ELECTRONIC SUPPLEMENTARY INFORMATION (ESI) for the paper:

Cyclodextrin complexes of the anticonvulsant agent valproic acid.

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Fig. S23 The PXRD patterns of a TMB complex crystallizing in the space group $P2_12_12_1$ (refcode XAQJII), a TMB·VAL complex (1:1) produced *via* co-precipitation, a representative isostructural TMB inclusion complex that crystallizes in $P2_12_12_1$ (refcode PAFSOE, with different unit cell data from XAQJII) and a different TMB·VAL complex produced *via* kneading.

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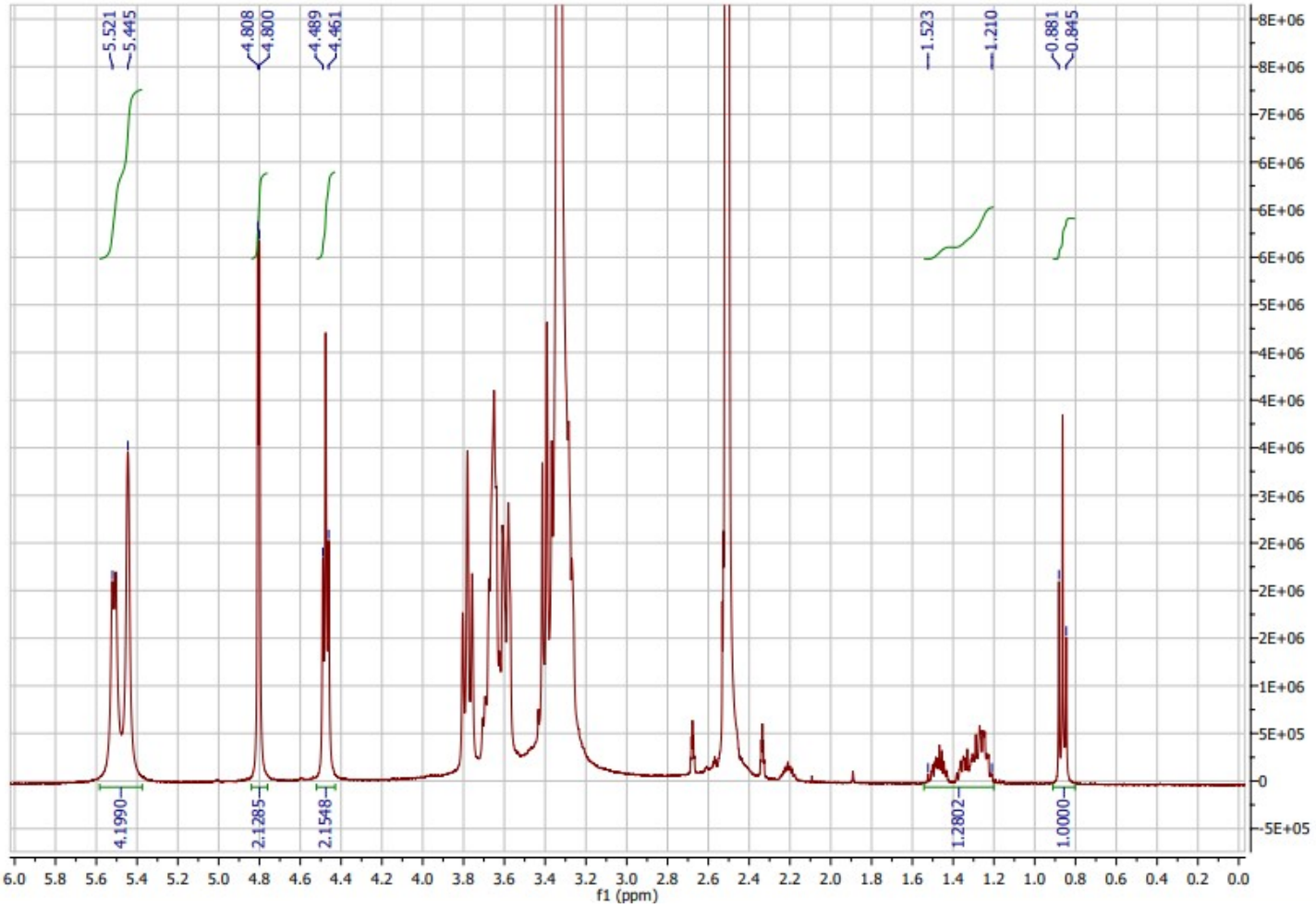

Fig. S1 The ^{1}H NMR spectrum of α-CD·VAL.

Table S1 The ^{1}H NMR spectral analysis of α-CD·VAL.

Assignment	δ (ppm)	Integration	Multiplicity	Proton representation (per molecule)	Stoichiometric ratio	Stoichiometric ratio (integer)
2 x C<u>H</u>$_3$ (valproic acid)	0.845-0.881	1.0000*	Triplet	6H	1.0000	1
4 x C<u>H</u>$_2$ (valproic acid)	1.210-1.523	1.2802	Multiplet	8H	0.9602	1
O<u>H</u>-6 (α-CD)	4.461-4.489	2.1548	Triplet	6H	2.1548	2
C<u>H</u>-1 (α-CD)	4.800-4.808	2.1285	Doublet	6H	2.1285	2
O<u>H</u>-2 and O<u>H</u>-3 (α-CD)	5.445-5.521	4.1990	Two separate doublets[1]	12H	2.0995	2

*reference integral

[1] The ^{1}H NMR spectrum displays one doublet and a singlet. This singlet peak would resolve into the second doublet at a higher resolution, or if more mass was available during the experiment.

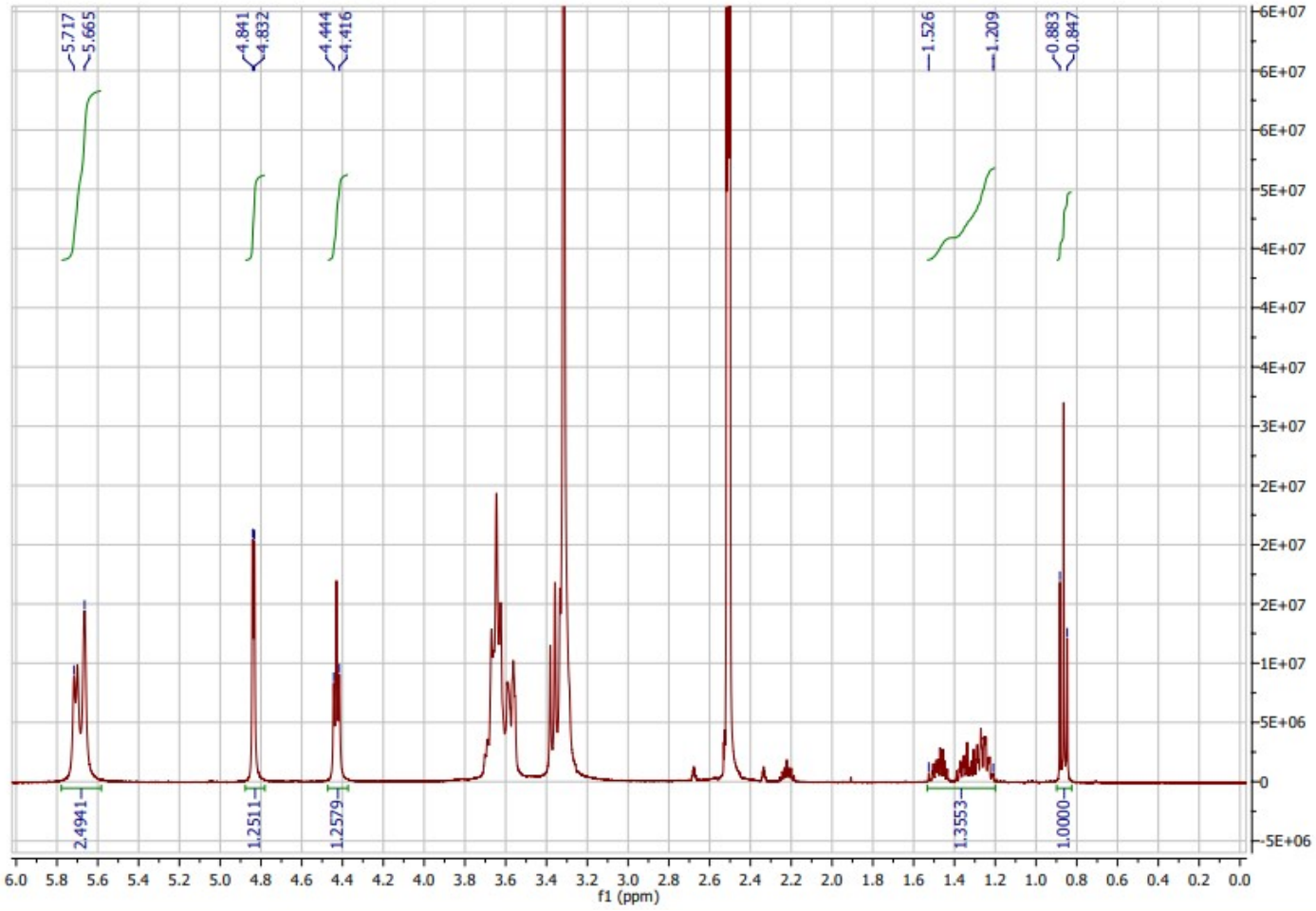

Fig. S2 The ^{1}H NMR spectrum of β-CD·VAL.

Table S2 The ^{1}H NMR spectral analysis of β-CD·VAL.

Assignment	δ (ppm)	Integration	Multiplicity	Proton representation (per molecule)	Stoichiometric ratio	Stoichiometric ratio (integer)
2 x C<u>H</u>$_3$ (valproic acid)	0.847-0.883	1.0000*	Triplet	6H	1.0000	1
4 x C<u>H</u>$_2$ (valproic acid)	1.209-1.526	1.3553	Multiplet	8H	1.0165	1
O<u>H</u>-6 (β-CD)	4.416-4.444	1.2579	Triplet	7H	1.1007	1
C<u>H</u>-1 (β-CD)	4.832-4.841	1.2511	Doublet	7H	1.0947	1
O<u>H</u>-2 and O<u>H</u>-3 (β-CD)	5.665-5.717	2.4941	Two separate doublets[2]	14H	1.2471	1

*reference integral

[2] The ^{1}H NMR spectrum displays one doublet and a singlet. This singlet peak would resolve into the second doublet at a higher resolution, or if more mass was available during the experiment.

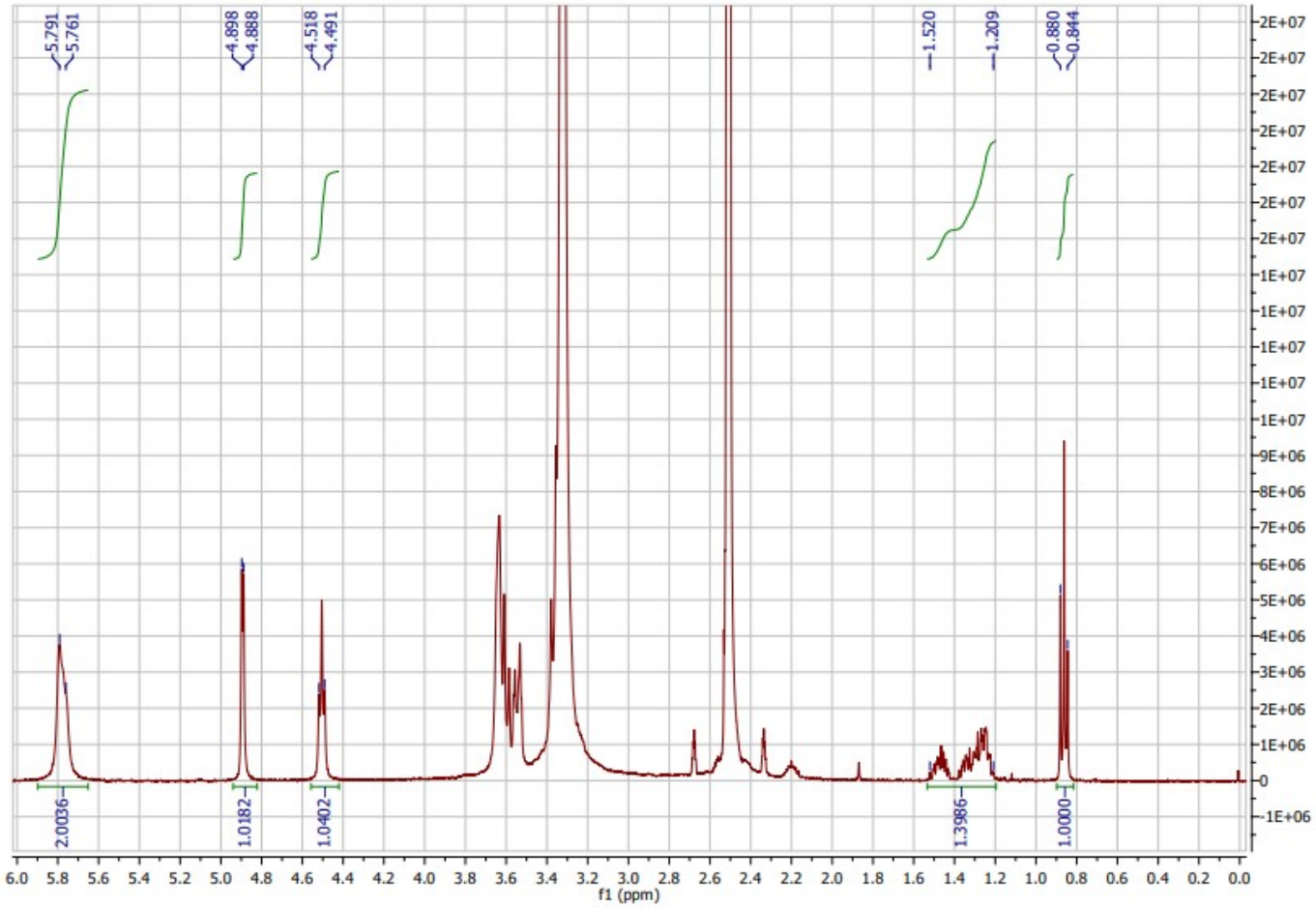

Fig. S3 The ^{1}H NMR spectrum of γ-CD·VAL.

Table S3 The ^{1}H NMR spectral analysis of γ-CD·VAL.

Assignment	δ (ppm)	Integration	Multiplicity	Proton representation (per molecule)	Stoichiometric ratio	Stoichiometric ratio (integer)
2 x C<u>H</u>$_3$ (valproic acid)	0.844-0.880	1.0000*	Triplet	6H	1.0000	4
4 x C<u>H</u>$_2$ (valproic acid)	1.209-1.520	1.3986	Multiplet	8H	1.0490	4
O<u>H</u>-6 (γ-CD)	4.491-4.518	1.0402	Triplet	8H	0.7802	3
C<u>H</u>-1 (γ-CD)	4.888-4.898	1.0182	Doublet	8H	0.7637	3
O<u>H</u>-2 and O<u>H</u>-3 (γ-CD)	5.761-5.791	2.0036	Two separate doublets[3]	16H	0.7514	3

*reference integral

[3] The ^{1}H NMR spectrum does not display adequate peak definition over this range; however, it is expected that these peaks would resolve into two separate doublets at a higher resolution, or if more mass was available during the experiment.

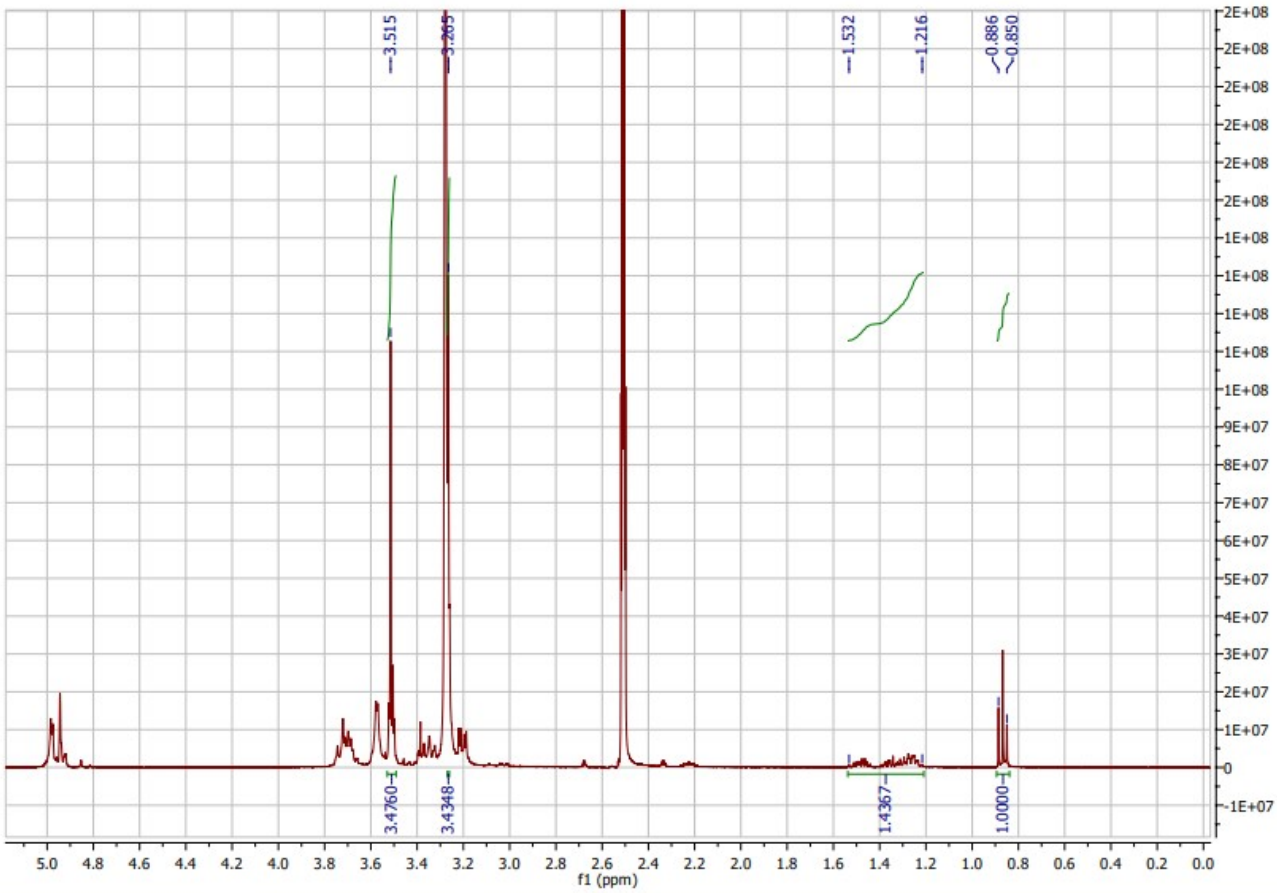

Fig. S4 The ^{1}H NMR spectrum of DMB·VAL.

Table S4 The ^{1}H NMR spectral analysis of DMB·VAL.

Assignment	δ (ppm)	Integration	Multiplicity	Proton representation (per molecule)	Stoichiometric ratio	Stoichiometric ratio (integer)
2 x C$\underline{H}_3$ (valproic acid)	0.850-0.886	1.0000*	Triplet	6H	1.0000	1
4 x C$\underline{H}_2$ (valproic acid)	1.216-1.532	1.4367	Multiplet	8H	1.0775	1
OC$\underline{H}_3$-6 (DMB)	3.265	3.4348	Singlet	21H	0.9814	1
OC$\underline{H}_3$-2 (DMB)	3.515	3.4760	Singlet	21H	0.9931	1

*reference integral

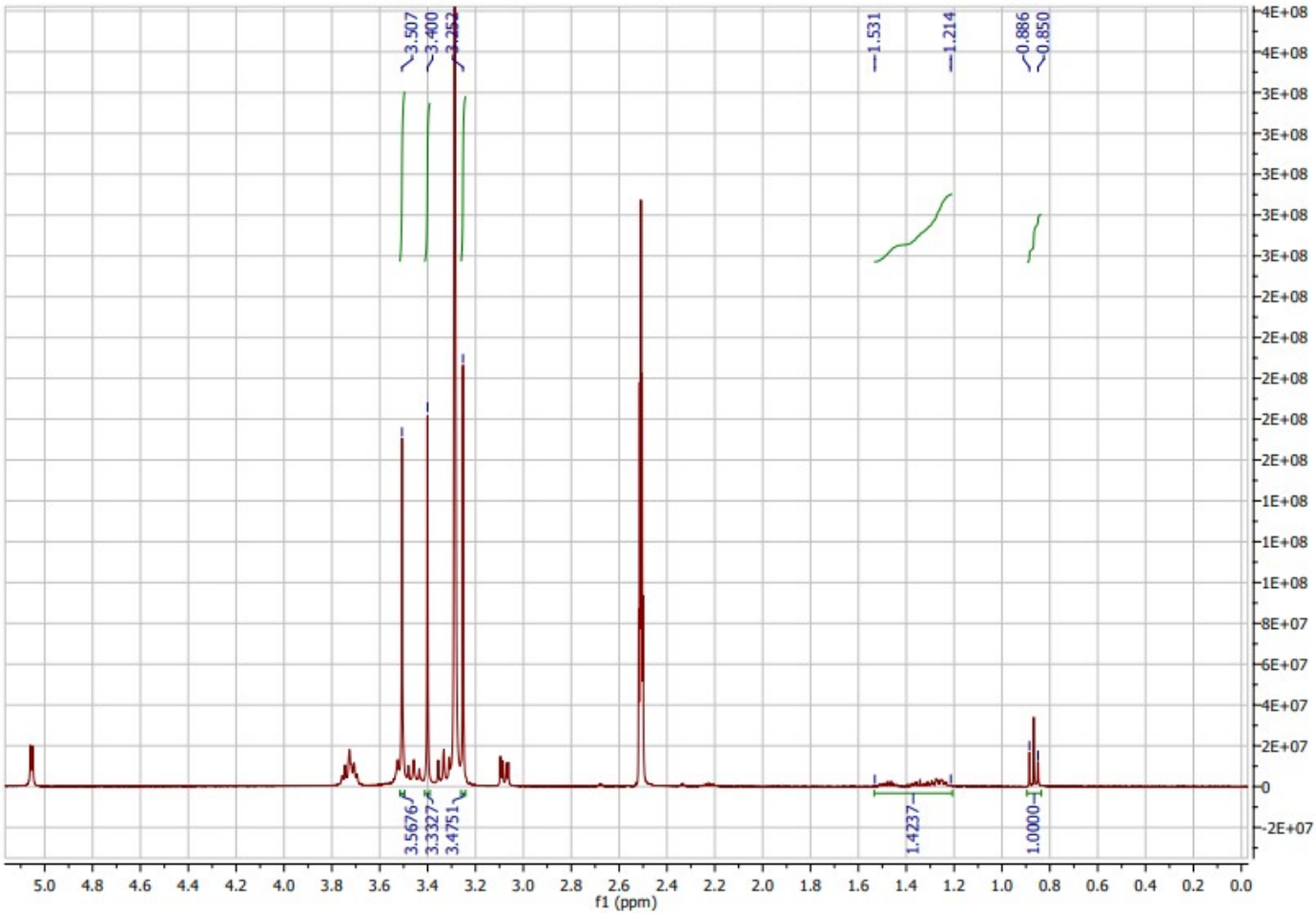

Fig. S5 The ^{1}H NMR spectrum of TMB·VAL.

Table S5 The ^{1}H NMR spectral analysis of TMB·VAL.

Assignment	δ (ppm)	Integration	Multiplicity	Proton representation (per molecule)	Stoichiometric ratio	Stoichiometric ratio (integer)
2 x C$\underline{H}_3$ (valproic acid)	0.850-0.886	1.0000*	Triplet	6H	1.0000	1
4 x C$\underline{H}_2$ (valproic acid)	1.214-1.531	1.4237	Multiplet	8H	1.0678	1
OC$\underline{H}_3$-6 (TMB)	3.252	3.4751	Singlet	21	0.9929	1
OC$\underline{H}_3$-3 (TMB)	3.400	3.3327	Singlet	21	0.9522	1
OC$\underline{H}_3$-2 (TMB)	3.507	3.5676	Singlet	21	1.0193	1

*reference integral

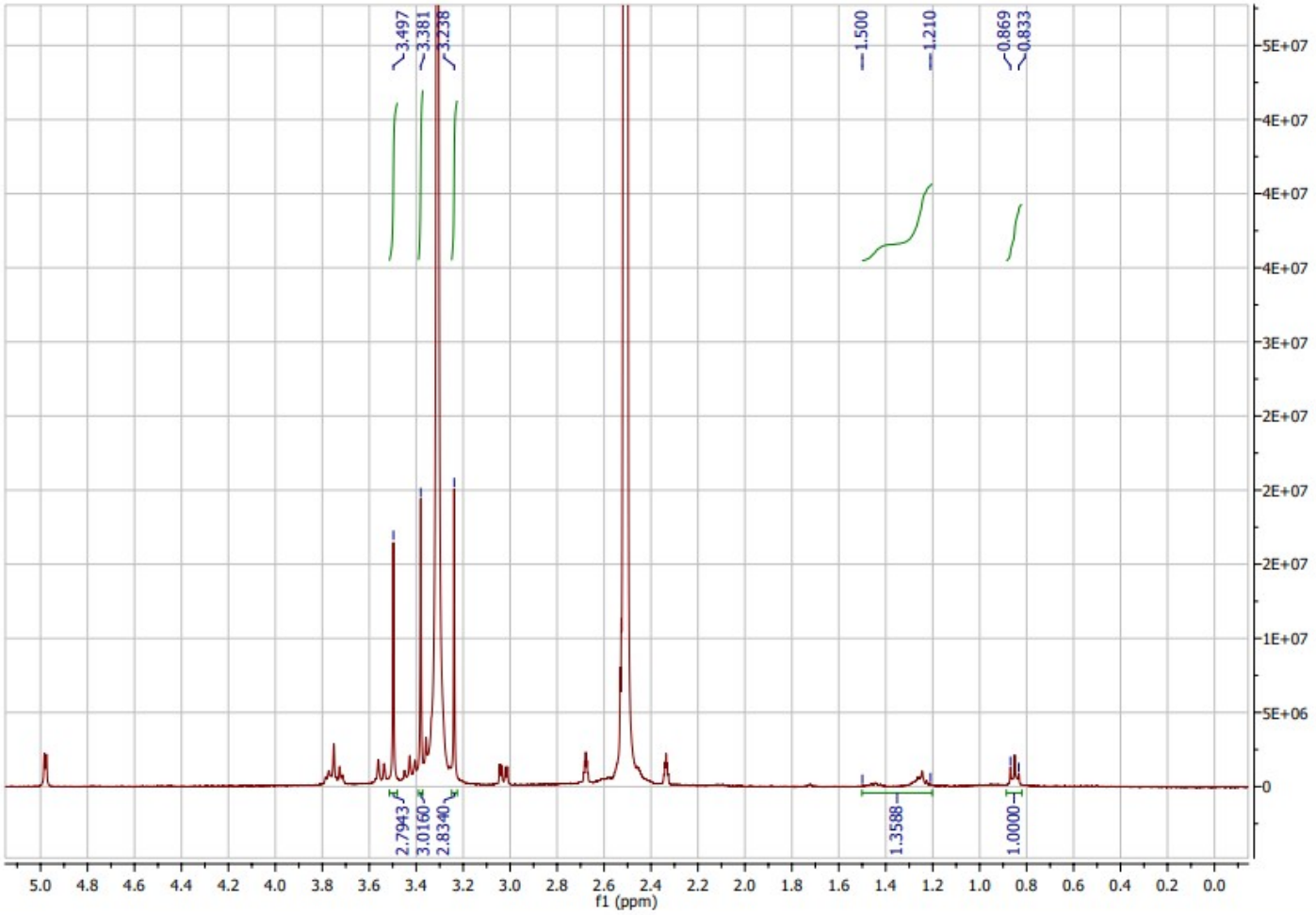

Fig. S6 The ^{1}H NMR spectrum of TMA·VAL.

Table S6 The ^{1}H NMR spectral analysis of TMA·VAL.

Assignment	δ (ppm)	Integration	Multiplicity	Proton representation (per molecule)	Stoichiometric ratio	Stoichiometric ratio (integer)
2 x C$\underline{H}_3$ (valproic acid)	0.833-0.869	1.0000*	Triplet	6H	1.0000	1
4 x C$\underline{H}_2$ (valproic acid)	1.210-1.500	1.3588	Multiplet	8H	1.0191	1
OC$\underline{H}_3$-6 (TMA)	3.238	2.8340	Singlet	18H	0.9447	1
OC$\underline{H}_3$-3 (TMA)	3.381	3.0160	Singlet	18H	1.0053	1
OC$\underline{H}_3$-2 (TMA)	3.497	2.7943	Singlet	18H	0.9314	1

*reference integral

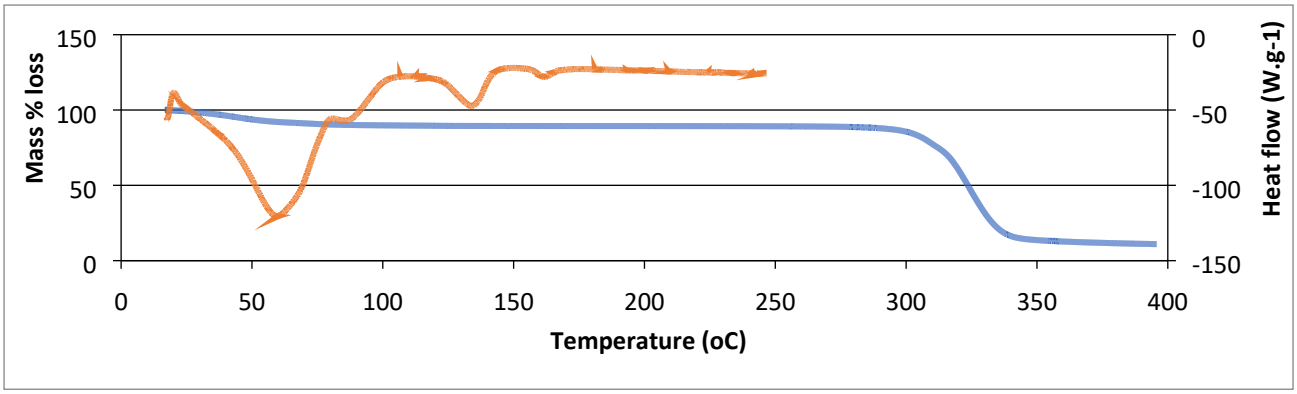

Fig. S7 Representative TGA curve for α-CD·VAL (n = 2) [blue] and a representative DSC trace for α-CD·VAL (n = 2) [red].

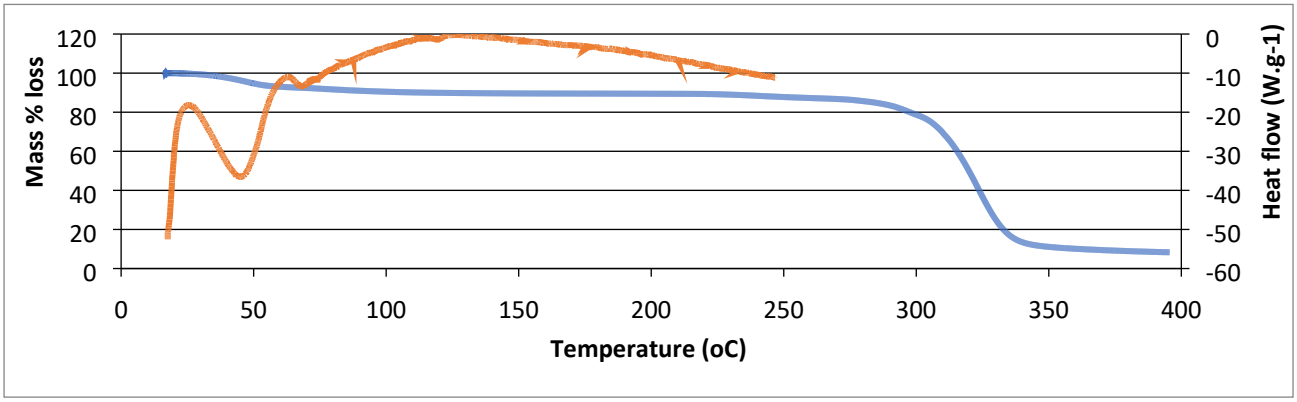

Fig. S8 Representative TGA curve for β-CD·VAL (n = 2) [blue] and a DSC curve for β-CD·VAL (n = 2) [red].

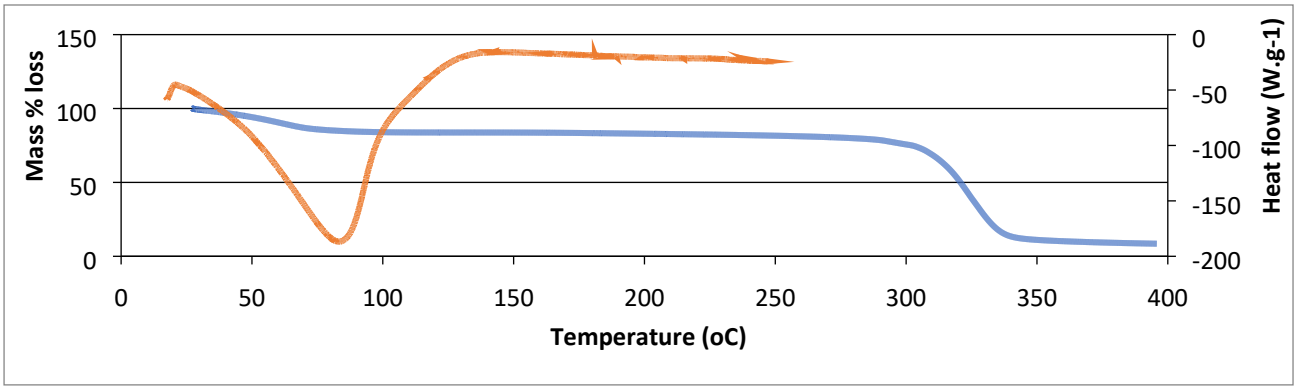

Fig. S9 Representative TGA curve for γ-CD·VAL (n = 2) [blue] and a DSC curve for γ-CD·VAL (n = 2) [red].

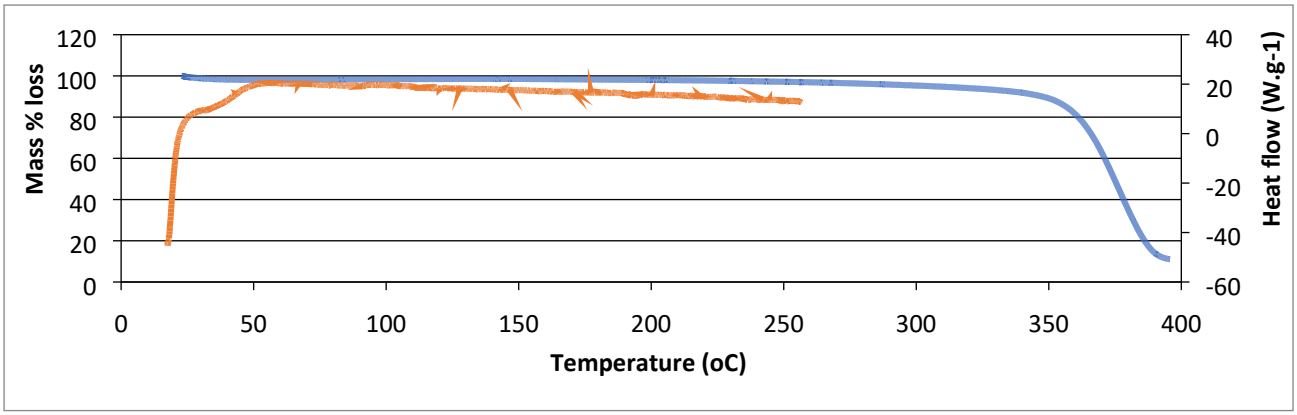

Fig. S10 Representative TGA curve for DMB·VAL (n = 2) [blue] and a DSC curve for DMB·CD·VAL (n = 2) [red].

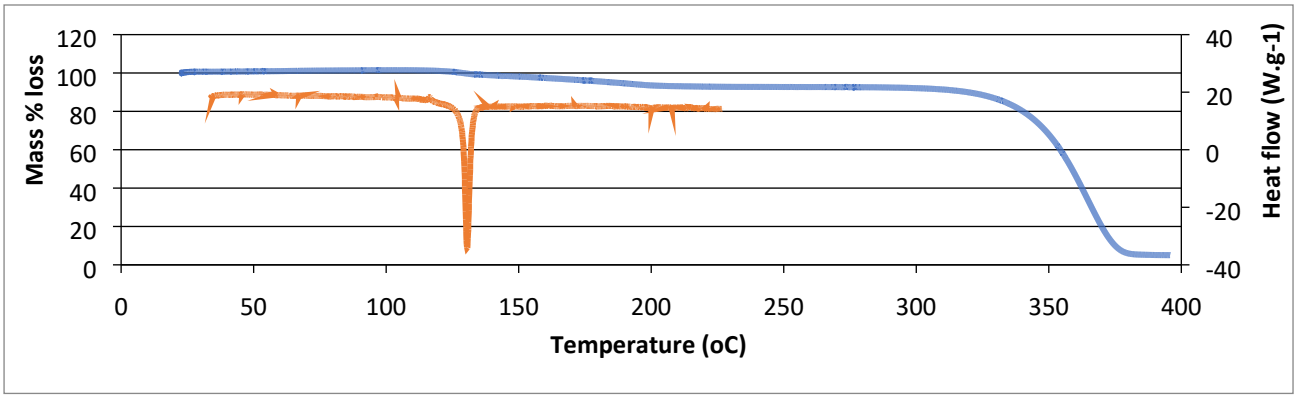

Fig. S11 Representative TGA curve for TMB·VAL (n = 2) [blue] and a representative DSC curve for TMB·CD·VAL (n = 3) [red].

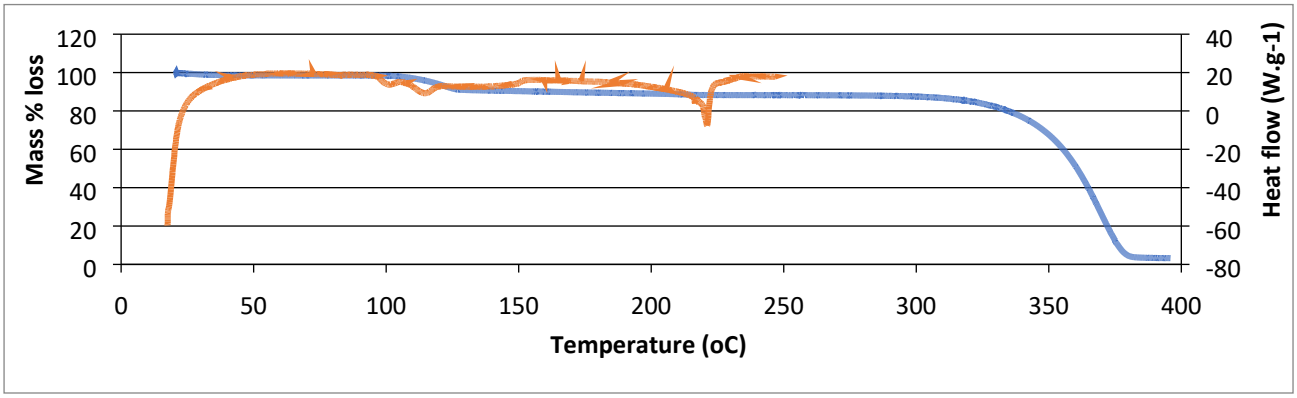

Fig. S12 Representative TGA curve for TMA·VAL (n = 2) [blue] and a representative DSC curve for TMA·CD·VAL (n = 2) [red].

Table S7 TGA and DSC measurements.

Complex	DSC	TGA
α-CD·VAL	1) Onset temp (1): 21.0 2) Peak temp. (1): 61.6 ± 1.8 3) Onset of shoulder endotherm: 81.1 °C ± 0.9 4) Onset temp (2): 120.9 ± 0.5 5) Peak temp. (2): 133.8 ± 0.1 6) Onset temp (3): 155.9 ± 0.3 Peak temp. (3): 161.5 ± 0.1	Dehydration: 10.4 ± 0.3 % (25.0 and 128.9 °C), which equates to 6.7 water molecules per α-CD molecule.
β-CD·VAL	Onset temp. (1): 25.2 °C Peak temp. (1): 47.9 Onset temp. (2): 65.5 °C Peak temp. (2): 67.9 °C Onset temp. (3): 118.0 °C Peak temp. (3): 120.0 °C	Dehydration: 11.5 ± 1.0 % (16.7 °C and 128.6 °C), which equates to 9.2 water molecules per β-CD molecule.
γ-CD·VAL	Onset temp. (1): 21.0 °C Peak temp. (1): 82.8 ± 0.1 °C	Dehydration: 16.4 ± 0.6 % (21.7 and 112.3 °C), which equates to 15.3 water molecules per γ-CD molecule.
DMB·VAL	Single shoulder: 25.5 – 49.0 °C	Dehydration: 2.1 ± 0.3 % (23.1 and 41.9 °C), which equates to 1.8 water molecules per DMB molecule.
TMB·VAL	Onset temp. (melt): 126.7 ± 0.8 °C Peak temp. (melt): 130.3 ± 0.1 °C	Guest loss: 8.3 ± 0.9 % (110.5 and 239.0 °C) (No dehydration occurred).
TMA·VAL	Onset temp. (1): 95.1 ± 0.6 °C Peak temp. (1): 101.5 ± 0.5 °C Onset temp. (2): 108.3 ± 0.7 °C Peak temp. (2): 114.6 ± 0.1 °C Shoulder range: 119.5 ± 0.1 °C to 152.3 ± 0.1 °C Onset temp. (3): 214.8 ± 2.2 °C Peak temp. (3): 220.0 ± 0.1 °C	Dehydration: 1.5 ± 0.1 % (20.8 °C and 38.2 °C), which equates to 1.2 water molecules per TMA molecule. Guest loss: 9.9 ± 0.7 % (99.4 °C and 214.8 °C)

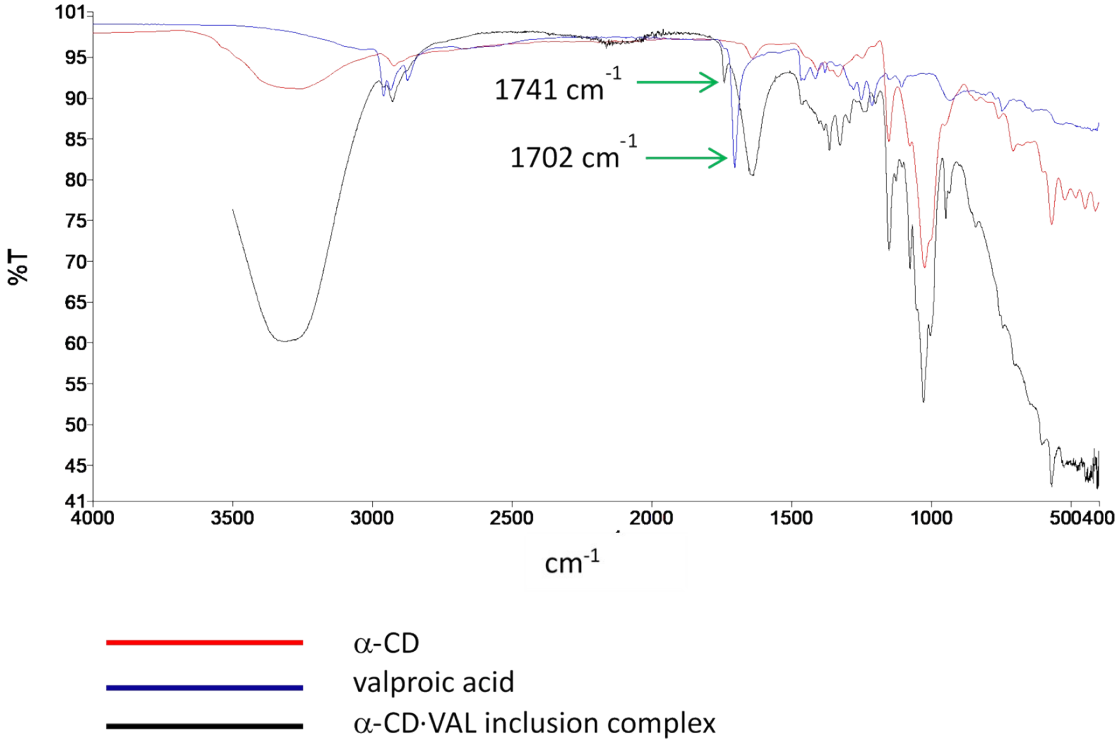

Fig. S13 FT-IR shift of the C=O band on inclusion of VAL in α-CD.

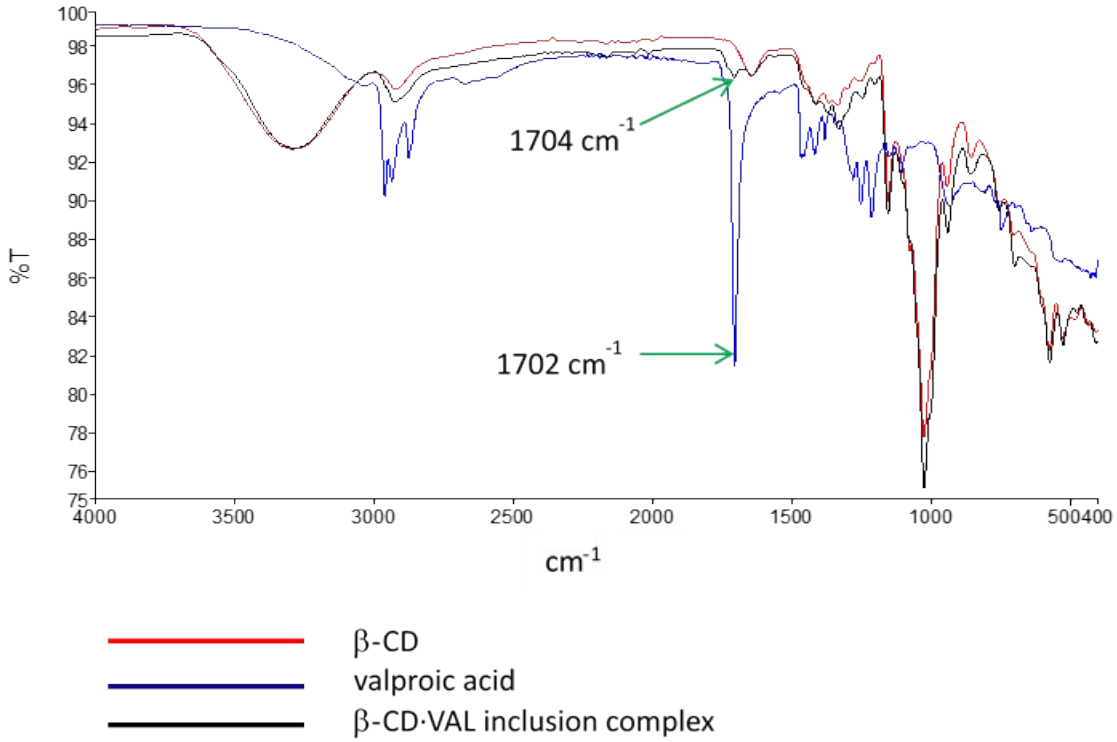

Fig. S14 FT-IR shift of the C=O band on inclusion of VAL in β-CD.

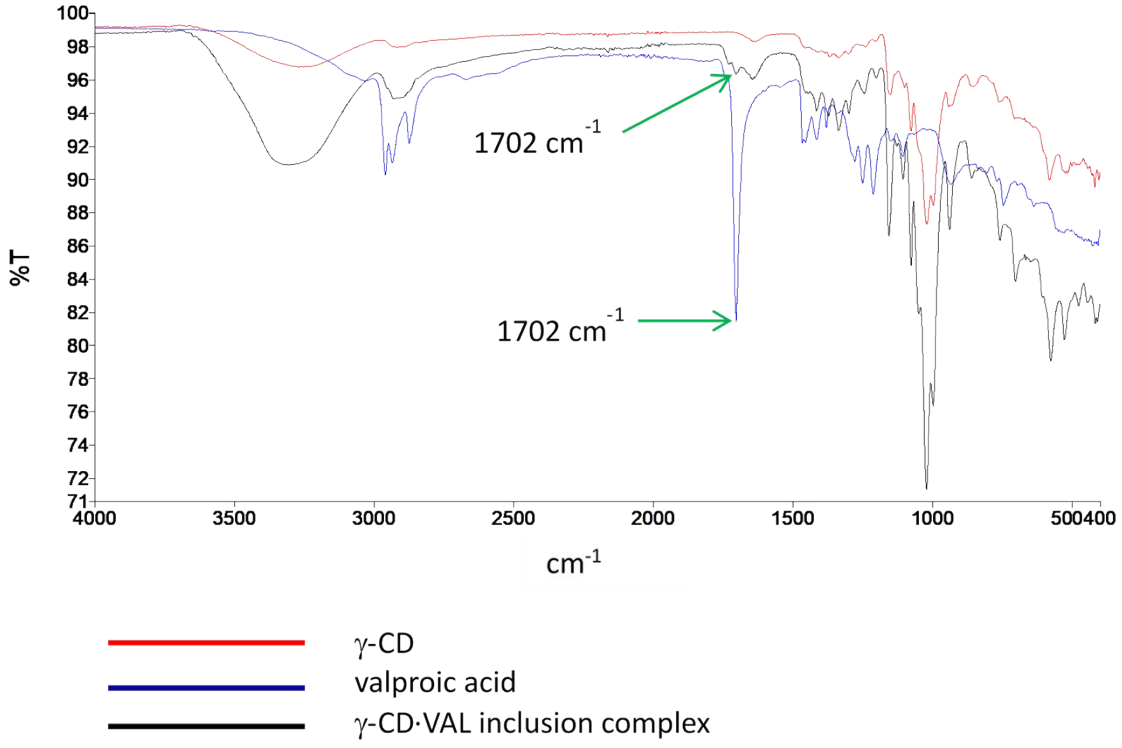

Fig. S15 FT-IR shift of the C=O band on inclusion of VAL in γ-CD.

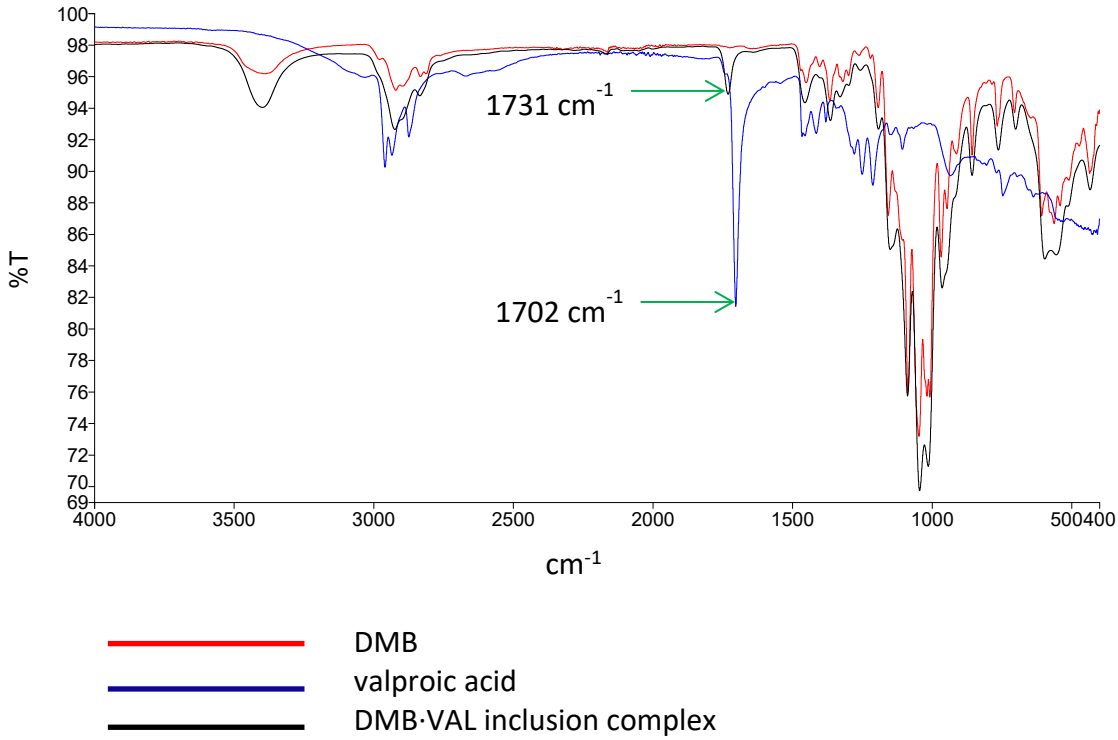

Fig. S16 FT-IR shift of the C=O band on inclusion of VAL in DMB.

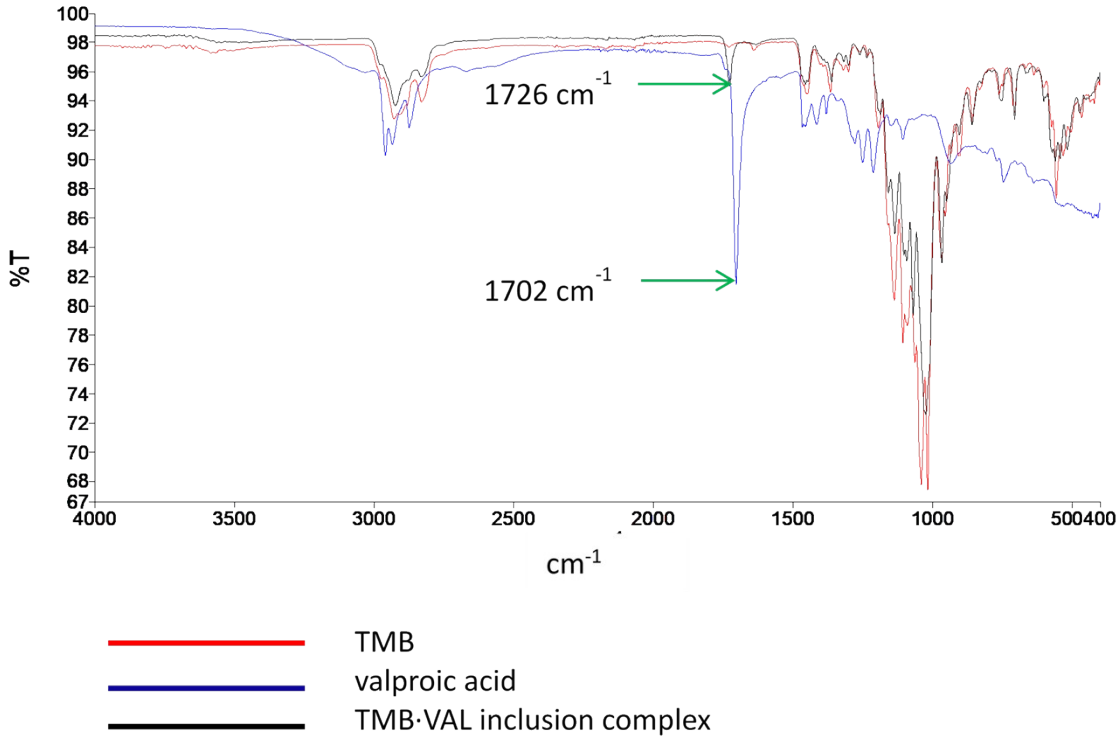

Fig. S17 FT-IR shift of the C=O band on inclusion of VAL in TMB.

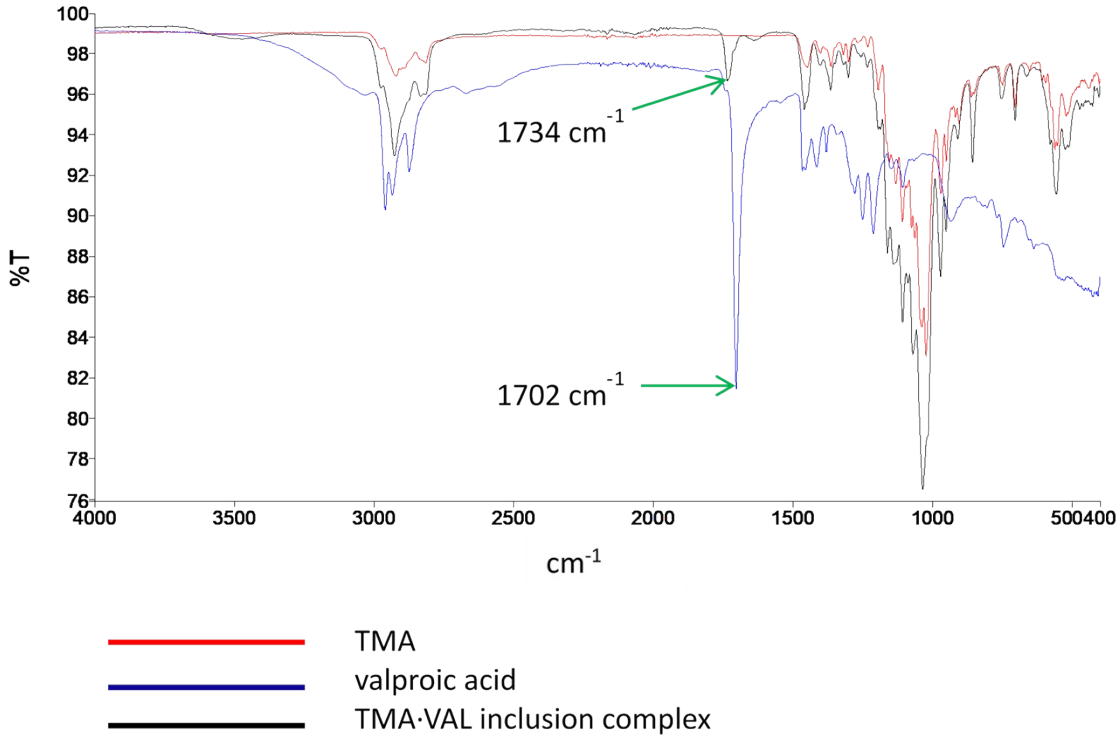

Fig. S18 FT-IR shift of the C=O band on inclusion of VAL in TMA.

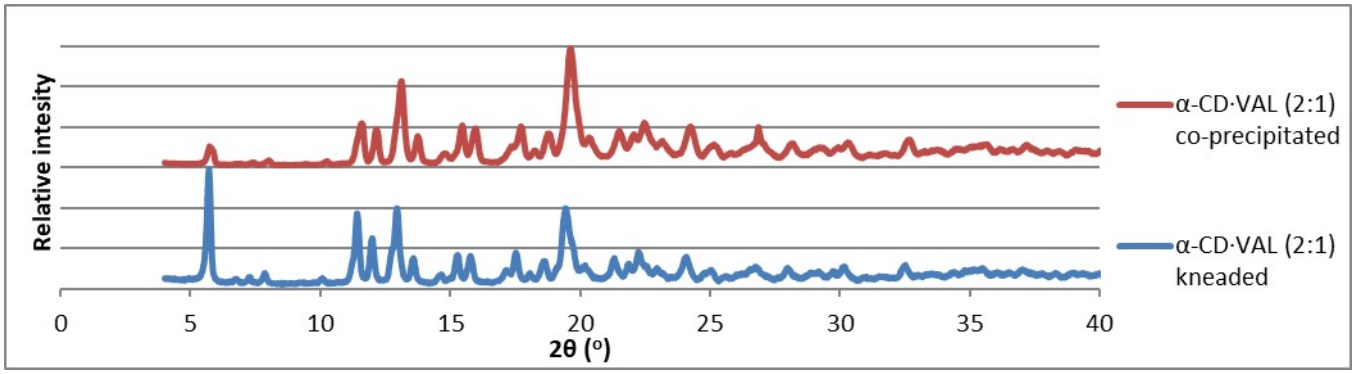

Fig. S19 PXRD patterns α-CD·VAL produced via co-precipitation (2:1) and kneading (2:1).

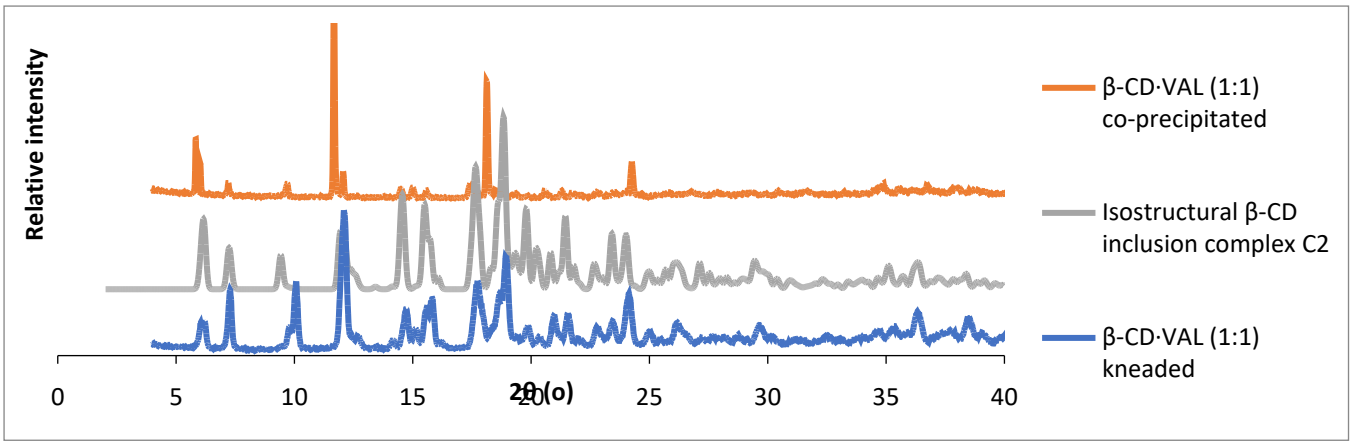

Fig. S20 PXRD patterns β-CD·VAL produced via co-precipitation (1:1) and kneading (1:1) and that of an isostructural β-CD inclusion complex crystallizing in the space group C2.

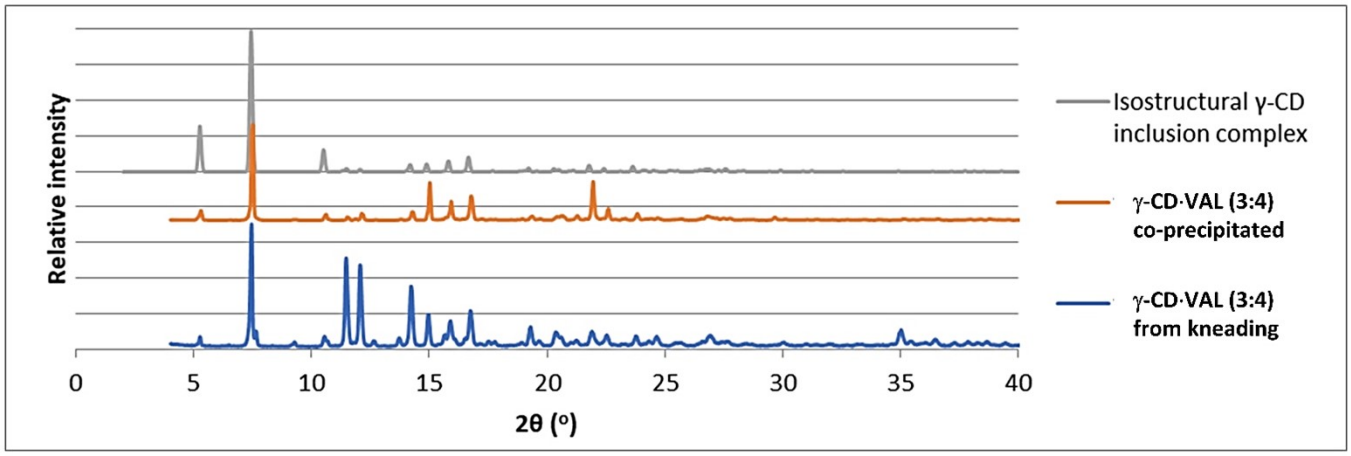

Fig. S21 The PXRD patterns of an isostructural γ-CD inclusion complex crystallizing in the space group $P42_12$, and the γ-CD·VAL inclusion complex produced via co-precipitation (3:4) and kneading (3:4).

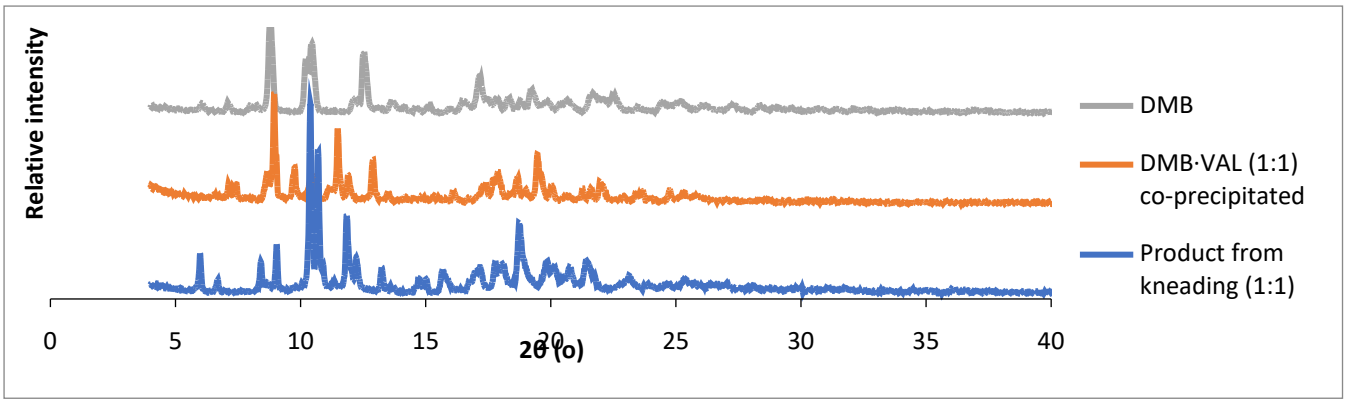

Fig. S22 PXRD patterns of the crystal form of DMB employed in this study (polymorph 1, CSD refcode QIYKEO), DMB·VAL produced via co-precipitation (1:1), and a product from kneading DMB and valproic acid.

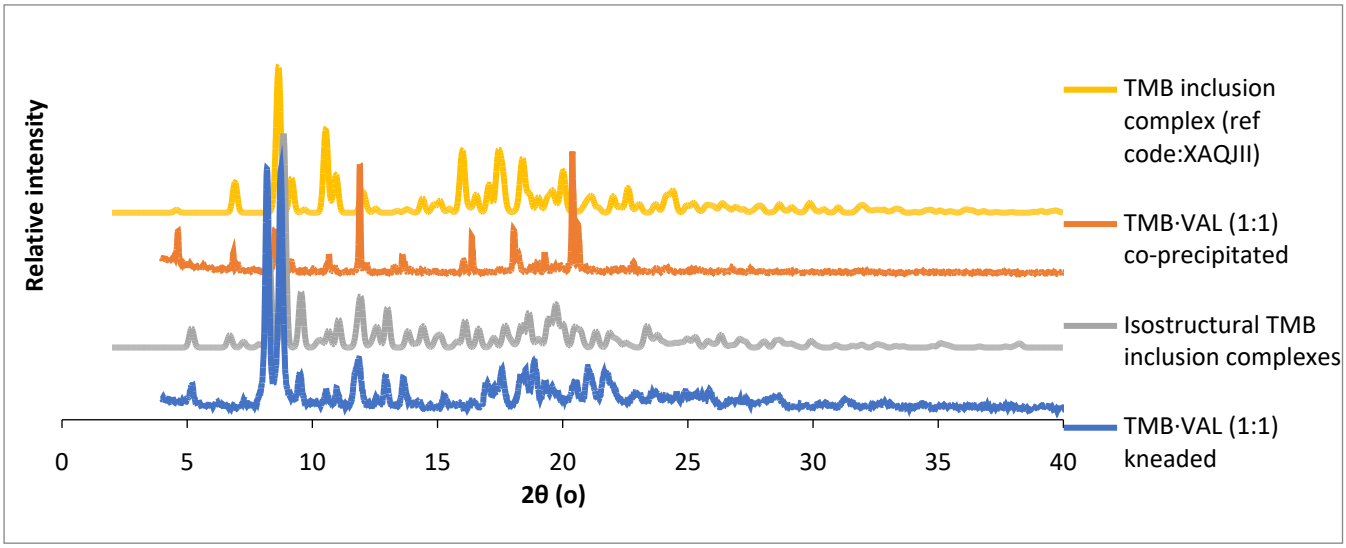

Fig. S23 The PXRD patterns of a TMB complex crystallizing in the space group $P2_12_12_1$ (refcode XAQJII), a TMB·VAL complex (1:1) produced *via* co-precipitation, a representative isostructural TMB inclusion complex that crystallizes in $P2_12_12_1$ (refcode PAFSOE, with different unit cell data from XAQJII) and a different TMB·VAL complex produced *via* kneading.

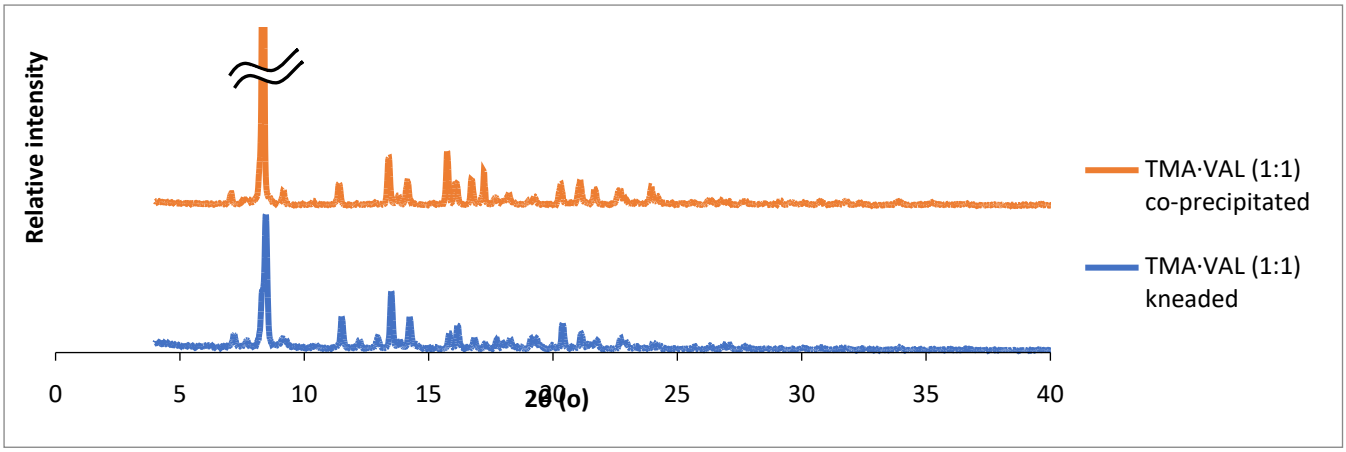

Fig. S24 The PXRD patterns of the TMA·VAL inclusion complex produced *via* co-precipitation (1:1) and kneading (1:1).

Table S8 Crystal Data and Refinement Parameters

	BCD·VAL	GCD·VAL	DMB·VAL	TMA·VAL
Complex formula	$2(C_{42}H_{70}O_{35})\cdot 2(C_8H_{16}O_2)\cdot 9.2H_2O$	$3(C_{48}H_{80}O_{40})\cdot 4(C_8H_{16}O_2)\cdot 49H_2O$	$(C_{56}H_{98}O_{35}).(C_{57}H_{100}O_{35})\cdot 2(C_8H_{16}O_2)\cdot 3.9H_2O$	$(C_{54}H_{96}O_{30})\cdot(C_8H_{16}O_2)\cdot 1.2H_2O$
Formula weight ($g.mol^{-1}$)	2900.67	5350.95	3035.06	1391.13
Temperature (K)	100(2)	293(2)	173(2)	100(2)
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
Crystal system	Monoclinic	Tetragonal	Triclinic	Orthorhombic
Space group	C2	$P42_12$	P1	$P2_12_12_1$
a (Å)	19.133(5)	23.745(4)	10.396(2)	15.337(3)
b (Å)	24.566(7)	23.745(4)	15.111(3)	20.728(4)
c (Å)	15.782(5)	23.100(5)	25.494(5)	23.104(5)
α (°)	90	90	83.247(4)	90
β (°)	108.873(6)	90	81.556(4)	90
γ (°)	90	90	89.475(4)	90
Volume ($Å^3$)	7019(3)	13025(5)	3934(1)	7345(3)
Z	2	2	1	4
Calculated density ($g.cm^{-3}$)	1.372	1.364	1.281	1.258
μ (mm^{-1})	0.123	0.123	0.106	0.101
F (000)	3108	5748	1635	3008
Crystal size (mm)	0.12 x 0.15 x 0.27	0.19 x 0.25 x 0.45	0.10 x 0.22 x 0.51	0.16 x 0.19 x 0.43
θ-Range scanned (°)	1.68 – 25.24	1.23– 25.56	1.36 – 25.04	2.71 – 20.29
Index range	h: -24, 24; k: -31, 31; l: -20, 20	h: -28, 28; k: -26, 28; l: -27, 27	h: -12, 12; k: -17, 17; l: -30, 30	h: -19, 19; k: -26, 25; l: -29, 29
No. of reflections collected	29021	149732	44688	67773
No. of unique reflections	15385	12162	26358	16290
Data completeness (%)	98.6	99.4	99.4	99.2
Data/restraints/parameters	15385/16/802	12162/8/655	26358/35/1664	16290/1/863
S (Goodness-of-fit on F^2)	1.122	1.73	1.191	1.017
Final R indices R_1, wR_2, [I > 2σ(I)]	0.0997, 0.2742	0.1431, 0.4024	0.1055, 0.2904	0.0676, 0.1482
R Indices, all data (R_1, wR_2)	0.1320, 0.3047	0.1554, 0.4101	0.1494, 0.3294	0.1342, 0.1761
Largest diff. peak and hole (e. $Å^{-3}$)	1.27, -0.42	0.55, -0.63	0.83, -0.47	0.38, -0.34

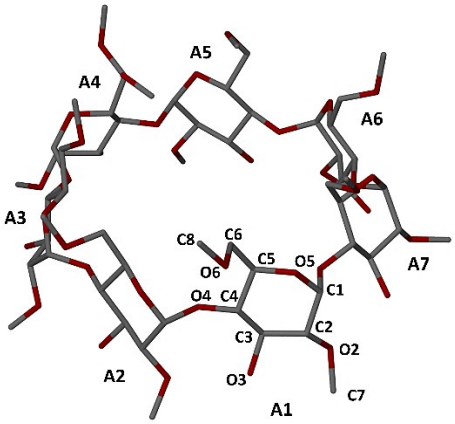

Fig. S25 Key to atomic and glucose residue numbering for DMB(A).

Table S9 Geometrical parameters for the host molecule A in DMB·VAL.

Residue	*l* (Å)	D (Å)	Φ (°)	d (°)	α[a] (Å)	D_3[b] (Å)	τ_2[c] (°)
A1	4.992	4.449	129.6	8.3	-0.086	2.97	11.4
A2	4.990	4.393	130.5	-3.3	-0.094	2.82	7.0
A3	5.208	4.342	124.7	-10.0	0.179	2.84	19.2
A4	5.037	4.422	129.7	15.8	0.015	2.96	22.7
A5	4.952	4.455	129.8	-8.0	-0.241	2.80	4.2
A6	5.111	4.311	127.2	0.1	0.189	2.80	6.8
A7	5.151	4.417	127.0	-2.8	0.038	2.83	22.7

[a] mean e.s.d. 0.005 Å; [b] mean e.s.d. 0.01 Å; [c] mean e.s.d. 0.5°

l, the distance of each O4 atom from the centroid of the O4-polygon;
D, the glycosidic O4···O4′ distance;
Φ the O4···O4′···O4′′ angle;
d, the O4···O4′···O4′′···O4′′′ torsion angle;
α, the deviation of each O4 atom from the mean O4-plane;
D_3, the O2···O3′ intra-ring distance;
τ_2 tilt angle: the angle between the plane containing O4, C4, C1 and O4′ of a given glucose ring and the mean O4-plane.

Fig. S26 Key to atomic and glucose residue numbering for DMB(B).

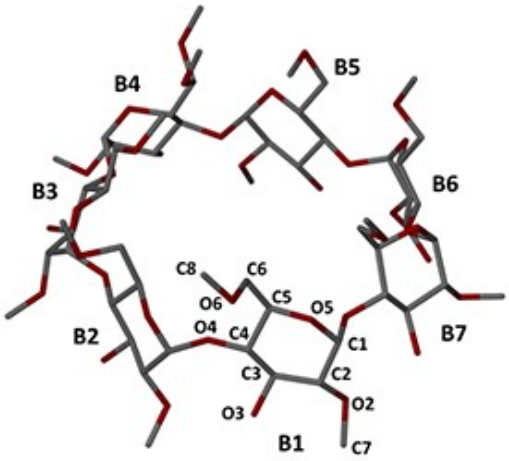

Table S10 Geometrical parameters for the host molecule B in DMB·VAL

Residue	*l* (Å)	D (Å)	Φ (°)	d (°)	α[a] (Å)	D_3[b] (Å)	τ_2[c] (°)
B1	5.000	4.426	129.1	12.6	-0.189	2.89	11.8
B2	5.075	4.433	128.8	-10.6	-0.097	2.85	6.4
B3	5.195	4.300	124.1	-8.0	0.311	3.27	27.5
B4	4.925	4.476	132.2	19.0	-0.074	2.98	23.8
B5	5.003	4.358	128.1	-9.3	-0.307	2.88	3.6
B6	5.156	4.342	125.9	-3.6	0.279	2.83	8.5
B7	5.061	4.469	128.9	-0.5	0.077	2.84	25.4

[a] mean e.s.d. 0.006 Å; [b] mean e.s.d. 0.01 Å; [c] mean e.s.d. 0.5°

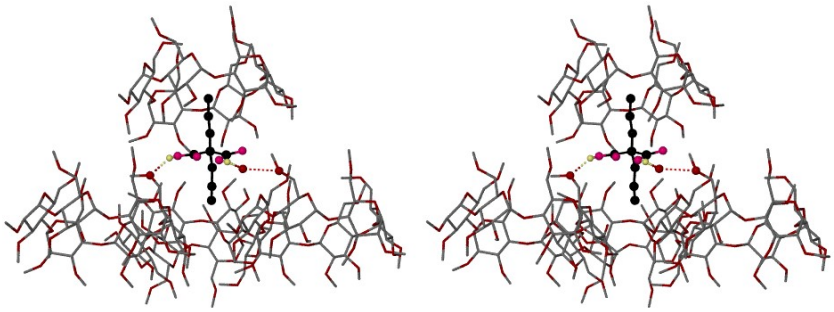

Fig. S27 Stereoview of the inclusion mode of the guest molecule VAL in TMA, showing the location of the protruding guest residue in an interstice at the junction of three neighbouring TMA molecules in the layer below. For clarity, the VAL molecules included in the three CD molecules have been omitted (as have H atoms, except those of the VAL -COOH group). Both disordered components of the -COOH group engage in H-bonding with neighbouring CD molecules.

Table S11 Geometrical parameters of the host molecule in TMA·VAL.

Residue	*l* (Å)	D(Å)	Φ (°)	d(°)	α[a] (Å)	D_3[b] (Å)	τ_2[c] (°)
A	4.381	4.377	115.6	-6.5	0.283	3.314	9.2
B	4.124	4.240	123.0	-9.7	-0.246	3.428	17.5
C	4.274	4.212	120.2	17.4	-0.040	3.279	33.5
D	4.385	4.336	114.8	-7.9	0.294	3.279	7.2
E	4.084	4.241	124.4	-8.6	-0.260	3.440	17.2
F	4.302	4.225	118.9	16.0	-0.030	3.156	30.0

[a] mean esd: 0.002 Å; [b] mean esd: 0.1°; [c] mean e.s.d. 0.12°

Calculations: Gravimetric solubility analysis

α-CD·VAL:

Experiment 1: Mass of penultimate and final increment of inclusion complex: 5.22 – 5.59 mg

Experiment 2: Mass of penultimate and final increment of inclusion complex: 5.22 – 5.49 mg

Fraction of valproic acid in α-CD·VAL:

$$\frac{144.211\ g/mol}{144.211\ g/mol\ +\ 2(972.846\ g/mol)\ +13.5(18.016)\ g/mol} = 0.061810$$

Therefore, the mass range of valproic acid solubilized in 1 ml H_2O is:

Experiment 1: 0.061810 x (5.22 – 5.59 mg) = **0.323 – 0.346 mg**

Experiment 2: 0.061810 x (5.22 – 5.49 mg) = **0.323 – 0.339 mg**

β-CD·VAL:

Experiment 1: Mass of penultimate and final increment of inclusion complex: 5.14 – 5.43 mg

Experiment 2: Mass of penultimate and final increment of inclusion complex: 4.97 – 5.18 mg

Fraction of valproic acid in β-CD·VAL:

$$\frac{144.211\ g/mol}{144.211\ g/mol\ +\ 1134.987\ g/mol\ +9.2(18.016)\ g/mol} = 0.099804$$

Therefore, the mass range of valproic acid solubilized in 1 ml H_2O is:

Experiment 1: 0.099804 x (5.14 – 5.43 mg) = **0.513 – 0.542 mg**

Experiment 2: 0.099804 x (4.97 – 5.18 mg) = **0.496 – 0.517 mg**

γ-CD·VAL:

Experiment 1: Mass of penultimate and final increment of inclusion complex: 6.92 – 7.15 mg

Experiment 2: Mass of penultimate and final increment of inclusion complex: 6.77 – 7.04 mg

Fraction of valproic acid in γ-CD·VAL:

$$\frac{144.211\ g/mol}{144.211\ g/mol\ +\ \frac{3}{4}(1297.128)\ g/mol\ +12.2(18.016)\ g/mol} = 0.10787$$

Therefore, the mass range of valproic acid solubilized in 1 ml H_2O is:

Experiment 1: 0.10787 x (6.92 – 7.15 mg) = **0.746 – 0.771 mg**

Experiment 2: 0.10787 x (6.77 – 7.04 mg) = **0.730 – 0.759 mg**