Electronic Supporting Information (ESI) for manuscript entitled:

A strategy for producing predicted polymorphs: catemeric carbamazepine form V

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1. Single-Crystal Structure analysis of CBZ form V

Data for this crystal structure were measured at 123 K with graphite monochromated Cu Kα radiation (λ = 1.54180 Å) using an Oxford Diffraction Gemini S instrument. All non hydrogen atoms were refined anisotropically. Hydrogen atoms of the amide group were refined isotropically, whereas other H atoms were placed in calculated positions utilizing riding modes. All structures were refined to converge against F^2 using the SHELXL-97 program.[1] A summary of data collection and refinement details is provided in Table S1. The asymmetric unit of CBZ form V is shown in Figure S1.

Table S1: Crystallographic details of CBZ form V structure

Compound reference	Carbamazepine form V
Chemical formula	$C_{15}H_{12}N_2O$
Formula Mass	236.27
Crystal system	Orthorhombic
a/Å	9.1245(5)
b/Å	10.4518(5)
c/Å	24.8224(11)
α/°	90.00
β/°	90.00
γ/°	90.00
Unit cell volume/Å^3	2367.2(2)
colour	Colourless
Temperature/K	123(2)
Space group	*Pbca*
No. of formula units per unit cell, *Z*	8
No. of reflections measured	5416
No. of independent reflections	2140
R_{int}	0.0624
Final R_1 values ($I > 2\sigma(I)$)	0.0450
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.0924
Final R_1 values (all data)	0.0872
Final $wR(F^2)$ values (all data)	0.1018
Goodness of fit on F^2	0.824

Using the reported method only a small number of individual crystals are obtained each time. Work is ongoing to obtain sufficient amounts of form V to allow a more complete physicochemical characterisation of this polymorph, including relative thermodynamic stability compared with other forms.

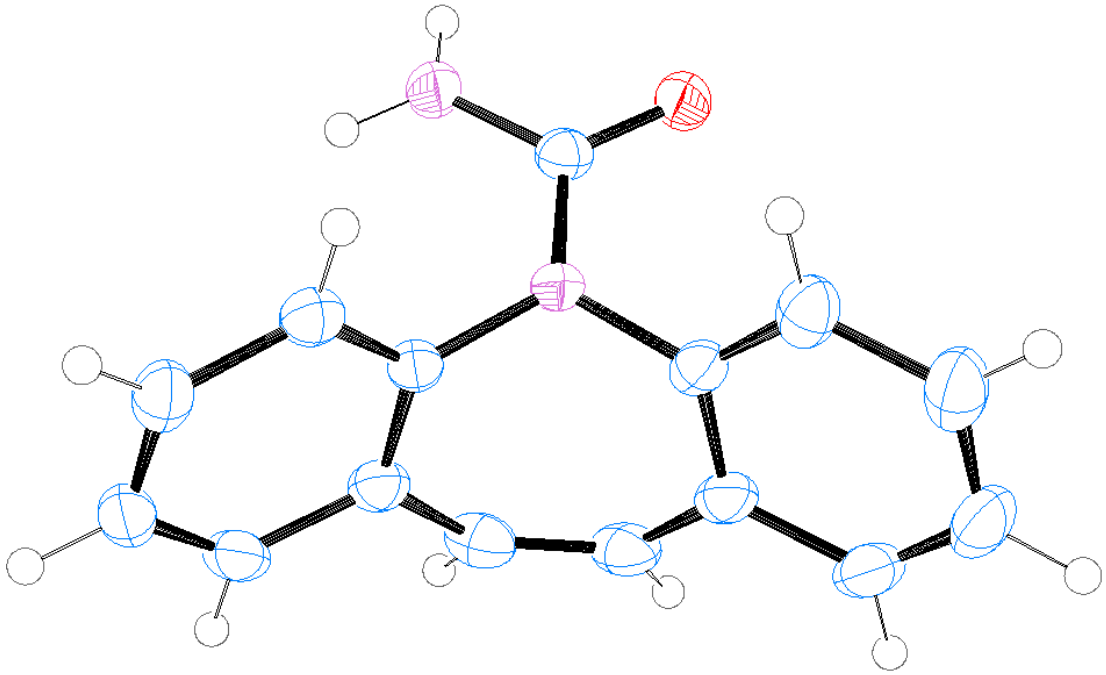

Figure S1. ORTEP diagram of CBZ form V (ellipsoids drawn at 50% probability level).

Table S2. Unit cells for **CBZ form V,** CBZ:DHC 50:50 solid-solution, DHC II and predicted CBZ structure.

Compound reference	CBZ form V	DHC form II[2]	50:50 solid solution[3]	Predicted [4]
Crystal system	Orthorhombic	Orthorhombic	Orthorhombic	Orthorhombic
a/Å	9.1245(5)	9.0592(4)	9.088(2)	9.312
b/Å	10.4518(5)	10.3156(5)	10.425(4)	10.598
c/Å	24.8224(11)	25.0534(12)	25.005(7)	24.882
α/°	90.00	90.00	90	90
β/°	90.00	90.00	90	90
γ/°	90.00	90.00	90	90
Unit cell volume/Å^3	2367.2(2)	2341.3	2369.0	2455.6
Temperature/K	123(2)	120	150	0
Space group	*Pbca*	*Pbca*	*Pbca*	*Pbca*

2. **Method for computational substitution calculations in Figure 3**.

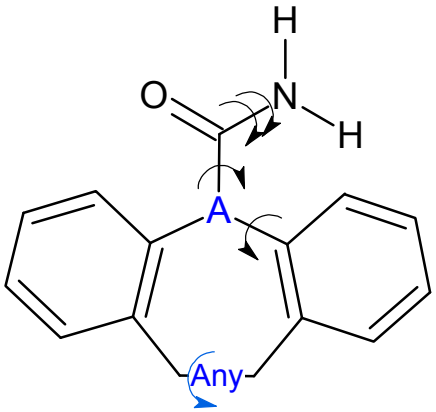

Figure S2. Generalized molecular structure of CBZ/DHC/CYH/CYT, showing the torsion angles whose structures were varied within the lattice energy minimization.

The atomic coordinates of hypothetical crystal structures were generated by substituting molecular structures so as to minimize the root-mean-square deviations of all atoms except hydrogens, with the C atom in CYH or CYT being matched to the N atom in CBZ or DHC. CYH and DHC have two low energy conformations differing in the orientation of the carboxamide group relative to the C10–C11 bond, both of which are observed in crystal structures. (The lower energy anti-conformer is observed in DHC I, II and III and the known solvate structures except that of the disordered DHC:DMSO, in which both the anti- and syn-conformers are both present with fractional occupancies of 0.81 and 0.19 respectively. The catemeric DHC form IV contains the syn-conformer.[5] CYH form II contains 3 molecules in the lower energy anti conformation and one in the syn conformation.) Hence, hypothetical structures containing both conformations were considered. The exception was the hypothetical structure of DHC in the Z'=4 CBZ I structure, where the conformations seen in the structural isomer CYH II were assumed.

The CrystalOptimizer algorithm[6] was used to simultaneously optimise the crystal structure and the molecular conformation within it by minimizing the lattice energy $E_{latt}=U_{inter}+\Delta E_{intra}$. Only the torsion angles (Fig S2) defining the two amide hydrogen positions, the rotation of the amide group with respect to the 7-membered ring, the angle of the amide to the ring, and, for CYH and DHC, the twist of the saturated bond of the 7-membered ring, were explicitly optimised within the crystal structure: all other intramolecular variables were defined by the constrained isolated molecule ab initio optimization. The intramolecular energy penalty for the conformational changes from the ab initio optimized structure, ΔE_{intra}, was calculated using GAUSSIAN03 at the RHF level of theory, with the 6-31G(d,p) basis set. The intermolecular lattice energy, U_{inter}, was calculated by DMACRYS using an isotropic atom-atom exp-6 potential with the FIT parameters[7] and all terms in the electrostatic energy up to R^{-5} calculated from the atomic multipoles up to hexadecapole. The atomic multipoles were obtained using GDMA2[8] to analyse the MP2/ 6-31G(d,p) charge density. The resulting lattice energy minima are shown in Table S3, and on Figure 3.

Table S3. Comparison of the experimental and lattice energy minima for the observed and computationally generated isostructural crystal structures of the CBZ family (Fig. 3)

Structure	Molecule	Form	Space Group	a / Å	b/ Å	c / Å	α / º	β / º	γ / º	E_{latt} / kJ mol^{-1}	U_{inter} / kJ mol^{-1}	ΔE_{intra} / kJ mol^{-1}	Density / g cm^{-3}
CBZI	CBZ	CBZI	P-1	5.171(<1)	20.574(2)	22.245(2)	84.12(<1)	88.01(<1)	85.19(<1)				1.339
				5.262	20.517	22.365	85.160	86.361	85.932	-124.80	-127.44	2.64	1.310
	CYT	CYTII	P-1	5.810(<1)	19.632(<1)	21.709(<1)	85.92(<1)	86.16(<1)	84.48(<1)				1.274
				5.641	19.937	21.891	86.126	84.945	84.868	-129.62	-131.13	1.51	1.282
	CYH	CYHII	P-1	5.649(<1)	19.564(<1)	22.074(<1)	84.22(<1)	88.41(<1)	83.60(<1)				1.307
				5.727	19.874	22.136	84.163	88.313	83.761	-129.68	-130.70	1.02	1.265
	DHC	hypothetical											
				5.442	21.179	22.430	83.763	89.522	86.076	-111.26	-113.96	2.69	1.235
CBZII	CBZ	CBZII	R-3	35.454(3)	35.454(3)	5.253(1)	90	90	120				1.235
			R-3	35.423(5)	35.243(5)	5.185(1)	90	90	120				1.305
				35.264	35.264	5.272	90	90	120	-121.97	-125.34	3.37	1.244
	CYT	CYTI	R-3	33.908(1)	33.908(1)	5.675(<1)	90	90	120				1.244
				34.249	34.249	5.639	90	90	120	-127.96	-128.76	0.81	1.228
	CYH	hypothetical											
		anti		34.378	34.378	5.637	90	90	120	-126.46	-128.17	1.71	1.229
		syn		35.743	35.743	5.666	90	90	120	-121.50	-123.08	1.58	1.131
	DHC	hypothetical											
		anti		35.140	35.140	5.433	90	90	120	-118.41	-120.80	2.39	1.226
		syn		36.072	36.072	5.461	90	90	120	-115.49	-118.50	3.02	1.157
CBZIII	CBZ	CBZIII	P21/n	7.537(1)	11.156(2)	13.912(3)	90	92.86(2)	90				1.343
				7.885	11.018	13.427	90	87.706	90	-128.76	-130.27	1.51	1.346
	CYT	hypothetical											
				6.768	11.657	16.993	90	112.179	90	-101.68	-102.13	0.45	1.259
	CYH	hypothetical											
		anti		7.671	11.871	13.789	90	87.682	90	-114.72	-118.50	3.78	1.256
		syn		7.572	11.710	14.115	90	91.072	90	-118.97	-121.93	2.95	1.260
	DHC	hypothetical											
		anti		7.547	11.612	13.986	90	91.382	90	-121.19	-123.03	1.84	1.292
		syn		7.804	11.736	13.545	90	94.080	90	-119.37	-121.42	2.06	1.279

CBZIV	CBZ	CBZIV	C2/c	26.609(4)	6.927(1)	13.957(2)	90	109.70(<1)	90				1.296
				26.856	6.916	25.429	90	31.853	90	-123.25	-124.98	1.73	1.259
	CYT	hypothetical											
				29.464	7.334	13.597	90	121.236	90	-105.30	-108.65	3.35	1.244
	CYH	hypothetical											
		anti		28.422	7.616	13.947	90	120.231	90	-104.61	-108.52	3.92	1.208
		syn		27.442	6.317	15.441	90	108.273	90	-118.54	-121.67	3.13	1.240
	DHC	hypothetical											
		anti		25.781	7.806	13.626	90	116.457	90	-120.99	-124.54	3.54	1.289
		syn		24.354	8.150	13.516	90	103.381	90	-112.78	-117.66	4.89	1.213
DHCI	CBZ	hypothetical											
				5.061	9.299	26.290	90	102.869	90	-122.08	-123.82	1.74	1.301
	CYT	hypothetical											
				5.500	9.218	24.666	90	99.697	90	-119.46	-124.01	4.55	1.268
	CYH	CYHI	P21/c	5.604(<1)	9.172(1)	23.579(3)	90	96.75(1)	90				1.310
				5.545	9.467	23.458	90	98.309	90	-135.24	-136.08	0.85	1.294
	DHC	DHCI	P21/c	5.505(1)	9.158(2)	24.266(7)	90	95.95(2)	90				1.301
				5.363	9.506	23.963	90	94.382	90	-130.00	-130.77	0.77	1.299
DHCII	CBZ	CBZV	Pbca	9.1245(5)	10.4518(5)	24.8224(11)	90	90	90				1.326
				9.517	10.245	24.833	90	90	90	-124.69	-125.50	0.81	1.296
	CYT	hypothetical											
				9.210	11.460	23.374	90	90	90	-125.08	-125.22	0.14	1.267
	CYH	hypothetical											
		anti		9.282	10.849	24.126	90	90	90	-131.81	-133.39	1.58	1.298
		syn		9.421	11.238	24.597	90	90	90	-116.83	-119.55	2.72	1.210
	DHC	DHCII	Pbca	9.059(<1)	10.316(<1)	25.053(1)	90	90	90				1.352
				9.281	10.467	24.718	90	90	90	-131.37	-132.04	0.68	1.318

DHCIII	CBZ	hypothetical											
				5.062	9.299	26.286	90.001	77.138	90.041	-122.07	-123.80	1.73	1.30
	CYT	hypothetical											
				5.505	9.220	25.251	89.968	74.182	90.198	-119.44	-123.91	4.47	1.27
	CYH	hypothetical											
		anti		7.044	8.681	22.580	80.243	83.326	71.604	-117.44	-118.98	1.54	1.22
		syn		5.656	8.516	28.515	88.383	73.451	90.318	-114.02	-115.01	0.99	1.20
	DHC	DHCIII	P-1	5.423(1)	9.200(5)	24.189(6)	87.59(3)	84.23(2)	88.93(3)				1.32
				5.363	9.515	24.139	89.998	81.521	89.980	-130.01	-130.70	0.69	1.30
DHCIV	CBZ	hypothetical											
				14.261	4.990	18.610	90	112.232	90	-121.46	-121.78	0.31	1.28
	CYT	hypothetical											
				12.709	5.586	18.625	90	106.600	90	-122.67	-123.93	1.26	1.23
	CYH	hypothetical											
		anti		11.637	7.001	16.726	90	99.472	90	-115.42	-117.07	1.65	1.17
		syn		13.445	5.554	18.118	90	104.728	90	-121.73	-123.09	1.36	1.21
	DHC	DHCIV	P21/c	13.207(6)	5.347(2)	18.891(7)	90	116.37(2)	90				
				13.246	5.418	18.853	90	115.587	90	-126.92	-132.20	5.28	1.30

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