Electronic Supplementary Information

Ionic cocrystals of etiracetam and levetiracetam: the importance of chirality for ionic cocrystals

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Hot Stage Microscopy experiment

According to VT-XRPD measurements on crystalline powder of $LEV_2{\cdot}CaCl_2{\cdot}2H_2O$, a possible recrystallization of the anhydrous form could occur at 250 °C; therefore we tried to obtain single crystals of anhydrous $LEV_2{\cdot}CaCl_2$ by heating the hydrated ICC $LEV_2{\cdot}CaCl2{\cdot}2H_2O$ in a Hot Stage Microscopy experiment (HSM) conducted immersing the powder in Fomblin®, a synthetic lubricant composed of carbon, oxygen and fluorine that remains liquid in a very wide range of temperatures (from –100 °C to 300 °C) and is thermally stable and chemically inert even at very high temperatures. The dehydration process could thus be detected (water bubbles formation) but no crystals could be observed at this temperature; the anhydrous form was then melted, and, after the stage was cooled down to room temperature, a few crystals were recovered of sufficient quality for X-ray structural determination, and they were found to be the hydrated form $LEV_2{\cdot}CaCl_2{\cdot}2H_2O$.

Superposition information for LEV2•CaCl2•2H2O and ETI2•CaCl2•2H2O.

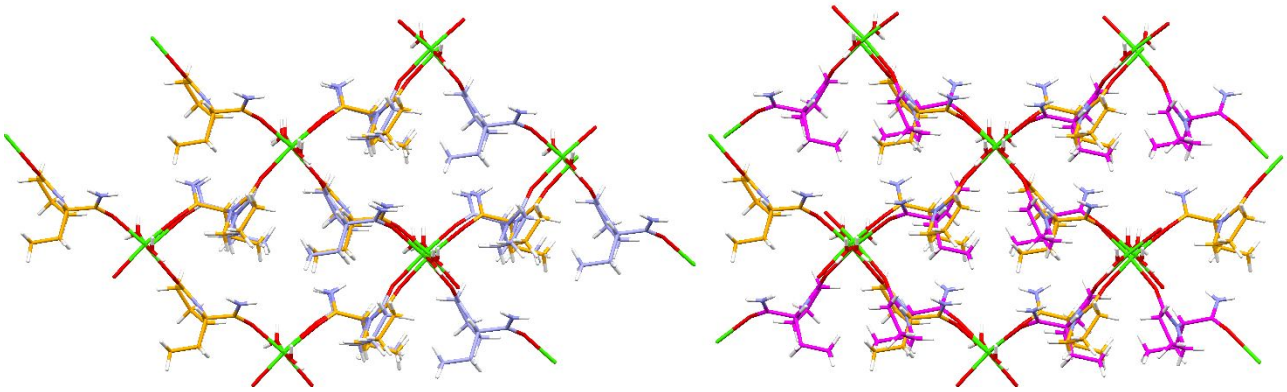

Fig. SI-1. Superposition details for $LEV_2{\bullet}CaCl_2{\bullet}2H_2O$ and $ETI_2{\bullet}CaCl_2{\bullet}2H_2O$. Both LEV and ETI crystallize in a C-centred unit cell with very similar unit cell parameters. Both structures show layers, where in ETI the layers contain either the R or S enantiomer. Superposition of the S-ETI layer onto the LEV layer shows a large similarity in crystal packing (Left). Superposition of the R-ETI layer onto LEV (right) reveals that the overall layer conformation is kept and that the molecules are able to adapt themselves to the local change in chirality.

Details of hydrogen bonds for cocrystals

Table S1. Hydrogen bond lengths/Å and angles/° for $LEV_2{\bullet}CaCl_2{\bullet}2H_2O$

D-H···A	d (D-H)	d (H···A)	d (D···A)	∠DHA
N3-H3A···Cl1	0.86	2.47	3.310(7)	166
N3-H3B···Cl2 [i]	0.86	2.42	3.215(7)	154
N4-H4A N···Cl2	0.86	2.5	3.257(7)	148
O5-H5A···Cl2 [ii]	0.82	2.34	3.151(6)	169
O5-H5B···Cl1 [iii]	0.82	2.33	3.143(5)	175
N4-H4B N···Cl1	0.86	2.36	3.214(7)	170
O6-H6A···Cl1	0.82	2.33	3.131(5)	165
O6-H6B···Cl2	0.82	2.39	3.138(6)	152

Symmetry codes: (i) 1/2 +x,1/2 +y,z; (ii) 1-x, y, 2-z; (iii) 3/2 –x,-1/2 +y,2-z.

Table S2. Hydrogen bond lengths/Å and angles/° for $ETI_2{\bullet}CaCl_2{\bullet}2H_2O$

D-H···A	d (D-H)	d (H···A)	d (D···A)	∠DHA
N2-H2A···Cl1 [ii]	0.77(5)	2.49(6)	3.248(5)	168(6)
N2-H2B···Cl1 [iii]	0.85(6)	2.48(6)	3.317(5)	167(4)
O3-H3A···Cl1 [i]	0.83(3)	2.32(3)	3.145(3)	172(3)
O3-H3B···Cl1	0.82(5)	2.30(5)	3.109(3)	170(4)

Symmetry codes: (i) 1-x,-y,1-z; (ii) 1-x,y,1/2-z; (iii) 1/2+x,1/2-y,-1/2+z.

Table S3. Hydrogen bond lengths/Å and angles/° for $LEV_2{\bullet}MgCl_2{\bullet}2H_2O$

D-H···A	d (D-H)	d (H···A)	d (D···A)	∠DHA
O2-H2A···Cl41 [iii]	0.82	2.52	3.193(2)	140

O2-H2B···Cl42 [iv]	0.82	2.48	3.227(2)	153
N13-H13A···Cl42	0.89	2.35	3.186(3)	156
N13-H13B···Cl41	0.89	2.34	3.215(3)	170
O22-H22A···Cl41 [i]	0.82	2.33	3.148(3)	172
O22-H22B···Cl42 [i]	0.82	2.45	3.191(3)	151
N33-H33B···Cl42 [i]	0.89	2.42	3.197(14)	146
N33-H33C···Cl41 [ii]	0.89	2.43	3.212(14)	147

Symmetry codes: (i) x,y,1+z; (ii) -1/2+x,-1/2+y,1+z; (iii) 2-x,y,1-z ; (iv) 3/2-x,1/2+y,1-z.

Table S4. Hydrogen bond lengths/Å and angles/° for ETI_2•$MgCl_2$•$6H_2O$

D-H···A	d (D-H)	d (H···A)	d (D···A)	∠DHA
N009-H00A···N008	0.79(4)	2.42(4)	2.767(4)	108(3)
N009-H00A···Cl1 [iii]	0.79(4)	2.54(4)	3.256(3)	152(4)
N009-H00B···Cl1 [ii]	0.91(4)	2.47(4)	3.375(3)	175(4)
O3-H3A···Cl1	0.74(4)	2.39(4)	3.110(3)	163(4)
O3-H3B···O2 [i]	0.84(4)	1.90(4)	2.738(3)	174(4)
O4-H4A···Cl1	0.77(4)	2.44(4)	3.154(3)	155(4)
O4-H4B···O5	0.96(4)	1.76(4)	2.699(4)	166(4)
O5-H5A···Cl1 [iii]	0.85	2.3	3.153(4)	178
O5-H5B···O2 [iv]	0.85	2.01	2.845(4)	168

Symmetry codes: (i) x,y,1+z; (ii) x,y,-1+z; (iii) -x,1-y,1-z; (iv) 1-x,1-y,-z.

Table S5. Hydrogen bond lengths/Å and angles/° for ETI_2•$MgCl_2$•$2H_2O$

D-H···A	d (D-H)	d (H···A)	d (D···A)	∠DHA
N2-H2A···Cl1 [i]	0.86	2.54	3.284(7)	145
N2-H2B···Cl1 [ii]	0.86	2.44	3.289(7)	170
O3-H3A···Cl1	0.88	2.39	3.164(5)	147
O3-H3B···Cl1 [i]	0.88	2.4	3.177(5)	148

Symmetry codes: (i) 1-x,1-y,1-z; (ii) 1/2+x,1/2+y,z.

Table S6. Hydrogen bond lengths/Å and angles/° for ETI_4•$MgCl_2$•$6H_2O$

D-H···A	d (D-H)	d (H···A)	d (D···A)	∠DHA
N2-H2A···O2 [i]	0.86	2.06	2.919(4)	176
N2-H2B···Cl1 [iii]	0.86	2.38	3.219(3)	167
N4-H4C···O4 [iv]	0.86	2.13	2.978(4)	169
N4-H4D···Cl1 [v]	0.86	2.42	3.252(3)	162
O5-H5A···O3	0.84(5)	1.93(5)	2.762(4)	174(4)
O5-H5B···O4 [ii]	0.77(5)	2.05(5)	2.797(3)	167(5)
O6-H6A···Cl1	0.85(4)	2.33(4)	3.145(3)	161(4)
O6-H6B···O7	0.82(6)	1.88(6)	2.697(4)	173(5)
O7-H7C···Cl1 [v]	0.85	2.48	3.266(4)	154
O7-H7D···O3	0.85	1.95	2.793(5)	173

Symmetry codes: (i) 1-x,2-y,2-z; (ii) 1-x,-y,1-z; (iii) 1-x,1-y,1-z; (iv) 2-x,-y,1-z; (v) 2-x,1-y,1-z.

Experimental XRPD vs calculated one from single crystal

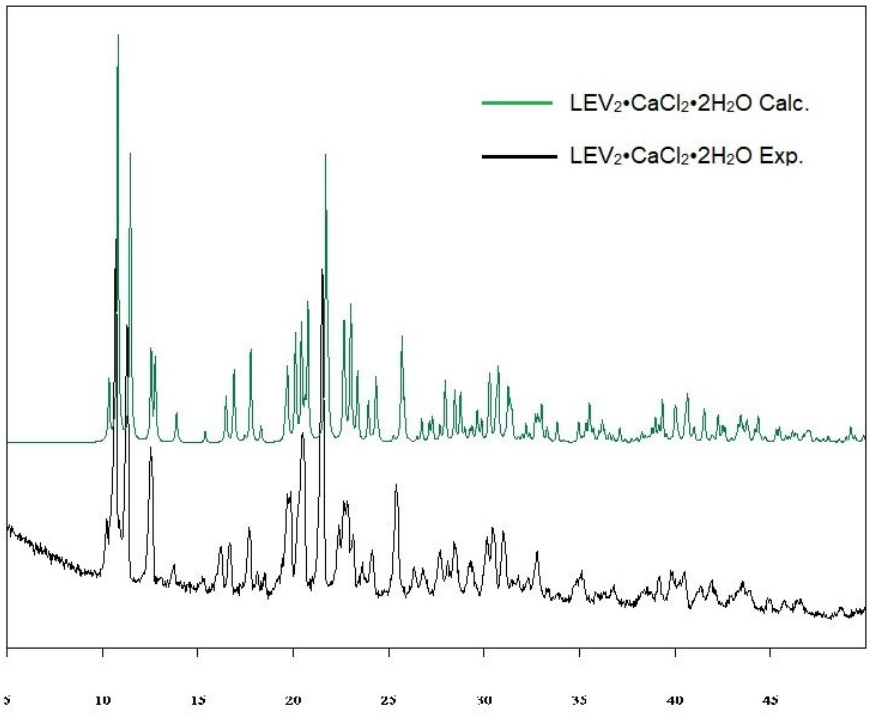

Fig. SI-2. $LEV_2 \cdot CaCl_2 \cdot 2H_2O$

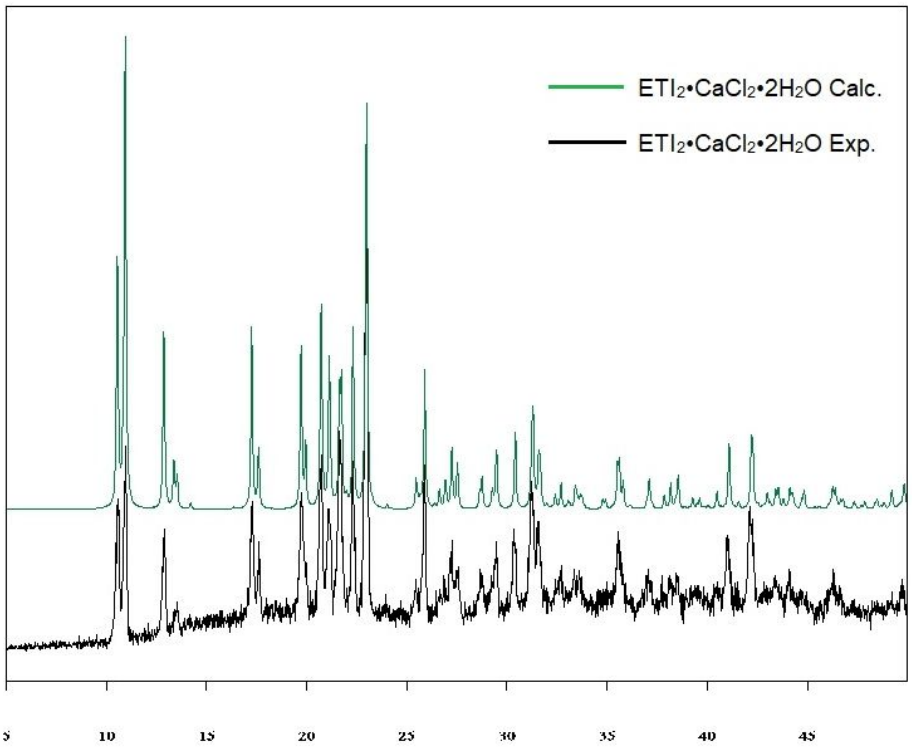

Fig. SI-3. $ETI_2 \cdot CaCl_2 \cdot 2H_2O$

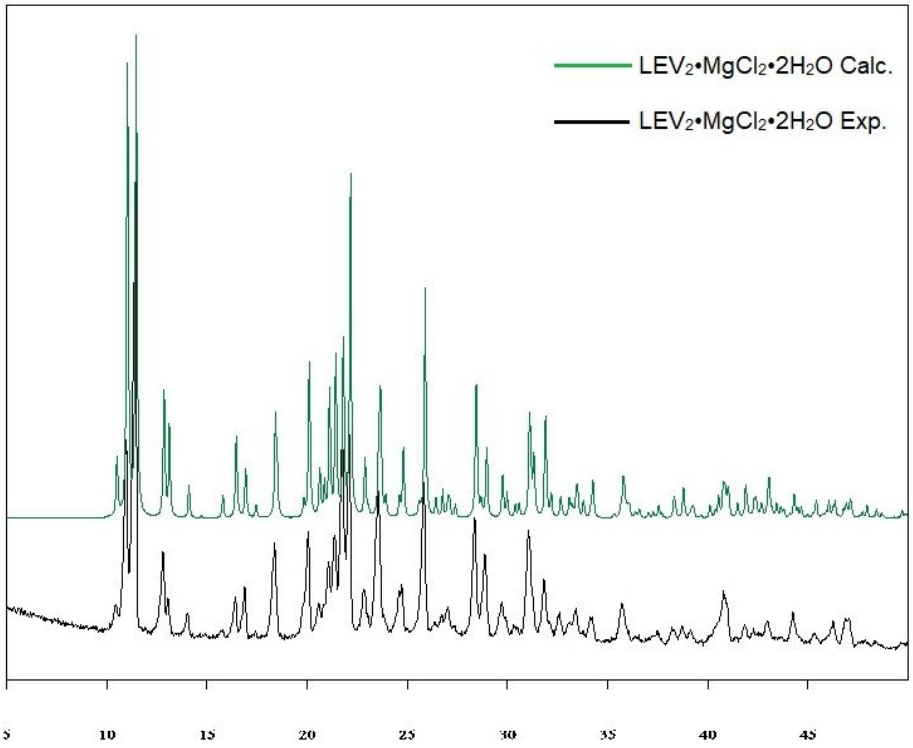

Fig. SI-4. $LEV_2 \cdot MgCl_2 \cdot 2H_2O$

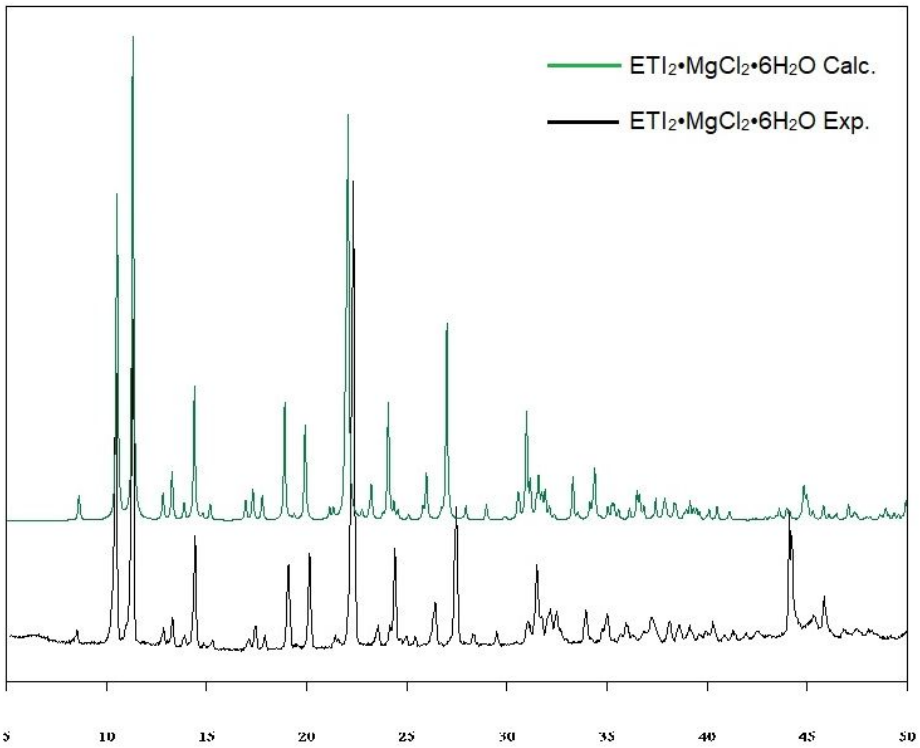

Fig. SI-5. $ETI_2 \cdot MgCl_2 \cdot 6H_2O$

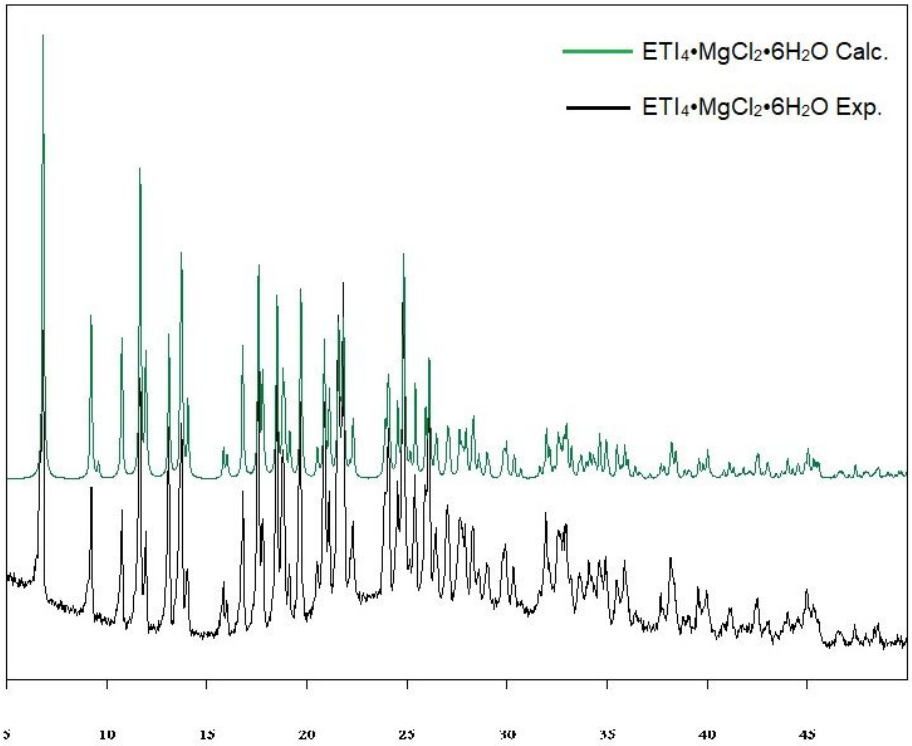

Fig. SI-6. $ETI_4 \cdot MgCl_2 \cdot 6H_2O$

DSC

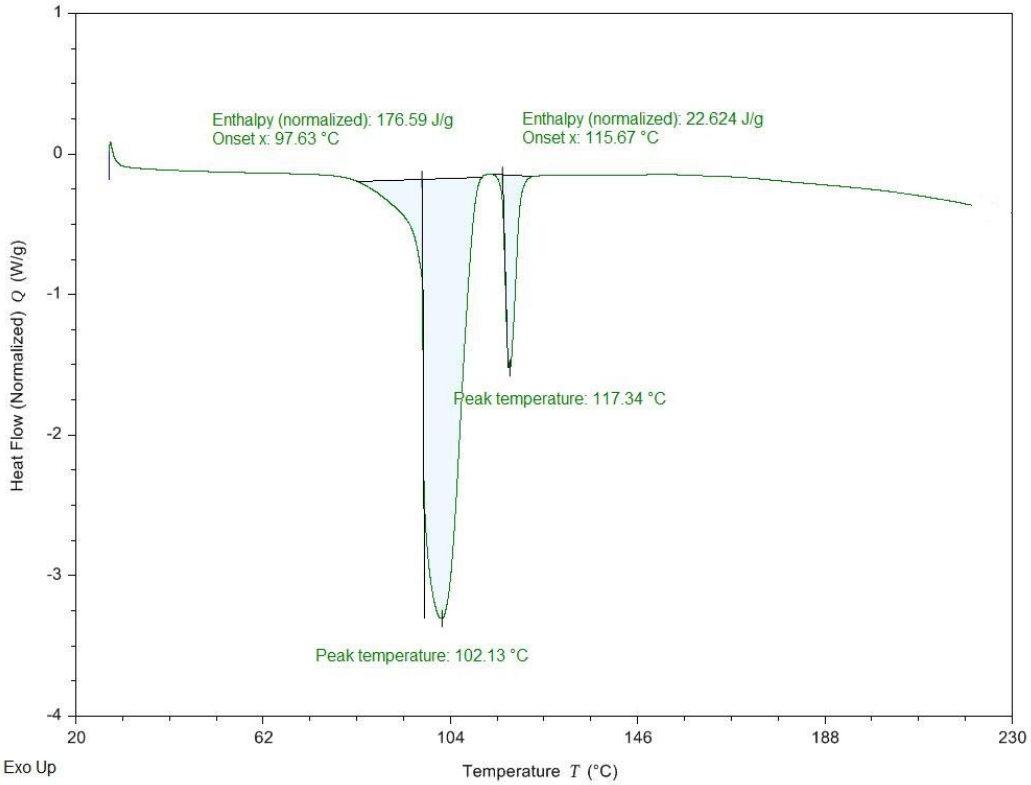

Fig. SI-7. DSC of $LEV_2 \cdot CaCl_2 \cdot 2H_2O$

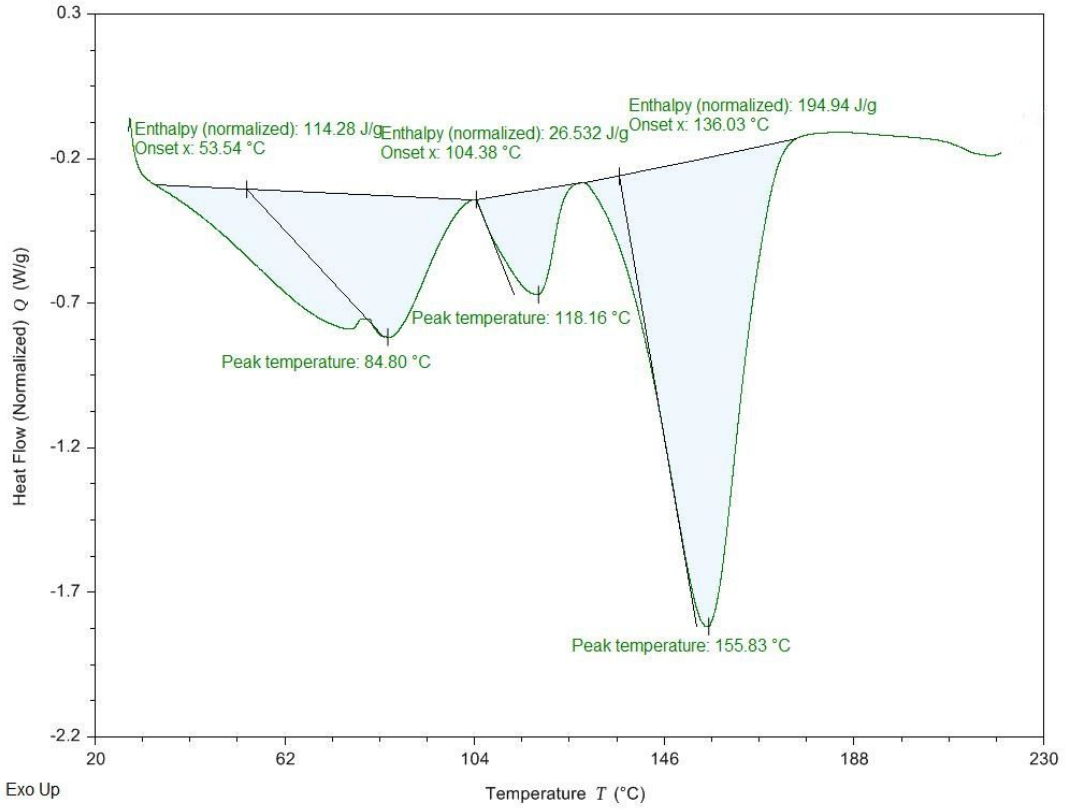

Fig SI-8. DSC of $ETI_2 \cdot CaCl_2 \cdot 2H_2O$

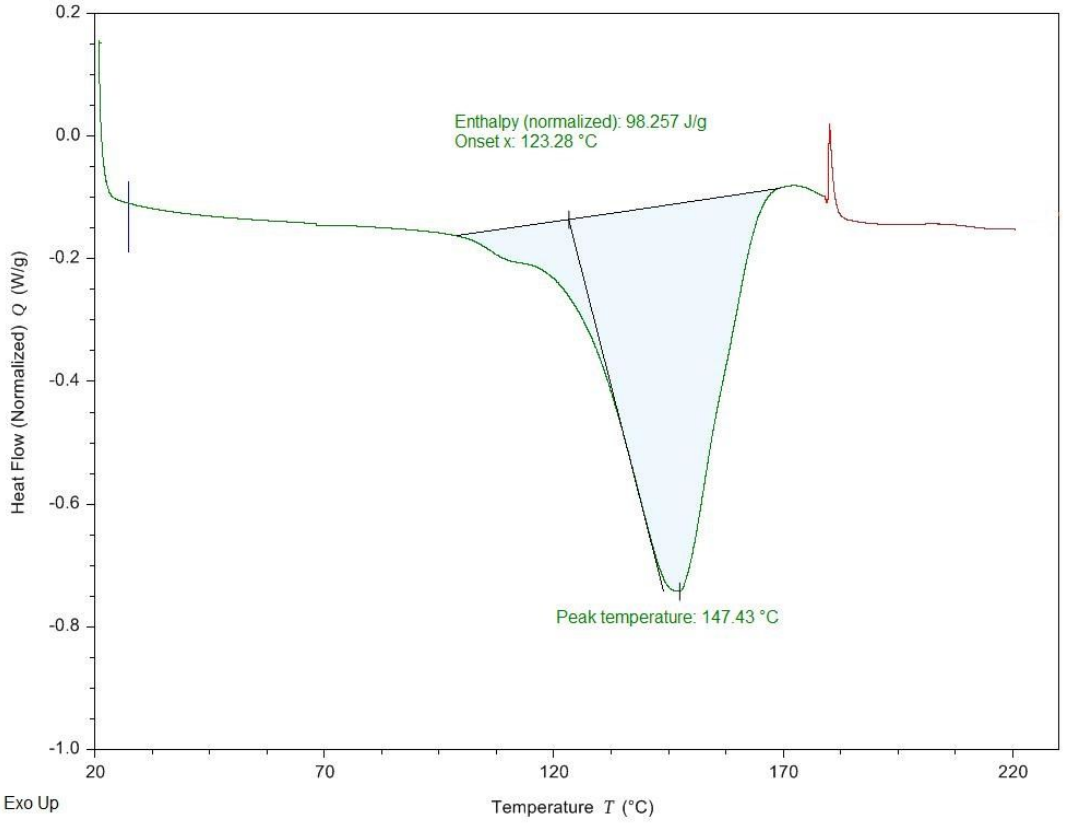

Fig. SI-9. DSC of $ETI_2 \cdot CaCl_2 \cdot 2H_2O$ (sample was kept for prolonged periods at 80 °C)

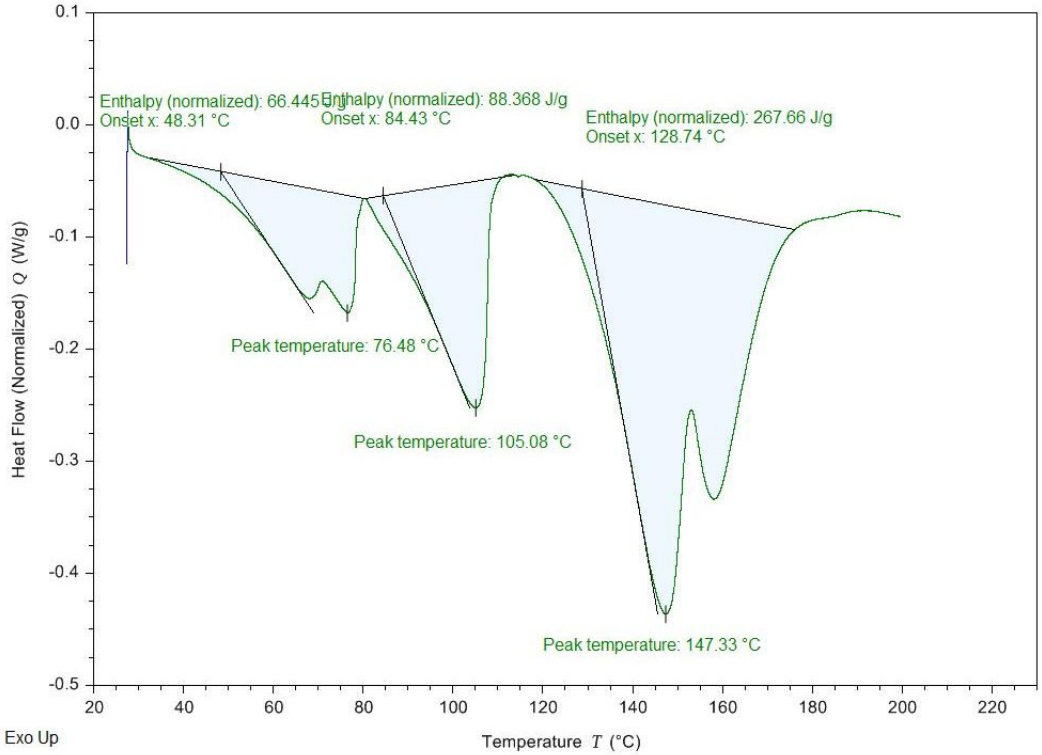

Fig. SI-10. DSC of $LEV_2 \cdot MgCl_2 \cdot 2H_2O$

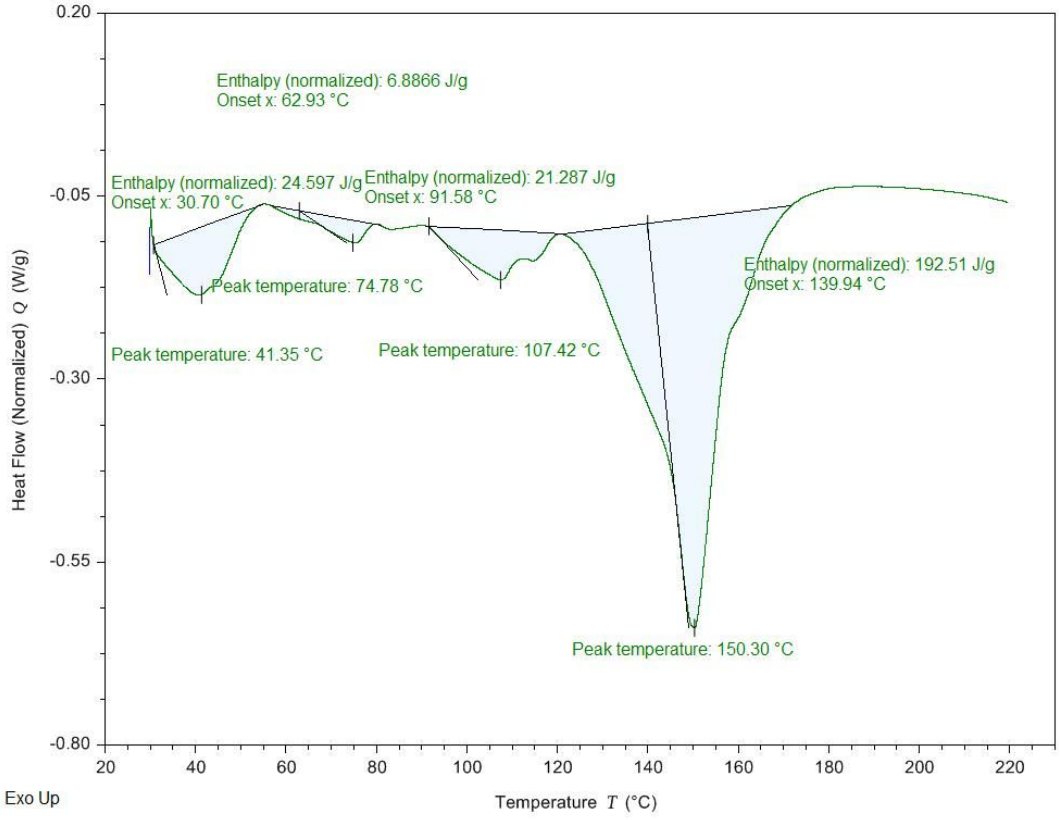

Fig. SI-11. DSC of $ETI_2 \cdot MgCl_2 \cdot 6H_2O$

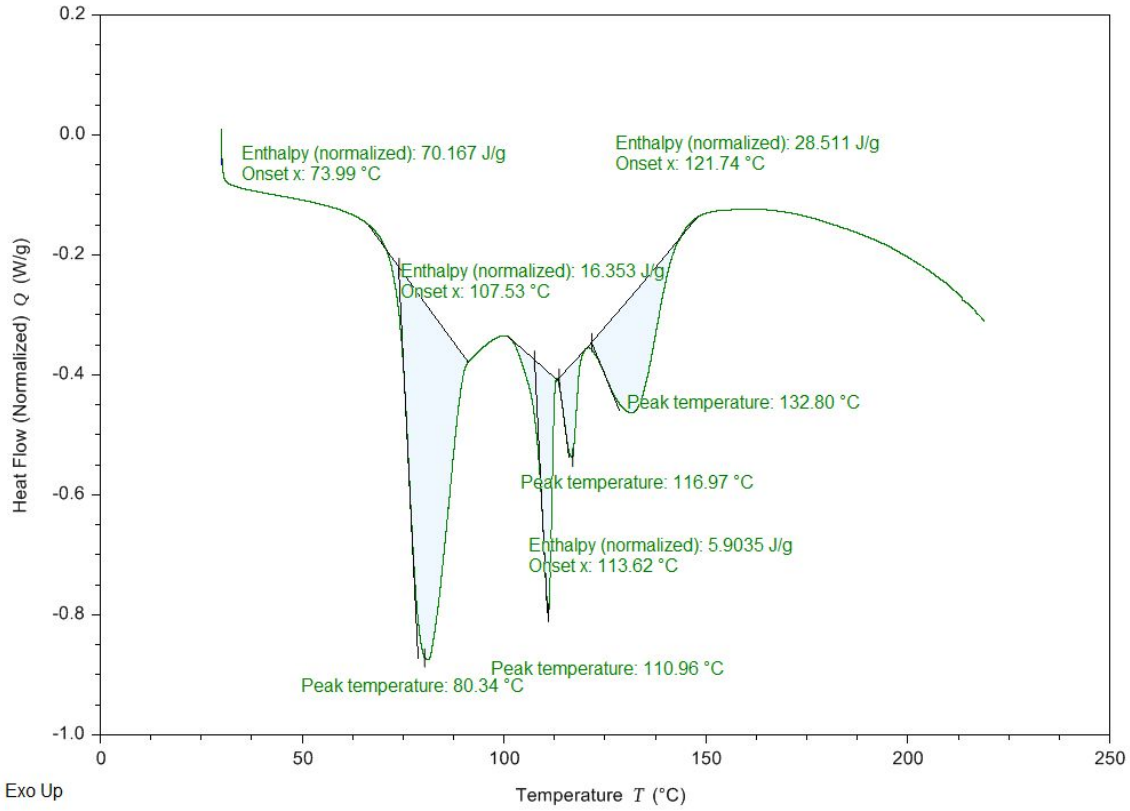

Fig. SI-12. DSC of $ETI_4 \cdot MgCl_2 \cdot 6H_2O$

VT XRPD

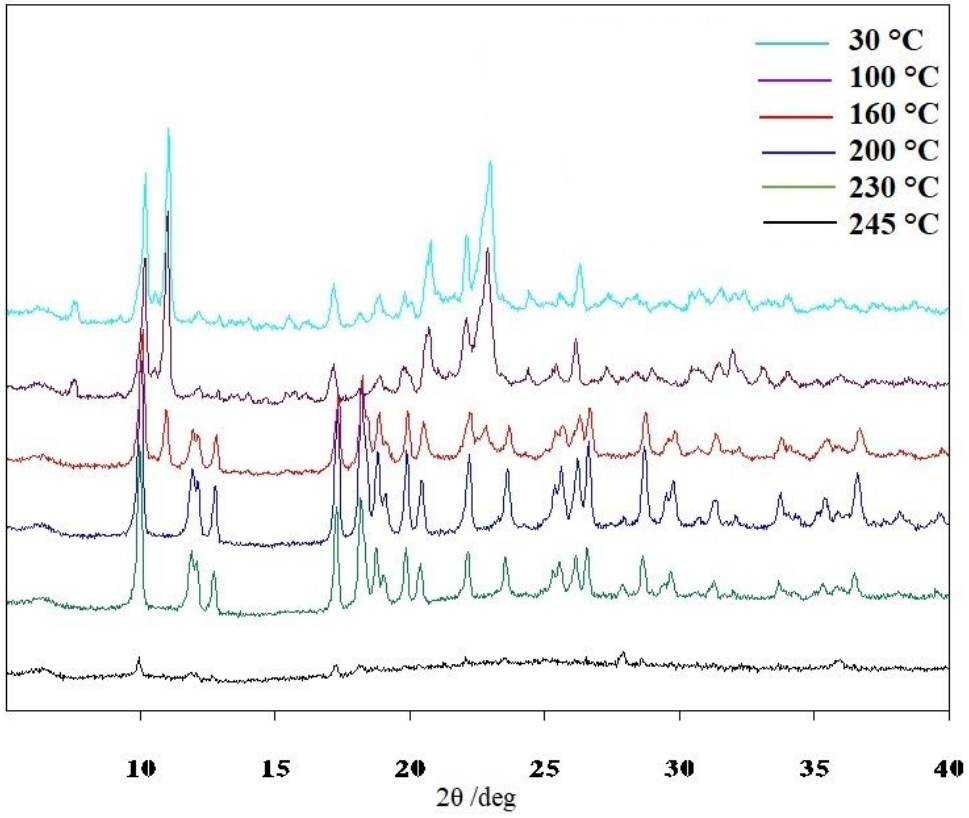

Fig. SI-13. VT XRPD of $ETI_4 \cdot MgCl_2 \cdot 4H_2O$