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Maryjane Tremayne [a c], Elizabeth J. Maclean [b] & Christopher Glidewell [a]

[a] School of Chemistry, University of St Andrews, St Andrews, KY16 9ST, U.K.

[b] CCLRC Daresbury Laboratory, Daresbury, Warrington, Cheshire, WA4 4AD, U.K.

[c] School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

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Structure Solution of Hydrogen Bonded Molecular Solids from Powder Diffraction Data

MARYJANE TREMAYNE[a*], ELIZABETH J. MACLEAN[b] and CHRISTOPHER GLIDEWELL[a]

[a]*School of Chemistry, University of St Andrews, St Andrews KY16 9ST, U.K. and* [b]*CCLRC Daresbury Laboratory, Daresbury, Warrington, Cheshire WA4 4AD, U.K.*

The crystal structures of 2,4,6-triisopropylbenzenesulfonamide and the 1: 1 adduct of hexamethylenetetramine and 1,2,3-trihydroxybenzene have been solved from synchrotron and laboratory X-ray powder diffraction data respectively. The structures were solved by application of a direct space structure solution approach using the Monte Carlo method and confirmed by Rietveld refinement. In the sulfonamide, the molecules are linked by N-H···O hydrogen bonds into two-dimensional sheets built from alternating eight and twenty-membered rings. In the cocrystal the molecules are linked by O-H···N hydrogen bonds to form puckered molecular ribbons that are in turn linked into a continuous 3D framework by C-H···π(arene) interactions.

Keywords: powder diffraction; hydrogen bonding; cocrystal; Monte Carlo method

INTRODUCTION

In organic molecular crystals, hydrogen bonds often constitute the strongest intermolecular synthon [1], and hence often dictate the preferred packing arrangement of the molecules. The general principles

* Present address: School of Chemistry, University of Birmingham, Edgbaston, Birmingham, B15 2TT. UK.

underlying the formation of hydrogen bonds are reasonably well understood, but there are at present few, if any, reliable methods for the prediction of hydrogen-bonding patterns. In general, the detailed description of hydrogen-bonding patterns in a given system must be derived from analysis of specific experimental data. Where crystals are available of a size and quality suitable for single-crystal X-ray or neutron diffraction, these techniques remain the method of choice. However, when no such material is available, resort must generally be made to powder X-ray diffraction.

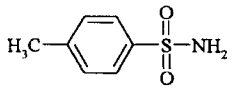
The use of powder X-ray diffraction for *ab initio* structure determination of purely organic molecular solids is a rapidly expanding field. Although traditional approaches to crystal structure solution have met with limited success when applied to these systems [2], considerable advances have been made in the application of direct space methods of structure solution to molecular crystals [3-8]. These methods approach structure solution by postulation of trial crystal structures constructed from known molecular connectivity, independently of the powder diffraction data. Direct space is explored using a range of global optimisation techniques, with each structural model assessed by comparison between the corresponding calculated diffraction pattern and the experimental diffraction data.

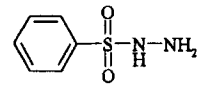
In this paper we describe the application, to compounds of which the primary interest is the hydrogen-bonding scheme, of a direct space method of structure solution based on the Monte Carlo algorithm. In the first instance we present the structure determination of 2,4,6-triisopropylbenzenesulfonamide [9], a compound containing 19 non-hydrogen atoms in the molecular unit and requiring torsional flexibility in structure solution, chosen as part of a long-running study of related compounds. We then report the structure determination of the 1:1 adduct of hexamethylenetetramine and 1,2,3-trihydroxybenzene: the first example of powder diffraction being used in the structure solution of an organic cocrystal. The hydrogen bonding patterns in these materials are then rationalised and codified in terms of the graph set approach [10,11].

SULFONYLAMINO AND RELATED COMPOUNDS

In previous work, we have reported the *ab initio* structure determination of three sulfonylamino compounds, using powder X-ray diffraction data collected using a conventional laboratory powder diffractometer [12]. The structures of 4-toluenesulfonamide $CH_3C_6H_4SO_2NH_2$ (I) and benzenesulfonylhydrazine $C_6H_5SO_2NHNH_2$ (II) were readily solved using

traditional direct methods programs while the structure of 4-toluenesulfonylhydrazine $CH_3C_6H_4SO_2NHNH_2$ (III) was solved using the maximum entropy and likelihood method MICE [13]. Similar data sets were recorded for 2-toluenesulfonamide $CH_3C_6H_4SO_2NH_2$ (IV), 2,4,6-trimethylbenzenesulfonylhydrazine $(Me)_3C_6H_2SO_2NHNH_2$ (V), and 2,4,6-tri-isopropylbenzenesulfonamide $(Me_2CH)_3C_6H_2SO_2NH_2$ (VI). Although these data enabled indexing of (V) and (VI), attempts at structure solution by traditional methods were unsuccessful. The diffraction pattern of (IV) could not be indexed from the data available. A new low-temperature data set for (VI) has been collected using synchrotron X-ray radiation, and details of the subsequent crystal structure determination are given below.


(I)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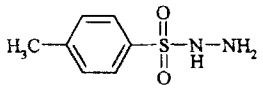
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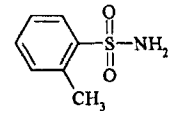
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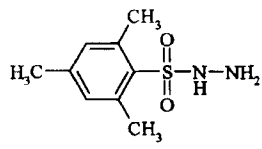
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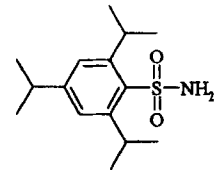

(VI)

2,4,6-tri-isopropylbenzenesulfonamide

The new X-ray diffraction data set was collected at station 2.3 of the SRS, Daresbury Laboratory at a temperature of 120(1) K. A large amount of ice formed on the capillary during the data collection and contributed some peaks to the diffraction pattern. These were excluded for the purposes of indexing, structure solution and the subsequent Rietveld refinement. Indexing gave a unit cell similar to that obtained from the corresponding ambient-temperature laboratory data [9].

Structure solution was carried out using the Monte Carlo method with a structural model constructed using standard bond lengths and angles which comprised the complete molecule (VI) excluding the methyl hydrogen atoms. Although the benzene ring was maintained as a rigid

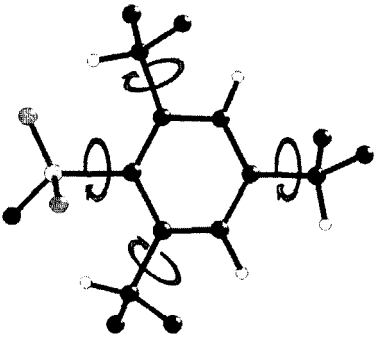


FIGURE 1. The structural fragment used in the structure solution of (VI) together with the internal rotations permitted in the Monte Carlo calculation.

body, the three isopropyl groups and the sulfonamide group were allowed to rotate freely and independently within the molecule as shown in Fig. 1.

The initial position, orientation, and intramolecular geometry of the structural fragment were chosen arbitrarily and the random movement of the molecule in the Monte Carlo calculation carried out by translation and rotation of the structural fragment within the unit cell simultaneously with the intramolecular rotations. After a total of 200000 Monte Carlo moves, the best structure solution (that with the lowest R_{wp}) corresponded to an R_{wp} value of 30.1%, whereas the R_{wp} was typically 47-61% for most random structures sampled.

This structure solution was then taken as the starting model for Rietveld refinement. The positions of all atoms were refined subject to soft restraints on the standard geometric parameters and the methyl H atoms were added to the molecule in positions consistent with standard geometry. Isotropic atomic displacement parameters were refined for the non-hydrogen atoms, but were constrained according to atom type or environment, i.e. S, O or N; aromatic, propyl ($CHMe_2$) or methyl C. The amino H atoms were placed in positions calculated from the coordinates of the hydrogen-bond donor and acceptors, but had no effect whatsoever on the refinement.

Hydrogen bonding and molecular conformation

The structure of (VI) is built from discrete molecules linked together by N-H···O hydrogen bonds. The conformation of the isopropyl groups is

such that the isopropyl C-H bonds all lie approximately parallel to the plane of the aryl ring, with the methyl substituents indicative of repulsive interactions between the isopropyl groups and the sulfonamido group. This conformation of the three independent isopropyl groups appears to be the norm for 2,4,6-tri-isopropyl species $(Me_2CH)_3C_6H_2X$ regardless of the identity of the α-atoms in the substituent X. In nearly all previously reported examples (see refs in [9]), the 2,4,6-tri-isopropylphenyl group was employed simply as a sterically bulky blocking group to protect some other part of the molecule, and none of these structure reports comment on its conformation. However, our analysis shows that the conformation of the isopropyl groups is essentially the same in all cases.

The NH_2 group in (VI) acts as a double donor of hydrogen bonds, with a sulfone oxygen in each of two different molecules acting as the acceptors. These interactions result in formation of C(4) spirals, based on the N-H···O=S motif and generated by 2_1 screw axes, and the generation of a cyclic $R^2_2(8)$ motif around the centres of inversion (Fig. 2). The C(4) motif of N-H···O=S hydrogen bonds is extremely common in sulfonamides [9,12], and the $R^2_2(8)$ motif has also been observed in sulfonamides [14,15], but these two motifs do not normally occur together in a single sulfonamide. The $R^2_2(8)$ rings have the effect of linking together two adjacent but anti-parallel C(4) spirals. The propagation of these two hydrogen-bond motifs by means of the combined action of 2_1 screw axes and centres of inversion leads to the generation of a continuous two-dimensional sheet parallel to (100) in which $R^2_2(8)$ and $R^6_6(20)$ rings alternate in a checkerboard pattern (Fig. 2). The tri-isopropylphenyl units lie on either side of the hydrogen-bonded sheet, so that the overall structure is that of a sandwich: a polar layer containing only S, O, N and H atoms lies between two non-polar hydrocarbon layers with only van der Waals contacts between adjacent sandwiches.

The initial room-temperature dataset collected using a laboratory X-ray source could be indexed, but the structure could not be determined using these data. The success achieved with low-temperature synchrotron data raises the possibility that the previous attempt at structure solution may have been hampered by the occurrence of intramolecular rotations at room temperature. While rotation of the sulfonamido group about the C-S bond is unlikely because of the hydrogen bonding, rotation of the isopropyl groups about the C(aryl)-$CHMe_2$ bonds seemed plausible. However, solid-state CP-MAS NMR investigations [16,17] have shown that such a rotation is not observed even at room temperature, and we conclude that it is a combination of

the superior resolution of the synchrotron data and the application of improved structure solution software which has now permitted structure determination.

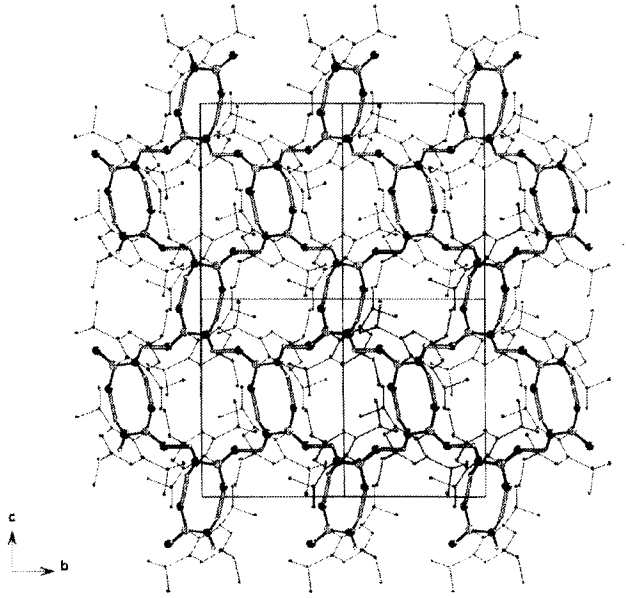


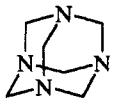
FIGURE 2. View of part of the crystal structure of (VI), showing the C(4) N-H···O=S chains parallel to [010] and the alternation of $R^2_2(8)$ and $R^6_6(20)$ hydrogen-bonded rings in the [100] plane: thin lines represent bonds to carbon, lines of intermediate thickness represent covalent S-N or S=O bonds, and thick lines represent N-H···O=S hydrogen bonds. All H atoms except those of the amide group are omitted for clarity.

ORGANIC COCRYSTALS

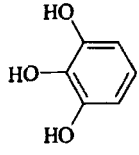
Previous studies have used single-crystal X-ray diffraction to explore the use of bis- and trisphenols in crystal engineering and the interaction of this type of phenol, acting as a hydrogen bond donor, with hexamethylenetetramine, $(CH_2)_6N_4$ (HMTA), as a hydrogen bond

acceptor [18]. However in the case of the 1:1 adduct of 1,2,3-trihydroxybenzene (pyrogallol, VII) and HMTA, investigation of the crystal structure has been carried out using powder diffraction data obtained from a conventional laboratory-based diffractometer.

In the application of direct space structure solution methods, the presence of more than one molecular fragment in the asymmetric unit makes the problem more complex both in terms of the number of degrees of freedom (ie. the number of structural parameters varied to generate new trial crystal structures), and to a certain extent, the effect on R-factor discrimination. There are a few examples of such materials solved from powder diffraction data using the direct space structure solution approach [19], a situation made more complicated here due to the presence of two entirely different entities in the cocrystal.



HMTA



(VII)

Pyrogallol–HMTA (1/1)

X-ray powder diffraction data were collected at room temperature on a high-resolution laboratory-based diffractometer using monochromatised $CuK\alpha_1$ radiation. Indexing gave a monoclinic unit cell and space group $P2_1/n$, consistent with the presence of one molecule of each component in the asymmetric unit.

The structural model used in the Monte Carlo structure solution comprised a complete HMTA molecule and a pyrogallol molecule (VII) excluding the hydrogen atoms on the three hydroxyl groups. Both these molecules were constructed using standard bond lengths and angles and treated as rigid bodies in the calculation. Trial structures were generated by translation and rotation of both molecules completely independently of each other 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 only additional constraint is a limit on the closest approach between the two independent bodies in the form of an artificially biased agreement factor The calculation was run for 500000 Monte Carlo moves and R_{wp} 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 structure was used as the starting model for Rietveld refinement and the positions of all atoms refined subject to soft restraints on the standard geometric parameters. As in the previous structure, isotropic atomic displacement parameters were refined for the non-hydrogen atoms only, and constrained according to atom type or environment, i.e. O, N, aromatic or methylene C. Diffraction data had been collected with the sample packed 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 the effects of the preferred orientation were minimised by use of the capillary data set for both solution and refinement, variation of a preferred orientation parameter in the [100] direction was required. A plot of the final Rietveld refinement for this structure is shown in Fig. 3. The hydroxyl H atoms were placed in positions calculated from the coordinates of the hydrogen-bond donor and acceptors, but were not included in the refinement.

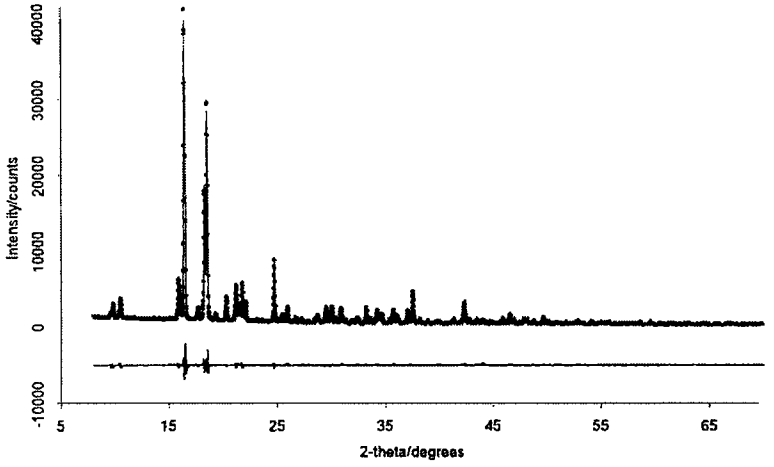


FIGURE 3. Final observed (circles), calculated (solid line) and difference (below) powder X-ray diffraction profile for the final Rietveld refinement of pyrogallol–HMTA (1/1). Agreement factors R_{wp} = 7.40%, R_p = 5.40% over the range $3°<2\theta<85°$; preferred orientation fraction = 0.807.

Hydrogen bonding and molecular packing

All three hydroxyl groups in the pyrogallol molecule act as hydrogen bond donors with three N atoms each from different HMTA molecules acting as acceptors. 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 around centres of inversion at (n, 0, ½) and (n+½, 0, ½) where n is an integer (Fig. 4). 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. 4). In hydrogen-bonded systems, HMTA generally acts as a double acceptor of hydrogen bonds [18]. Rather less frequently, HMTA behaves as an acceptor of just one hydrogen bond [18,20], or as in this case, of three hydrogen bonds [21-23].

Two symmetry-related ribbons (related by the action of glide planes) run through each unit cell, along the lines (n, ½, 0) and (n, 0, ½). These ribbons are 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. Propagation of these two types of C-H···π(arene) interactions based on aromatic and aliphatic C-H bonds respectively links all the parallel ribbons into a single bundle, so that the overall supramolecular structure is three-dimensional.

CONCLUDING REMARKS

This study demonstrates the structure determination and subsequent rationalisation of the hydrogen-bonding schemes of two molecular systems from powder diffraction data. In the case of 2,4,6-tri-isopropylbenzenesulfonamide, the molecule was permitted considerable torsional flexibility in structure solution by the Monte Carlo method. Comparison of the structure found for this material with those of a range of other systems containing the 2,4,6-tri-isopropylphenyl fragment has revealed a common conformation, within which there is, in fact, just one two-fold choice, the orientation of the 4-substituent. Clearly, significant economy in the Monte Carlo structure solution could have been attained

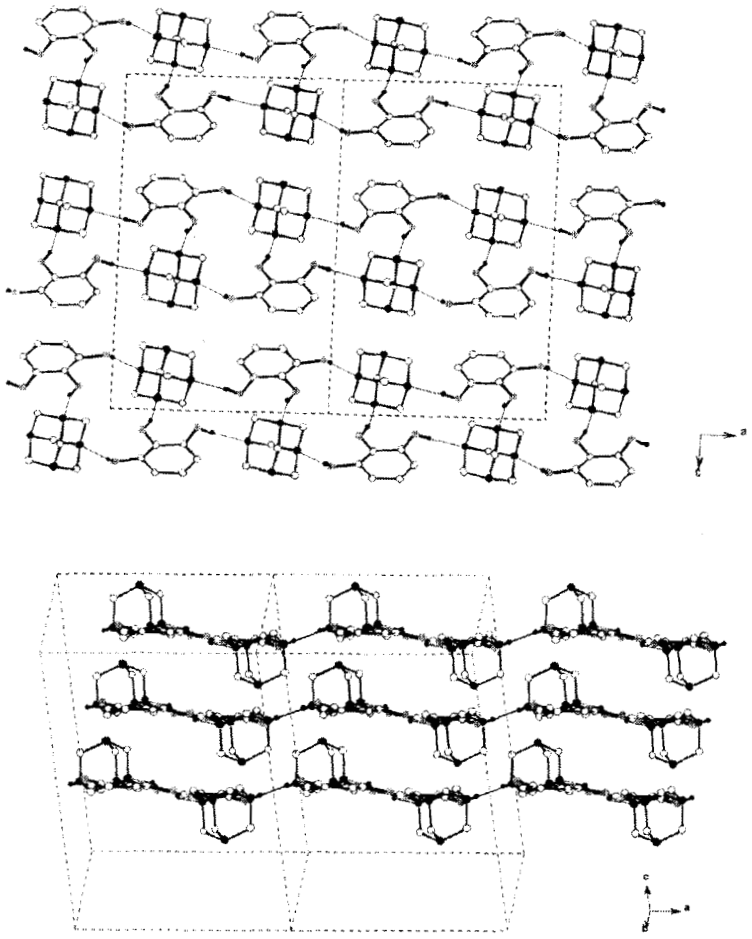


FIGURE 4. The crystal structure of pyrogallol–HMTA (1/1), showing the alternating O-H···N hydrogen-bonded $R^4_4(18)$ rings generating puckered molecular ribbons running parallel to [100]: carbon atoms are indicated by open circles, nitrogen atoms are black and oxygen atoms are light grey. The hydrogen atoms are shown by small black spheres and hydrogen bonds represented by thin lines. H atoms not involved in any hydrogen bonding are omitted for the sake of clarity.

by incorporation of prior conformational information, such as that derived from exhaustive analysis of the information in the CSD regarding the intramolecular rotation of the isopropyl groups in this structure. However, the effects of widespread use of conformational probabilities on the efficiency of global optimisation techniques are not clear. We have also shown, in the solution of the pyrogallol–HMTA 1:1 adduct, that it is possible to determine the crystal structures of relatively complex systems 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.

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