Melting point–solubility–structure correlations in chiral and racemic model cocrystals

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1. Cocrystal formation

All chemicals were purchased from Sigma Aldrich and were used without further purification. **BIPY•PTA** cocrystals were prepared by mixing a 1:1 stoichiometric amount of 4,4'-bipyridine hydrate, BIPY.H_2O (66 mg, 0.38 mmol) and *p*-toluic acid, PTA (51 mg, 0.38 mmol) and dissolving them in a minimum amount of dimethyl sulfoxide (DMSO) until the solution became clear and left to evaporate at room temperature. Colourless block shape crystals were obtained after few weeks (Mp = 158.9-161.2 ^{o}C). Cocrystals of **BIPY•racPBA** were prepared by dissolving 63 mg (0.36 mol) of BIPY.H_2O and 60 mg (0.37 mol) of *rac*-2-phenylbutyric acid (racPBA) in 3 ml methanol. The solution was stirred until it became clear and left to crystallise at room temperature. Block shape colourless crystals were obtained after two weeks (Mp = 80.5-84.0 ^{o}C). The cocrystal **BIPY•racPSA** was prepared by dissolving 125 mg (0.72 mol) of BIPY.H_2O and 140 mg (0.72 mol) of racemic phenylsuccinic acid (racPSA) in 2.8 ml of isopropanol until the solution became clear, and was left to crystallise at room temperature. Block shape yellow crystals were obtained after 1 week (Mp = 148.4-150.4 ^{o}C). 79 mg (0.43 mmol) of the 1,2-bis(4-pyridyl)ethane (ETBIPY) and 84 mg (0.43 mmol) of (rac)PSA were dissolved in 1:1 mixture of propanol/water. Colourless crystals of **ETBIPY•racPSA** were obtained within a few days via a slow evaporation method (Mp = 185.8-187.9 ^{o}C). ETBIPY (74 mg, 0.40 mmol) and (S)-PSA (78 mg, 0.40 mmol) were dissolved in a minimal amount of DMSO. The solution was allowed to slowly evaporate at room temperature to yield colourless block crystals of **ETBIPY•(S)PSA** after four weeks (Mp = 147.4-151.4 ^{o}C). Considerable effort was invested to prepare BIPY•(S)PBA and BIPY•(S)PSA but without success.

2. X-ray crystallography

Intensity data for all the structures were collected on a Bruker DUO APEX II[1] diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073 Å) at 173K using an Oxford Cryostream 700. Data collection and cell refinement were performed using SAINT-Plus[2] and the space groups were determined from systematic absences using XPREP[3] and further justified by the refinement results. Accurate unit cell parameters were refined on all data. The structures were solved using SHELXS-97[4] and refined using full-matrix least squares methods in SHELXL-2016/4[4] within the X-Seed[5] graphical user interface. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms bound to carbon atoms were placed at idealized positions and refined as riding atoms. Hydroxyl hydrogen atoms were located in the difference electron density map and were constrained into idealized positions with suitable AFIX instruction. Crystal data and hydrogen bond details are given in Table S1 and Table S2, respectively. CCDC deposit numbers 1912005-1912009 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

Table S 1 Crystal data for discussed compounds

Compounds	BIPY•PTA	BIPY•racPBA	BIPY•racPSA	ETBIPY•racPSA	ETBIPY•(S)PSA
Molecular formula	$C_{26}H_{24}N_2O_4$	$C_{15}H_{16}NO_2$	$C_{20}H_{18}N_2O_4$	$C_{22}H_{22}N_2O_4$	$C_{22}H_{22}N_2O_4$
Formula weight (g.mol^{-1})	428.47	242.29	350.36	378.41	378.42
Crystal system	monoclinic	monoclinic	monoclinic	triclinic	triclinic
Space group	$P2_1/c$ (No.14)	$P2_1/c$ (No.14)	$P2_1/n$ (No.14)	$P\bar{1}$ (No. 2)	$P1$ (No. 1)
a(Å)	7.8077(16)	5.695(11)	9.3729(19)	6.5593(13)	6.5705(13)
b(Å)	6.1034(12)	32.968(7)	18.545(4)	9.2837(19)	9.2493(18)
c(Å)	22.881(5)	7.2241(14)	11.135(2)	16.826(3)	17.129(3)
α(°)	90.00	90.00	90.00	82.39(3)	92.82(3)
β(°)	91.67(3)	109.74(3)	113.89(3)	81.52(3)	99.52(3)
γ(°)	90.00	90.00	90.00	69.63(3)	110.25(3)
V(Å^3)	1089.9(4)	1276.7(5)	1769.8(7)	946.4(3)	956.8(4)
Z	2	4	4	2	2
ρcalc (g.cm^{-3})	1.306	1.260	1.315	1.328	1.314
μ(MoKα) (mm^{-1})	0.089	0.084	0.093	0.092	0.091
F(000)	452	516	736	400	400
Crystal size (mm)	0.14×0.18×0.33	0.10×0.15×0.15	0.18×0.23×0.32	0.09 × 0.12 × 0.24	0.10× 0.37× 0.40
Temperature (K)	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
Theta min-max (°)	2.61, 28.29	2.47, 28.25	2.20, 28.37	2.35, 27.33	1.21, 28.29
Dataset	-8:10; -6:8; -30:18	-7:7; -43:43;-9:9	-12:12; -24:24; -6:14	-8: 8; -11: 11; 0: 21	-8: 8; -12:12; -22: 22
Final R indices	R_1=0.0470,	R_1=0.0626,	R_1=0.0415,	R_1= 0.0777,	R_1= 0.0489,
[I>2.0 σ(I)]	wR_2=0.1188	wR_2=0.1317	wR_2=0.1024	wR_2= 0.1634	wR_2=0.0969
R indices (all data)	R_1=0.0710,	R_1=0.0777,	R_1=0.0581,	R_1= 0.1195,	R_1=0.0398,
	wR_2=0.1330	wR_2=0.1379	wR_2=0.1115	wR_2= 0.1803	wR_2=0.0918
Tot., uniq.data, R(int)	5002, 1910, 0.0235	10554, 2470, 0.0297	12630, 3351, 0.0299	4116, 2860, 0.0494	9350, 8032, 0.0435
N_{ref}, N_{par}	2697, 144	3116, 165	3351, 237	2680, 255	8032, 509
S	1.038	1.084	1.040	1.060	1.038
Max. and av. Shift/error	0.00, 0.00	0.00, 0.00	0.000, 0.000	0.00, 0.00	0.00, 0.00
Min. and max. resd. Dens.	-0.223, 0.309	-0.223, 0.490	-0.189, 0.261	-0.299, 0.322	-0.191, 0.235

Table S 2 Hydrogen bonding metrics for discussed compounds

Compounds	d(D-H) (Å)	d(H···A) (Å)	d(D···A) (Å)	D-H···A (°)	Symmetry operator
BIPY•PTA					
O3-H3···N1	0.84	1.84	2.6748(2)	178.0	
C1-H1···O2*	0.95	2.35	3.241(2)	156.9	x, y+1, z
BIPY•racPBA					
O3-H3···N1	0.84	1.80	2.618(2)	165.6	
C4-H4···O2*	0.95	2.63	3.276(2)	126.1	-x+1, -y, -z
C5-H5···O2*	0.95	2.74	3.342(3)	122.1	-x+1, -y, -z
C5-H5···O2	0.95	3.21	3.735(3)	116.7	
BIPY•racPSA					
O3-H3···N1	0.84	1.82	2.6573(14)	175.9	
O2-H22···N2*	0.84	1.82	2.6578(15)	171.9	-x+3/2, y+1/2, -z+1/2
C1-H1···O4*	0.95	2.38	3.3105(18)	166.7	x+1/2, -y+1/2, z+1/2
C8-H8···O2*	0.95	2.55	3.421(2)	153.1	x+3/2, -y+1/2, z+1/2
C10-H10···O1*	0.95	2.60	3.354(2)	136.8	x+1/2, -y+1/2, z-1/2
C17-H17···O3*	1.00	2.42	3.3727(18)	158.3	x-1/2, -y+1/2, z-1/2
ETBIPY•racPSA					
O1-H1···N1B	0.84	1.80	2.622(4)	167.5	
O3-H3···N1A	0.84	1.77	2.609(3)	173.4	
C5A-H5A···O4	0.95	2.69	3.349(4)	127.4	
C1B-H1B···O2	0.95	2.98	3.527(4)	117.9	
C5B-H5B···O1*	0.95	2.64	3.435(4)	141.7	-x+1, -y, -z+1
ETBIPY•(S)PSA					
O1C-H1C···N2A	0.84	1.77	2.601(3)	172.5	
C10A-H10A···O2C	0.95	2.74	3.382(3)	125.4	
O3C-H3C···N2B	0.84	1.80	2.631(3)	169.3	
C11B-H11B···O4C	0.95	2.64	3.319(4)	128.4	
O3D-H3D···N1B	0.84	1.79	2.628(3)	172.8	
C5B-H5B···O4D	0.95	2.65	3.331(3)	128.7	
O1D-H1D...N1A*	0.84	1.77	2.601(3)	168.6	x, y-1, z+1
C5A-H5A...O2D*	0.95	2.72	3.377(3)	127.2	x, 1+y, z-1

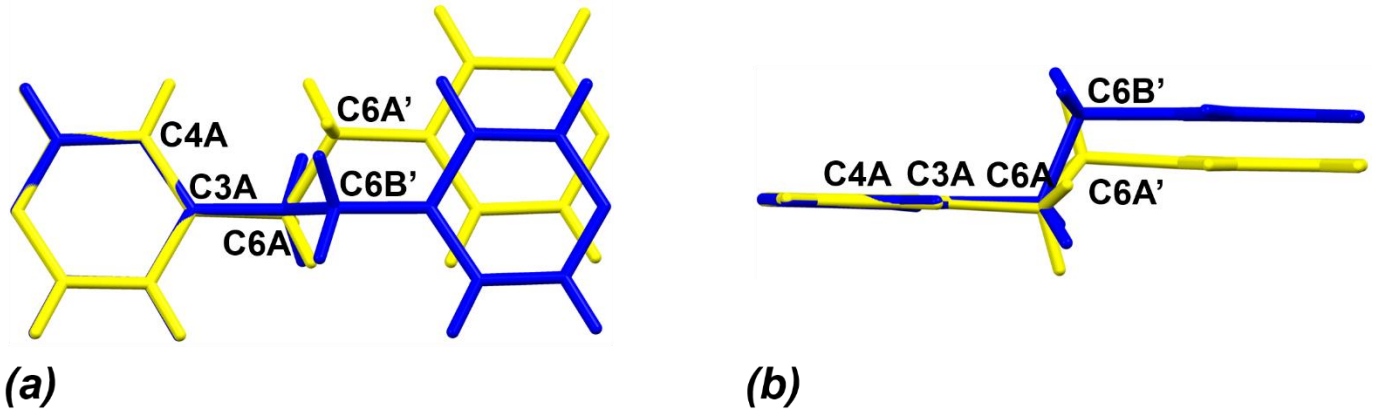

Figure S 1 Overlap of the two different conformers of ETBIPY (molecule A- yellow, molecule B- blue) in ETBIPY•racPSA from the top (a) and side view (b). Atoms used to describe torsional differences are labelled accordingly.

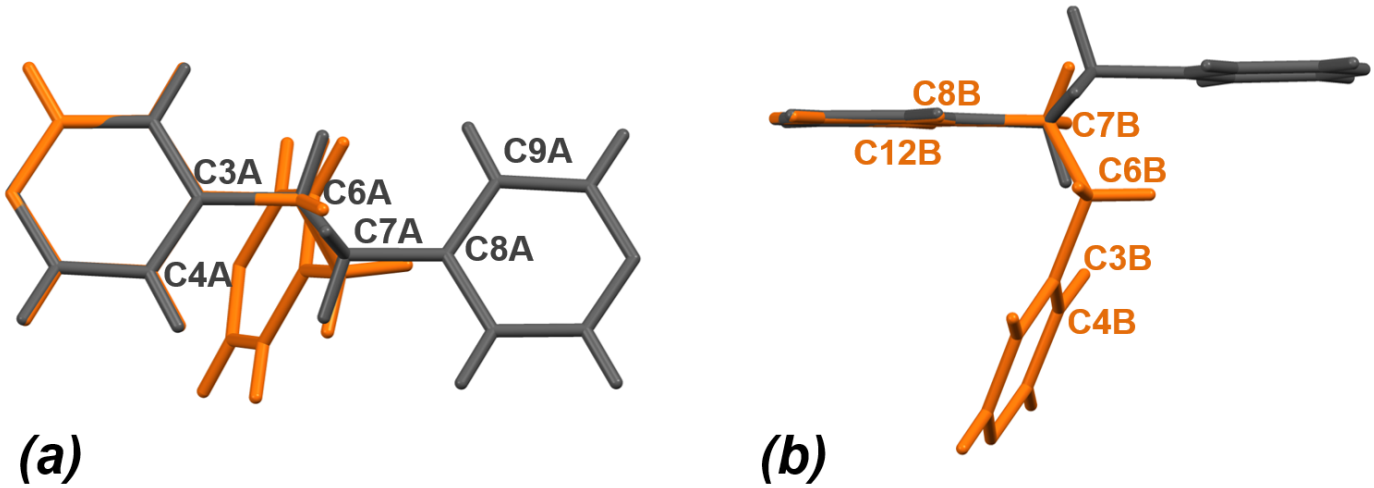

Figure S 2 The difference between the two symmetrically independent ETBIPYs (molecule A- grey, molecule B- orange) in ETBIPY•(S)PSA from the top (a) and side view (b). Atoms used to describe torsional differences are labelled accordingly.

3. Thermal analysis of cocrystals

Differential Scanning Calorimetry (DSC) was carried out using a Perkin Elmer Pyris 6 under a N2 gas purge (flow rate of 20.0 ml/min). Experiments were conducted over a temperature range of 30 °C to 350 °C. DSCs for multicomponent crystals and their relevant starting materials are shown in Fig. S3-S7.

The DSC curve of BIPY•PTA shows one endotherm corresponding to the melting point of the crystal (T_{on}= 158.9 °C, T_{peak}= 161.2 °C). The melting point of the cocrystal is located between the melting points of the two starting material, BIPY (T_{on}= 108.6 °C, T_{peak}= 111.2 °C) and PTA (T_{on}= 178.0 °C, T_{peak}= 181.8 °C). BIPY tend to hydrate during the sample preparation (grinding) for DSC measurement thus the first endotherm observed on the DSC curve is related to the loss of water of the BIPY•H_2O. (**Figure S3**)

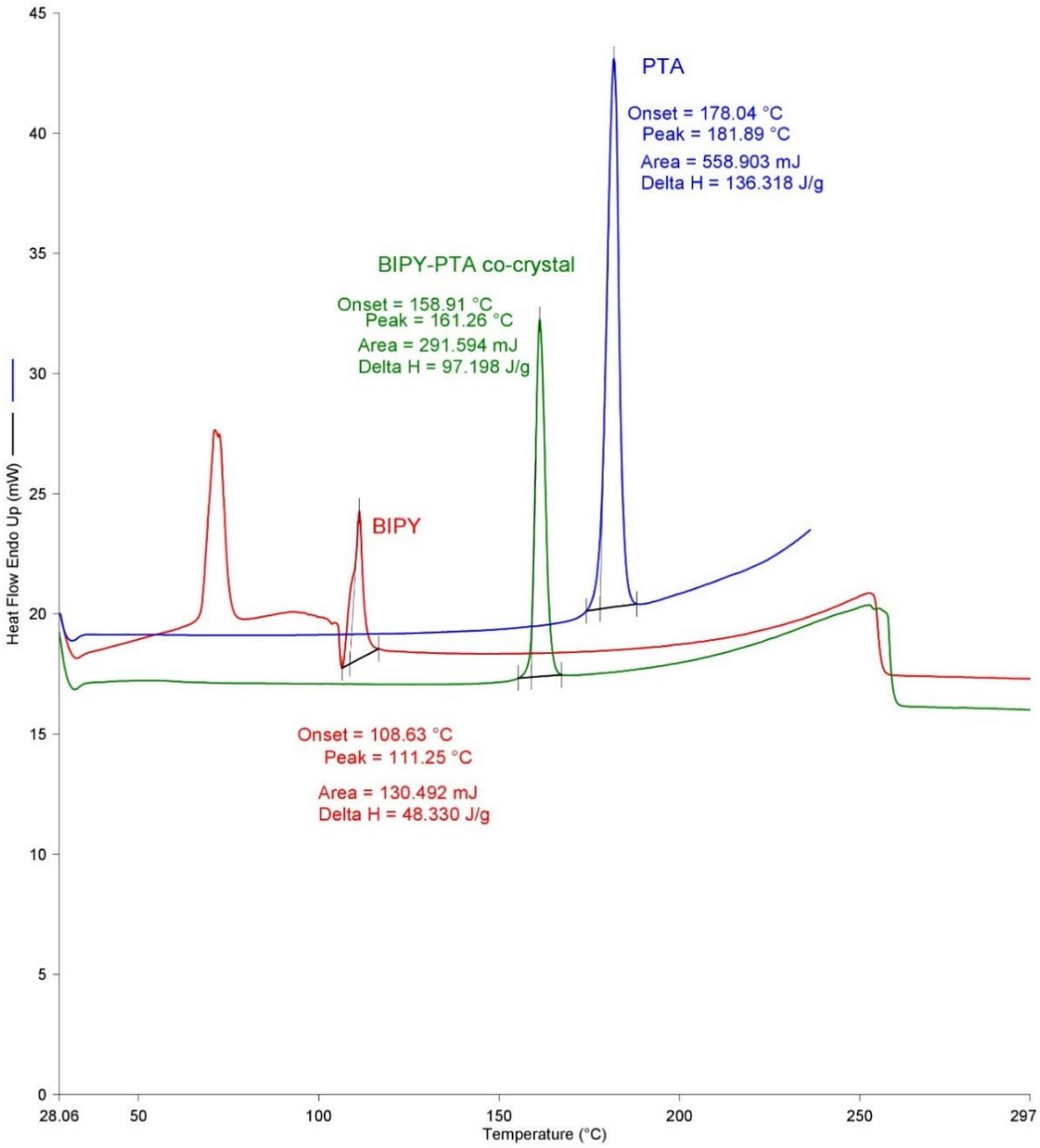

Figure S3 DSC curve of BIPY•PTA and the individual starting materials, BIPY and PTA.

The DSC curve of BIPY•racPBA crystals shows one endotherm corresponding to the melting point of the crystal (T_{on}= 80.5 °C, T_{peak}= 84.1 °C). (**Figure S4**)

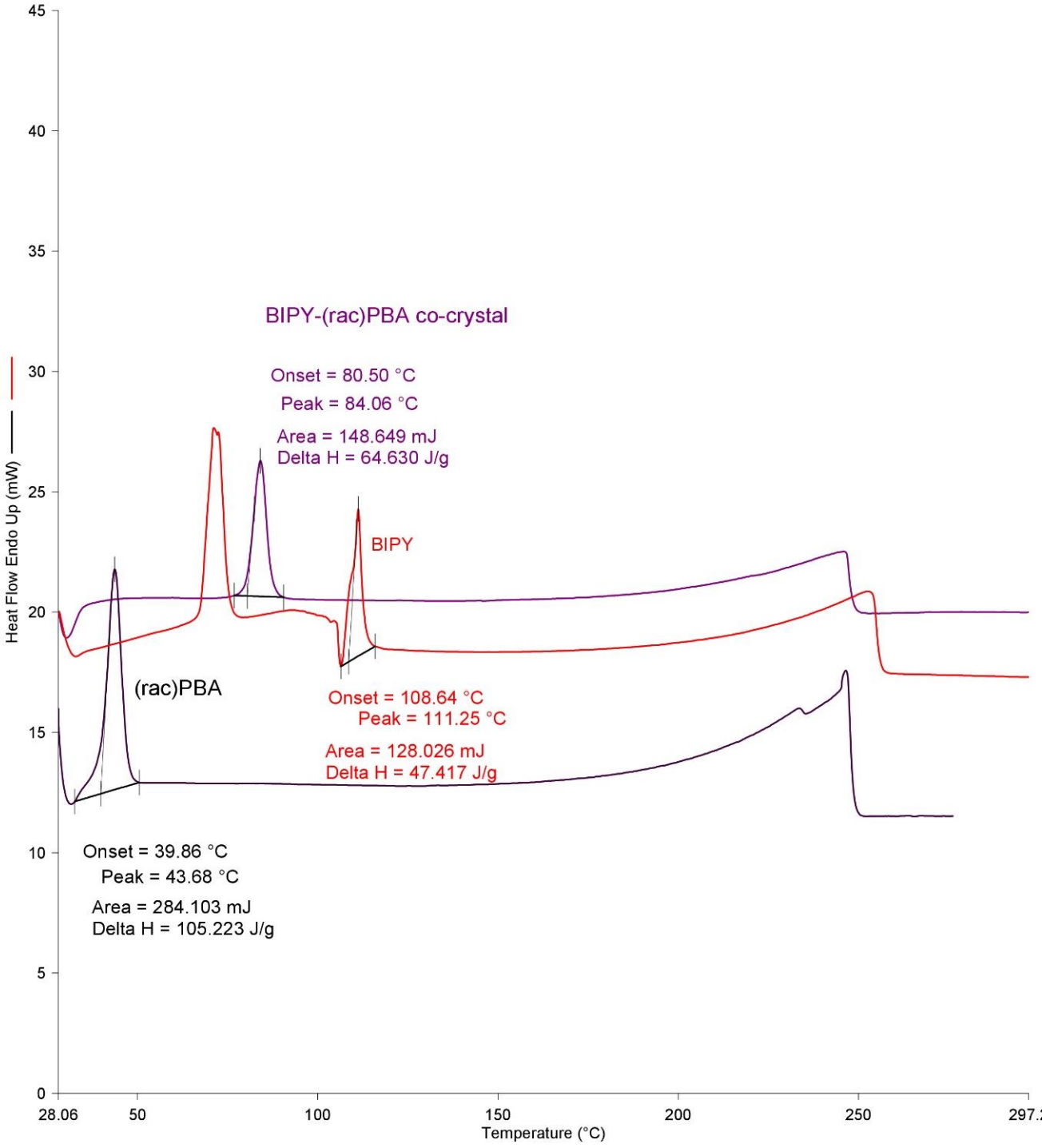

Figure S4 DSC curve of BIPY•racPBA.

The DSC curve of BIPY•racPSA crystals shows one endotherm corresponding to the melting point of the crystal (T_{on}= 148.4 °C, T_{peak}= 150.4 °C). (**Figure S5**)

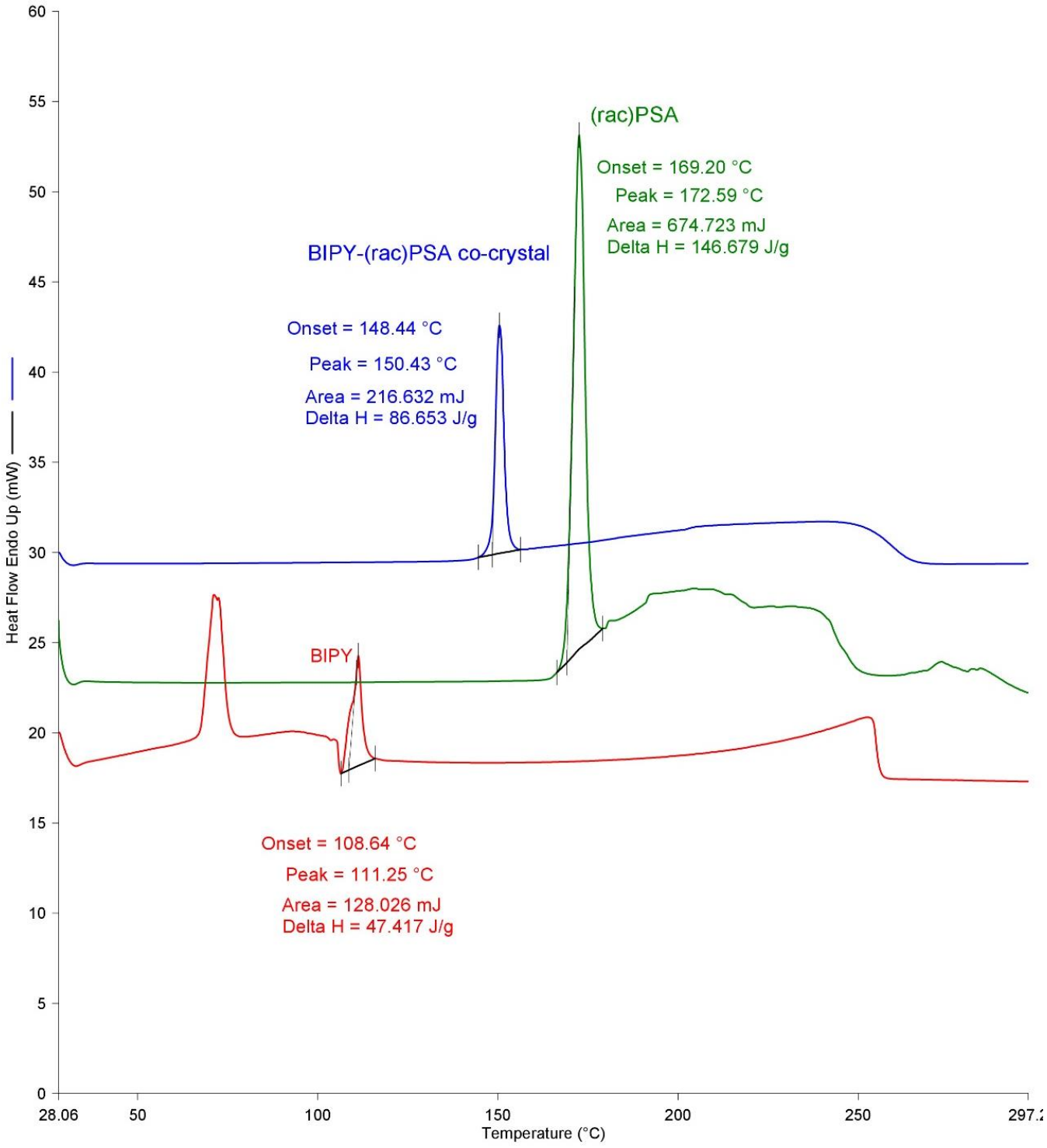

Figure S5 DSC curve of BIPY•racPSA.

The DSC curve of ETBIPY•racPSA crystals shows one endotherm corresponding to the melting point of the crystal (T_{on}= 185.8 °C, T_{peak}= 188.0 °C) (**Figure S6**).

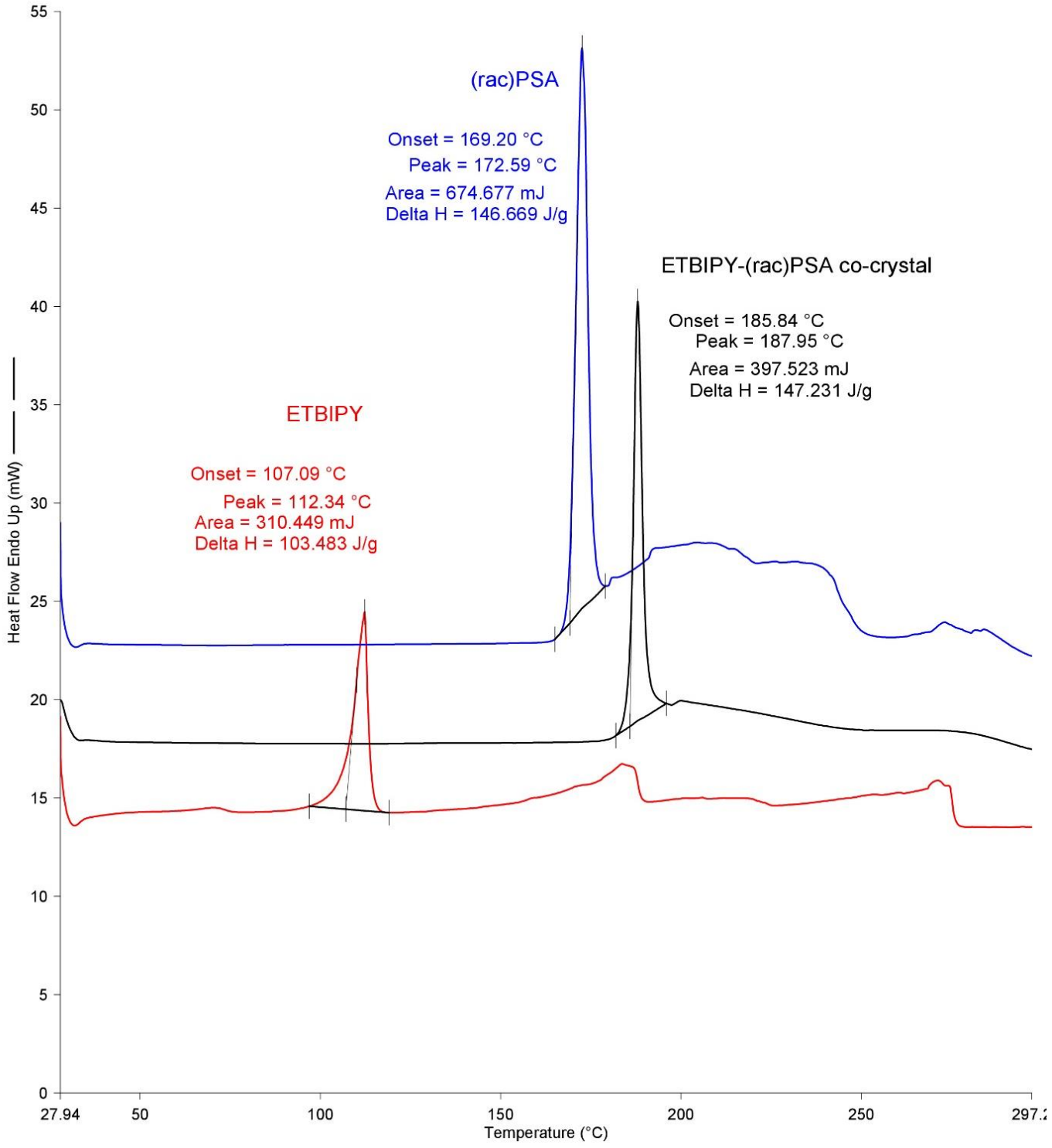

Figure S6 DSC curve of ETBIPY•racPSA.

The DSC curve of ETBIPY•(S)PSA crystals shows a more complex melting process. The melting point of the cocrystal (T_{on}= 147.0 °C, T_{peak}= 151.4 °C) is between the melting points of the two starting material, ETBIPY (T_{on}= 107.1 °C, T_{peak}= 112.3 °C) and (S)-PSA (T_{on}= 178.2 °C, T_{peak}= 182.5 °C). (**Figure S7**).

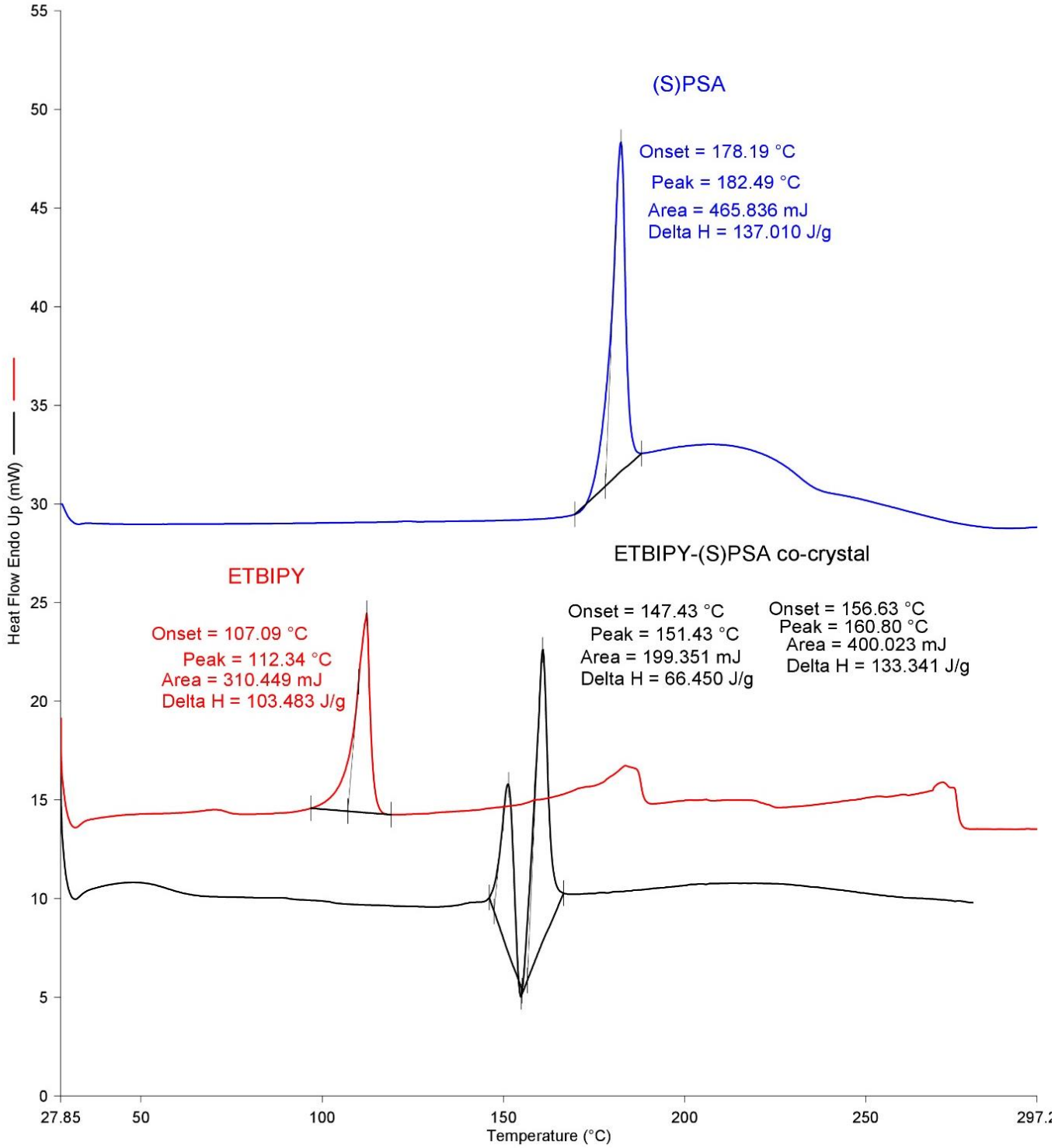

Figure S7 DSC curve of ETBIPY•(S)PSA

4. Powder X-ray analysis

Powder X-ray diffraction (PXRD) data were recorded on a Bruker D2 phaser diffractometer using CuKα radiation (1.54184 Å) generated at 30 kV and 10 mA. Simulated powder patterns of crystal structures were calculated using Mercury[6] and compared with the experimental patterns to confirm bulk phase purity. In order to determine whether the cocrystals can be obtained mechanochemically, the starting materials were ground with a mortar and pestle for thirty minutes and the resulting compounds were analysed by PXRD.

Powder X-ray analysis was conducted to show that the structure detected by using one single crystal only (**Figure S8-S12**, green- single crystal, calculated) is representative to the bulk material (**Figure S8-S12**, red- bulk). Also PXRD analysis was used to show if the cocrystal can be prepared via a more environmental friendly method by using a minimal amount of solvent. The two starting material were ground in a 1:1 ratio with several drops of solvent and after 30 mins the PXRD pattern was collected (**Figure S8-S12**, blue- grinding) and was compared to the pattern of the starting materials (**Figure S8-S12**, light blue- BIPY or ETBIPY, purple- acid). The single crystal structure is representative to the bulk material in all cases.

The patterns for the single crystal and the ground material of BIPY•PTA are quite similar and clearly differ from the starting compounds. However, the match is not perfect and several peaks related to BIPY and PTA are still noticeable, therefore partial reaction occurred. In all the other structures the PXRD obtained from the ground material were poor quality and thus the outcome of the grinding experiments are inconclusive.

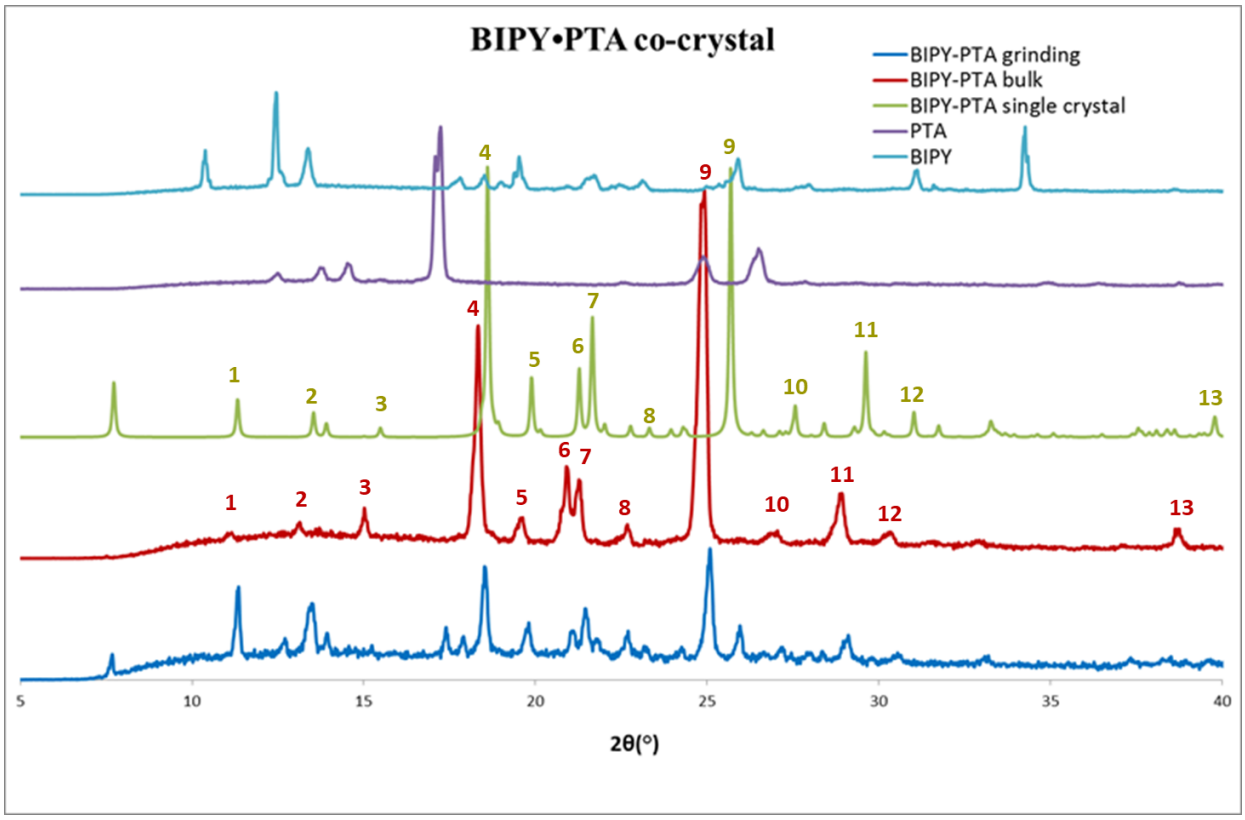

Figure S8 Comparison of PXRD patterns: pure BIPY(light blue), pure PTA (purple), the pattern generated from single crystal structure of BIPY•PTA (green), PXRD pattern of the bulk of the crystallisation (BIPY•PTA bulk -red) and the result of the solvent drop grinding (BIPY•PTA blue).

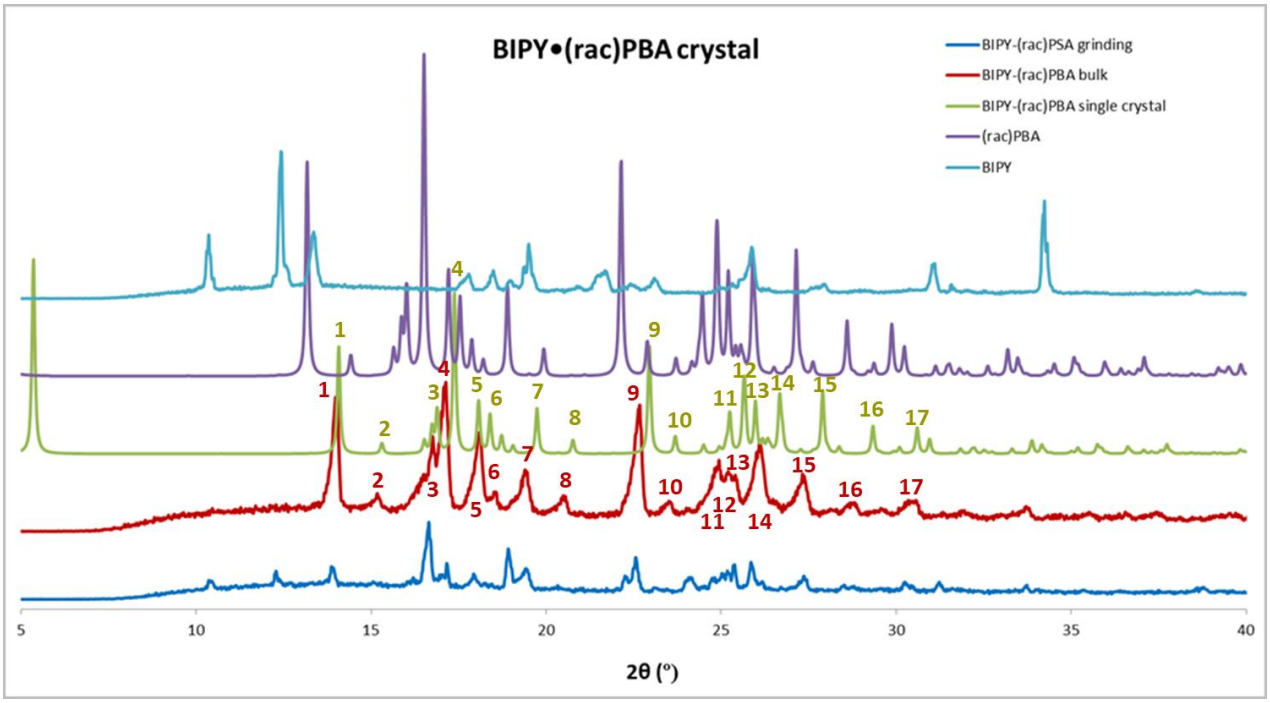

Figure S9 Comparison of PXRD patterns: pure BIPY (light blue), pure racPBA (purple), the pattern generated from single crystal structure of BIPY•racPBA (green), PXRD pattern of the bulk of the crystallisation (BIPY•racPBA bulk-red) and the result of the solvent drop grinding (BIPY•racPBA blue).

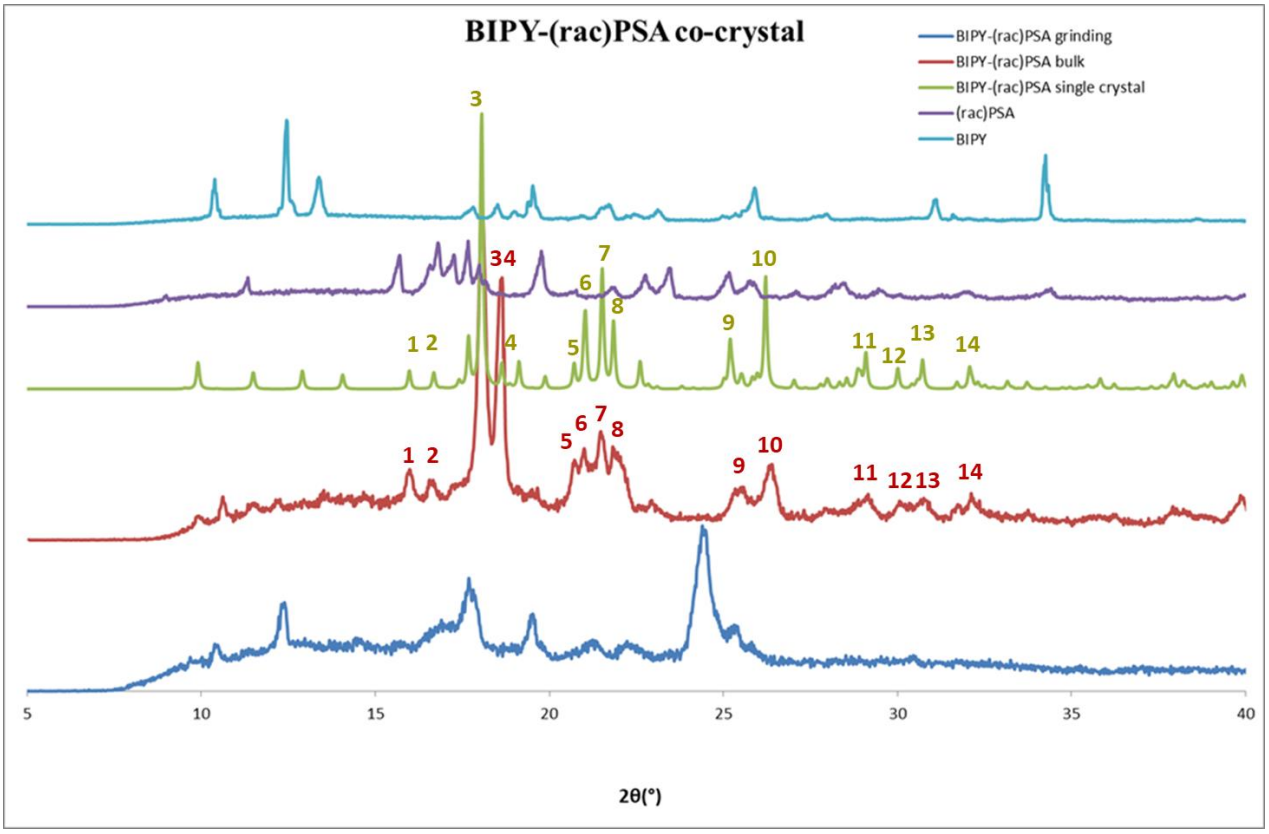

Figure S10 Comparison of PXRD patterns: pure BIPY(light blue), pure racPSA (purple), the pattern generated from single crystal structure of BIPY•racPSA (green), PXRD pattern of the bulk of the crystallisation (BIPY•racPSA bulk-red) and the result of the solvent drop grinding (BIPY•racPSA blue).

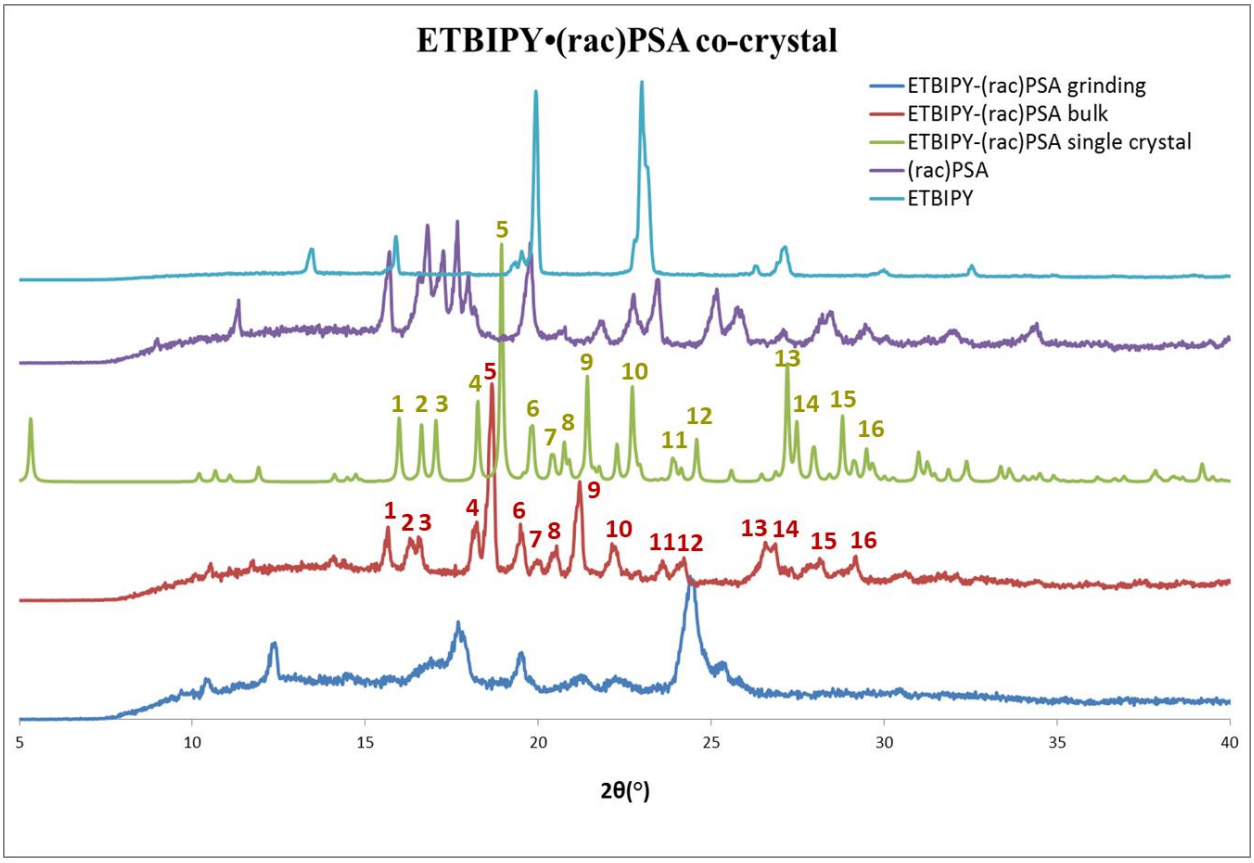

Figure S11 Comparison of PXRD patterns: pure ETBIPY (light blue), pure racPSA (purple), the pattern generated from single crystal structure of ETBIPY•racPSA (green), PXRD pattern of the bulk of the crystallisation (ETBIPY•racPSA bulk- red) and the result of the solvent drop grinding (ETBIPY•racPSA blue).

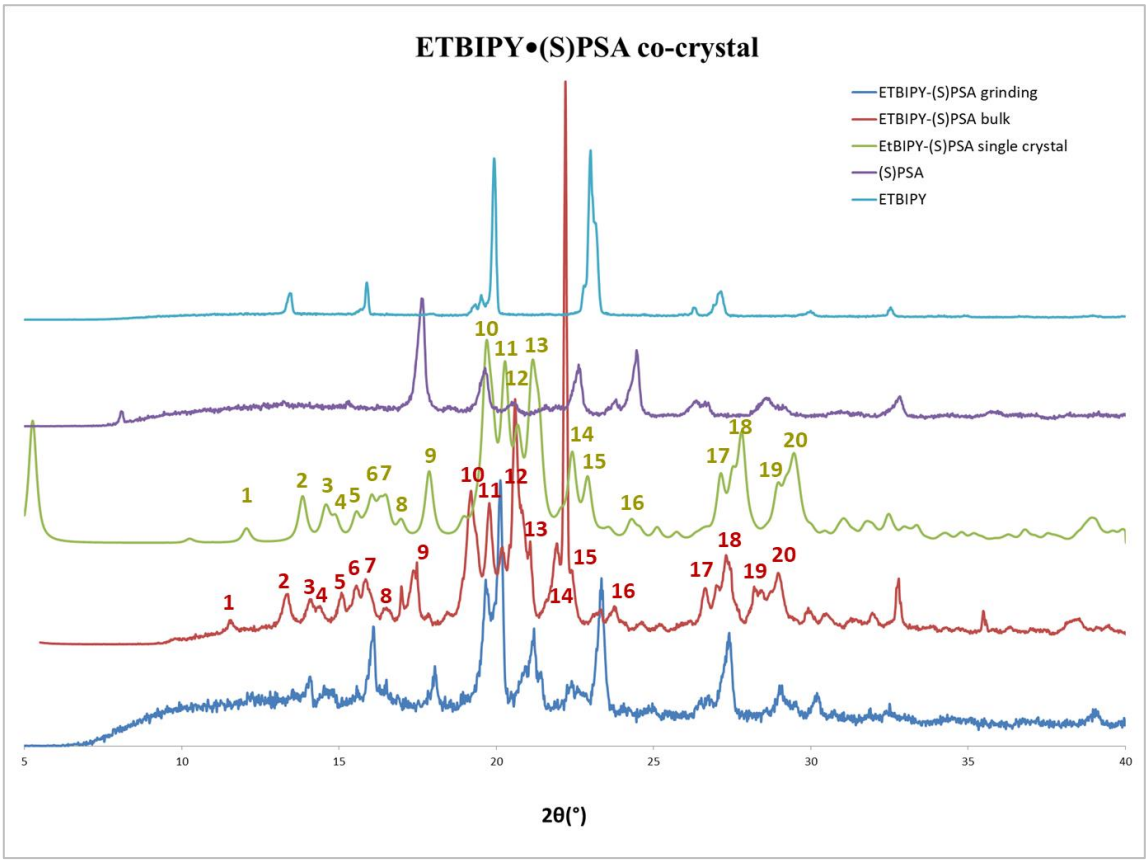

Figure S12 Comparison of PXRD patterns: pure ETBIPY (light blue), pure (S)PSA (purple), the pattern generated from single crystal structure of ETBIPY•(S)PSA (green, full with at half maximum set to 0.3), PXRD pattern of the bulk of the crystallisation (ETBIPY•(S)PSA bulk- red) and the result of the solvent drop grinding (ETBIPY•(S)PSA blue).

5. Energy calculations and energy frameworks

The lattice energies for the fragments in the molecular systems considered in this work were calculated with the aid of equation 1,

$$E_{lat} = \frac{1}{2} \sum_{R_{AB}<R} N * E_{tot}^{AB} \quad (1)$$

where N is the number of molecular pairs in the cluster with a particular interaction energy. For BIPY•PTA, BIPY•racPBA and BIPY•racPSA the interaction energies were calculated with CrystalExplorer[7] at the HF/3-21G level of theory for a 20 Å radius and the results were visualised in the form of energy frameworks in Figure S13, S14 and S15, respectively.

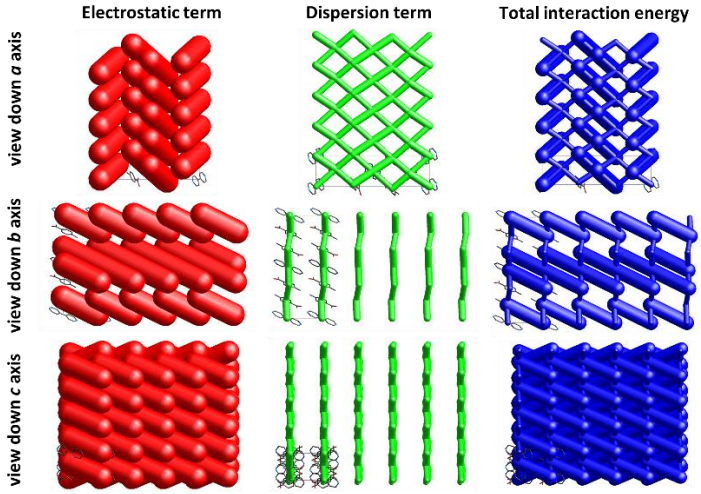

Figure S13 Energy frameworks for BIPY•PTA

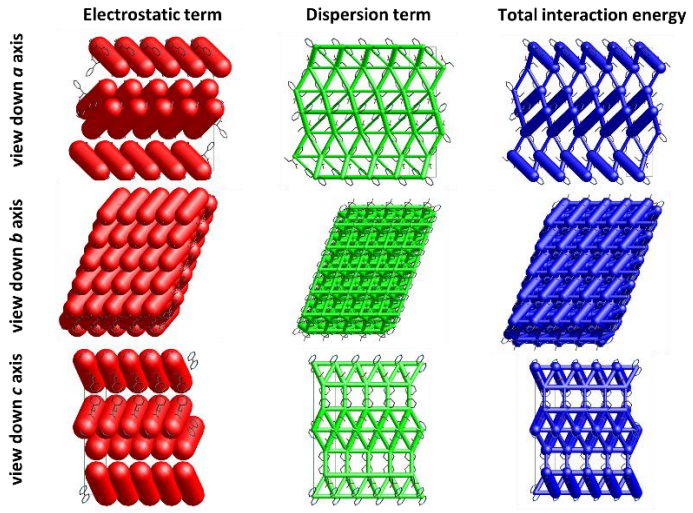

Figure S14 Energy frameworks for BIPY•racPBA

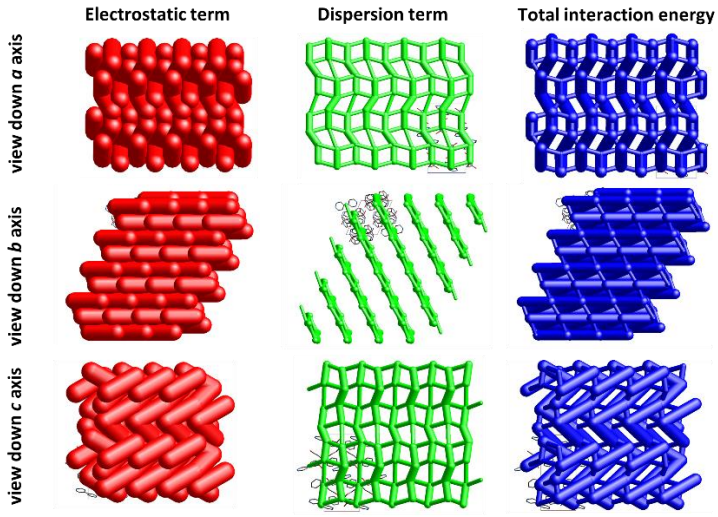

Figure S15 Energy frameworks for BIPY•racPSA

In the case of ETBIPY•racPSA a stoichiometric ratio of 1:(2 x ½) was used and in the case of ETBIPY•(S)PSA a stoichiometric ratio of 2:2 was used when calculating the interaction energy sum for the crystal structures (Figure S16). For the ETBIPY•racPSA the ratio mentioned above was used due to the crystal consisting of one full PSA molecule and two half ETBIPY molecules. The results listed in Table S3 revealed that the crystal of ETBIPY•(S)PSA has lower lattice energy values than ETBIPY•racPSA.

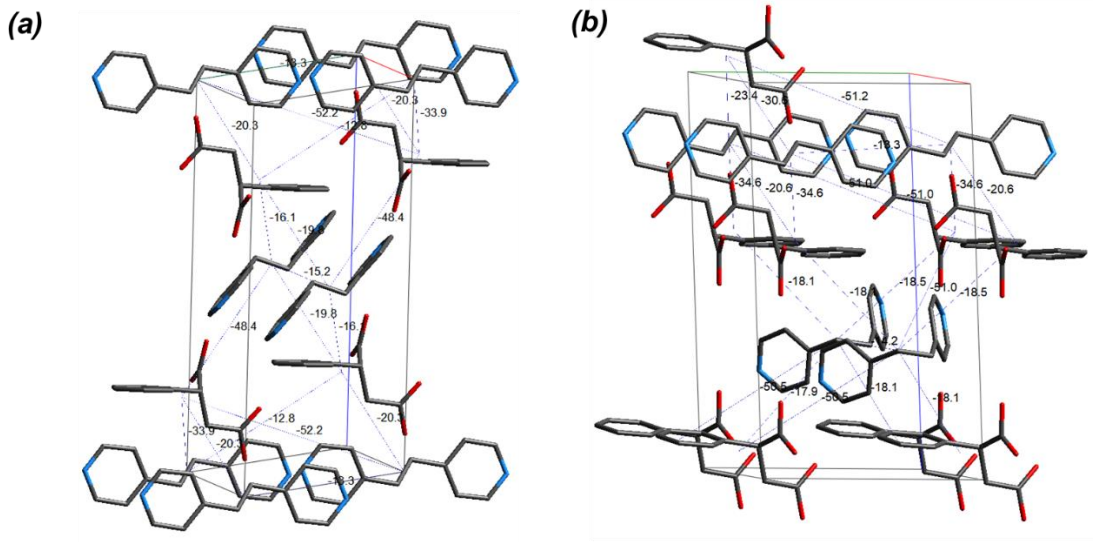

Figure S16 Interaction energies in ETBIPY•racPSA (a) and ETBIPY•(S)PSA (b) crystals (CE-B3LYP model, 20 Å radius).

Table S3 Lattice energies obtained from CrystalExplorer for the molecular structures considered in this work

Molecule	*Model*	*Radius (Å)*	*Lattice Energy (kJ mol^{-1})*
ETBIPY•racPSA	CE-HF	20	-227.94
ETBIPY•(S)PSA	CE-HF	20	-268.83
ETBIPY•racPSA	CE-B3LYP	20	-213.18
ETBIPY•(S)PSA	CE-B3LYP	20	-282.70

To visualise the subtle differences in the supramolecular architecture of the chiral and the racemic crystals in terms of energetics, interaction energies calculated using the CE-B3LYP model for a 20 Å radius were used to create the energy frameworks (Figure S17). The energy framework of both structures are very similar when the electrostatic contributions are compared but subtle differences are noted in the dispersion components (see black arrows on Figure S17). The net interaction energy framework reveals layers where weaker interaction is observed in the ETBIPY•(S)PSA structure.

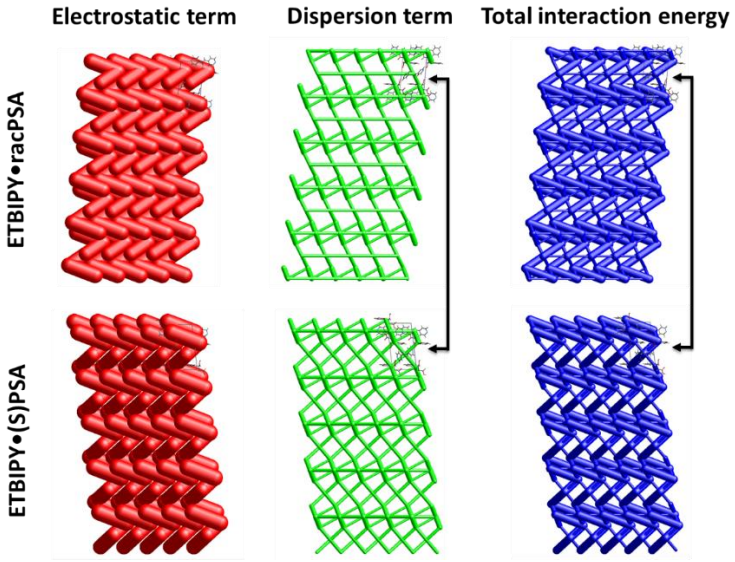

Figure S17 Energy frameworks for ETBIPY•racPSA and ETBIPY•(S)PSA. The energy scale factor is 300 and the energy threshold is 12 kJ mol^{-1}. Structures are shown down the *a* axis.

6. Hirshfeld surface analysis (additional fingerprint plots)

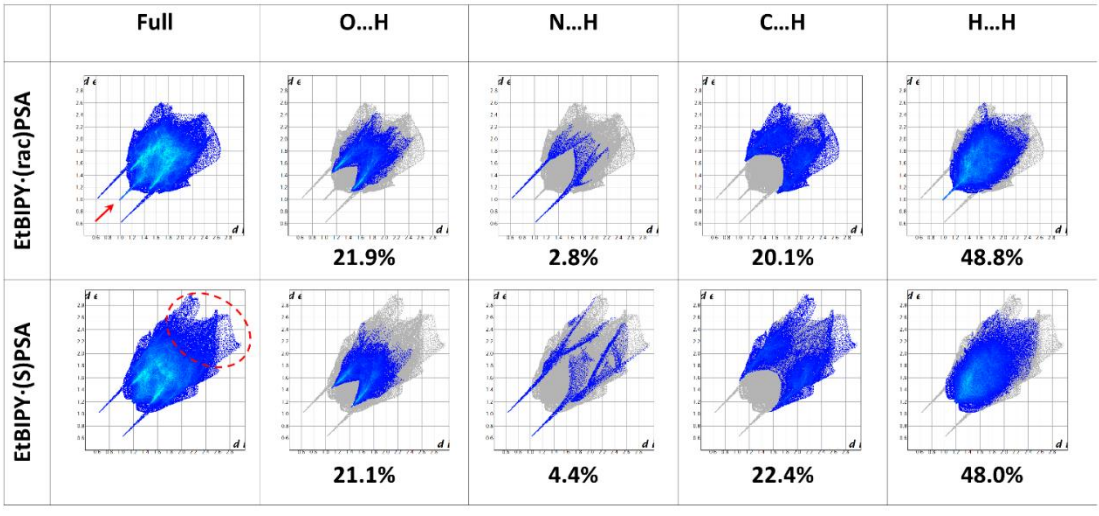

Figure S18 Fingerprint plots calculated for the supramolecular units (ETBIPY•racPSA: *(R)PSA…ETBIPY (molA)…(S)PSA…ETBIPY(molB)*; ETBIPY•(S)PSA: *ETBIPY (molA)…(S)PSA(molD)…ETBIPY(molB)… (S)PSA(molC)*). The overall of shape of the plots differs in the H…H interactions: a short spike (red arrow) resulted from the proximity of the ortho hydrogen of the pyridine ring (H1B) and the hydrogen atom on the chiral carbon (H13). The more extended C…H interactions of the chiral crystal (red circle) suggest a less efficiently packed crystal. It is interesting to note that there is no significant difference between the % distributions in the different interactions.

7. Solubility measurements results

Table S4 Solubility values for BIPY, PTA, racPSA, racPBA and their cocrystals measured in water and ethanol.

	solvent	mass of vial	mass of vial+ solvent	mass of vial+ solvent+ compound	mass of compound	mass of solvent	mass of paper	mass of paper+ undissolved compound	mass of undissolved	mass of dissolved	volume of solvent	solubility	solubility	average solubility
unit		(g)	(g)	(g)	(g)	(g)	(g)	(g)	(g)	(g)	(mL)	(g/g)	(mg/mL)	(mg/mL)
BIPY	ethanol	150.1820	159.2330	160.8580	1.6250	9.0510	3.179	3.544	0.3650	1.2600	11.4715	0.1392	**excluded**	
		154.0390	158.1430	159.3060	1.1630	4.1040	3.218	4.025	0.8070	0.3560	5.2015	0.0867	**68.44**	
		151.9580	157.0250	158.1420	1.1170	5.0670	3.181	3.796	0.6150	0.5020	6.4221	0.0991	**78.17**	**73.30**
	water	151.7790	167.6150	168.6020	0.9870	15.8360	3.193	3.716	0.5230	0.4640	15.8360	0.0293	**29.30**	
		151.8670	167.4590	168.3040	0.8450	15.5920	3.238	3.530	0.2920	0.5530	15.5920	0.0355	**35.47**	
		154.2250	168.6620	169.5210	0.8590	14.4370	3.214	3.664	0.4500	0.4090	14.4370	0.0283	**28.33**	**31.03**
PTA	ethanol	143.3110	150.9000	153.1050	2.2050	7.5890	3.257	4.882	1.6250	0.5800	9.6185	0.0764	**60.30**	
		139.0110	149.9200	151.5340	1.6140	10.9090	3.187	3.836	0.6490	0.9650	13.8264	0.0885	**69.79**	
		143.2600	151.8740	153.2960	1.4220	8.6140	3.212	4.288	1.0760	0.3460	10.9176	0.0402	**excluded**	**65.05**
	water	118.5850	132.0510	152.7300	20.6790	13.4660	3.198	4.569	1.3710	19.3080	13.4660	1.4338	**1433.83**	
		122.5150	133.7230	154.5640	20.8410	11.2080	3.205	4.505	1.3000	19.5410	11.2080	1.7435	**1743.49**	
		122.9810	134.2790	154.8110	20.5320	11.2980	3.157	4.429	1.2720	19.2600	11.2980	1.7047	**1704.73**	**1627.35**
racPSA	ethanol	141.1650	151.4940	152.1750	0.6810	10.3290	3.233	3.512	0.2790	0.4020	13.0913	0.0389	**30.71**	
		141.3680	151.1360	151.6620	0.5260	9.7680	3.208	3.472	0.2640	0.2620	12.3802	0.0268	**21.16**	
		142.6380	149.3060	150.3710	1.0650	6.6680	3.203	3.935	0.7320	0.3330	8.4512	0.0499	**39.40**	**30.42**
	water	141.8750	149.1490	149.6430	0.4940	7.2740	3.17	3.58	0.4100	0.0840	7.2740	0.0115	**11.55**	
		140.8270	154.3690	154.8560	0.4870	13.5420	3.179	3.525	0.3460	0.1410	13.5420	0.0104	**10.41**	
		140.6640	154.1940	154.6910	0.4970	13.5300	3.203	3.552	0.3490	0.1480	13.5300	0.0109	**10.94**	**10.97**
racPBA	ethanol	141.9430	148.3940	149.5920	1.1980	6.4510	3.123	3.671	0.5480	0.6500	8.1762	0.1008	**79.50**	
		134.1450	142.1640	143.1880	1.0240	8.0190	3.121	3.583	0.4620	0.5620	10.1635	0.0701	**55.30**	
		136.0300	139.6160	140.6030	0.9870	3.5860	3.152	4.061	0.9090	0.0780	4.5450	0.0218	**excluded**	**67.40**
	water	142.2340	147.4650	147.8060	0.3410	5.2310	3.128	3.21	0.0820	0.2590	5.2310	0.0495	**49.51**	
		133.4820	145.7280	146.7480	1.0200	12.2460	3.151	3.389	0.2380	0.7820	12.2460	0.0639	**63.86**	
		131.0030	139.8190	140.1490	0.3300	8.8160	3.186	3.303	0.1170	0.2130	8.8160	0.0242	**excluded**	**56.69**

	solvent	mass of vial	mass of vial+ solvent	mass of vial+ solvent+ compound	mass of compound	mass of solvent	mass of paper	mass of paper+ undissolved compound	mass of undissolved	mass of dissolved	volume of solvent	solubility	solubility	average solubility
unit		**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(mL)**	**(g/g)**	**(mg/mL)**	**(mg/mL)**
BIPY-PTA	ethanol	148.5160	156.6860	157.0040	0.3180	8.1700	3.3	3.413	0.1130	0.2050	10.3549	0.0251	**19.80**	
		151.2420	159.9360	159.6360	-0.3000	8.6940	3.296	3.384	0.0880	-0.3880	11.0190	-0.0446	**excluded**	
		124.7620	131.8630	132.2700	0.4070	7.1010	3.304	3.49	0.1860	0.2210	9.0000	0.0311	**24.56**	**22.18**
	water	149.1460	161.0560	161.3800	0.3240	11.9100	3.298	3.413	0.1150	0.2090	11.9100	0.0175	**17.55**	
		145.0740	152.8070	153.0370	0.2300	7.7330	3.3	3.503	0.2030	0.0270	7.7330	0.0035	**excluded**	
		151.3320	163.7690	164.0830	0.3140	12.4370	3.218	3.364	0.1460	0.1680	12.4370	0.0135	**13.51**	**15.53**
BIPY-PSA	ethanol	138.8950	141.8950	148.0860	6.1910	3.0000	3.213	3.298	0.0850	6.1060	3.8023	2.0353	**excluded**	
		138.7890	141.7190	144.1040	2.3850	2.9300	3.2	3.314	0.1140	2.2710	3.7136	0.7751	**611.54**	
		143.2000	145.5400	147.0000	1.4600	2.3400	3.189	3.303	0.1140	1.3460	2.9658	0.5752	**453.84**	**532.69**
	water	142.1710	150.9450	151.1260	0.1810	8.7740	3.13	3.161	0.0310	0.1500	8.7740	0.0171	**excluded**	
		136.7560	142.8800	143.1080	0.2280	6.1240	3.168	3.229	0.0610	0.1670	6.1240	0.0273	**27.27**	
		140.3770	145.9140	146.2200	0.3060	5.5370	3.183	3.329	0.1460	0.1600	5.5370	0.0289	**28.90**	**28.08**
BIPY-PBA	ethanol	123.1610	130.3240	130.6900	0.3660	7.1630	3.2	3.431	0.2310	0.1350	9.0786	0.0188	**14.87**	
		121.4670	130.8170	131.2520	0.4350	9.3500	3.19	3.402	0.2120	0.2230	11.8504	0.0239	**18.82**	
		123.7870	129.8680	130.1550	0.2870	6.0810	3.22	3.41	0.1900	0.0970	7.7072	0.0160	**12.59**	**15.42**
	water	123.3280	134.0040	134.2410	0.2370	10.6760	3.247	3.491	0.2440	-0.0070	10.6760	-0.0007	**excluded**	
		122.0850	128.4750	128.8580	0.3830	6.3900	3.127	3.313	0.1860	0.1970	6.3900	0.0308	**30.83**	
		123.0450	130.0760	130.6380	0.5620	7.0310	3.224	3.422	0.1980	0.3640	7.0310	0.0518	**51.77**	**41.30**

Table S5 Solubility values for ETBIPY, racPSA, S-PSA and its cocrystals measured in water and ethanol.

	solvent	mass of vial	mass of vial+ solvent	mass of vial+ solvent+ compound	mass of compound	mass of solvent	mass of paper	mass of paper+ undissolved compound	mass of undissolved	mass of dissolved	volume of solvent	solubility	solubility	average solubility
unit		**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(mL)**	**(g/g)**	**(mg/mL)**	**(mg/mL)**
ETBIPY	ethanol	148.7450	153.0880	154.7400	1.6520	4.3430	3.1870	4.3650	1.1780	0.4740	5.5044	0.1091	**86.11**	
		150.9410	157.7070	159.1010	1.3940	6.7660	3.2140	4.1150	0.9010	0.4930	8.5754	0.0729	**57.49**	
		152.5810	158.1060	159.6620	1.5560	5.5250	3.1750	3.6720	0.4970	1.0590	7.0025	0.1917	**excluded**	**71.80**
	water	147.7390	154.6590	155.0120	0.3530	6.9200	3.2430	3.2940	0.0510	0.3020	6.9200	0.0436	**43.64**	
		151.0000	158.1060	159.1190	1.0130	7.1060	3.2160	3.2700	0.0540	0.9590	7.1060	0.1350	**134.96**	
		152.7480	161.2160	169.5210	8.3050	8.4680	3.1860	3.2500	0.0640	8.2410	8.4680	0.9732	**973.19**	**89.30**
racPSA	ethanol	141.1650	151.4940	152.1750	0.6810	10.3290	3.2330	3.5120	0.2790	0.4020	13.0913	0.0389	**30.71**	
		141.3680	151.1360	151.6620	0.5260	9.7680	3.2080	3.4720	0.2640	0.2620	12.3802	0.0268	**21.16**	
		142.6380	149.3060	150.3710	1.0650	6.6680	3.2320	3.9350	0.7030	0.3620	8.4512	0.0543	**42.83**	**31.57**
	water	141.8750	149.1400	149.6430	0.5030	7.2650	3.1700	3.5800	0.4100	0.0930	7.2650	0.0128	**12.80**	
		140.8270	154.3690	154.8560	0.4870	13.5420	3.1790	3.5250	0.3460	0.1410	13.5420	0.0104	**10.41**	
		140.6640	154.1940	154.6910	0.4970	13.5300	3.2030	3.5520	0.3490	0.1480	13.5300	0.0109	**10.94**	**11.38**
(S)PSA	ethanol	139.7880	147.4790	147.9160	0.4370	7.6910	3.2430	3.5600	0.3170	0.1200	9.7478	0.0156	**12.31**	
		143.3180	151.7210	152.1020	0.3810	8.4030	3.2100	3.5100	0.3000	0.0810	10.6502	0.0096	**7.61**	
		141.1490	148.8810	149.1100	0.2290	7.7320	3.2300	3.4560	0.2260	0.0030	9.7997	0.0004	**excluded**	**9.96**
	water	140.4880	151.9270	152.3110	0.3840	11.4390	3.1380	3.2000	0.0620	0.3220	11.4390	0.0281	**28.15**	
		142.0700	151.0830	151.7050	0.6220	9.0130	3.1700	3.2200	0.0500	0.5720	9.0130	0.0635	**excluded**	
		141.7590	151.3080	151.6760	0.3680	9.5490	3.2400	3.2800	0.0400	0.3280	9.5490	0.0343	**34.35**	**31.25**
ETBIPY-racPSA	ethanol	139.2280	143.1900	143.2740	0.0840	3.9620	3.1860	3.2440	0.0580	0.0260	5.0215	0.0066	**5.18**	
		142.7850	145.1370	145.2090	0.0720	2.3520	3.2170	3.2540	0.0370	0.0350	2.9810	0.0149	**excluded**	
		137.3360	141.6100	141.7040	0.0940	4.2740	3.1800	3.2510	0.0710	0.0230	5.4170	0.0054	**4.25**	**4.71**
	water	139.3790	145.0620	145.1650	0.1030	5.6830	3.2480	3.3340	0.0860	0.0170	5.6830	0.0030	**excluded**	
		137.9110	144.3020	144.3740	0.0720	6.3910	3.1960	3.2280	0.0320	0.0400	6.3910	0.0063	**6.26**	
		141.7170	148.2480	148.3390	0.0910	6.5310	3.2340	3.2760	0.0420	0.0490	6.5310	0.0075	**7.50**	**6.88**
ETBIPY-(S)PSA	ethanol	142.3110	147.4700	149.3990	1.9290	5.1590	3.2020	3.3850	0.1830	1.7460	6.5387	0.3384	**267.03**	
		133.1220	138.3680	139.8500	1.4820	5.2460	3.1880	3.3500	0.1620	1.3200	6.6489	0.2516	**198.53**	
		139.7020	147.5380	148.2440	0.7060	7.8360	3.1730	3.2710	0.0980	0.6080	9.9316	0.0776	**excluded**	**232.78**

	solvent	mass of vial	mass of vial+ solvent	mass of vial+ solvent+ compound	mass of compound	mass of solvent	mass of paper	mass of paper+ undissolved compound	mass of undissolved	mass of dissolved	volume of solvent	solubility	solubility	average solubility
unit		**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(g)**	**(mL)**	**(g/g)**	**(mg/mL)**	**(mg/mL)**
	water	134.0770	141.3890	142.9540	1.5650	7.3120	3.1980	3.2230	0.0250	1.5400	7.3120	0.2106	**210.61**	
		142.2150	149.5630	151.6610	2.0980	7.3480	3.2660	3.3110	0.0450	2.0530	7.3480	0.2794	**279.40**	
		136.3670	144.7000	145.6310	0.9310	8.3330	3.1900	3.2180	0.0280	0.9030	8.3330	0.1084	**excluded**	**245.00**

8. References

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