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The Crystal Structure of Anhydrous β-Caffeine as Determined from X-ray Powder-Diffraction Data

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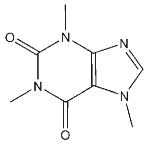
Abstract: The crystal structure of the low-temperature form of anhydrous caffeine has been determined by using X-ray powder-diffraction data with a combined simulated-annealing/Rietveld method. Anhydrous caffeine crystallises with five crystallographically independent molecules in a monoclinic *C*-centred unit cell with dimensions of $a=43.0390(17)$, $b=15.0676(6)$ and $c=6.95314(14)$ Å and a β angle of 99.027(2)°.

Keywords: caffeine · organic crystals · real-space methods · structure elucidation · X-ray diffraction

Introduction

Despite the widespread use of caffeine, it still has the ability to surprise, mostly in relation to its biological activity[1] including the recently discovered genetic disposition of humans to the compound.[2] In addition, the solid-state crystal structures of caffeine remain, at least in part, mysterious even after almost 50 years of investigation.



caffeine

Caffeine crystallises from aqueous solutions as the monohydrate, the crystal structure of which was first determined by Sutor in 1958.[3] This monohydrate rapidly loses water and even under careful experimental conditions the crystal structure contains only 0.84 water molecules per caffeine molecule (based on the least-squares refinement).[4]

At room temperature and relative humidity (below 60%) the monohydrate converts quantitatively to the anhydrous β form of caffeine. The dehydration process has been investigated extensively and a mechanism has been postulated in which water leaves the crystal through the channel structure, whereas optical microscopy suggests that the mechanism involves simultaneous re-nucleation of caffeine into the anhydrous form.[5–7] Consequently, the single crystals are destroyed during this dehydration process. The structure of the resulting anhydrous form has already been speculated upon by Cesàro and Starec[8] and recently a detailed computational study provided further insight into the aggregation of caffeine in the solid state.[9] Upon heating anhydrous caffeine above 150 °C, a further phase transition is observed that yields the α form of caffeine.[10] After the sample is cooled to room temperature, this α form is metastable and remains unchanged in sealed containers for prolonged times. Mechanical pressure in the form of grinding or tabletting initiates the conversion of α-caffeine into β-caffeine.[11] The different crystal forms of caffeine have been characterised previously by means of X-ray powder diffraction and lately a new diffraction pattern has been added to the ICCD database that shows additional peaks in the powder pattern of the β phase, without indexing the pattern.[12] The high-temperature α phase is characterised by a much simpler powder-diffraction pattern, which is compatible with rhombohedral metric symmetry of the unit cell. The high symmetry of the α phase was noticed by Cesàro and Starec[8] and very recently its crystal structure was solved by using X-ray powder diffraction.[13] However, the crystal structure of the anhydrous, low-temperature form remains elusive; although, Edwards et al. reported an attempt to solve the crystal structures of the two anhydrous forms from powder-diffraction data in their paper on the re-determination of the crystal structure of caffeine monohydrate.[4]

With the advent of novel powerful methods for the collection of high-resolution powder-diffraction data and the introduction of powerful algorithms to solve crystal structures

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in direct space, previous problems are now within reach of being solved.[14–22] In the present work, these new tools were applied to the long-standing problem of solving the crystal structure of the β form of caffeine, and a model of the crystal structure that is consistent with X-ray diffraction data is presented.

Results and Discussion

To establish the absence of any phase mixtures, commercially available caffeine was subjected to X-ray powder diffraction at room temperature and at elevated temperatures. In addition, a control experiment was carried out in which caffeine was recrystallised from an aqueous solution. The powder diffractograms obtained were all in agreement with patterns published previously, and during heating the expected phase transitions were observed. High-quality powder-diffraction data were subsequently collected by using $Cu_{K\alpha 1}$ radiation.

The powder pattern of β-caffeine could be indexed completely by using the program TREOR,[23] which gave a unit cell with dimensions of $a=42.405$, $b=15.029$ and $c=6.938$ Å and angles of almost 90°. From the absence of all $h+k+l=2n+1$ reflections, a body-centred unit cell was inferred. However, profile fitting (Le Bail method) of the powder pattern under the constraint of an orthorhombic unit cell resulted in unacceptable differences between the observed and calculated profiles, although a good χ^2 value of 1.9 could be achieved. Lowering the symmetry to monoclinic improved the agreement considerably to give an χ^2 value of 1.4. From the systematic absences of the *hkl* reflections it was not possible to deduce whether a primitive or a centred unit cell is present. Additionally, several space groups were possible, for example, *Pc*, $P2_1/c$, *Cc* or *C*2/*c*, which could not be assigned unambiguously from the powder data.

Fortunately, this dilemma could be solved by investigating a microcrystal found serendipitously in a recrystallisation batch. This crystal yielded the same unit cell dimensions as the indexed powder pattern, and moreover, it was possible to unambiguously identify the Laue symmetry and monoclinic axis. After transformation from monoclinic *I* to monoclinic *C*, the extinction symbol was found to be *C*1*c*1, which would be in agreement with either space group *Cc* or *C*2/*c*. The large volume of the unit cell and the small molecular volume means that the number of molecules per unit cell cannot be reliably deduced by means of the 18 Å^3-per-atom rule. However, through careful pycnometric measurements of the density of solid anhydrous caffeine, a density of $\rho=1.483(10)\,\mathrm{Mg\,m^{-3}}$ was determined, which is in agreement with the value reported by Cesàro and Starec[8] ($\rho=1.50(1)\,\mathrm{Mg\,m^{-3}}$), and with that recently obtained by using transitiometry ($\rho=1.47\,\mathrm{Mg\,m^{-3}}$),[24] but differs from that reported by Edwards et al.[4] From the density and the unit-cell volume, a total of 20 molecules per unit cell was calculated. Based on this information the space group was assigned as *Cc*, because the point-group symmetry of caffeine is C_s, which is not compatible with any special position in *C*2/*c*. However, occupation of a special position would be required to fit 2.5 molecular formula units into the asymmetric unit.

A model of the molecular geometry was constructed, based on the single-crystal structure of the monohydrate, for solving the structure by using the program TOPAS.[25] Five independent molecules were placed at arbitrary positions and in arbitrary orientations in the unit cell and treated as rigid bodies. A least-squares minimisation routine (based on the Rietveld technique[26]) was used to refine this model until convergence was achieved, before random shifts by means of a simulated annealing process were applied to the positions and orientations. During the minimisation, rotational parameters and positional parameters of the rigid bodies and a scaling factor were refined. Profile and background parameters were kept fixed at values obtained from a Le Bail fit to speed up the calculations. This minimisation was followed by further least-squares cycles after each new model had been generated by using the Monte Carlo mechanism. All calculations were done in real space by using step intensities without any preceding intensity extraction. Each of the minimisation cycles are real Rietveld refinements, which allow the positions of rigid bodies to be allocated even if the Monte Carlo model generated is rather different from the correct positions. This represents a unique feature of the chosen software because very complex structures can be tackled by using this procedure. The procedure was repeated until the minimisation routine had converged more than 15000 times. The resulting best model was used for further calculations. To test that the minimum found was correct, individual molecules were rotated by 180° along the molecular axis—because the molecular shape of the caffeine molecule mimics C_s symmetry, with the exception of the *N*-methyl group that is attached to the five-membered ring—and the minimisation process was repeated. No lower minima were found during these calculations. The model was used to perform a final Rietveld refinement by refining all necessary structural and profile parameters. Observed, calculated and difference powder patterns are shown in Figure 1.

The crystal structure of anhydrous caffeine viewed along the *c* axis is shown in Figure 2. The hydrogen atoms, which were included in the structure factor calculations in fixed positions that correspond to the monohydrate, have been omitted and only one layer of molecules is shown. The next layer is generated through the *c*-glide plane in such a way that the projection of the mirror image of each of the five molecules can be directly superimposed onto its counterpart. The resulting columns of caffeine molecules are parallel to the *c* axis and the normals of the molecular planes of the caffeine molecules within each column are tilted in the *a*,*c* plane (Figure 3). The crystal structure obtained from this experiment resembles the predicted structure of β-caffeine in many ways.[9] Setting the axes to space group *Ia* results in a unit cell whose metric symmetry is almost orthorhombic, and which might be considered the 5×1 supercell of the one

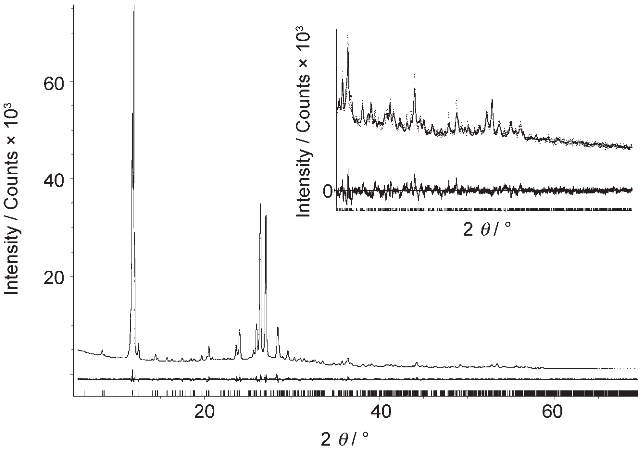

Figure 1. Final Rietveld plot of the low-temperature phase of anhydrous caffeine. Observed intensities are shown as dots, and the calculated diffraction pattern is shown as a continuous line (upper trace). The difference pattern is shown in the lower trace and positions of Bragg peaks are indicated by short vertical bars. The inset shows the 2θ range 35–70° with counts scaled by a factor of ten.

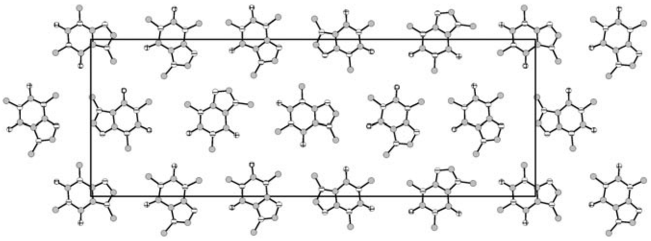

Figure 2. The crystal structure of the low-temperature form of anhydrous caffeine viewed along the *c* axis, with hydrogen atoms omitted. The *a* axis is oriented horizontally and the crystal packing along the *c* axis has been truncated to include only molecules whose geometrical centre lies in the range $0.3 \leq z \leq 0.8$.

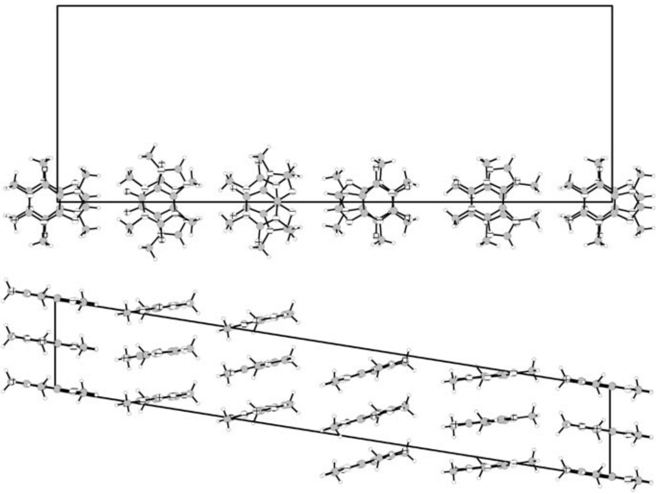

Figure 3. Formation of molecular stacks parallel to the *c* axis; the vertical distance between the centroids of the molecules is equivalent to $0.5c = 3.477$ Å. The viewing directions are along the *c* axis (top) and along the *b* axis (bottom); the *a* axis lies in the plane of the page.

found through energy minimisation by Gavezotti and Carlucci.[9] Both the predicted crystal structure and that obtained experimentally include stacks of molecules (Figure 4), however, all the low-energy forms of the predicted crystal structures exhibit caffeine molecules oriented in an anti-parallel fashion, whereas this motif is absent in the experimental structure. To obtain anti-parallel stacks of molecules by utilising the *c*-glide plane symmetry element, the molecular axis would have to align parallel to the *b* axis. Figure 2 shows that in the experimental structure the molecular axes of the five independent molecules are aligned between 45 and 90° to the *b* axis, which yields stacks of molecules that are oriented in an almost parallel fashion.

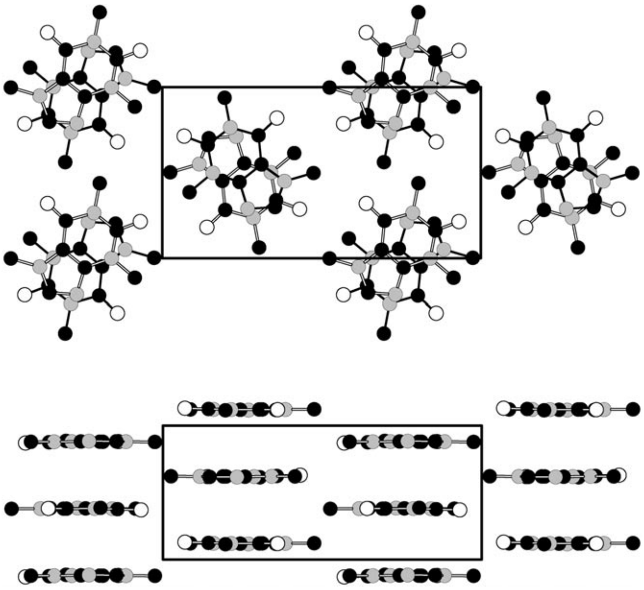

Figure 4. Predicted orthorhombic crystal structure of anhydrous caffeine according to Carlucci and Gavezotti.[9] Although a comparable intermolecular spacing along the stacking direction is observed in both model and experiment, the experimental crystal structure is not characterised by anti-parallel dimers of caffeine molecules as proposed in the theoretical study.

The crystal-packing structure obtained by means of the Rietveld refinement contains a small number of short C⋯C, C⋯N and C⋯O contacts, which are up to 0.6 Å shorter than the sum of the van der Waals radii. These contacts must be attributed to errors remaining in the molecular orientations of the five independent rigid bodies. There has been no attempt to include further penalty restraints in the Rietveld refinement, either as a hard sphere or through a Lennard-Jones-type potential. Given the good convergence of the stable Rietveld refinement, it is unlikely that a better agreement between the calculated and the observed powder pattern would have been obtained. Instead, the remaining discrepancies between the observed and the calculated powder patterns prompted the consideration of a disorder model, possibly in space group *C*2/*c*. Although no evidence was found for the latter space group, the agreement between the calculated and the observed powder patterns could be substantially improved through the introduction of another five rigid bodies that are tied to the existing molecules through a unity occupancy constraint. The procedure used to find the positions of the disordered molecules is comparable to the one described above. The positions of the disordered molecules were refined individually by using the combined simulated-annealing/Rietveld technique. The disorder parameter for individual pairs of molecules varies between 15 and 36%. Although this disorder model led to a further reduction of the differences between the observed and calculated diffraction patterns, this structural model was not pursued further. There are several reasons for questioning this structural model. Firstly, refining ten independent rigid bodies has not been sufficiently validated for treatment by the Rietveld method owing to the complexity of the problem. The wide range of occupancies for the five pairs of caffeine models is questionable, and the individual pairs do not occupy spatially closely related sites, but distribute themselves over the whole unit cell. Finally, all samples of anhydrous caffeine display superimposable diffraction patterns after re-formation of the low-temperature phase from the high-temperature phase. The initial formation of the anhydrous low-temperature phase from the monohydrate may very well lead to complex disordered crystal packing, whereas it is unlikely that the same highly disordered crystal packing is reconstituted from the highly symmetric high-temperature phase.

Conclusion

The main conclusion of this work is that the previously unknown unit cell of the low-temperature form of anhydrous caffeine was found and determined unambiguously. A structural model for the β form has been postulated based on an alternating direct space structure solution and Rietveld refinement by using TOPAS. The possibility of an even more complicated structure that may include a modulated (incommensurate) structure remains.

Experimental Section

General: Caffeine was obtained from Merck (Darmstadt, Germany). Batches of caffeine monohydrate were recrystallised from hot aqueous solutions. Diffractometer data for structure solution were collected by using a Bruker D8 Vario1 instrument with $\mathrm{Cu}_{K\alpha 1}$ radiation and a positional sensitive detector (Braun). Data were collected in Debye–Scherrer geometry on a sample in a 0.3 mm capillary. During data collection at room temperature the capillary was rotated.

The density of caffeine powder was measured in *n*-heptane at 295 K. A 25 mL pycnometer was filled four times with caffeine (approximately 1.5 g). Trapped air was removed ultrasonically. The density determined was $\rho = 1.483(10)\ \mathrm{Mg\,m^{-3}}$.

Crystal data: $C_8H_{10}N_4O_2$; $M_r = 194.20$; $a = 43.0390(17)$, $b = 15.0676(6)$, $c = 6.95314(14)$ Å; $\beta = 99.027(2)°$; $V = 4453.2(3)$ Å^3; $T = 298$ K; $\rho = 1.44824(9)\ \mathrm{Mg\,m^{-3}}$; $\lambda = 1.540598$ Å; space group *Cc* (no. 9); $Z = 20$. Rietveld refinement, which included 6 background parameters, 10 profile parameters and a total of 56 independent parameters, yielded the following background-corrected agreement factors (%): $R'_{\mathrm{exp}} = 2.76$, $R'_{wp} = 5.70$ and $R'_p = 4.33$, with the corresponding values of $R_{\mathrm{exp}} = 1.91$, $R_{wp} = 3.94$ and $R_p = 2.88$ obtained without background subtraction. $R_{\mathrm{Bragg}} = 1.07$, and a goodness-of-fit of 2.07 were reached by using 987 reflections within the 2θ range of 5.50 to 70.00°.

Acknowledgements

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