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Structural Studies of the Polymorphs of Carbamazepine, Its Dihydrate, and Two Solvates

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Abstract:

High-field cross-polarisation magic-angle spinning ^{13}C NMR spectra are presented for the four known polymorphs of anhydrous carbamazepine, for a dihydrate, and for two solvates. These are all distinctive, despite relatively low spectral dispersion, and give immediate information about the crystallographic asymmetric unit. The results for the trigonal and the two monoclinic forms are consistent with the published crystal structures. That of the triclinic form was found to contain four molecules in the crystallographic asymmetric unit, which has recently been confirmed by an X-ray diffraction study. NMR shows that the dihydrate has one molecule in the asymmetric unit, and the full crystal structure derived from single-crystal X-ray diffraction work is reported herein. It is found to be ordered and monoclinic, in contrast to the reported disordered orthorhombic structure. The discrepancy is attributed to the common occurrence of multiple micro-twinning. Shielding computations using a method which takes explicit account of the repetition inherent in a crystal lattice are reported for the P-monoclinic form and are compared to the experimental chemical shifts. The NMR data of all the forms are discussed in relation to variations in the molecular geometry of the hydrogen-bonded dimers (except in the case of two solvates). Chemical shift variations are explored as a function of the amide torsion using the Gaussian computer program.

Introduction

Polymorphism and solvate formation represent major problems to pharmaceutical industry in terms of patent establishment and protection, reliability of production, and stability on storage and in processing. Methods of studying the structure and properties of polymorphs and solvates are therefore of paramount importance. Traditionally, single-crystal X-ray diffraction is the preferred way to establish structure, but it is appreciated that this is subject to many difficulties from factors such as static or dynamic disorder, crystal suitability, twinning, etc. In cases where no suitable single crystal can be obtained, structure solution from powder X-ray data has been demonstrated to be a very promising and successful alternative.[1] However, there are limitations to this method, and it is increasingly recognised that solid-state magic-angle spinning (MAS) NMR is a powerful tool for providing additional and complementary structural information. We are therefore pursuing general strategies of combining MAS NMR, X-ray diffraction, and computational methods[2−9] to examine both structure and molecular-level dynamics of polymorphic systems and solvates.

In the present paper, we have been examining carbamazepine (**I**), 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide. This compound has found clinical use for the treatment of neuralgia and epilepsy. It is known to exist in at least four anhydrous polymorphic modifications (Grzesiak et al.[10] and references therein), two of which are monoclinic, one is trigonal and the final one is triclinic. The P-monoclinic form is the thermodynamically stable modification under ambient conditions. As commonly occurs in polymorphic systems, there is some confusion in the literature on the numerical numbering for these forms, a situation summarised by Grzesiak et al.[10] It is safe, however, to refer to them by their Bravais lattices, since the two monoclinic modifications can be distinguished as P-lattice and C-lattice. The crystal structures of the P-monoclinic[11−13] and trigonal[14] structures have been

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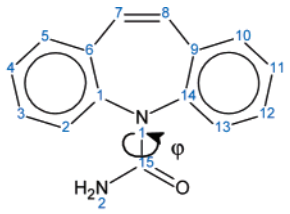
known for over 15 years. More recently, the structure of the C-monoclinic form has been published,[15] which was designated as a new form IV by the authors. However, this form had already been discovered in 1968 by Kuhnert-Brandstätter et al.[16] (called form II) and was observed later by many other authors.[17−20] At the time that most of the NMR work described here was carried out, the crystal structure of the triclinic form (the stable modification at high temperature) was unknown, but recently that, too, has been solved.[10] According to Grzesiak et al.,[10] the four forms are close in energy, the stability order at room-temperature being P-monoclinic > triclinic > C-monoclinic > trigonal. Thermochemical data[17,21] and the densities[10] clearly indicate an enantiotropic relationship between the P-monoclinic form and the triclinic form, and there is no doubt that the P-monoclinic form shows the lowest free energy of all the forms at and below room temperature. From the thermochemical data evaluated by Grzesiak et al.,[10] it may be deduced that the C-monoclinic form and the P-monoclinic form also represent an enantiotropic pair. However, the C-monoclinic and the triclinic form are monotropically related according to Grezsiak et al.[10] but enantiotropically related according to Krahn and Mielck.[17] The trigonal form is obviously the least stable of all anhydrous forms. Because of the fast transformation of the trigonal form, its melting point could not be determined so far, and therefore the thermodynamic relationship of this polymorph to other anhydrous forms remains unclear.

We have obtained cross-polarisation magic-angle spinning (CPMAS) carbon-13 spectra at high field (11.1 T) for all four anhydrous forms, and these are discussed below.

The dihydrate of carbamazepine has been studied in numerous publications [e.g., refs 17, 20, 22−33]. According to McMahon et al.,[28] a dihydrate obtained from the P-monoclinic form behaves differently to one produced from the triclinic form. The two hydrates showed slightly different thermochemical behaviour, but the powder X-ray diffraction patterns and spectroscopic data are practically identical. Therefore the authors concluded that there is no evidence that supports the existence of two different dihydrate forms. In the present paper we report both the ^{13}C CPMAS spectrum and the full crystal structure of the dihydrate. Its structure has been reported in the literature[23] to be disordered orthorhombic (space group *Abam*), with the carbamezapine molecule assumed to have a spurious symmetry plane arising from rotational disorder of the amide group. The appearance of disorder is exacerbated by the similarity of the diffracting powers of oxygen and NH_2, as present in the amide grouping.

Several other solvates exist (see, for example, Terrence et al.,[34] Hilfiker et al.,[20] Fleischman[35] and Lowes et al.[14]), and we show here the ^{13}C CPMAS spectra of acetone[34] and dioxane[20] solvates. The structure of the acetone solvate has been solved.[34] It falls into the $P\bar{1}$ space group and contains one molecule in the asymmetric unit.



Carbamazepine (**I**),
showing the atomic numbering and the internal rotation coordinate

Low-field ^{13}C CPMAS spectra of an unidentified carbamazepine polymorph (probably P-monoclinic) and of its mixtures with a dihydrate have been presented.[24] The proton relaxation time of the anhydrous form was found to be very long, a fact which was exploited to quantify the relative proportions of the dihydrate in the mixtures. Spectral resolution was relatively poor, in part because of second-order effects on the signals of carbons bonded to nitrogen [Harris & Olivieri[36] and references therein].

Experimental Section

Samples. The various polymorphs were obtained by standard literature procedures. The purchased commercial product (Pfannenschmidt, D-Hamburg, Batch No. 8902 L417) contained the P-monoclinic form. The triclinic form was obtained by annealing the P-monoclinic form at 170 °C for 1 h in an oven. The C-monoclinic form was obtained by drying the dihydrate over phosphorus pentoxide at room temperature and the trigonal form by crystallization from toluene. The solvates were crystallized from a dioxane or acetone solution by evaporation of a part of the solvent at room temperature. The dihydrate was obtained by recrystallization from a wet ethanol solution.

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NMR. Solution-state spectra were recorded using a Varian Unity 300 spectrometer. Carbon-13 CPMAS data for the acetone and dioxane solvates were obtained at 75.43 MHz using a Varian Inova 300 spectrometer whilst the remaining ^{13}C spectra were measured at 125 MHz using a Varian Infinity 500 spectrometer. The Inova was fitted with a 7.5 mm o.d. rotor system (spin rates 5.0 kHz), whilst a 3.2 mm o.d. rotor (spin rates 8−10 kHz) was used with the Infinity (but a 5 mm rotor, at 9−10 kHz spin rate, for the monoclinic forms). The chemical shifts were referenced via a replacement sample of adamantane (methylene carbon chemical shift assigned as +38.4 ppm relative to the signal for TMS). Contact times ranged between 1 and 5 ms. Recycle delays were chosen following initial experiments and varied greatly, being 5−10 s for the trigonal and triclinic forms and the dioxane solvate. A value of 300 s was employed for the acetone solvate. The two monoclinic forms have very long proton spin−lattice relaxation times at ambient probe temperature, so recycle delays of 600 s were required. In consequence, numbers of transients also covered a wide range, from only 64 for P-monoclinic to 8640 for the triclinic. All samples were measured at ambient probe temperature (ca. 22 °C). High-speed (22 kHz) proton MAS spectra were also obtained using the Infinity spectrometer (with the 3.2 mm o.d. rotor system). For the anhydrous polymorphs these showed only a broad band, though the line width at half-height varied with the sample (ca. 1.8 kHz for the triclinic form but ca. 2.3 kHz for the C-monoclinic form); no separate signal was seen for the hydrogen-bonded protons.

Computations for the P-Monoclinic Form. NMR shielding tensors were calculated for all atoms in the crystal structure using the fully periodic Gauge Including Projector Augmented Wave method (GIPAW).[37] This enables calculations to be made of shielding tensors with all-electron accuracy from computational techniques based on the use of pseudopotentials. For all calculations we use density functional theory within the Perdew−Berke−Ernzerhof generalised gradient approximation.[38] The charge density and electronic wave functions are described using a plane-wave basis set. To improve the computational efficiency of our approach we use pseudopotentials to describe the interactions of the valence electrons with the core ion. For the geometry optimisation we use the CASTEP electronic structure code[39] and employ "ultrasoft" pseudopotentials[40] with a maximum planewave energy of 400 eV. For the calculation of the shielding constants we use the PARATEC [PARAllel Total Energy Code, by B. Pfrommer, D. Raczkowski, A. Canning, and S. G. Louie, Lawrence Berkeley National Laboratory (with contributions from F. Mauri, M. Cote, Y. Yoon, C. Pickard, and P. Haynes). For more information, see www.nersc.gov/projects/paratec] and Trouiller−Martins[41] norm-conserving pseudopotentials with a maximum planewave energy of 950 eV. Integrals over the Brillouin zone use a Monkhorst−Pack[42] grid with a sample spacing of 0.6 $Å^{-1}$.

The computations of the effect of varying the torsion angle were carried out on a single-molecule basis using the Gaussian 98 program.[43] The structure of an isolated carbamazepine molecule as in the crystalline P-monoclinic state (CCSD code CBMZPN01) was used as the starting point. The dihedral angle, N2C15N1C14 (φ, see (**I**)), was systematically changed from 0° to 90°. The structure was then optimised at the B3LYP/6-31G* level of theory (DFT method), while keeping φ constant at its designated value. The optimised geometry was then used to calculate NMR shielding parameters, also at B3LYP/6-31G*.

Semiempirical molecular orbital calculations were performed using MOPAC[44] with, for purposes of comparison, the AM1 and PM3 methods. Geometry optimisation was performed using the eigenvector following procedure specified with the keyword EF.

X-ray Diffraction. X-ray measurements for carbamazepine dihydrate were performed on a Bruker SMART CCD 1K area-detector diffractometer. *Crystal data*: $C_{15}H_{12}N_2O\cdot 2H_2O$; $M_r = 272.34$; $T = 120(2)$ K; λ(Mo Kα) = 0.710 73 Å; monoclinic, space group $P2_1/c$ (No. 14), $a = 10.066(2)$ Å, $b = 28.719(5)$ Å, $c = 4.831(1)$ Å, $\beta = 103.45(1)°$, $V = 1358.2(5)$ $Å^3$; $D_c = 1.332$ g cm^{-3}; $Z = 4$; μ(Mo Kα) = 0.09 mm^{-1}. 12 555 reflections (2385 unique, $R_{int} = 0.089$) were collected by a combination of five sets of narrow ω-scans, covering the full sphere of reciprocal space. The structure was solved by direct methods[45,46] and refined by full-matrix least squares against F^2 of all data using SHELXTL 6.12 software (Bruker AXS, Madison, WI, 2001). Both the peak profiles and the intensity statistics of reflections indicated a twinned crystal. The refinement converged at $R = 0.086$ for 1757 reflections with $I > 2\sigma(I)$ and $wR(F^2) = 0.266$ for all data. A correction for merohedral twinning,[47] assuming the twin law (−1 0 −1/0 −1 0/0 0 1), reduced these R indices to 0.073 and 0.214, respectively, and drastically improved the refinement of hydrogen atoms. The intensity contributions from the two twin components were refined to 0.829(5) and 0.171(5).

All non-hydrogen atoms were refined in anisotropic approximation. All the hydrogen atoms were located in the difference Fourier map; those at carbon atoms were included as "riding" in idealised positions, whilst those of the NH_2

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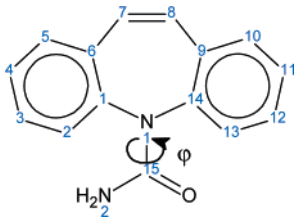
Table 1. **Carbon-13 chemical shifts (in ppm) for carbamazepine polymorphs and solvates and for a solution in $CDCl_3$[a]**



Carbon number	Solution state	Trigonal	P-monoclinic	C-monoclinic	Triclinic	Dihydrate	Acetone solvate	Dioxane solvate
15	157.41	159.0	159.0	159.9	159.3	158.5	159.8	158.4
1,14	139.84	141.7 140.0	140.4 137.3	138.8 136.9	141.7 139.8	140.9 140.1	141.5 139.5	142.1 140.4
6,9	134.83	135.6 134.3	134.7x2?	134.0	136.7, ~136 135.6x2 134.5x2, 133.9x2	135.2 134.7	?,136.7	136.1x2
7,8	130.27	131.2 130.6 129.0x2? 127.9	132.0 131.0 129.2x3?	129.3x? 128.7x?	132.5, 132.1 131.1, 130.9 130.0x4?, 129.3 128.9x4?	131.2x2 130.0 129.5x3? 128.9x2?	130.9x4? 129.4x2? 128.2x4?	133.5? 130.6 128.9
2,13	129.40							
4,11	129.30							
5,10	128.58							
3,12	127.55	126.2	127.3	125.5	126.7x2? 125.9x4?	126.8 125.9		125.8 124.1
1,14 (average)		140.9	138.9	137.9	140.8	140.0	140.5	141.3
1,14 (splitting)		1.7	3.1	1.9	1.9	1.8	2.0	1.7

[a] The solid-state chemical shifts are considered to be accurate to ±0.2 ppm, whilst the solution state shifts are an order of magnitude more accurate.

group and of the water molecules were refined freely in isotropic approximation. Notwithstanding appreciable variations of the bond distances (N−H 0.77(4) and 0.97(5) Å; O−H 0.79(6) to 1.12(6) Å), the location of these hydrogens is chemically reasonable.

The full structural information in CIF or other electronic format is available as electronic Supporting Information and has been deposited at the Cambridge Crystallographic Data Centre, dep. no. CCDC-278591.

NMR Results

A proton-decoupled ^{13}C NMR spectrum, obtained at 125 MHz and ambient temperature, of a solution of carbamazepine in deuteriochloroform, reveals the existence of eight peaks, consistent with a symmetrical structure on the NMR time scale. Assignments of the peaks can be made using (^{13}C, ^{1}H) HETCOR and (^{1}H, ^{1}H) COSY two-dimensional spectra, and the results are given in Table 1. Two of the signals are significantly broadened, presumably because internal rotation about the ring nitrogen to C15 bond (see (**I**)) is insufficiently rapid at ambient temperature to completely average the chemical shifts of the relevant pairs of carbons.

CPMAS ^{13}C spectra of the four anhydrous polymorphs, the dihydrate, an acetone solvate, and a dioxane solvate, obtained at 125 MHz, are displayed in Figure 1. Several deductions can be made. First, although the dispersion of most of the signals is not good (since all the carbons, except for that of the amide group, are aromatic or ethylenic), all the forms are clearly distinguishable by their spectra, which can therefore be used as fingerprints for recognition purposes.

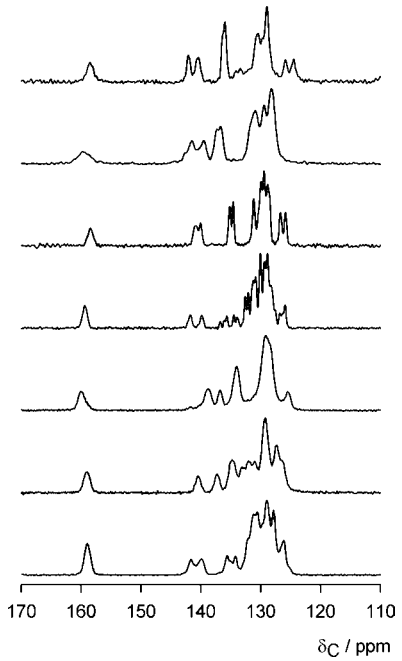


Figure 1. **Carbon-13 CPMAS spectra, obtained at 125 MHz, of various forms of carbamazepine. Bottom to top: trigonal; P-monoclinic; C-monoclinic; triclinic; dihydrate; acetone solvate; dioxane solvate.**

Second, it is clear that both the trigonal form and the dihydrate have a whole molecule as the crystallographic asymmetric unit, since the signals from the C1/C14 and C6/C9 pairs of carbons are each split into two components (as is the C3/C12 pair for the dihydrate). The observation of

Table 2. **Calculated ground-state energies and mean atomic forces of the three reported crystal structures of the P-monoclinic form of carbamazapine after relaxation of the hydrogen positions[a]**

CCSD structure	ground state energy/eV	mean force/eV Å^{-1}	
		backbone	hydrogens
CBMZPN01	−14 050.962	0.5282	0.0104
CBMZPN02	−14 050.902	0.6228	0.0085
CBMZPN10	−14 051.167	0.5369	0.0070

[a] The calculations were performed with the fully periodic planewave-pseudopotential method.

single peaks for the amide carbon militates against the possibility that the asymmetric unit consists of two half-molecules in these cases. The situation for the two monoclinic forms is not so clear. The resonances of the triclinic form are more complex; in particular, five lines are observed for the C6/C9 pair of carbons, three of them being of double intensity (and one of these showing an incipient splitting in a dipolar dephased spectrum, not illustrated), which suggested to us that there are eight crystallographically different sites for these carbons, i.e., four molecules in the asymmetric unit. Since we made this observation, this suggestion has been confirmed by a single-crystal X-ray study.[10]

Whilst there are clear differences between the spectra of all the forms studied, it is difficult to make quantitative comparisons because of the overlap of signals from the predominant aromatic carbons and the broadening influence of the quadrupolar nitrogens. However, it can be said that the carbonyl signal shows a small but significant variation from 158.4 to 159.9 ppm. The average shift for C1 and C14 varies a little more widely, from 137.9 to 140.9 ppm. This pair of carbons is the only one to provide crystallographic splittings from all of the forms; these are notably constant (between 1.7 and 2.0 ppm) with the exception of the P-monoclinic form (splitting 3.1 ppm).

Shielding Computations

Computations of the shielding for the P-monoclinic form of carbamazepine were undertaken using the planewave pseudopotential[47] formalism and the GIPAW method,[37] which takes explicit account of the repetition inherent in a crystal lattice. The three separate independent determinations of the crystal structures for this polymorph available in the Cambridge Crystal Structure Database (CCSD) were used as starting points. As is our recommended practice, the hydrogen atoms (only) in the structures were first allowed to relax their positions. Table 2 lists the ground state energies, the mean forces on each backbone atom and the mean forces on each hydrogen atom for structures CBMZPN01, CBMZPN02, and CBMZPN10 after relaxation. As expected, these differ only a little between the structures. As we find the CBMZPN10 structure to have the lowest ground-state energy we focus on this structure and report the calculated isotropic shielding constants in Table 3.

Comparisons with the experimental data are limited because only carbons 15, 1/14, and 6/9 can be definitively assigned for the P-monoclinic form, though the C3/12 resonance is probably at 127.3 ppm. Agreement with experiment appears to be moderately good. As with previous investigations of molecular crystals,[5] the carbonyl carbon shows the largest deviation from experiment (3.9 ppm). The shift difference between the C15 and C1/C14 signals is computed to be 19.46 ppm whilst experimentally it is 20.2 ppm. Similar results for the C15 to C6/9 shift difference are 22.28 and 24.3 ppm. The total spectral range predicted by the computations is 30.0 ppm, which is comparable to the experimental value of 31.7 ppm. A more valuable test lies in comparing data for "crystallographic splittings", i.e., those arising from nonequivalence caused by lack of molecular symmetry in the crystalline state. For C1/14, the computed splitting is 3.1 ppm (observed 3.3 ppm) whilst for C6/9 it is 0.7 ppm (unresolved in the spectrum and so <1 ppm). The C1/14 result is particularly interesting since it suggests we can use the computations to assign shifts to the geometry of the molecule in the solid state. Thus we assign the peak at 137.3 ppm in the spectrum of the P-monoclinic form to C1 as shown in scheme **I** (i.e., the carbon near to the NH_2 group), whereas that at 140.4 ppm is assigned to C14 (i.e., the carbon near to the carbonyl oxygen atom). The severe overlapping of peaks in the region below 133 ppm prevents any detailed comparison between experimental and computed values.

Table 3. **Calculated isotropic chemical shifts for the P-monoclinic form of carbamazepine (CBMZPN10)[a]**

carbon number	chemical shift/ppm
15	155.1
14	142.2
1	138.9
9	136.3
6	135.6
8	134.0
10	133.2
7	133.1
5	129.7
13	129.0
3	129.0
4	126.5
2	126.2
12	125.7
11	125.1

[a] The calculation used the hydrogen optimised geometry with the fully periodic GIPAW method. The chemical shifts were obtained from the computed shielding constants using a reference shielding of 169.5 ppm obtained from previous work on molecular crystals.[5]

To study the effect of amide torsion of carbamazepine on the ^{13}C chemical shifts, calculations were performed using Gaussian 98. Figure 2 shows the results. The crosses represent carbon atoms on one ring, and the triangles represent carbon atoms on the other ring. It is clear that the shielding of the nearest carbons to the C15−N1 bond, namely 1, 14, 2, and 13, together with C-15 itself, are most affected by internal rotation about that bond.

An important issue in the study of polymorphism is the extent to which a change in molecular geometry, between the gas phase and the solid-state configuration, can be accommodated in optimising the molecular packing forces. Clearly, calculations of shielding for both an isolated molecule of carbamazepine and molecules treated within a

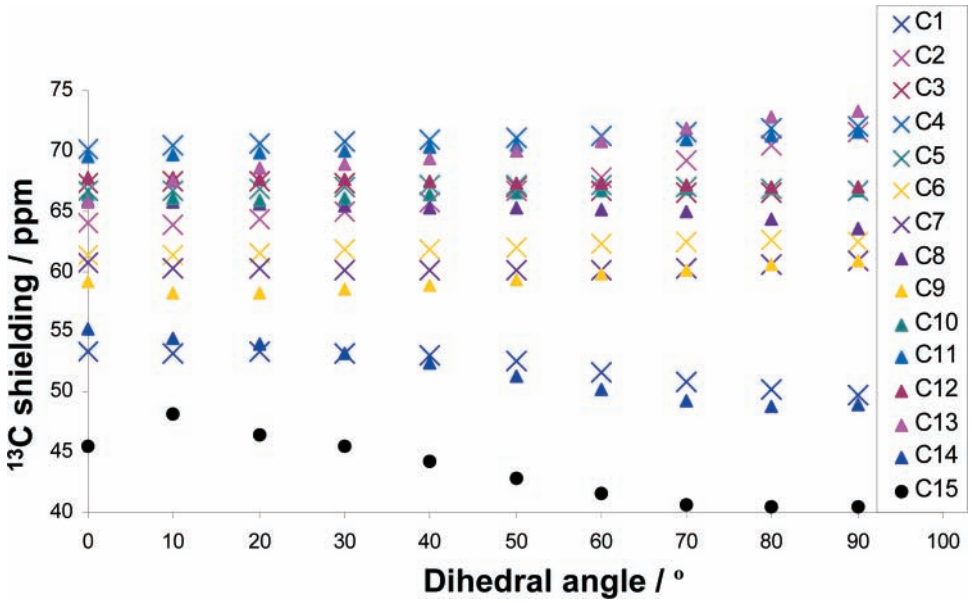


Figure 2. **Effect of amide torsion angle (defined as N2−C15−N1−C14) on the chemical shift of an isolated molecule of carbamazepine, computed using the Gaussian 98 program.**

fully periodic formalism are valuable when attempting to resolve the relative importance in determining observed chemical shifts of, respectively, changes in molecular geometry and intermolecular interactions. The molecular geometries determined, respectively, for the P-monoclinic and trigonal phases were examined for any significant differences. It was noted that for the P-monoclinic and trigonal forms of carbamazepine the difference in the torsion angle C15−N1−C14−C9 that describes the orientation of the carboxamide group is ca. 13°, whereas the difference in the torsion angle N2−C15−N1−C14 (that varied in the shielding computations) is ca. 5°. A reaction coordinate calculation was performed using MOPAC with the AM1 method in which the torsion angle C15−N1−C14−C9 was varied from 80° to 140°, with full relaxation of the other degrees of freedom describing the molecular structure. The calculation indicated that a change in this torsion had a minimal impact on the calculated heat of formation <4 kJ/mol. Hence it can be concluded that this parameter is, potentially, labile and can be affected significantly by the requirement to optimise the intermolecular interactions.

Crystal Structures

We find the structure of the dihydrate to be monoclinic (space group $P2_1/c$). The asymmetric unit comprises one complete carbamazepine molecule (in agreement with the NMR spectrum) and two water molecules. The structure, like those of the anhydrous carbamazepine polymorphs, contains dimers of carbamazepine molecules related via a crystallographic inversion centre and linked via a pair of N−H···O hydrogen bonds. A network of hydrogen bonds, involving the remaining sites of the amido group and the water molecules, links dimers into a double layer, parallel to the crystallographic (0 1 0) plane, as shown in Figures 3 and 4. Note that all the hydrophilic parts of the structure are sandwiched within the layer, while the layers contact each other by hydrophobic parts of carbamazepine molecules and

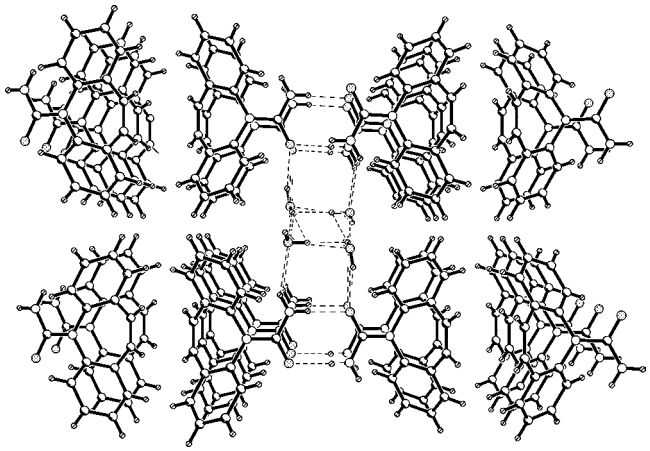


Figure 3. **Hydrogen-bonded network of carbamazepine dihydrate, showing the stacking of the carbamazepine molecules.**

therefore are held together only by van der Waals interactions. Water molecules occupy channels, running inside the layer in the directions parallel to the crystal axis *c*. Each channel contains four parallel (and cross-linked) chains of water molecules.

Previous studies of carbamazepine dihydrate[23,48] (one of which is in the Cambridge database with code FEFNOT) solved the structure in the orthorhombic space group *Abam* (an alternative setting of *Cmca*), with half of carbamazepine molecule and one water molecule per asymmetric unit. This implied the carbamazepine molecule was bisected by a crystallographic mirror plane, with the amido group disordered between two orientations which differ by a 180° rotation around the N1−C15 bond. However, swapping the acceptor (O) and donor (NH_2) of hydrogen bonds requires a concerted rotation of *all* amido groups and *all* water molecules in a whole layer, or at least in a whole chain of dimers (parallel to the *a* axis), as shown in Figure 4, left. Therefore the mirror plane is only a statistical artifact,

(48) Griesser, U. J. Ph.D. Thesis, 1991.

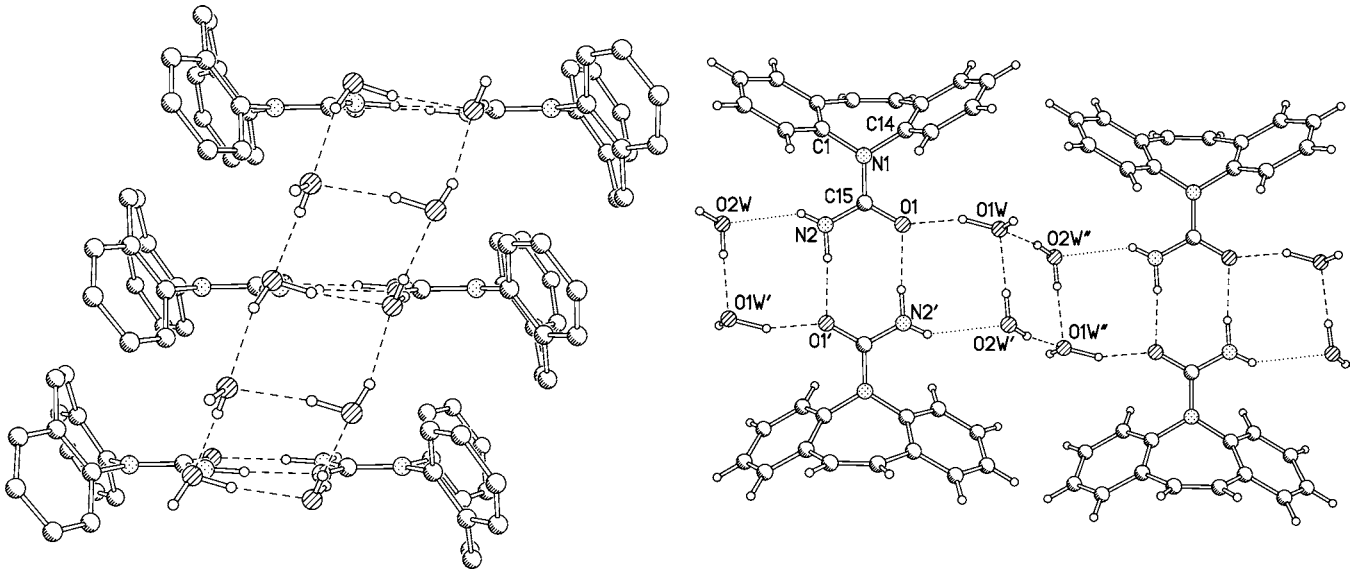


Figure 4. **A more detailed picture of the carbamazepine dihydrate hydrogen-bonded network, viewed down the *a* axis (left) and projected onto the (1 0 0) plane (that is, the twinning plane) (right).**

resulting from chains of opposite polarity being distributed throughout the crystal. Each individual molecule, dimer, and their local environment have no mirror symmetry, just as the case in the monoclinic structure.

In fact, the monoclinic lattice that we found, can be converted by the transformation

$$\begin{pmatrix} 0 & -1 & 0 \\ -1 & 0 & 0 \\ -1 & 0 & -2 \end{pmatrix}$$

into a *pseudo*-orthorhombic lattice of twice the volume, with the parameters very similar to those of FEFNOT (a = 28.839(9) Å, b = 4.924(2) Å, c = 19.748(5) Å at room temperature). The discrepancy factor between Laue equivalents, R_{int}, was not very much higher than that for the monoclinic setting (0.147 against 0.089). However, whilst in our case the β and γ angles of the lattice in the "orthorhombic" setting approached 90° within 0.01−0.02°, α showed an irreducible deviation by 0.4°. Furthermore, the least squares refinement of the orthorhombic cell was somewhat unstable. Although the structure could be solved in the orthorhombic space group and the results (including the mode of disorder) were similar to those of FEFNOT, the refinement was rather unsatisfactory, with the conventional $R > 0.10$. It is noteworthy that both previous studies also resulted in high *R*-factors and other unsatisfactory features.

An alternative explanation can be a pseudo-merohedral twinning of the monoclinic crystal by the twin law:

$$\begin{pmatrix} -1 & 0 & -1 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix}$$

that is, by reflection in the mirror plane perpendicular to the *a* axis (equivalent to the spurious mirror plane in the orthorhombic model). Indeed, a correction of reflection intensities on assumption of such twinning (see Experimental Section) much improved the results in our refinement, confirming the original hypothesis. We found the twin component contributions to relate as 5:1, while the previous studies probably dealt with 1:1 twinning, more perfectly emulating the orthorhombic symmetry. It can be argued that the distinction between disorder and twinning is essentially one of *scale*. A symmetrical disorder on a molecular level produces indisputably a new structure, i.e., a polymorph. At the opposite extreme is the situation where twin components are optically observable and can even be separated mechanically, but this is not so in our case. A careful investigation with a polarizing microscope failed to identify the component crystals of twins or boundaries between them. It is likely, therefore, that the twinning occurs on a microscopic level (multiple micro-twinning or penetration twinning). The distinction between such twinning and domain-type disorder (with domain sizes of tens to hundreds of Å) is a subtle one, and it is not impossible that we have encountered a borderline example. However, in the absence of any experimental data on the boundary dimensions, this remains a speculation.

Of course, given the nature of the hydrogen-bonded dimers, disorder among them is not surprising. However, we have no corroborating evidence of disorder. The NMR clearly shows the asymmetric unit is a full molecule, but of course the local environment within the dimers dominates the chemical shifts. The NMR evidence proves that if rotational disorder of the amide group exists for the dihydrate, it must be spatial in nature, not dynamic; i.e., internal rotational rates about the C15−N1 bond must be less than the NMR time scale (lifetimes > ca. 5 ms). It should be stressed that there were no discernible differences between the ^{13}C spectra of samples providing monoclinic and orthorhombic structures. The existence of two more-or-less identical structures differing only in order/disorder (the latter requiring a superlattice of the former) is most unlikely.

We also initially obtained an orthorhombic space group from other samples of carbamazepine dihydrate but were then able to refine the X-ray results in terms of the $P2_1/c$ structure,

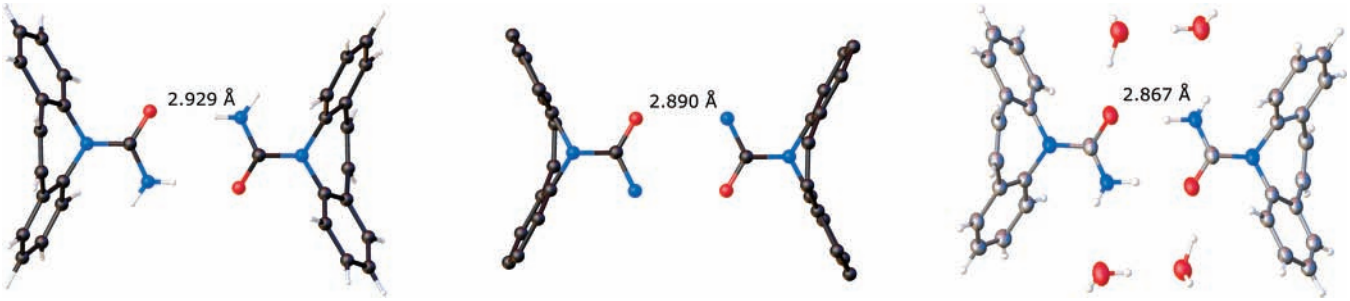
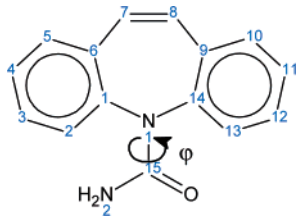


Figure 5. **Carbamazepine dimers in (left) the P-monoclinic form, (centre) the trigonal form, and (right) the dihydrate.**

Table 4. **Some key molecular angles in the forms of carbamazepine[a]**



		intramolecular angles[a]			
structure	database code	α[b]	β	γ	δ
triclinic[c]	CBMZPN11 (O1)	−179.6	−17.7	55.0	70.7
	CBMZPN11 (O2)	−176.8	−15.2	54.1	71.2
	CBMZPN11 (O3)	−175.7	−11.8	54.9	69.2
	CBMZPN11 (O4)	−176.7	−15.9	55.1	71.9
P-monoclinic	CBMZPN01	−170.6	2.2	53.4	61.4
	CBMZPN02	−170.4	1.8	53.3	62.9
	CBMZPN10	−170.7	1.6	53.3	61.5
trigonal	CBMZPN03	−176.1	−13.4	55.2	70.3
C-monoclinic	CBMZPN12	−172.4	−7.5	49.8	68.1
dihydrate	this work	179.6(3)	0.9(5)	55.8(1)	54.5(1)

[a] The angles are defined as follows (see also Figure 6): φ, torsion angle C14−N1−C15−N2; β, torsion angle C1−N1−C15−N2; γ, dihedral angle between benzene rings; δ, dihedral angle between N2, O1, C15, N1 and C1, C6, C9, C14 planes. [b] The signs are given in relation to Figure 6 and of the molecule given as the asymmetric unit in the cif file. [c] Four independent molecules.

as discussed herein but with 50/50 twinning. We have studied and are still studying this twinning phenomenon in more detail. The results will be published in a relevant journal dedicated to crystallography, since further discussion is not appropriate in the present article.

Further Discussion

All the structures of the carbamazepine forms show hydrogen-bonded dimers, with a centre of inversion between the two molecules, as illustrated in Figure 5. The distance between the hydrogen-bonded oxygen and nitrogen atoms varies over a range of 0.047 Å. Some key angles, in the carbamazepine molecules forming the dimers, which may influence the NMR chemical shifts, are listed for all the anhydrous forms and the dihydrate in Table 4 (see also Figure 6). It can be seen that the angle between the phenyl rings (γ) is remarkably constant (between 53.3° and 55.7°), with the notable exception of the C-monoclinic form (49.8°). Likewise, the amide group is always closely planar. The quaternary atoms C1, C6, C9, and C14 are also coplanar or very nearly so. However, the torsional angles (φ and β) vary substantially, the P-monoclinic form showing a particularly low magnitude for β. The data in Table 4 imply that the environment of N1 varies widely in its departure from planarity, the angle $\varphi-\beta$ involving bonds C1/N1 and C14/N1 ranging from 160.8° to 180.8°. For the dihydrate, the N1 environment is notably planar and coplanar with the amide group. The actual ring angle at N1 lies within the narrow bounds 116.1° to 117.5° in the various forms, whereas the hinge angle (δ) varies widely, from 61.4° to 71.9°, with an outlier of 54.6° for the dihydrate. [This angle is closely related to, though not identical with, the torsion angle C15−N1−C14−C9 identified as labile by the MOPAC computations.]

Remarkably, the trigonal form has the crystal volume per molecule of 318 Å^3, compared to 291−293 Å^3 for the other forms. Having examined the crystal packing of the trigonal form, we note that the structure contains infinite channels, coaxial with the 3-fold axes, with the diameter of over 5 Å (the shortest cross-channel distances H···H of 7.6 Å minus twice the van der Waals radius of H, 1.1−1.2 Å), enough to accommodate small solvent molecules, such as water, methanol, acetonitrile, etc. Given the near-uniform width of the channels and hydrophobic nature of their walls, solvent molecules can be both statically and dynamically disordered along the channel, without affecting either the X-ray diffraction or the (solid-state) NMR patterns substantially. The solvent-accessible voids comprise 428 Å^3 per unit cell (or 7.5% of the total volume). Without solvent, the structure has a space-filling coefficient $\rho = 0.645$. It is well-known[49−51] that, at ambient conditions, ρ of molecular crystals usually lies between 0.65 and 0.77, whilst crystal structures with lower ρ are unstable and tend to transform into a denser polymorph or, if possible, enclose solvent molecules in the voids. Thus we can hypothesize the trigonal form of carbamazepine may readily contain nonstoichiometric quantities of water or some other small solvent molecules.

Whilst we can speculate on the NMR chemical shifts, it is difficult to relate the small observed differences between forms to molecular geometry variations without more precise signal assignments. However, it is clear from the Gaussian computations that the dihedral (torsion) angle φ has a potentially significant influence and from the crystal structures that other geometric factors are likely to be important.

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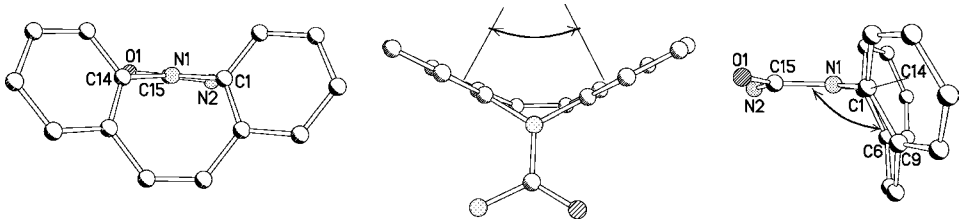

Figure 6. **Definitions of the angles reported in Table 4: (left) angles φ and β; (centre) angle γ; (right) angle $(180^\circ - \delta)$.**

It is an open question whether intermolecular effects need to be taken into account. It is interesting to note that the unusually large C1/C14 crystallographic splitting of 3.1 ppm for the P-monoclinic form correlates with the notably low hinge angle δ. However, such a correlation is not obvious for the dihydrate, which has an even lower hinge angle (though perhaps there is compensation from the planarity around N1 for this form). More insight may arise from fully periodic computations with improved functionals for all the forms with known crystal structures and for notional variations in the hinge angle and departure from planarity at N1. We do intend to pursue this line of enquiry in due course, but it is a major project which will take considerable time.

In conclusion, it can be stated that, although the molecular geometries of the forms of carbamazepine are closely similar, all seven can be clearly distinguished by their ^{13}C MAS NMR spectra, which show (by crystallograpic splittings) that all forms except the triclinic have one complete formula unit in the asymmetric unit, whilst the triclinic form has four, in agreement with past and recent diffraction results. In particular, the dihydrate has a full formula unit, which is inconsistent with the disorder reported in the reported orthorhombic structure in the literature, if dynamic (but not if static). Our reinvestigation of this structure shows it to be monoclinic rather than orthorhombic. The discrepancy with the literature is thought to arise from the common occurrence of micro-twinning. Various computations have shown the effects of torsional variations on chemical shifts, and those carried out using the fully periodic planewave/pseudopotential methodology offer promise of being able to predict and/or explain shift differences between analogous atoms in different independent molecules in the unit cell.

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Supporting Information Available

Crystal and structural data for carbamazepine dihydrate in pdf and cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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