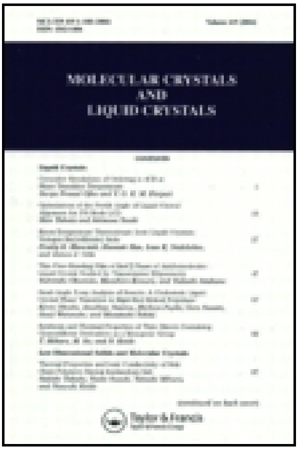

Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals

Determining the Crystal Structures of Organic Solids using X-Ray Powder Diffraction Together with Molecular and Solid State Modeling Techniques

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Determining the Crystal Structures of Organic Solids using X-Ray Powder Diffraction Together with Molecular and Solid State Modeling Techniques

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An overview of recent work directed to the crystallographic structure solution of organic solids using a combination of X-ray powder diffraction and a grid-based direct space search for trial structures is presented. A number of study cases illustrate the application and potential of this approach. Additionally, the inherent limitations of powder diffraction as an isolated tool for structure determination are discussed together with an outline of ways to address these limitations in the future.

Keywords: Powder diffraction; structure solution; organic crystal structures; systematic search; polymorphism; molecular modeling

INTRODUCTION

Currently the Cambridge Structural Database (CSD) [1,2] holds *ca.* two hundred thousand crystal structures of organic and organometallic compounds, which is but a small fraction of known organic materials. A large number of molecular materials display nucleation characteristics that are not favourable with respect to obtaining crystals suitable enough, in terms of size and perfection, for structure determination *via* single crystal diffraction. Fast growth coupled with a large nucleation rate, for example, will result in the precipitation of many small crystallites. Too small a crystallite size will preclude the use of single crystal diffraction for structure determination, even though the individual micro–crystals may be of high quality. Given the relationship between crystal structure and crystal growth characteristics it is fair to assume that our current knowledge of the crystal chemistry of molecular solids is biased towards types of structures that easily form single crystals. The implications of this, in terms of the design and preparation of advanced organic materials in the solid state are obvious.

Recent years have seen a number of developments enabling the determination of crystal structures of organic, molecular materials *via* powder diffraction. Several methods used for structure solution from powder diffraction data have been developed [3–10]. Although they are based upon different approaches to the problem of finding the "best" structure, all have one element in common, in that they perform the search for trial structures in direct space.

One fundamental question has to be raised: if one employs a quasi–global optimisation technique such as simulated annealing [5, 10] or a genetic algorithm [4], how certain can one be that the final structural model is the best possible to describe the experimental data? Certainly, the computational advantage these two methods have over others is quickly lost if they must be applied several times until a statistically relevant pattern emerges.

This paper provides an overview of our methodology, paying particular attention to the systematic approach to trial structure generation. Selected case studies are used to highlight the development of the procedure and the benefits of this approach as well as potential problems in structure solution from powder diffraction in general.

METHODOLOGY

For molecular crystals the general strategy for structure solution from powder diffraction data can be divided into four stages:

- Generation of the molecular fragment contained in the asymmetric unit.
- Determination of lattice parameters and space group.
- Trial structure generation.
- Rietveld refinement [11, 12].

Initially, a probe molecule or molecular fragment must be generated. The probe molecule is described in terms of internal coordinates and then optimised using either semi–empirical molecular orbital methods [13] or molecular mechanics methods employing established force fields [14, 15] or a combination of both. The main purpose of the geometry optimisation is to provide accurate bond angles and bond lengths. For molecules possessing torsional degrees of freedom, the minimum energy structure *in vacuo* may not necessarily correspond to the conformation adopted in the solid state [16]. Providing that the subsequent trial structure generation includes parameters to describe the significant torsional degrees of freedom, an accurate prediction of the molecular conformation is not required at this stage. In certain cases an alternative approach may be to derive a structural model based upon crystallographic data from similar molecules with known structures.

Trial Structure Generation: Development of the Grid Search Procedure

Of the different direct space search methods [3–10] in use today for trial structure generation, the grid search is conceptually the simplest. In this a grid can be defined in an n–dimensional search space with a probe molecule being placed on every point on that grid. The best packing arrangement can then be found by locating the grid-point which is associated with either the lowest lattice energy or the best fit of a calculated diffraction pattern to experimental data, R_{wp}, defined as

$$R_{wp} = \left(\frac{(w_i(y_{i,o} - y_{i,c}))^2}{w_i y_{i,o}^2} \right)^{\frac{1}{2}} \qquad (1)$$

Prior to the development of an automated grid search procedure the trial structure generation was performed manually. This was found to be feasible only for simple, rigid molecules, where the molecular symmetry constrains the molecule to coincide with a given symmetry element of the space group. In the case of 6,13–dichlorotriphendioxazine (DCTPD) [17, 18], for example, the molecule possesses a centre of symmetry packing with the space group $P2_1/c$. The centre of the molecule is confined to the origin of the unit cell, and hence only rotations of the molecule need be considered in the search. As a consequence the search can be performed by manually changing the orientation of the molecule. The individual structures generated are then assessed in terms of their simulated X-ray diffraction patterns and calculated lattice energy.

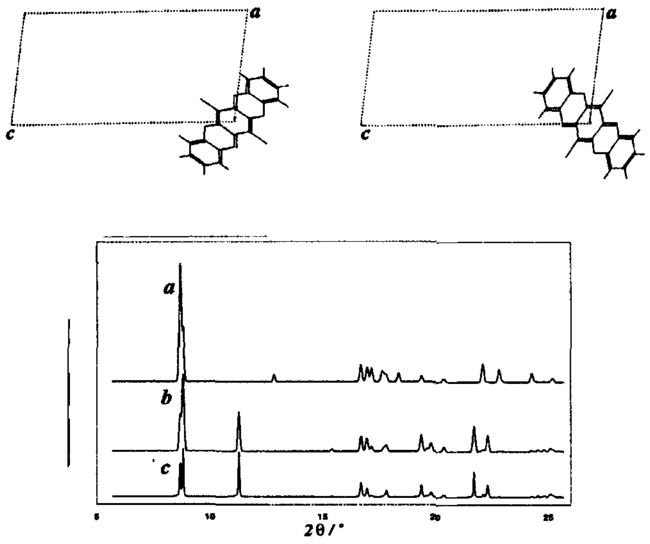

Figure 1: Comparison of the simulated powder X–ray diffraction pattern with the experimental diffraction pattern (c) for DCTPD in two different orientations. The initial orientation (top left) yields the simulated diffraction pattern **a**, the structure used in subsequent Rietveld refinements (top right) yields the diffraction pattern **b**.

Figure 1 shows the simulated powder pattern for DCTPD in two different orientations. The simulated diffraction pattern of the structure generated initially gives an acceptable fit to the experimental data, except for the (102) peak at 12° 2θ, which has a very low intensity in the calculated pattern, and the $(\bar{1}02)$ peak, which was found to be absent in the experimental data. From this observation it was deduced that a simple rotation of the molecule by 90° would be required to improve fit of the simulated data with respect to the experimental powder pattern.

In the general case, any grid search method scales as $\prod_{i=1}^{n} x_i$, where x is the number of steps for the i^{th} of $n \geq 6$ parameters (three translations and three rotations for rigid molecules plus any number of torsional degrees of freedom for molecules with conformational flexibility). As a consequence, it quickly becomes untenable to search for starting structures for Rietveld refinement manually. However, one can greatly reduce the computational effort required by introducing "chemical sense" *via* the concept of close contacts between non–bonded atoms, defined *via* standard van der Waals distances. In its implementation the screening procedure draws upon the concept of decision trees [19]: Initially the molecule is divided into fragments, one of which is defined as the parent. The parent will be a rigid fragment, whereas child fragments may have torsional degrees of freedom. A tree is defined where major branchpoints represent the parent fragment at different positions and orientations in the unit cell. Emanating from these points are all structures that differ only in the coordinates of the child fragments. Initially, the parent fragment is subjected to a distance screen, whereby any two non–bonded atoms must have a separation greater than a predefined cut–off distance. If this fragment passes the test, the child fragments are assessed consecutively in the same manner. If at any time one of the molecular fragments fails the distance screen, the remainder of that particular branch is eliminated from the search without further consideration. It is problematic to base such a procedure upon the weighted profile fit factor R_{wp}.

Only those trial structures that do not have close contacts between non–bonded atoms are assessed and ranked in terms of R_{wp} and a calculated lattice energy. The latter can be assessed *via* the atom–atom approximation associated with the use of empirical force field parameters [20, 21]. Depending upon the initial step sizes selected in the grid search, and in cases where discrepancies are manifest between the two ranking procedures, optimisation of the best trial structures may be necessary to cluster similar structures.

The best trial structure after ranking is subjected to Rietveld refinement [11, 12] in order to determine the optimum structure with respect to the experimental diffraction data.

EXAMPLE CASE STUDIES

In this section we outline some examples of crystal structures solved using the methodology outlined above.

Rigid Molecules

The simplest structures to solve are those containing rigid molecules without torsional degrees of freedom. In those cases where symmetry considerations require the molecule to reside in a well defined region of the unit cell, the search for trial structures suitable for Rietveld refinement can be carried out manually. Prior to the development of our automated search procedure [3], this was the only method available for "systematic" trial structure generation.

Triphendioxazine based molecular crystals

The following cases are examples where the search for trial structures was performed manually. Triphendioxazine (TPD, Figure 2) is the basic chromophore unit for a number of commercially important dyes. Due to the low solubility of these materials in most common solvents, single crystals are not easily obtained and structure solution *via* powder diffraction is an attractive route.

TPD is a centrosymmetric molecule and crystallises in a centrosymmetric space group [18, 22]. The X-ray powder diffraction patterns were indexed [23–25] resulting in the lattice parameters **a** = 6.88 Å, **b** = 5.2 Å, **c** = 17.74 Å, and β = 93.617°, the systematic absences being consistent with the space group $P2_1/c$. As density considerations require two molecules in the unit cell, it becomes clear that the asymmetric unit must contain half a molecule. The molecular centre of symmetry therefore must coincide with the origin of the unit cell. This reduces the number of degrees of freedom to be considered in the search to those describing rotations of the molecular fragment about the origin.

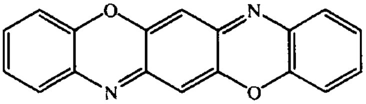

Figure 2: Triphendioxazine

As in the case of TPD, 6,13-Dichlorotriphendioxazin (DCTPD, Figure 3) crystallises in a centrosymmetric space group [17, 18]. The lattice parameters were determined to be **a** = 8.72 Å, **b** = 4.89 Å, **c** = 17.15 Å, and β = 97.87° and systematic absences are consistent with the spacegroup $P2_1/c$. Again, the number of molecules in the unit cell is 2, and the same considerations apply for the search procedure as in the previous example of TPD.

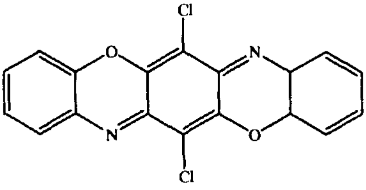

Figure 3: 6,13-Dichlorotriphendioxazine

By targeting key materials in the manner employed for TPD and DCTPD (and also 2,9-Bis(3-N,N-dimethylamino)-propylamino-6,13-dichlorotriphendioxazine, which is discussed below) it is possible to gain an understanding of the crystal chemistry of these systems, especially as they are not amenable to single crystal techniques. In particular, these systems allow us to address the interplay of steric interactions which determine the overall efficiency with which the molecules can pack within the unit cell in juxtaposition to the desireability of forming specific interactions such as hydrogen bonds. In TPD the structure is characterised by weak hydrogen bonds between the oxygen and nitrogen atoms of one molecule and hydrogen atoms of a neighbouring molecule in the crystallographic a-direction; π-π stacking in the crystallographic b-direction is also evident. The presence of the chlorine atoms in TPD-analogue DCTPD subtly changes the packing motif, resulting in the weak hydrogen bonds being replaced by chlorine hydrogen interactions with a concomitant expansion of the lattice in the a-direction from 6.88 Å to 8.72 Å.

Metal-free phthalocyanine

Metal-free phthalocyanine (Figure 4) is known to exhibit polymorphism, with at least three crystal structures, the α-form [26], the β-form [27], as well as the X-form [28], having been reported.

Although the crystal structure of the X-form had been determined previously from powder diffraction [28], the poor quality of the reported structure together with a large R-factor merited a reinvestigation. The unit cell differs from that previously reported in that a larger value of the angle β found together with a reduction in the magnitude of the a-axis [29]. Systematic absences are consistent with the space group $P2_1/a$ with two molecules in the unit cell. Symmetry considerations constrain the centre of symmetry of the molecule to coincide with the origin of the unit cell. As in the case of TPD and DCTPD only rotations of half the molecule about the unit cell origin need be considered in the systematic search procedure.

The best trial structure for Rietveld refinement against the experimental powder diffraction data was established on the basis of calculated lattice energy alone. The final refined structure is significantly different when compared to the previously published structure. A clear manifestation of this can be seen in the calculated lattice energies: for the structure determined by a systematic search the calculated lattice energy is -43.6 kcal mol^{-1}, whereas the previously reported crystal structure results in a physically unrealistic lattice energy of +81 kcal mol^{-1}. When comparing the X–form of metal–free phthalocyanine to the β–form, both present a similar packing motif. Adopting the classification of Gavezotti and Desiraju [30] for hydrocarbon packing motifs, both structures were found to represent a herringbone packing arrangements. The factor distinguishing the two structures was found to be the angle between the planes of the molecules. In the X–form, this angle is 50°, in the β–form a larger angle of 89° is observed. The greater angle in the β–form results in a greater packing efficiency and a lower calculated lattice energy of -45.5 kcal mol^{-1}

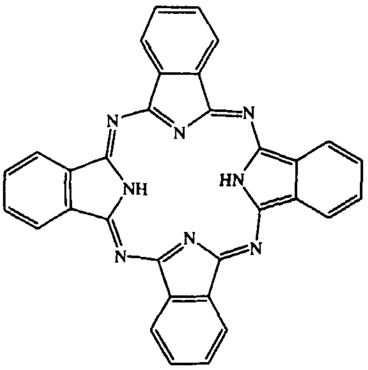

Figure 4: Metal–free Phthalocyanine

Predicting Polymorphs using a Systematic Search Approach

In the absence of experimental diffraction data, but with prior knowledge of the lattice parameters, the systematic search procedure can be employed as a powerful tool for predicting likely crystal structures.

Phenazine

The heterocyclic molecule Phenazine (Figure 5) exists in two known polymorphic forms [31–33] commonly referred to as the α– and the β–forms.

The crystal structure of the α–polymorph was determined by single crystal methods [31], whereas only lattice parameters and space group have been reported for the β–polymorph [32]. The cell parameters for β–phenazine were found to be **a** = 11.64 Å, **b** = 11.58 Å, **c** = 6.88 Å, and β = 99.32°. The space group is $P2_1/n$ with four molecules in the unit cell. In this case the asymmetric unit contains one molecule. Hence three translational and three rotational degrees of freedom needed to be considered in the systematic search. Analysis of the data revealed that the α–phase could be classified as adopting a γ packing motif, whereas the best structure found in the search procedure for the β–phase was consistent with a sandwich herringbone motif.

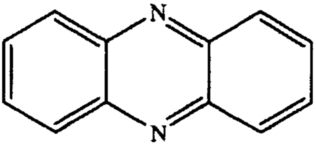

Figure 5: Phenazine

Perylene

Perylene (Figure 6) is a simple polyaromatic molecule which also exists in two polymorphic forms, α– and β–perylene.

Both polymorphs the α– and the β–form have structures determined previously by single crystal methods [34, 35]. For the β–polymorph, however, the reported crystal structure [35] was of poor quality as evidenced by the weighted R–factor of 17%. The lattice parameters of this phase are **a** = 9.78 Å, **b** = 5.90 Å, **c** = 10.59 Å, and β = 96.75°. The space group is $P2_1/c$ with two molecules in the unit cell. Again, the molecular centre of symmetry is constrained to lie on the origin of the unit cell, and only rotations of the molecule about this point need be considered. For β–perylene the systematic search results in a structure [33] that is clearly different compared to the published structure, yet exhibits a similar γ–type packing arrangement. In contrast, α–perylene adopts a sandwich herringbone arrangement.

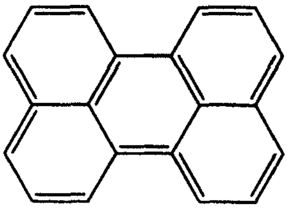

Figure 6: Perylene

Molecules with Conformational Flexibility

Molecules with conformational flexibility add a further layer of complexity to the systematic search procedure.

2,9–Bis(3-N,N-dimethylamino)-propylamino–6,13–dichlorotriphendioxazine

2,9–Bis(3-N,N-dimethylamino)-propylamino–6,13–dichlorotriphendioxazine (DATPD, Figure 7) is related to the TPD family described above, but unlike the other materials examined, the (3-N,N-dimethylamino)-propylamino side groups result in substantial torsional flexibility.

The unit cell was found to be triclinic with **a** = 8.77 Å, **b** = 13.02 Å, **c** = 8.34 Å, α = 114.06°, β = 108.72°, and γ = 74.05° [18], consistent with a single molecule in the unit cell. A manual search for trial structures was performed in the space group $P\bar{1}$. Assuming that the molecule makes use of its centre of symmetry in the solid state, it can be constrained to coincide with the inversion centre, i.e. the asymmetric unit contains half a molecule. Thus only rotational and torsional degrees of freedom were considered in the search. The flexibility of the (3-N,N-dimethylamino)-propylamino side groups requires substantially more effort in generating trial structures. Substantial differences between the final calculated diffraction pattern from Rietveld refinement and the experimental data cast doubt on the quality of the final trial structure. Clearly, with a structure such as DATPD the manual search procedure exceeds its limitations.

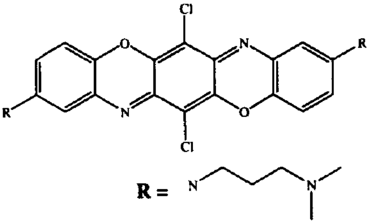

Figure 7: 2,9–Bis(3-N,N-dimethylamino)-propylamino–6,13–dichlorotriphendioxazine

Meta–stable benzophenone

Benzophenone (Figure 8) was the first organic molecular material identified as existing in different polymorhic forms [36]. It crystallises in a stable form (α) with orthorhombic symmetry [37], as well as in a meta–stable (β) form, which displays monoclinic symmetry.

The meta–stable phase was obtained by crystallisation from the supercooled melt. It was found to recrystallise to the stable phase in a monotropic phase transition which can be induced by mechanical stress or contact with the stable phase.

The lattice parameters of the meta–stable phase [38] were determined as **a** = 16.22 Å, **b** = 8.15 Å, **c** = 16.33 Å, and β = 112.91°. The volume of the unit cell is approximately twice that found for the

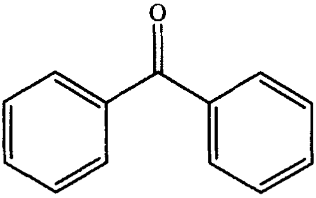

Figure 8: Benzophenone

stable phase. Systematic absences are consistent with the space group C2/c with eight molecules in in the unit cell and one molecule in the asymmetric unit. Benzophenone has two torsional degree of freedom which define the relative orientation of the phenyl rings with respect to each other as well as the keto–group. Both of these torsions were allowed to vary during the systematic search procedure.

Whereas the stable phase of benzophenone crystallises in the non–centrosymmetric space group $P2_12_12_1$ [37] and hence contains only one enantiomer (arising from the fact that the molecule and its mirror image are non–superimposable), the meta–stable phase is centrosymmetric and and contains both enantiomers. An important parameter that can be expected to vary considerably both between the polymorphic forms as well as between the *in vacuo* molecular structure and the solid state [16] is the interplanar angle between the two phenyl rings. The interplanar angle is 54.4° in the stable phase and and 64.5° in the meta–stable phase. The calculated value for an isolated molecule using the semi–empirical AM1 parametrisation is 56.0°. These differences serve to illustrate the subtle balance between intra– and inter–molecular interactions in adopting the optimal packing arrangement during the crystallisation process. However, it is worthwhile to note that benzophenone is a prime example for demonstrating the weaknesses of semi–empirical molecular orbital calculations. It is well known [39, 40], that any calculated minimum energy conformation very much depends upon the parametrisation used. Whereas AM1 was specifically developed to reproduce molecular geometries, other methods may produce poor results. One must therefore exercise extreme caution when comparing calculated with experimental structures.

Meta–Stable Phenyl Salycilate

Phenyl salicylate (salol, Figure 9) is of interest due to its similarity to benzophenone. The additional ether bond gives the molecule greater conformational flexibility and the phenolic hydroxyl group adds potential for intermolecular hydrogen bonding. As in the case of benzophenone the crystal structure of the stable phase is known from single crystal diffraction studies [41], The meta–stable phase crystallises from the supercooled melt. Due to its propensity for spontaneously recrystallising to the stable phase, it was crystallised *in situ* in a sealed capillary. The lattice parameters were determined from the powder diffraction data [42] as **a** = 17.40 Å, **b** = 5.98 Å, **c** = 10.69 Å, and β = 108.99°. The space group is $P2_1/n$ with four molecules in the unit cell.

Similar to benzophenone, the salol molecule is not superimposable with its mirror image. In contrast to the former, both the stable and the meta–stable phase of salol crystallise in centrosymmetric space groups. The space group of the stable phase is Pbca and differs from the meta–stable phase in the arrangement of different enantiomers with respect to each other. The difference for the two phases in the interplanar angle between the phenyl rings is not as pronounced as in benzophenone. The stable phase of salol has an angle of 70.15° whereas the same angle in the meta–stable phase is 73.54°.

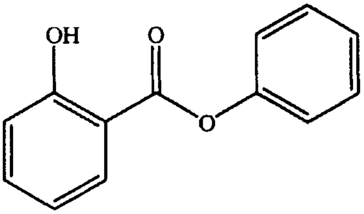

Figure 9: Phenyl Salicylate

Primidone

Primidone (5–ethyl–5–phenyl–hexahydropyrimidine–4,6–dione, Fig. 10) is an anticonvulsive agent closely related to the barbiturate family of pharmaceuticals.

It occurs in two known polymorphic forms. Primidone A is monoclinic [43] with lattice parameters **a** = 12.25 Å, **b** = 7.09 Å, **c** = 14.81 Å, and β = 117.82°, space group $P2_1/c$, and contains four molecules in the unit cell, whereas Primidone B [44] is orthorhombic (space group Pbca, eight molecules per unit cell) with lattice parameters **a** = 10.27 Å, **b** = 7.92 Å, and **c** = 27.54 Å. Both structures are known from single crystal diffraction experiments and were used to explore the viability of the systematic search procedure for systems with more than one internal degree of freedom. In the systematic search approach two torsional angles were varied, namely those describing the orientation of the phenyl and ethyl group with respect to the pyrimidine–dione ring. In both cases, the best trial structure

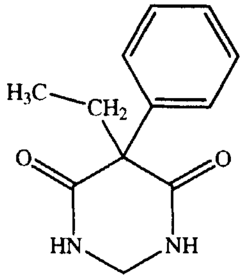

Figure 10: Primidone

from the systematic search closely resembles the known crystal structure (Table 1).

Table 1: Comparison of the systematic search results for primidone A and primidone B with the known crystal structures. The calculated lattice energies are given for the optimised crystal structures and trial structures together with the RMS fit of the best structure from the systematic search to the respective crystal structure.

Polymorph	Calculated Lattice Energy of Crystal Structure	Calculated Lattice Energy of Best Trial Structure	RMS Fit
Primidone A	-41.45 kcal mol^{-1}	-41.16 kcal mol^{-1}	0.22%
Primidone B	-42.55 kcal mol^{-1}	-42.55 kcal mol^{-1}	0.43%

Primidone A and primidone B can both be characterised in terms of chains of hydrogen bonded molecules, with each individual molecule forming a pair of N–H···O hydrogen bonds with each of two neighbouring molecules. The different polymorphs merely differ in the relative orientation of the chains with respect to each other.

1,3–Dimethylxanthine (Theophylline)

1,3–Dimethylxanthine (Figure 11, Theophylline) is a pharmaceutical used in the treatment of respiratory diseases. It is an interesting case for structure solution, due to its inherent ability to form a number of different intermolecular hydrogen bonds.

The unit cell of anhydrous theophylline was found to be orthorhombic with **a** = 24.58 Å, **b** = 3.83 Å, and **c** = 8.49 Å. Systematic absences are consistent with the space group $Pna2_1$. A systematic search results in two different structures [45] with almost identical lattice energy and R_{wp}. In both trial structures the theophylline molecules form an extensively hydrogen bonded network, but the particular hydrogen bonding motifs exhibited by the individual structures differ considerably. In the first solution, one characteristic interaction is a N···H–N hydrogen bond between the imidazole rings of two neighbouring molecules.

Another feature particular to this structure is the apparent existence of a bifurcated weak O···H–C hydrogen bond, where one hydrogen stems from a methyl group of a neighbouring molecule and the second hydrogen from the imidazol CH of a second neighbouring molecule. The second structure contains an N–H· · ·O hydrogen bond, as well as a weak O· · ·H–C hydrogen bond, where the hydrogen stems from a methyl group. Although a single crystal structure has been reported recently [46] postulating the first of the trial structures as the crystal structure, nevertheless the other trial structure is equally significant in terms of the objective measures used in this study. A preliminary study employing distributed multipole analysis indicates that the first structure is indeed the most stable, but further work is required before a definitive statement as to the nature of the crystal structure of anhydrous theophylline can be made.

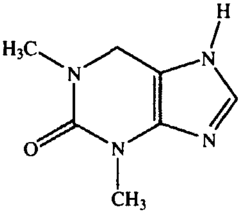

Figure 11: Theophylline

OUTLOOK

Development of the systematic search approach for structure solution from powder diffraction data is still ongoing, but the validity and usefulness of the technique has been demonstrated. Clearly, this rigorous and exhaustive approach does not represent the fastest method available, however, it is the most robust as all feasible packing arrangements are elucidated. The search algorithm is ideally suited to parallelisation and a more sophisticated implementation is under development. The extension of the systematic search to systems with considerable conformational flexibility and to systems with more than one molecule in the asymmetric unit, such as salts or solvates appears to be problematic in terms of the scaling of the search space, but it can be achieved given current advances in computing technology. The robustness of this technique make this a highly desirable goal.

Substantial further research is required to identify means of distinguishing distinct structures that are characterised by almost identical ranking based upon the criteria used. If these structures result in similar fits to the diffraction data, better data (but not necessarily diffraction data) may be required. Since factors such as preferred orientation and sample strain can severely affect the accuracy of the measured intensities in the diffraction pattern, ambiguity will always remain. Texturing effects can be removed by employing a three dimensional detector array. However, there remains the more fundamental problem of having sufficient data for structure solution. Increasingly complex molecules require an increasing number of parameters to describe their structure. The number of independent data points in a powder diffraction patterns is inherently limited by both instrumental resolution and peak overlap. Invariably, a point will be reached, where the number of parameters required to describe a particular model will exceed the number of parameters that can justifiably be used given a particular set of data. A solution to this problem is to use information obtainable from other experimental or computational techniques, as indeed the method discussed here already does. Other data that could be utilised include, for example, solid state Nuclear Magnetic Resonance data, which can identify, amongst other important information, the number of molecules in the asymmetric unit and provide information on hydrogen bonding, or infra–red spectroscopy, which can also be utilised to identify hydrogen bonding motifs.

Lattice energy calculations using improved force fields or sophisticated quantum mechanical approaches including the use of distributed multipole analysis [47,48] may enhance our ability to resolve similar structures.

A further development in the foreseeable future will be the extension of the methodology to include structures for which lattice parameters cannot be determined unambiguously due to severe peak overlap at low scattering angles. This requires a substantial amount of expertise and prior knowledge so as to determine sensible ranges for the lattice parameters based upon a knowledge of the molecular geometry. Clearly, the discrimination of structures based upon lattice energy will make such an approach to structure solution feasible and provide a valuable stage *en route* to genuine structure prediction.

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