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Direct-space structure solution from laboratory powder diffraction data of an organic cocrystal: 1,2,3-trihydroxybenzene–HMTA (1/1)†

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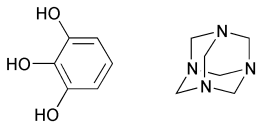
The crystal structure of an organic cocrystal, 1,2,3-trihydroxybenzene–hexamethylenetetramine (1/1), has been solved from conventional laboratory X-ray powder diffraction data that are significantly affected by preferred orientation, using a direct space structure solution approach based on the Monte Carlo method.

A sound knowledge and understanding of the role that intermolecular forces play in supramolecular assembly is generally obtained from systematic crystallographic studies. Where crystals are available of suitable quality for single-crystal diffraction, these techniques remain the method of choice. However, when no such material is available, this valuable structural information can often be obtained from powder diffraction data.

The use of X-ray powder diffraction for *ab initio* structure determination of purely organic molecular solids is a rapidly expanding field, mainly due to the considerable advances in the development of direct space methods of structure solution.[1–6] Here we report the first application of such a method to the structure determination of an organic cocrystal containing two different molecular building blocks, the 1 : 1 adduct of 1,2,3-trihydroxybenzene [$C_6H_3(OH)_3$; pyrogallol **1**] and hexamethylenetetramine [$(CH_2)_6N_4$; HMTA **2**] from conventional laboratory powder diffraction data. Despite the presence of two different molecular components in the structure and evidence of significant preferred orientation in the data, the Monte Carlo method employed here smoothly generated a starting structure for Rietveld refinement. This structure determination demonstrates both the power of this technique as a tool in the systematic study of intermolecular interactions and as an emerging force in the field of crystal engineering, and the feasibility of using lower resolution powder data collected using laboratory-based powder diffractometers rather than relying on the availability of synchrotron radiation for solving structures with this degree of complexity.



1 **2**

Previous studies have used single-crystal X-ray diffraction to explore the use of bis- and tris-phenols in crystal engineering and the interaction of this type of phenol, acting as a hydrogen bond donor, with HMTA as a hydrogen bond acceptor.[7] However in the case of pyrogallol–HMTA (1/1), investigation of the crystal structure was carried out using powder diffraction data. This type of material is an ideal target for the direct space structure solution technique as it is the organization of these well-defined building blocks within the crystal structure that is of greatest importance.

The direct-space methods approach structure solution by postulation of trial crystal structures constructed from known molecular connectivity, independently of the powder diffraction data. The trial structures are generated by movement of a structural model around the unit cell including variation of molecular conformation when required, and each structure assessed by comparison between the corresponding calculated diffraction pattern and the experimental diffraction data. The structure solution, or global minimum, is then located using a global optimization strategy such as Monte Carlo[2,6] (the method used here), simulated annealing[3,5] or genetic algorithm techniques.[4]

In the application of direct space structure solution methods, the presence of more than one molecule in the asymmetric unit makes the problem more complex in terms of the number of degrees of freedom (*i.e.* the number of structural parameters varied to generate new trial crystal structures), and to an extent, the effect on *R*-factor discrimination. There are few examples of such materials solved from powder diffraction data using the direct space structure solution approach,[8] a situation made more complicated here due to the presence of two entirely different molecules in the cocrystal with the location of each molecule in the unit cell being unique and non-superimposable. The exact hydrogen-bonded relationship between the molecules in this system was not predictable in advance.

The powder diffraction pattern was indexed on a monoclinic unit cell (space group $P2_1/n$) consistent with the presence of one molecule of each component in the asymmetric unit. Hence the structural model used in the Monte Carlo structure solution comprised a complete HMTA molecule and a pyrogallol molecule excluding the hydrogen atoms on the three hydroxyl groups. Both molecules were constructed using standard bond lengths and angles, and treated as rigid units during structure solution, although not in the subsequent refinement. Trial crystal structures were then generated by completely independent translation and rotation of the two molecular components within the unit cell. With more than one independent molecule required to define the structure, the number of degrees of freedom required for random movement is increased (from 6 to 12 in this case) without conformational flexibility being introduced. The calculation was run for 500000 Monte Carlo moves and R_{wp} was found to be typically 52–68% for most random structures whereas the best structure solution corresponded to an R_{wp} value of 18.9%. This solution was used as the starting model for a successful Rietveld refinement (Fig. 1).

Diffraction data had been collected in both disc and capillary geometries and it was clear from the difference in relative intensities of related peaks in these data that there was a significant degree of preferred orientation present. Although these effects were minimized by the use of the capillary data for both solution and refinement, variation of a preferred orientation parameter was still required in refinement.‡ In such cases, this distortion of the data often has a disastrous effect on traditional structure solution, whereas in our experience, direct-

† Electronic supplementary information (ESI) available: atomic coordinates and metrical parameters for 1,2,3-trihydroxybenzene–HMTA (1/1). See http://www.rsc.org/suppdata/cc/b0/b007189g/

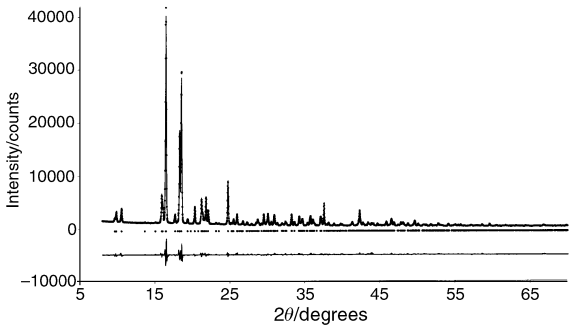


Fig. 1 Final observed (circles), calculated (solid line) and difference (below) X-ray powder diffraction profile for the final Rietveld refinement of pyrogallol–HMTA (1/1). Reflection positions are also marked.

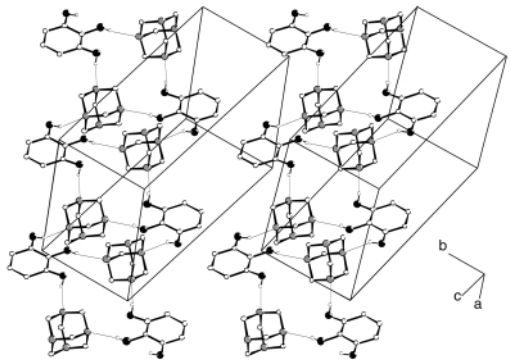


Fig. 2 Stereoview of the crystal structure of pyrogallol–HMTA (1/1) showing the alternating O–H···N rings generating a puckered molecular ribbon. Only hydrogen atoms involved in hydrogen bonding are shown and hydrogen bonds are indicated by thin lines. Intermolecular O···N distances are 2.90(1), 2.79(1) and 2.69(1) Å.

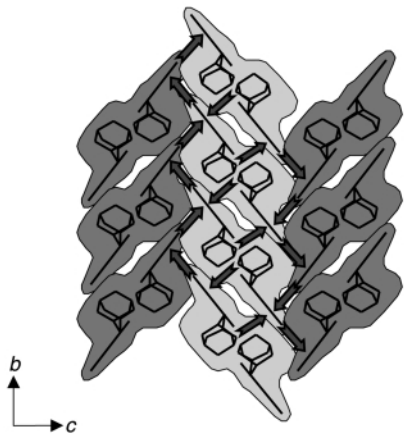


Fig. 3 A schematic diagram of the crystal structure of pyrogallol–HMTA (1/1) with each ribbon shown end-on and represented by a shaded area with the molecular units indicated by black lines. C–H···π(arene) interactions within each stack (light areas) and between neighbouring stacks (dark areas) are indicated by block arrows. C···π(arene) distances, *i.e.*: to the centroid of the ring, are 3.64(1) Å and 3.69(1) Å, respectively.

space methods appear to be more robust, presumably because a substantial amount of structural knowledge is included in the calculation through the use of a structural model.

In the structure, all three hydroxyl groups in the pyrogallol molecule act as hydrogen bond donors, and hence three N atoms in each HMTA molecule act as acceptors. This differs from the majority of systems, in which HMTA acts as a double acceptor of hydrogen bonds:[7] rather less frequently HMTA behaves as an acceptor of just one hydrogen bond, a full complement of four hydrogen bonds, or as in this case, of three hydrogen bonds.[7–9]

O–H···N hydrogen bonds are formed from the hydroxyl groups in the 1 and 3 positions linking alternating pyrogallol and HMTA molecules in a chain running parallel to the [100] direction. Pairs of these chains are linked by further O-H···N hydrogen bonds from the hydroxyl groups in the 2 positions to another N atom in each HMTA unit forming two distinct cyclic $R^4_4(18)$ motifs. The result is a lightly-puckered molecular ribbon running parallel to the [100] direction in which the HMTA cages lie alternately above and below the plane (Fig. 2). These ribbons are then linked into a continuous three-dimensional framework by C–H···π(arene) interactions. There are edge-to-face interactions between pyrogallol units in neighbouring ribbons, occupying one face of each ring: the other face of each ring is involved in a C–H···π(arene) interaction with a C–H bond from an HMTA unit in a neighbouring ribbon. The latter C–H···π(arene) interactions link sets of neighbouring parallel ribbons into columns stacked in the [010] direction, while those between the pyrogallol units link neighbouring stacks together to form a herringbone pattern (Fig. 3). Propagation of these two types of C–H···π(arene) interactions based on aromatic and aliphatic C–H bonds links all the parallel ribbons into a single bundle, so that the overall supramolecular structure is three-dimensional.

In this study we have shown that it is possible to determine the crystal structures of relatively complex materials such as cocrystals with multiple fragments in the structure solution process, from conventional laboratory X-ray powder diffraction data that is significantly affected by the presence of preferred orientation. The successful application of direct space techniques to the structure solution of materials containing a greater number of independent structural fragments or molecules with a considerable degree of conformational flexibility from powder data of this quality is clearly a possibility. Subsequent rationalization of the intermolecular forces in this system show an unpredicted network of both weak and strong hydrogen bonds, demonstrating the invaluable contribution that powder diffraction will have in improving our understanding of non-covalent forces and their role in crystal packing.

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Notes and references

‡ *Crystal data* for pyrogallol–HMTA (1/1), $C_{12}H_{18}N_4O_3$: M_r = 266.30, monoclinic, a = 10.7691(2), b = 7.0107(2), c = 16.7519(4) Å, β = 91.402(2)°, V = 1264.38(3) Å^3, space group $P2_1/n$ (no. 14), Z = 4, D_c = 1.39 g cm^{-3}, T = 273 K.

Sample preparation: a microcrystalline sample produced by crystallisation of a methanol solution containing equimolar quantities of **1** and **2**.

Data collection and Rietveld refinement: the powder diffraction data were collected on a Stoe STADI/P diffractometer using Cu-Kα_1 radiation, and a linear PSD. Data were measured over $5 < 2\theta < 75°$ in 0.02° steps for 15 h. In refinement, all atom postions (except the hydroxyl H atoms which were given calculated positions) were refined subject to soft constraints, and isotropic atomic displacement parameters (refined for non-H only) constrained according to atom type. Final refinement gave R_{wp} = 7.40%, R_p = 5.40% for 654 reflections and 117 parameters; preferred orientation fraction = 0.807.

CCDC 182/1828. See http://www.rsc.org/suppdata/cc/b0/b007189g/ for crystallographic files in .cif format.

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