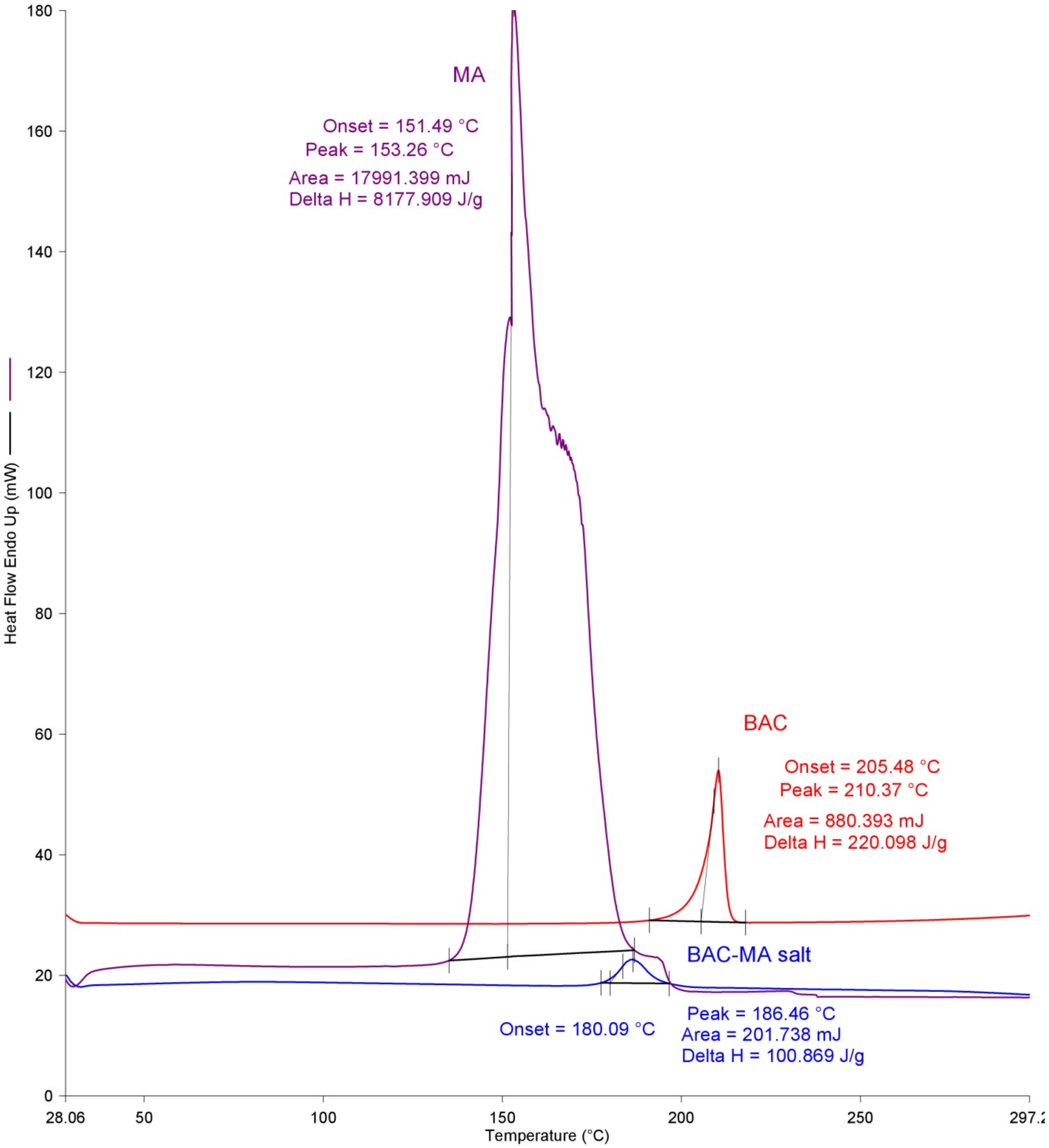

__Figure S11__ DSC curves of (BAC$^+$)(MA$^-$) and the starting materials.

The DSC curve of (BAC$^+$)(PTSA$^-$)•IPA crystals shows one endotherm corresponding to the melting point of the crystal (T_{on}= 169.6°C, T_{pea}k= 171.3°C). The melting point of the salt is located between the melting points of the two starting material, BAC (T_{on}= 205.5°C, T_{peak}= 210.4°C) and PTSA (T_{on}= 101.5°C, T_{peak}= 106.8°C). (**Figure S12**)

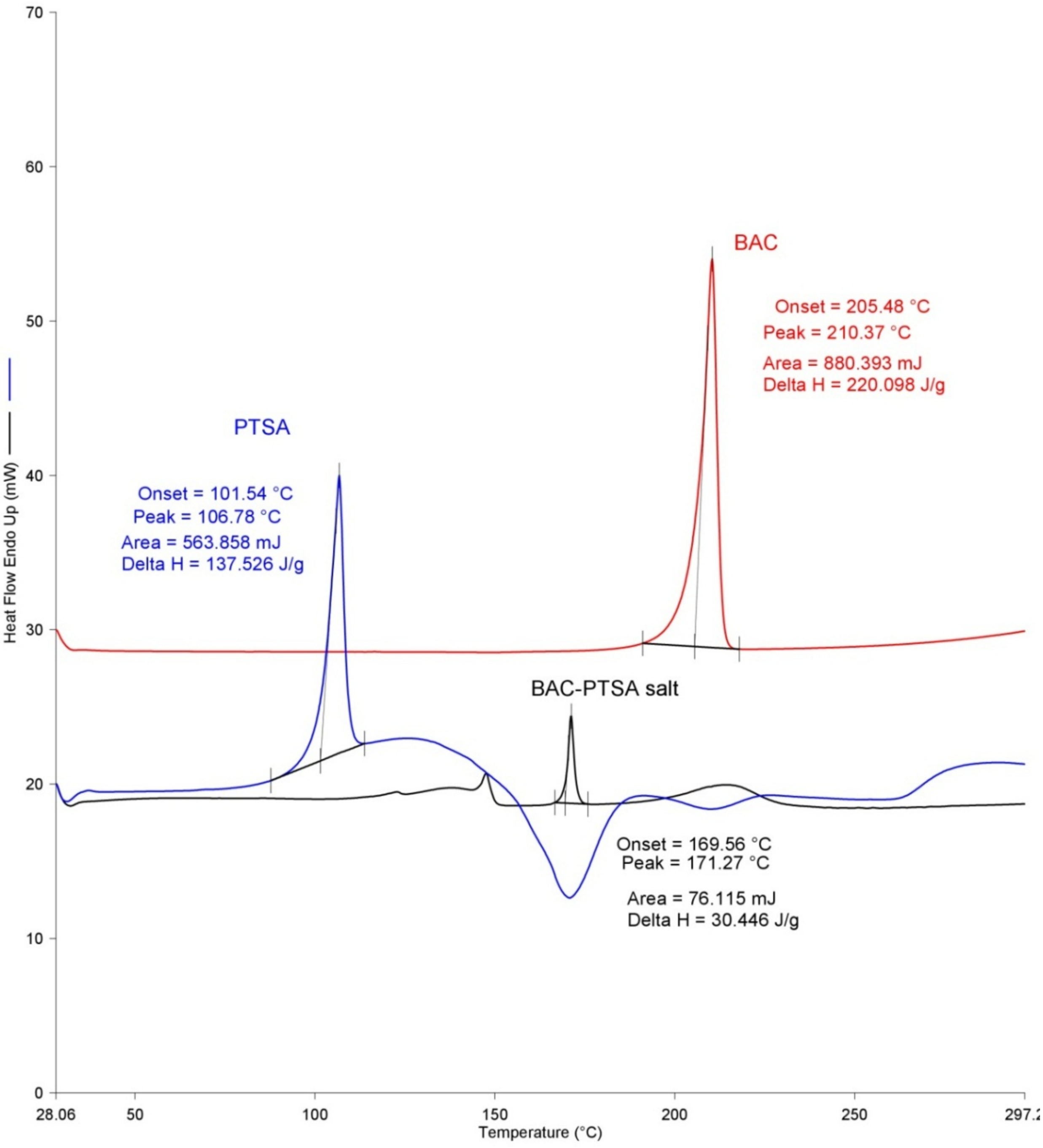

__Figure S12__ DSC curve of (BAC$^+$)(PTSA$^-$)•IPA and the starting materials.

Hirshfeld surface analysis

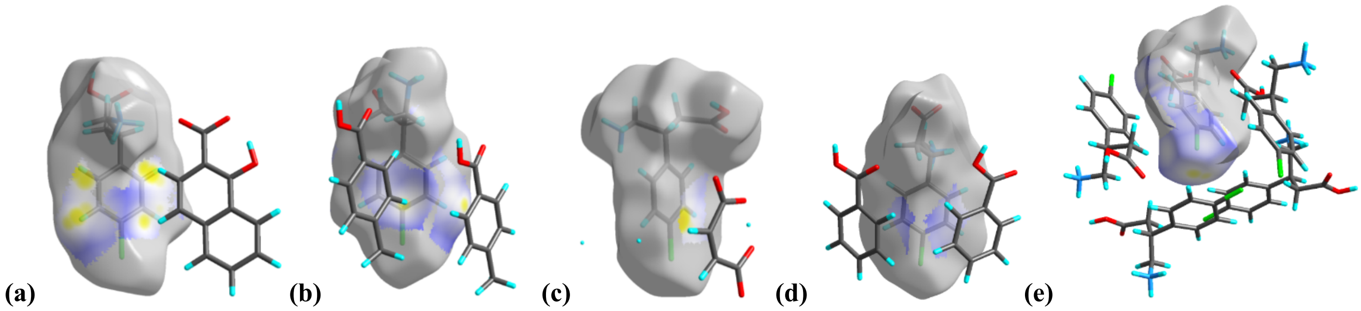

Figure S13 *Interactions represented on Hirshfeld surfaces: (a) C-H···π interactions in (BAC$^+$)(HNA$^-$) and (b) BAC•PTA, C···C interactions in (c) (BAC$^{+)}$(MA$^-$) and (d) Molecule A in BAC•BA and Cl···H and the Cl···C interactions in (2BAC$^+$)(OA$^-$) (e).*