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The Solid-State Structure of 3-Hydroxy-4-methyl-2(3*H*)-thiazolethione: Prediction and Measurement

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Abstract—The solid-state structure of 3-hydroxy-4-methyl-2(3*H*)-thiazolethione has been determined using the synchrotron radiation source at Station 9.8, Daresbury SRS (UK). The structure has been verified by Rietveld refinement against laboratory powder X-ray diffraction data. Ab initio crystal structure prediction is successful on specification of an initial *pseudo*-centrosymmetric sub-unit constructed via O–H···S hydrogen bonds. In general, such sub-units (or supermolecules) may be identified using crystal-engineering principles.

Introduction

The solid-state structure adopted by a material has a profound influence upon its physicochemical properties and reactivity.[1] Structural variants of a given molecule (e.g. polymorphs, hydrates) exhibit different properties including thermal stability, solubility and dissolution rate.[2–4] Such differences are especially relevant to the pharmaceutical industry, for example, where the inadvertent production of an unexpected polymorph or hydrate can lead to the administration of ineffective or toxic dosages.[5] In addition, the specification of the structure of the solid form of a pharmaceutical compound is essential for effective patent protection. Clearly, determination of the solid-state structures of organic materials is of vital importance.

The technique of choice for determination of solid-state structure is single-crystal X-ray diffraction, providing when successful a complete, unambiguous model of the molecular and solid-state structure of a material. Advances in instrumentation, in particular the development of CCD area-detectors, have led to data collection times measured in hours rather than days and in most cases the technique is considered to be routine. Indeed the limiting factor is often the failure to obtain single crystals of sufficient size and quality for analysis using standard laboratory equipment. In the absence of single crystals suitable for X-ray analysis, determination of the solid-state structure of an organic material becomes markedly more complex.

The complementary approach of structure solution directly from powder X-ray diffraction (PXRD) data is a non-trivial task; compression of the diffraction data from three dimensions into one results in extensive peak overlap from which the extraction of individual reflection intensities (required for direct methods or Patterson methods) is difficult. This problem may be overcome by the application of 'whole-profile' fitting techniques, as used in the Rietveld method.[6] The challenging step in this methodology is the generation of a starting model close enough to the actual structure for successful refinement. Current approaches utilise direct-space strategies in which trial structures are generated independently of the diffraction data and assessed by their goodness of fit to the measured PXRD pattern.[7,8] The fit may be quantified by the weighted profile *R*-factor (R_{wp}) and the parameters used to define the structural model may then be optimised so as to yield the lowest value of R_{wp}. Thus, structure solution becomes a problem of global optimisation. Techniques based upon Monte Carlo and genetic algorithm optimisation methods are currently the subject of extensive research and have provided numerous successes.[9,10] A potential drawback for the routine application of direct-space strategies, however, is the requirement for the previous determination of unit-cell parameters and space group. This step is not trivial and may not always be possible, particularly for low-symmetry organic materials analysed with laboratory X-ray sources.

An alternative approach to the structure solution stage has arisen from the application of synchrotron X-ray sources to

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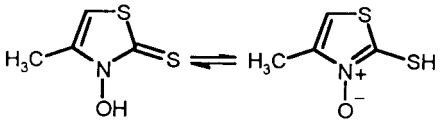
Table 1. Crystal data and structure refinement details

Empirical formula	$C_4H_5NOS_2$
M (g mol^{-1})	147.21
T (K)	150(2)
Crystal system	Orthorhombic
Space group	*Pbca*
Crystal size (mm)	0.20×0.03×0.01
Radiation (λ/Å)	Synchrotron (0.6891)
a (Å)	6.5345(17)
b (Å)	13.345(4)
c (Å)	28.032(7)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	2444.6(11)
Z	16
μ (mm^{-1})	0.763
Reflections collected	12137
Unique reflections	2340
R_{int}	0.099
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (eÅ^{-3})	0.930, −0.672
$R1$ ($I>2\sigma(I)$)	0.142
w$R2$ ($I>2\sigma(I)$)	0.254
S	1.433

single-crystal diffraction analysis. The high-flux X-ray beam available from a synchrotron source can produce diffracted intensity sufficient for structure determination from crystals which would previously have been defined as single powder grains. The recent introduction of Station 9.8 at Daresbury SRS (UK)[11] has already produced several excellent examples.[12–14] Such facilities have redefined the limits at which it becomes necessary to employ PXRD structure solution methods. Collection of PXRD data remains, nevertheless, advisable since it is important to ensure that structures obtained from selected microcrystalline fragments are representative of the bulk material. This may be achieved qualitatively by comparison of the observed PXRD pattern with that simulated from the single-crystal model, or in a more quantitative manner by subjecting the single-crystal model to Rietveld refinement against the PXRD data.

Solid-state structure determination may alternatively be approached on the basis of prediction rather than measurement. The ab initio prediction of solid-state structures is particularly attractive since it is based only on molecular information, i.e. no unit-cell information is required. The space group must still be supplied, although a search in all 230 possibilities could theoretically be performed. In practice, the choice of space group for organic crystals is usually restricted to one of seven: $P1$, $P\bar{1}$, $P2_1$, $P2_1/c$, $P2_12_12_1$, *Pbca* and $C2/c$.[†] Numerous prediction methodologies have appeared in the literature, one of which has been adapted to form a commercially available package,[15,16] in which Monte Carlo simulated annealing search methods are employed. The structures generated are assessed initially on the basis of their calculated lattice energies to give a number of low-energy crystal structures which are said to have a 'high probability' of being observed experimentally.[17] In practice, the method generates a set of energetically reasonable models, among which the actual one may be present. For solid-state characterisation purposes, PXRD patterns simulated from the proposed models must be compared with the measured pattern. Where the comparison is favourable, the models may be advanced to the Rietveld refinement stage.[18] The structure prediction method is dependent on the availability of suitable force fields for the material of interest, although the Dreiding force field has been shown to be suitable for most organic molecules.[19]

We are currently studying the solid-state chemistry of cyclic thiohydroxamic acids which find application as preservatives,[20] and also as alkoxy radical precursors in synthetic procedures.[21] Despite extensive study resulting from these applications, there has been little solid-state information reported for these materials. The only reported crystallographic studies of which we are aware are those of 1-hydroxy-2(1*H*)-pyridinethione[22,23] and 3-hydroxy-4-(*p*-tolyl)-2(3*H*)-thiazolethione.[23] It is likely that this lack of crystallographic information results largely from difficulty encountered in obtaining single crystals of sufficient size for X-ray analysis. In this paper, we consider the solid-state structure of 3-hydroxy-4-methyl-2(3*H*)-thiazolethione (**1**). Structure determination using standard laboratory instruments has not been possible for this material; crystals of sufficient size for X-ray analysis invariably give rise to poorly shaped diffraction peaks (suggesting that they are not single). The solid-state structure of **1** has, therefore, been determined using a microcrystalline fragment at Station 9.8, Daresbury SRS (UK) and refined against laboratory PXRD data. The viability of ab initio structure prediction has also been explored for **1**.



1a **1b**

Results

Solid-state structure of 1 from synchrotron single-crystal data

Details of the single-crystal refinement are given in Table 1. **1** crystallises in the space group *Pbca* with two independent molecules in the asymmetric unit (Fig. 1). The possibility of tautomerism exists (**1a↔1b**); both independent molecules were assigned as the thione tautomer on the basis of the C–S and N–O bond distances (N(1)–O(1)=1.380(10), N(2)–O(2)=1.374(11) Å cf. N–O$_{av}$=1.396(12) Å; C(1)–S(1)=1.687(10), C(5)–S(3)= 1.679(11) Å cf. $C{=}S_{av}$= 1.671(24) Å).[24‡] This was confirmed by the location of H(100) and H(101) in difference Fourier maps. The molecules form *pseudo*-centrosymmetric dimers via O–H···S hydrogen-bond interactions (H(101)···S(1)= 2.27(2), H(100)···S(3)=2.22(2) Å). The deviations from exact centrosymmetry are small (insignificant within the

[†] The selection is made on the basis of well-known space group statistics. While the possibility remains for adoption of a different space group, these seven provide a good starting set.

[‡] It has been shown that both 1-hydroxy-2(1*H*)-pyridinethione and 3-hydroxy-4-(*p*-tolyl)-2(3*H*)-thiazolethione also exist as the thione tautomer in the solid state.[22,23]

Table 2. Details of the Rietveld refinement

Space group	*Pbca*
a (Å)	6.6041(2)
b (Å)	13.4664(4)
c (Å)	28.1938(12)
V (Å^3)	2507.4(2)
Data range (°)	$5 \leq 2\theta \leq 85$
No. profile points	7990
No. parameters	30
Peak shape function	Thompson et al.[25] (Pseudo-voigt)
Asymmetry model	Finger et al.[26]
Background	Linear interpolation (10 terms)
Preferred-orientation model	March-Dollase[27]
Preferred-orientation axis	002
Preferred-orientation ratio	0.78(2)
R_{exp} [a]	0.0321
R_p [b]	0.0442
R_{wp} [b]	0.0839

[a] $R_{exp} = [(N-P)/\sum_i^N w_i y_i(\text{obs})^2]^{1/2}$

[b] $R_{wp} = [\sum_i w_i[y_i(\text{obs}) - y_i(\text{calc})]^2 / \sum_i w_i[y_i(\text{obs})]^2]^{1/2}$. N is the number of profile points, P is the number of parameters, y_i(obs) and y_i(calc) are the observed and calculated intensities at the point i, and w_i is the weight for the ith point (standard weighting scheme applied).[28] For R_p, unit weights are employed.

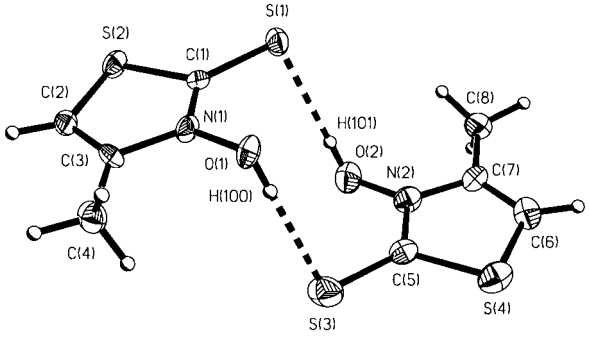


Figure 1. Asymmetric unit of **1** showing displacement ellipsoids at 50% probability. Hydrogen bonds are indicated by dotted lines.

precision of the results), but the centres of symmetry do not coincide with crystallographic centres of symmetry. The dimers are linked by C–H···O interactions (C(2)···O(1)=3.351(12), H(2)···O(1)=2.43 Å; C(6)···O(2)=3.410(14), H(6)···O(2)=2.52 Å) into chains running parallel to the *a* direction (Fig. 2).

Rietveld refinement of 1

The single-crystal structure of **1** shows a relatively large conventional *R*-factor ($R1=0.142$), suggesting inadequacies in either the structural model or the data quality. The large internal *R*-factor ($R_{int}=0.099$) suggests the latter to be the case. This may be indicative of crystal decay, or perhaps suggest that the microcrystalline fragment was not single. It should be noted from the cell parameters of **1** that *b* is approximately twice *a* and *c* is approximately twice *b*, an arrangement likely to result in crystal twinning. Repeated powder X-ray diffraction measurements of a bulk sample gave no indication of decay in the X-ray beam. To ensure, therefore, that the structure was correct and representative of the bulk material, Rietveld refinement against laboratory PXRD data was performed.

The structure obtained from the single-crystal study

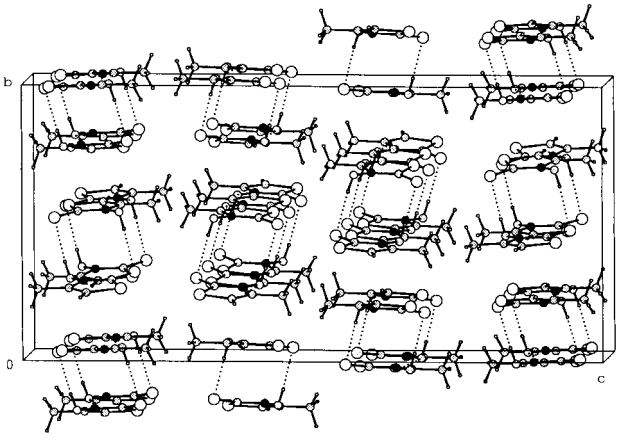
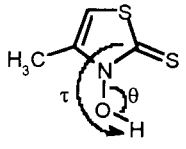


Figure 2. View of **1** along the *a* direction showing the centrosymmetric dimers linked into chains by C–H···O interactions. Hydrogen-bond interactions are indicated by dotted lines.

was employed as the starting model with the molecular geometries fixed and the molecules allowed to rotate and translate as rigid bodies. Hydrogen atoms, including H(100) and H(101) were included as part of the rigid body definition. An alternative treatment of H(100) and H(101) would be to exclude them from the rigid body definition and place them along the O(1)···S(3) and O(2)···S(1) vectors. In the final model, the positions of H(100) and H(101) were found to lie exactly along the O(1)···S(3) and O(2)···S(1) vectors such that any choice based on the merits of each approach would be somewhat arbitrary. Attempts to refine the model using bond distance restraints in place of rigid-body constraints led to unreasonable deviations in the molecular geometry with no appreciable improvement to the profile fit. A single isotropic displacement parameter common to all atoms was refined. Comparison of data collected in transmission geometry with data collected in Debye–Scherrer mode suggested significant preferred orientation in the flat-plate sample and this was accounted for in the refinement. Details of the refinement are given in Table 2 and the final difference curve is shown in Fig. 3. The final *R*-factors and the goodness of the profile fit confirm that the structure obtained from the single-crystal diffraction is indeed correct and representative of the bulk material.

Ab initio structure prediction

The first step for the ab initio structure prediction of **1** is the determination of the molecular conformation. The molecule is essentially rigid; the only significant degree of freedom is the position of the hydrogen atom of the hydroxyl group, specified by the two parameters, θ and τ (Scheme 1). Gas-phase geometry optimisation (MOPAC-AM1) gives the values shown in Table 3. It has been noted previously, however, that molecular conformations in the solid state



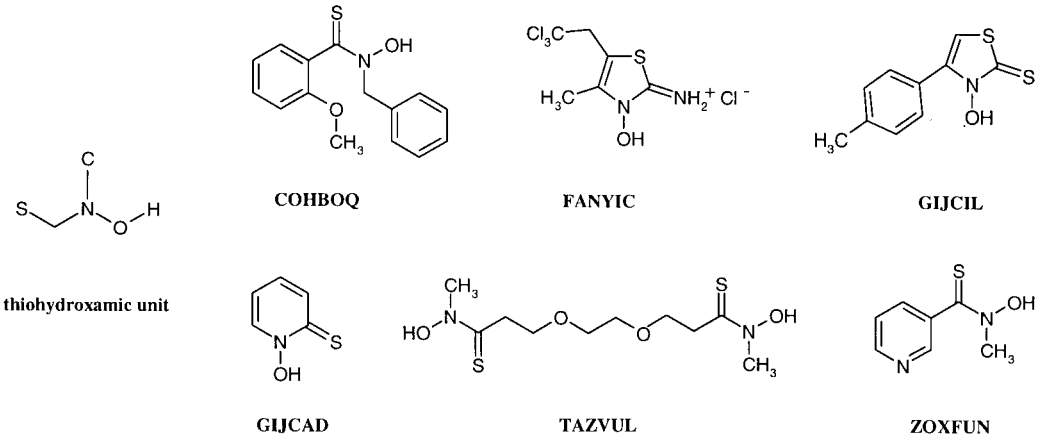
Scheme 1.

Table 3. Conformational parameters for derivatives of **1**

		θ (°)	$\lvert\tau\rvert$ (°)
1	H(100)	111(1)	92(1)
	H(101)	111(1)	93(1)
	Gas-phase optimised	106.0	45.3
2		102(4)	69(4)
3		110(3)	94(4)
GIJCIL[23]		111(1)	86(2)
FANYIC[32]		103(1)	107(2)
ZOXFUN[34]		108(1)	102(2)

often differ from those determined by theoretical gas-phase calculations.[29] It is highly probable that the position of the hydrogen atom in the solid state will be different from that of the gas-phase molecule as a result of intermolecular forces within the crystal. It is advisable, therefore, to make use of observed conformational preferences for the prediction of solid-state structures, i.e. examine the conformations found in similar molecules in the Cambridge Structural Database (CSD).[30] A search for the thiohydroxamic acid unit (shown in Scheme 2) in organic-only structures recovered only six examples (refcodes: COHBOQ,[31] FANYIC,[32] GIJCAD,[22,23] GIJCIL,[23] TAZVUL[33] and ZOXFUN[34]—see Scheme 2). Three of these examples, including the cyclic thiohydroxamic acid, 1-hydroxy-2(1*H*)-pyridinethione (GIJCAD), contain *intra*molecular O–H···S bonds. For cyclic thiohydroxamic acids based on the 5-membered thiazole ring, however, the greater O···S distance and smaller O–H···S angle required for intramolecular interaction, mean that *inter*molecular O–H···S interactions are likely to be favoured. Intermolecular interactions are observed in FANYIC, GIJCIL and also in the non-cyclic ZOXFUN. In addition to these examples, we are aware of two other relevant structures not yet included in the CSD which contain intermolecular O–H···S interactions: 3-hydroxy-4-[(3-oxo-4-methyl-2(3*H*)-thiazol-2-yl)thio]-2(3*H*)-thiazolethione (**2**), and a hydrated phase of **1**, denoted **3** (see Table 3).[35] The values of θ and τ observed in all of these structures are listed in Table 3. Clearly, there is a wide range and averaging the values will give little insight for such a limited sample. It was considered that the best guide to the solid-state conformation of **1** was given by the hydrate phase **3** since this contains the 3-hydroxy-4-methyl-2(3*H*)-thiazolethione molecule itself rather than some derivative of it. The geometry of **1** in the hydrate was, therefore, used as the molecular conformation for the structure predictions. Indeed, it emerges that subsequent comparison with the single-crystal structure of **1** confirms the conformation is very close to that observed.

Structure predictions were performed in the six primitive space groups $P1$, $P\bar{1}$, $P2_1$, $P2_1/c$, $P2_12_12_1$, and $Pbca$ with one molecule specified in the asymmetric unit and then with



Scheme 2.

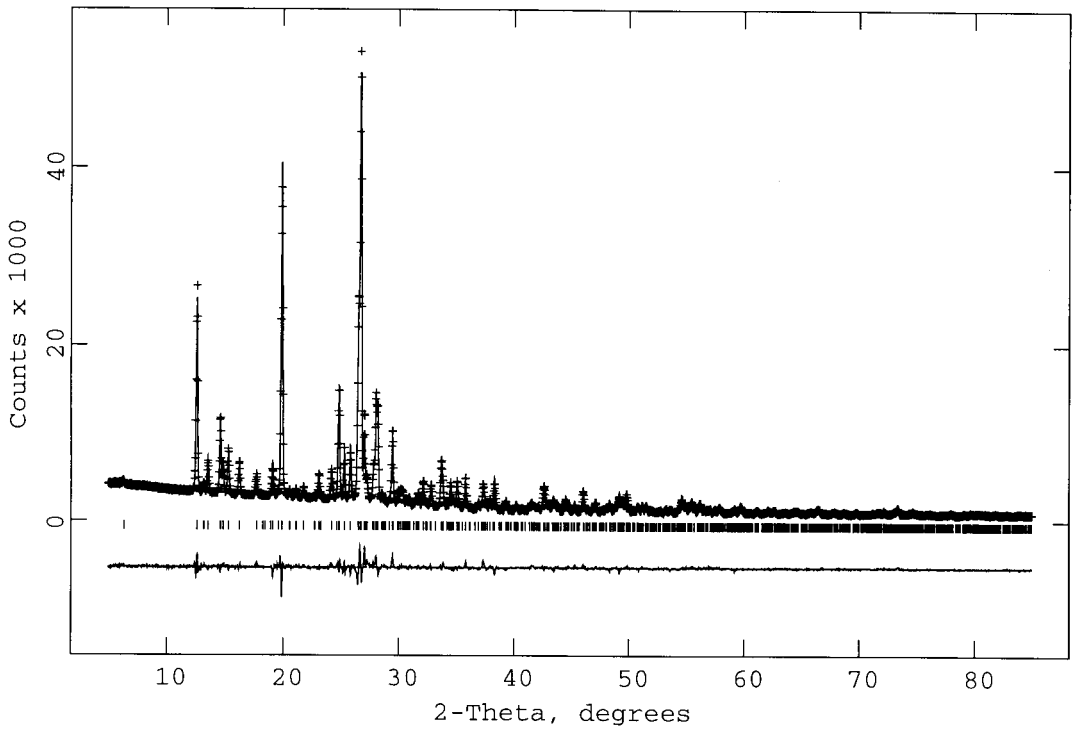


Figure 3. Calculated (solid line), observed (crosses) and difference PXRD profiles for the Rietveld refinement of **1**. Reflection positions are indicated by tick marks.

two independent molecules. The recurring feature within the predicted structures is the dominance of O–H···O hydrogen bonds; of the 10 lowest-energy structures in the search with two independent molecules (lattice energies ranging from −100.45 to −89.85 kJ mol^{-1}), only one exhibits O–H···S interactions. For all of the searches performed, however, there were no resulting models which gave a simulated PXRD pattern similar to that observed. Thus, ab initio structure prediction of **1** was not successful.

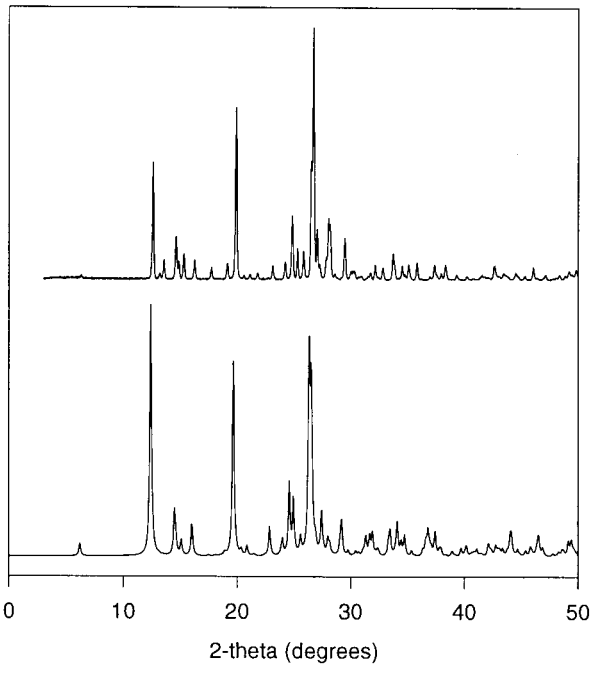


Figure 4. Observed (top) PXRD pattern for **1** and the pattern simulated from the predicted model **m16** (bottom). The relative peak intensities in the observed pattern are subject to preferred orientation effects.

Discussion

The failure of the ab initio structure prediction may be rationalised by consideration of the solid-state structure of **1**, as determined by the single-crystal and Rietveld studies. The two molecules in the asymmetric unit are related by *pseudo*-inversion symmetry, i.e. two non-superimposable conformations exist. Within the present structure prediction methodology, only a single conformation is generally specified at the outset. The only means by which the dimer motif may be generated from the single conformer in this case is to utilise a crystallographic centre of symmetry. The structure cannot then be constructed successfully even in the correct space group since there are not enough centres of symmetry remaining. This example clearly illustrates the difficulty involved with predicting structures in which two distinct molecular conformations are present.

To examine the viability of the structure prediction method in the absence of these complicating factors, the dimeric unit (Fig. 1) derived from the single-crystal structure was employed as a rigid starting model. At this stage, predictions were performed only in the observed space group *Pbca*. The resulting set of models included one (the 16th lowest-energy model, denoted **m16**) which showed an excellent qualitative fit to the observed PXRD data (Fig. 4). The lattice parameters (a=6.697, b=13.537, c=28.540 Å) are comparable with those observed for **1**, and the model was progressed to the Rietveld refinement stage. Lattice parameters and background coefficients were refined initially with peak profile

coefficients fixed to those for **1** and no refinement of the atomic coordinates. This step led to convergence with R_p=0.0934 and R_{wp}=0.1426. Subsequent rigid-body refinement in the manner outlined previously led to a final structure identical to that produced by the previous Rietveld refinement of **1**. Thus, on specification of a suitable structural sub-unit, the structure prediction process is successful, and provides a starting model of sufficient quality for subsequent refinement. Such an approach may in general provide a means to overcome the difficulties encountered where multiple crystallographically independent molecules are present.

Identification of structural sub-units as an intermediate step in structure prediction has been suggested previously in the 'molecular nuclei' approach.[36] For crystal structures containing a single independent molecule, each molecule must be related to its neighbours by some symmetry operator. Symmetry operators can, therefore, be used to generate clusters of molecules which, when translated in three dimensions in space, build structures in the most common space groups. The suitability of each molecular coupling generated by the action of a symmetry operator must be assessed in terms of its intermolecular potential energy. Using standard atom–atom potential calculations parameterised for crystals, a measure of the stability of the coupling in the solid state may be obtained. It is noted, however, that a strong interaction does not necessarily mean that the coupling will be observed in the crystal structure where other intermolecular interactions will have significant influence; this may be likened to the observation that molecular conformations in the solid state are likely to differ from those in the gas phase due to the influence of intermolecular interactions, and the two observations may be treated in a similar manner. It has been noted that for ab initio structure predictions it is advisable to employ molecular conformations observed to be most stable in the solid state.[29] Similarly, the ultimate measure of the stability of a molecular coupling in the solid state is its repeated observation within crystal structures. Identification and utilisation of consistently occurring molecular couplings is, of course, the foundation of crystal engineering.

Specification of the molecular conformation in the first step of the structure prediction may logically be extended to specification of the *supramolecular* conformation via consideration of an appropriate synthon. The supermolecule may then be employed as a rigid body in the structure prediction process. The methodology is subtly different from that of the molecular nuclei approach in that the supermolecule need not necessarily be constructed by the action of a symmetry operator, but may correspond to any frequently observed structural sub-unit. In this manner, it becomes possible to treat systems containing multiple crystallographically independent molecules. In practice, couplings are usually generated via the action of a symmetry operator (for example, the well-known centrosymmetric carboxylic acid dimer). This does not adversely affect the method, however, since the correct structure should be generated in the appropriate sub-group of the correct space group. Although the initial specification of a supermolecule may not strictly be considered as an ab initio structure prediction, utilisation of the methodology in conjunction with experimental PXRD data may prove to be a valuable tool for the elucidation of 'difficult' crystal structures.

Conclusion

To appreciate fully the influence of the solid-state structure of organic materials on their physicochemical properties and reactivity, reliable structure determination methods are required for all materials, not just those which readily form large single crystals. Utilisation of facilities such as Station 9.8 at Daresbury allow for structure determination for more 'difficult' materials. Combination of this resource with powder X-ray diffraction data provides a comprehensive approach for the elucidation of solid-state structures. An alternative approach to structure determination is the ab initio prediction of crystal structures. The example presented here illustrates that existing prediction methodology may be enhanced by the initial specification of a suitable structural sub-unit or supermolecule. The identification and utilisation of structural sub-units is, of course, crystal engineering. It is envisaged that the combination of the chemical and structural information available to the crystal engineer with existing structure prediction methodology could lead to a powerful structure prediction procedure.

Experimental

3-Hydroxy-4-methyl-2(3*H*)-thiazolethione was obtained from Aldrich Chemical Co. The material was recrystallised from dichloromethane to leave needles of **1**, m.p. 92–93°C; (Found: C, 32.5; H, 3.4; N, 9.2. $C_4H_5NOS_2$ requires C, 32.6; H, 3.4; N, 9.5%).

Single-crystal X-ray diffraction

Data were collected for **1** at Daresbury SRS (UK), Station 9.8 using a Bruker AXS Smart CCD area-detector diffractometer.[37] A crystal of dimensions 0.20×0.03×0.01 mm^3 was cut from a needle grown by slow evaporation of a solution of **1** in ethanol. Intensities were integrated from several series of exposures.[38] Each exposure covered 0.2° in ω, with an exposure time of 4 s and the total data set comprised more than a hemisphere. The unit cell parameters were refined using LSCELL[39] and the data were corrected for absorption and incident beam decay.[40] The structure was solved by direct methods using SHELXS-97[41] and refined on F^2 using SHELXL-97.[42]

Powder X-ray diffraction (PXRD)

PXRD analysis of **1** was carried out using a Stoe STADI-P high-resolution diffractometer with Ge(111)-monochromated Cu K_α radiation (λ=1.5406 Å) and a position-sensitive detector (PSD) covering ca. 6° in 2θ. The pattern was measured in transmission geometry over the 2θ range 3–85° with a step size of 0.5° and a count time of 360 s per step (total data collection time ca. 16 h). Rietveld refinement was carried out using the GSAS package.[43]

Computational details

All molecular-modelling applications were carried out within the *Cerius*^{2} (ver. 4.0) package.[44] Structure predictions were performed using the *Polymorph Predictor* module. The Dreiding forcefield with default parameters[19] was employed using the Ewald long-range summation method for electrostatic and van der Waals interactions.[45,46] In all cases, electrostatic potential derived charges were calculated using the MOPAC (AM1) semi-empirical molecular orbital program;[47] these have been shown to be superior for general organic molecules.[16] Lattice energy calculations were performed using the *Crystal Packer* module. Energy minimisation was carried out initially with rigid-body rotations and translations within a fixed unit cell. In a subsequent minimisation step, unit-cell parameters were also relaxed (within the symmetry constraints of the crystal system). To assess the suitability of the Dreiding forcefield for the study of **1** the observed single-crystal structure was subjected to rigid-body energy minimisation. The final minimised model has $E_{\text{latt}}=-95.5$ kJ mol^{-1} with unit-cell parameters a=6.472, b=13.559, c=28.458 Å. The mean change in cell lengths of 0.234 Å (maximum change of 0.426 Å in c) is small and indicates that the force field provides an adequate description of the intermolecular interactions.

Acknowledgements

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