A predicted dimer-based polymorph of 10,11-dihydrocarbamazepine (Form IV)†

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A novel polymorph of 10,11-dihydrocarbamazepine (form IV), which had been predicted to be thermodynamically feasible, was obtained from the vapour phase and displays an $R_2^2(8)$ hydrogen bonded dimer motif in contrast to the catemeric motifs in forms I–III.

10,11-Dihydrocarbamazepine (DHC) is a recognised impurity in carbamazepine (CBZ), a dibenzazepine drug used in the treatment of epilepsy.[1] Here, DHC is of particular interest as part of a wider investigation that combines experimental searches with crystal structure prediction (CSP) to explore the basic science underpinning structural diversity in CBZ and the closely related analogues, DHC, cyheptamide (CYH) and cytenamide (CYT) (Fig. 1). In this communication, we present the single-crystal structure of a new dimer-based polymorph of DHC, form IV,† that was successfully predicted by CSP methods. We also report on the structural relationships between DHC polymorphs as indicated by the XPac program.[2]

DHC forms I (monoclinic),[3] II (orthorhombic)[4] and III (triclinic)[5] all display the catemeric C(4) hydrogen-bonded motif shown in Fig. 2, as does a 1:1 CBZ:DHC[6] solid solution. Notably, the dominance of the catemer motif in non-solvated DHC structures is in marked contrast to the known polymorphs of CBZ[7] and CYT[8] that contain only the dimer motif. CSP studies on DHC (this work) as well as CBZ,[9] CYH and CYT† have identified thermodynamically competitive populations of hypothetical crystal structures that are based on either the catemer motif or an $R_2^2(8)$[10] dimer. However, prior to this report only CYH had been crystallised in both dimer and catemer motifs.[11]

The CSP results for DHC were challenged by employing a diverse range of experimental crystallisation conditions in a search for predicted polymorphs and, in particular, potential dimeric structures.

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† Electronic supplementary information (ESI) available: Summary of results for solution crystallisations and CSP on DHC, also further details on results of XPac comparisons of DHC I–IV. [Note, detailed CSP results for CYH and CYT are outwith the scope of this report and will be published in detail in a subsequent report]. CCDC reference number 739821. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b914365c

Fig. 1 CBZ and related structural analogues DHC, CYH and CYT.

The crystallisation methods used included an automated parallel solution crystallisation study[12,13] supplemented by manual solution crystallisations, solvate desolvation plus recrystallisation from both the melt and vapour phase. In total, 170 automated and manual solution recrystallisations were implemented using a library of 71 solvents under 4 different conditions (details in the ESI).† These produced DHC I, II and III in addition to six crystalline solvates (formic acid,[14] formamide,[15] acetic acid,[16] butyric acid, triflouroacetic acid and DMSO[17]). A dimeric DHC motif is observed in the crystalline DMSO solvate, but in the other four known solvate structures (see ESI)† DHC molecules form an $R_2^2(8)$ motif with the carboxylic acid or amide group of the solvent molecule in preference to a solvated DHC dimer or catemer. Desolvation of polycrystalline samples of these solvates, including DHC:DMSO, produced DHC I and/or II (see ESI). Crystallisation of DHC from the melt failed due to rapid and complete decomposition upon melting to produce 10,11-dihydro-5H-dibenzo[b,f]azepine.[18]

Single-crystals of form IV were obtained, together with those of form I and II, by crystallisation from the vapour phase via sublimation.‡ Single-crystal analysis was carried out on a small needle shaped crystal at 123(2) K. The single-crystal structure is shown in Fig. 3 overlaid with the matching predicted structure (ak2, Table S4 in ESI†) found in the CSP search ~10 kJ mol^{-1} above the global minimum.

Fig. 2 The C(4) catemer motif observed in DHC forms I–III (form I shown) and also in CYH form I and in a 1:1 solid solution of DHC:CBZ (N–H⋯O and N–H⋯π contacts shown as dashed lines).

Fig. 3 Crystal structure of DHC IV viewed down the *b*-axis showing the centrosymmetric $R_2^2(8)$ dimers (N–H···O contacts shown as dashed lines). The predicted structure ak2 is overlaid (red sticks). A comparison of form IV and ak2 using the packing similarity tool in Mercury 2.2[19] yields an RMS value of 0.33 Å for a 15 molecule coordination group.

DHC can adopt one of two molecular conformations depending on the orientation of the carboxamide group relative to the C_{10}–C_{11} bond (Fig. 4). 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. DHC form IV however contains the *syn*-conformer that is estimated to be <2 kJ mol⁻¹ less stable than the *anti*,§ a value consistent with the values expected for conformational polymorphism. Using the approximate crystal energy landscape (as in ref. 9, details in the ESI),† generated assuming the molecule adopted one of these gas-phase optimised conformations, DHC II was found to be the most stable structure. It also showed catemer-based structures generated from the *syn* conformation that were almost as stable as forms I and III (*e.g.* fc13 in the ESI).† Dimer-based structures were significantly less stable (by about 5 kJ mol⁻¹) with DHC form IV further destabilised by the conformational energy penalty associated with the *syn*-conformer. A previously published CSP study on DHC[20] also predicted form II as the global minimum, and found the lowest energy *syn*-conformer (catemeric) structure and lowest energy dimeric structure to be *ca.* 7 and 6 kJ mol⁻¹ above the global minimum, respectively. At the time, these authors estimated that structures greater than 5 kJ mol⁻¹ above the global minimum were unlikely to be observed.[20]

The packing arrangement of DHC molecules in form IV was compared to the other three polymorphs using the XPac method and the same procedures applied previously to 25 CBZ related structures,[21] CYH I and II[11] and CYT I and II.[8] Three supramolecular constructs[2] (SCs) are observed more than once across the four DHC polymorph structures and their structural relationships are illustrated in Fig. 4. The 1D SCs A and A_1 are observed in DHC I, III and IV, whilst the catemer, B, is observed in I, II and III. Fig. 4 also highlights two motifs that occur only once across the four DHC structures considered in the analysis, namely the 0D hydrogen-bonded dimer in IV (C) and an offset 1D stack of DHC molecules (D) in form II. The combination of SCs A_1 and B in DHC I (monoclinic) and III (triclinic) results in structures with a high degree of 3D correspondence.

A previous XPac analysis of forms I and II of the related molecule CYH,[11] identified that the 1D stack equivalent to A in Fig 4. is preserved in both structures, despite the change in hydrogen bonding (catemer → dimer) that accompanies the CYH I → II thermal phase transition. Similarly for DHC, the importance of space-filling effects is evident, with non-hydrogen bonded 1D stacks of DHC molecules
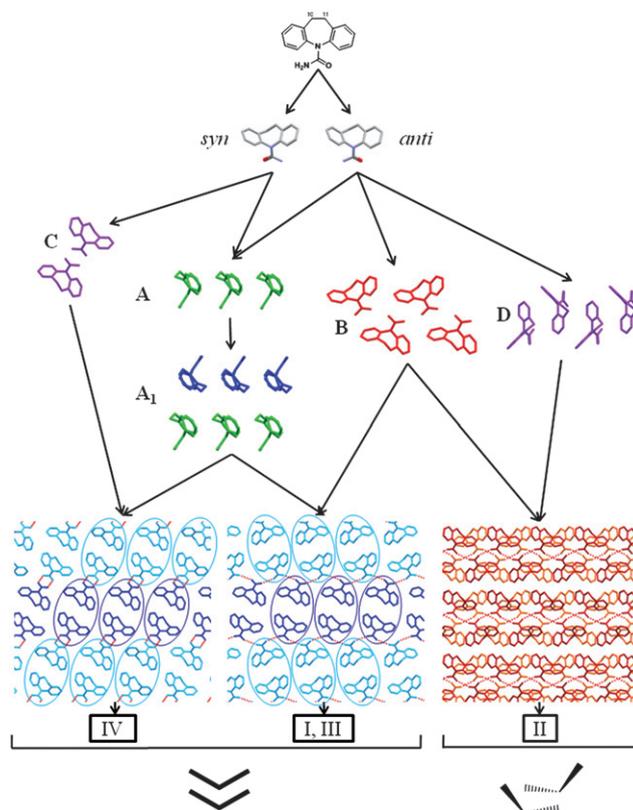
Fig. 4 Tree diagram illustrating the similarity relationships between DHC I, II, III and IV. From top to bottom: DHC and the *syn*- and *anti*-conformers; SC A, a 1D stack; 1D SC A_1 composed of two inversion related A stacks (A_1 comprises *anti*-conformers in I and III and *syn*-conformers in IV); SC B, a 1D catemeric arrangement. A, A_1 and B are each viewed perpendicular to the SC translation vector. Motifs C, a 0D dimer, and D, an offset 1D stack are observed only in forms IV and II, respectively. The packing diagrams for I, III and IV are viewed parallel to the A_1 translation vector and the blue ovals highlight the different relative orientations of the A_1 stacks in the catemeric (I, III) and dimeric (IV) structures. The diagrams at the base of the figure illustrate which of the two principle 1D stacking arrangements are observed in the structures (*i.e.* A_1 in I, III and IV and D in II).

(SC A_1) observed in forms I, III and IV. The catemer and dimer hydrogen bonding motifs in these structures therefore arise from altered packing of the common molecular stack, A_1, as highlighted in the packing diagrams in Fig. 4.

In general terms, the discovery of this new dimer-based polymorph of DHC provides another example of the successful application of CSP technologies to identify favourable packing motifs and crystal structures. An important caveat in the context of informing experimental polymorph discovery however, is the need to consider the predicted structures within a reasonably large energy range as being possible, given the likely error in calculating relative crystal energies. It has recently been shown that the relative energies of predicted CBZ structures are sensitive to the modelling of molecular flexibility[22,23] and intermolecular forces, although the explicit modelling of the distortion of the charge distribution within the crystal[24] may be less important for DHC.[20] Whilst reliable calculations of the relative ambient free energies of organic crystals are a major challenge to computational chemistry, the discovery of DHC IV confirms that the approximate lattice energy landscape provides a meaningful

Table 1 Dimer and catemer hydrogen bonding motifs in the crystal structures of CBZ, DHC, CYT and CYH

	Polymorphs	$R_2^2(8)$	C(4)
CBZ	4	4	—
DHC	4	1	3
CYH	2	1	1
CYT	2	2	—

indication of potential solid-state diversity, establishing a rationale for experimental investigation of the true crystal energy landscape. In the case of DHC, there are other predicted structures that may reasonably be expected to crystallise in preference to the *syn*-dimer based DHC IV, such as ak61 (see ESI) that shows identical packing of the more stable *anti*-conformer. Clearly, nucleation is important in determining which energetically feasible structures are actually observed as polymorphs, however, the concomitant formation of DHC I, II and IV from the vapour phase illustrates the considerable challenge of predicting the impact of kinetic factors involved in crystallisation.

In conclusion, DHC IV represents an important advance in defining the true extent of solid-state structural diversity of the molecules in Fig. 1, as summarised in Table 1. With two of the four compounds (DHC and CYH) having now been shown to adopt both dimer and catemer based crystal structures in accordance with CSP, the continued challenge to experimental and computational technologies is to provide confirmation of whether CBZ and CYT can or cannot form polymorphs based on the catemer motif.

Acknowledgements

Notes and references

‡ 20 mg of DHC, obtained from Aldrich, was placed in a 10 mL glass volumetric flask in which a glass fibre was suspended. A small crystal of CYT I was attached to the fibre. The container was sealed and placed on a hot plate at 100 °C and left for 24 h after which fine crystals were observed on the glass fibre. Individual crystals were identified using single-crystal diffraction, confirming the presence of forms I, II and IV in the recrystallised sample. Although there is no evidence to suggest DHC IV grew on the surface of the CYT I crystal, further studies are ongoing to assess the reproducibility of DHC IV in the absence of heterochemical seeds and to obtain bulk samples of form IV for characterisation of the physical properties. DHC IV. $C_{15}H_{14}N_2O$, $M_r = 238.28$, Bruker-AXS Kappa Apex II instrument, Mo radiation ($\lambda = 0.71073$ Å), Experimental structure [values for predicted ak2]: monoclinic, $P2_1/c$, $a = 13.207(6)$ [13.897], $b = 5.347(2)$ [5.215], $c = 18.891(7)$ [19.430] Å, $\beta = 116.37(2)$ [117.13]°, $V = 1195.23$ Å^3, $T = 123(2)$ K, $\mu = 0.085$ mm^{-1}, 16837 reflections measured, 2353 unique ($R_{int} = 0.0824$), $\theta_{max} = 26.0°$, 171 parameters, $R = 0.043$ [based on F and 1566 data with $F^2 > 2\sigma$ (F^2)], $R_w = 0.098$ (based on F^2 and all 2353 unique reflections), $S = 1.03$.

§ The *syn*-conformer is estimated to be less stable than the *anti* by 1.7 kJ mol^{-1} at the MP2 level (ESI) and 1.43 at the SCF level with a 6–31G(d,p) basis set, and 1.67 kJ mol^{-1} (DFT calculations with PW91 functional and DNP basis set) ref 20, by full optimisation of the two conformers.

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