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Structural Characterization of Industrially Relevant Polymorphic Materials from Powder Diffraction Data

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Abstract:

To fully characterize a polymorphic system, it is necessary to know the structural properties of all polymorphs formed by the molecule of interest. Traditionally, single-crystal X-ray diffraction techniques have been used for this purpose, although different polymorphic forms of a given molecule can differ significantly in crystal quality and in many cases only one or a few of the polymorphs yield single crystals that are suitable for investigation by single-crystal X-ray diffraction. Structural characterization of the other polymorphs must be carried out using *powder* X-ray diffraction. Fortunately, recent years have seen significant developments in techniques for determining crystal structures of molecular solids directly from powder diffraction data. This article highlights the current scope of these techniques and highlights some examples involving studies of polymorphic materials of industrial relevance.

1. Introduction

In the case of molecular solids, polymorphism arises when a given type of molecule is able to form different crystal structures.[1−4] Although the different polymorphs have the same chemical composition, their solid-state properties are generally different as a consequence of their different crystal structures. In recent years, there has been considerable interest within industry in being able to find and characterize as many polymorphs as possible of the active molecule of interest (for example, a drug or pigment) so that the polymorph with the most desirable properties for the targeted application can be selected. It is then essential that the desired polymorph can be produced reliably and reproducibly on scale-up and that it remains stable during subsequent processing and marketing. Given these issues, the quest to produce and fully characterize all accessible polymorphs of a given drug substance has become an area of intense activity within pharmaceuticals and other industries.

To fully characterize a polymorphic system, it is important to establish the crystal structures of the different polymorphs, and single-crystal X-ray diffraction techniques have traditionally been used for this purpose. However, the requirement for single-crystal samples of appropriate size and quality imposes a natural limitation on the scope of this technique, as many materials can be prepared only as microcrystalline powders. In many cases, different polymorphs of a given molecule differ in crystal quality, such that only one or a few of the polymorphs can be studied by single-crystal X-ray diffraction. For the other polymorphs, structure determination must be carried out using powder X-ray diffraction data. While structure determination from single-crystal X-ray diffraction data is now essentially routine (provided of course that appropriate single crystals can be grown), carrying out complete structure determination from powder X-ray diffraction data is substantially more challenging, particularly in the case of molecular solids. Nevertheless, in recent years[5−9] there have been considerable advances in the power and scope of techniques for this purpose, thus enabling full structural characterization of molecular crystals that are not suitable for investigation by single-crystal X-ray diffraction methods.

This contribution highlights the current scope of techniques for determining the structures of molecular solids directly from powder diffraction data and highlights some examples from industrial areas of research.

2. Structure Determination from Powder Diffraction Data

Although the single-crystal and powder X-ray diffraction patterns of a given material contain the same intrinsic information, this information is distributed in three-dimensional space in the single-crystal diffraction pattern, whereas it is compressed into one dimension in the powder diffraction pattern. As a consequence, there is generally considerable overlap of peaks in the powder diffraction pattern, which obscures information on the intensities of *individual* diffraction maxima and hence impedes (or in some cases prohibits) the process of carrying out crystal structure determination using the powder diffraction data. As molecular solids typically have large unit cells and low symmetry, the problem of peak overlap is often particularly severe for such materials.

The three stages involved in crystal structure determination from diffraction data are (Figure 1) (i) unit cell determination and space group assignment, (ii) structure solution, and (iii) structure refinement. The aim of *structure solution* is to obtain an initial approximation to the structure,

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(1) Dunitz, J. D. *Pure Appl. Chem.* **1991**, *63*, 177.
(2) Caira, M. R. *Top. Curr. Chem.* **1998**, *198*, 164.
(3) Bernstein, J.; Davey, R. J.; Henck, J.-O. *Angew. Chem., Int. Ed.* **1999**, *38*, 3441.
(4) Bernstein, J. *Polymorphism in Molecular Crystals*; Oxford University Press: Oxford, 2002.
(5) Cheetham, A. K.; Wilkinson, A. P. *Angew. Chem., Int. Ed. Engl*. **1992**, *31*, 1557.
(6) Harris, K. D. M.; Tremayne, M. *Chem. Mater*. **1996**, *8*, 2554.
(7) Langford, J. I.; Louër, D. *Rep. Prog. Phys*. **1996**, *59*, 131.
(8) Meden, A. *Croat. Chem. Acta* **1998**, *71*, 615.
(9) Harris, K. D. M.; Tremayne, M.; Kariuki, B. M. *Angew. Chem., Int. Ed*. **2001**, *40*, 1626.

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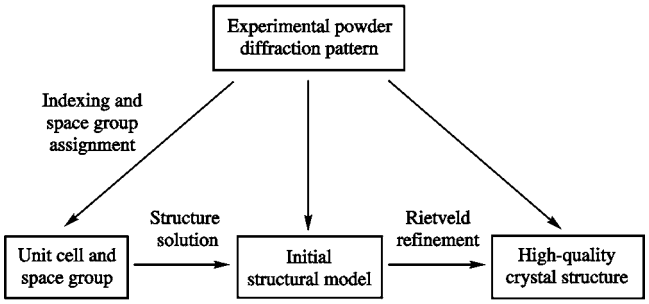


Figure 1. **Diagram illustrating the different stages involved in determination of a crystal structure from powder diffraction data.**

using the unit cell and space group determined in the first stage, but starting with no knowledge of the actual arrangement of atoms or molecules within the unit cell. If the structure solution is a sufficiently good approximation to the true structure, a good quality structure can then be obtained by *structure refinement*. For powder diffraction data, structure refinement can be carried out fairly routinely using the Rietveld profile refinement technique,[10,11] and unit cell determination is carried out using standard indexing procedures.[12−15]

The techniques currently available for structure solution from powder diffraction data can be categorized as "traditional" and "direct-space" approaches. The *traditional* approach follows a close analogy to the analysis of single-crystal diffraction data, in that the intensities $I(hkl)$ of individual reflections are extracted directly from the powder diffraction pattern and are then used in the types of structure solution calculation that are used for single-crystal diffraction data. However, as discussed above, peak overlap in the powder diffraction pattern can limit the reliability of the extracted intensities $I(hkl)$, which can lead to difficulties in subsequent attempts to solve the structure using these intensity data. In contrast, the *direct-space* approach follows a close analogy to global optimization procedures, which find applications in many areas of science. Indeed, our initial work on the development of the direct-space strategy[16] originated from identifying the opportunity to combine our existing experience in computer simulation of solids (involving global optimization based on consideration of energy)[17] together with our experience in the application of traditional techniques for powder structure solution.[18]

In the direct-space approach, trial structures are generated in direct space, independently of the experimental powder diffraction data, and the suitability of each trial structure is assessed by direct comparison between the powder diffraction pattern calculated for the trial structure and the experimental powder diffraction pattern. This comparison is quantified using an appropriate *R*-factor. Our implementations of the direct-space strategy have used the weighted powder profile *R*-factor R_{wp} (the *R*-factor normally employed in Rietveld refinement), which considers the entire digitized intensity profile point-by-point, rather than the integrated intensities of individual diffraction maxima. Thus, R_{wp} takes peak overlap implicitly into consideration. Furthermore, R_{wp} uses the digitized powder diffraction data directly as measured, without further manipulation of the type required when extracting individual peak intensities from the powder diffraction pattern.

The basis of the direct-space strategy for structure solution is to find the trial crystal structure corresponding to lowest *R*-factor and is equivalent to exploring a hypersurface $R(\Gamma)$ to find the global minimum, where Γ represents the set of variables that define the structure. In principle, any technique for global optimization may be used to find the lowest point on the $R(\Gamma)$ hypersurface, and much success has been achieved in using Monte Carlo/simulated annealing[16,19−28] and genetic algorithm[29−36] methods in this field. In addition, grid search[37−41] and differential evolution[42] methods have also been employed. Most reported crystal structure deter-

(10) Rietveld, H. M. *J. Appl. Crystallogr*. **1969**, *2*, 65.
(11) Young, R. A.; Ed. *The Rietveld Method*; International Union of Crystallography: Oxford, 1993.
(12) Visser, J. W. *J. Appl. Crystallogr*. **1969**, *2*, 89.
(13) Werner, P.-E.; Eriksson, L.; Westdahl, M. *J. Appl. Crystallogr*. **1985**, *18*, 367.
(14) Boultif, A.; Louër, D. *J. Appl. Crystallogr*. **1991**, *24*, 987.
(15) Shirley, R. A. *The Crysfire System for Automatic Powder Indexing*; The Lattice Press: 41 Guildford Park Avenue, Guildford, Surrey GU2 5NL, England, 1999.
(16) Harris, K. D. M.; Tremayne, M.; Lightfoot, P.; Bruce, P. G. *J. Am. Chem. Soc*. **1994**, *116*, 3543.
(17) Harris, K. D. M. *J. Phys. Chem. Solids* **1992**, *53*, 529.
(18) Lightfoot, P.; Tremayne, M.; Harris, K. D. M.; Bruce, P. G. *J. Chem. Soc., Chem. Commun*. **1992**, 1012.
(19) Ramprasad, D.; Pez, G. B.; Toby, B. H.; Markley, T. J.; Pearlstein, R. M. *J. Am. Chem. Soc*. **1995**, *117*, 10694.
(20) Kariuki, B. M.; Zin, D. M. S.; Tremayne, M.; Harris, K. D. M. *Chem. Mater*. **1996**, *8*, 565.
(21) Tremayne, M.; Kariuki, B. M.; Harris, K. D. M. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 770.
(22) Andreev, Y. G.; Lightfoot, P.; Bruce, P. G. *J. Appl. Crystallogr*. **1997**, *30*, 294.
(23) Engel, G. E.; Wilke, S.; König, O.; Harris, K. D. M.; Leusen, F. J. J. *J. Appl. Crystallogr*. **1999**, *32*, 1169.
(24) MacLean, E. J.; Tremayne, M.; Kariuki, B. M.; Harris, K. D. M.; Iqbal, A. F. M.; Hao, Z. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1513.
(25) Miao, P.; Robinson, A. W.; Palmer, R. E.; Kariuki, B. M.; Harris, K. D. M. *J. Phys. Chem*. **2000**, *104*, 1285.
(26) Tanahashi, Y.; Nakamura, H.; Yamazaki, S.; Kojima, Y.; Saito, H.; Ida, T.; Toraya, H. *Acta Crystallogr*. **2001**, *B57*, 184.
(27) Pagola, S.; Stephens, P. W.; Bohle, D. S.; Kosar, A. D.; Madsen, S. K. *Nature* **2000**, *404*, 307.
(28) Shankland, K.; McBride, L.; David, W. I. F.; Shankland, N.; Steele, G. *J. Appl. Crystallogr*. **2002**, *35*, 443.
(29) Kariuki, B. M.; Serrano-González, H.; Johnston, R. L.; Harris, K. D. M. *Chem. Phys. Lett*. **1997**, *280*, 189.
(30) Harris, K. D. M.; Johnston, R. L.; Kariuki, B. M. *Acta Crystallogr*. **1998**, *A54*, 632.
(31) Kariuki, B. M.; Psallidas, K.; Harris, K. D. M.; Johnston, R. L.; Lancaster, R. W.; Staniforth, S. E.; Cooper, S. M. *Chem. Commun*. **1999**, 1677.
(32) Turner, G. W.; Tedesco, E.; Harris, K. D. M.; Johnston, R. L.; Kariuki, B. M. *Chem. Phys. Lett*. **2000**, *321*, 183.
(33) Cheung, E. Y.; McCabe, E. E.; Harris, K. D. M.; Johnston, R. L.; Tedesco, E.; Raja, K. M. P.; Balaram, P. *Angew. Chem., Int. Ed*. **2002**, *41*, 494.
(34) Cheung, E. Y.; Harris, K. D. M.; Johnston, R. L.; Hadden, K. L.; Zakrzewski, M. *J. Pharm. Sci.* **2003**, *92*, 2017.
(35) Habershon, S.; Harris, K. D. M.; Johnston, R. L. *J. Comput. Chem.* **2003**, *24*, 1766.
(36) Shankland, K.; David, W. I. F.; Csoka, T. *Z. Kristallogr*. **1997**, *212*, 550.
(37) Reck, G.; Kretschmer, R.-G.; Kutschabsky, L.; Pritzkow, W. *Acta Crystallogr*. **1988**, *A44*, 417.
(38) Masciocchi, N.; Bianchi, R.; Cairati, P.; Mezza, G.; Pilati, T.; Sironi, A. *J. Appl. Crystallogr*. **1994**, *27*, 426.
(39) Dinnebier, R. E.; Stephens, P. W.; Carter, J. K.; Lommen, A. N.; Heiney, P. A.; McGhie, A. R.; Brard, L.; Smith, A. B., III. *J. Appl. Crystallogr*. **1995**, *28*, 327.
(40) Hammond, R. B.; Roberts, K. J.; Docherty, R.; Edmondson, M. *J. Phys. Chem*. **1997**, *B101*, 6532.
(41) Chernyshev, V. V.; Schenk, H. *Z. Kristallogr*. **1998**, *213*, 1.
(42) Seaton, C. C.; Tremayne, M. *Chem. Commun*. **2002**, 880.

minations of organic molecular solids from powder diffraction data have used the direct-space strategy, although we note that there have also been a number of successful structure determinations of such materials using the traditional approach.

Finally, we note that, in general, structure solution from powder diffraction data has a good chance of success only if the experimental powder diffraction pattern contains reliable information on the intrinsic relative intensities of the diffraction maxima, which requires that there is no "preferred orientation" in the powder sample. Preferred orientation arises when the crystallites in the powder are oriented preferentially in certain directions, and can be particularly severe when the crystal morphology is strongly anisotropic (e.g., long needles or flat plates). When there is a nonrandom distribution of crystallite orientations in the sample, the measured relative peak intensities differ from the intrinsic relative diffraction intensities, limiting the prospects for determining reliable structural information from the powder diffraction pattern. To circumvent this difficulty in our work, we employ a straightforward screening procedure[43] to ensure that powder samples are free of preferred orientation *before* recording high-quality powder diffraction data for use in structure determination calculations.

3. Methodology for Direct-Space Structure Solution

In the direct-space approach for structure solution, the structure is defined by a "structural fragment", which represents the atoms (or a subset of the atoms) in the asymmetric unit. The structural variables (i.e. the set Γ discussed above) represent the position, orientation, and intramolecular geometry of each molecule in the asymmetric unit. The position is defined by the coordinates $\{x,y,z\}$ of the centre of mass or a selected atom, and the orientation is defined by rotation angles $\{\theta,\phi,\psi\}$ around a set of orthogonal axes. In general, the bond lengths and bond angles are fixed (either using standard values for the type of molecule under study or using the known geometry of a similar molecule), and the intramolecular geometry is specified by a set of variable torsion angles $\{\tau_1,\tau_2,...,\tau_n\}$ that define the molecular conformation. Thus, in general, there are $6+n$ variables, $\Gamma = \{x, y, z, \theta, \phi, \psi, \tau_1, \tau_2, ..., \tau_n\}$, for each molecule in the asymmetric unit.

Much of our current research is focused on the development, implementation, and optimization of new techniques for structure determination from powder diffraction data, with emphasis on tackling the specific challenges encountered for molecular solids. Most of our current work in this field employs the genetic algorithm technique for structure solution. In the genetic algorithm, a population of trial structures, each defined by the variables in the set Γ, is allowed to evolve subject to the rules and operations that govern evolution in biological systems. Initially, the population comprises a set of randomly generated structures. The variables in the set Γ represent the "genetic code" that uniquely characterizes each member of the population. The

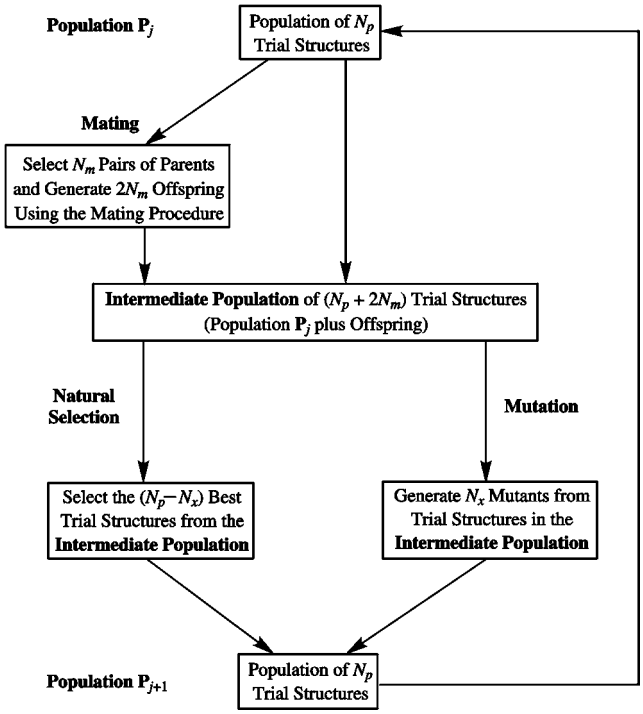


Figure 2. **Flowchart representing the evolution of the population from one generation (population P_j) to the next generation (population P_{j+1}) in the genetic algorithm technique for structure solution from powder diffraction data.**

quality ("fitness") of each structure depends on its value of R_{wp}. The population is allowed to evolve through several generations by means of mating, mutation, and natural selection. In mating, a number of pairs of structures ("parents") are selected, and new structures ("offspring") are generated by swapping genetic information between the two parents. In mutation, some structures are selected from the population and random changes are made to parts of their genetic code to create mutant structures. In natural selection, only the best structures are allowed to pass from one generation to the next generation. A schematic flowchart illustrating the procedure for evolution of the population from one generation to the next generation in the genetic algorithm technique for structure solution is shown in Figure 2. After the population has been allowed to evolve for a sufficiently large number of generations, the evolutionary process is such that the best structure in the population (i.e., with lowest R_{wp}) should be close to the correct crystal structure. Other features of our genetic algorithm technique include an implementation of Lamarckian evolution[32] (in which each new structure generated in the genetic algorithm calculation is subjected to local minimization of R_{wp} with respect to the variables in Γ) and a parallel genetic algorithm[35] (involving the separate evolution of different subpopulations, with migration of structures between subpopulations allowed to occur in a controlled manner). Full details of our genetic algorithm method are given elsewhere,[29,30,32,35] and the method is implemented in the program EAGER.[44]

(43) Cheung, E. Y.; Harris, K. D. M.; Foxman, B. M. *Cryst. Growth Des.* **2003**, *3*, 705.

(44) Habershon, S.; Turner, G. W.; Kariuki, B. M.; Cheung, E. Y.; Hanson, A.; Tedesco, E.; Albesa-Jové, D.; Chao, M. H.; Lanning, O. J.; Johnston, R. L.; Harris, K. D. M. *EAGER*; University of Birmingham, 2003.

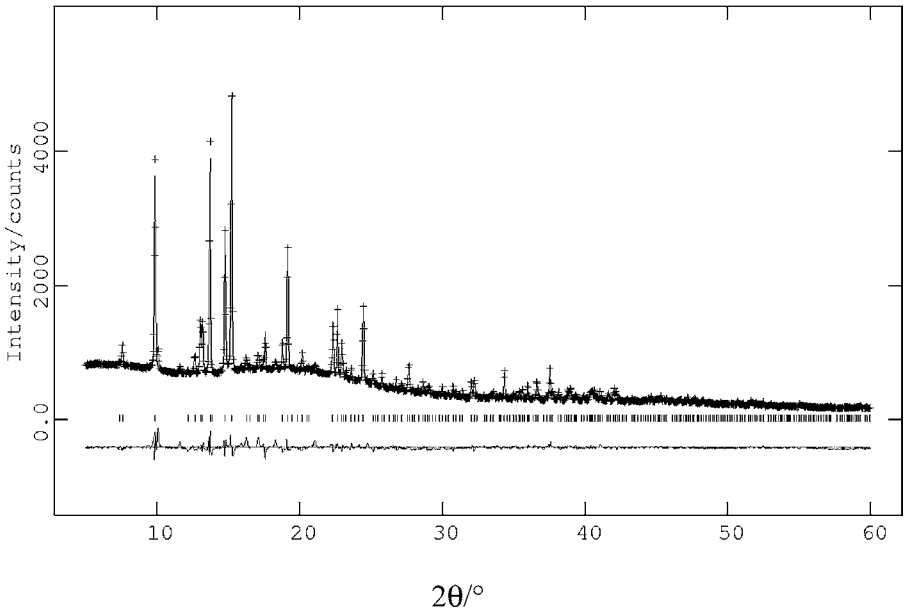
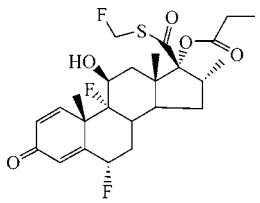


Figure 3. **Experimental (+ marks), calculated (solid line), and difference (lower line) powder X-ray diffraction profiles for the Rietveld refinement of Form 2 of FP. Reflection positions are marked. The calculated powder diffraction profile is for the final refined crystal structure shown in Figure 4.**

4. Examples of Structure Determination from Powder Diffraction Data in Cases Relating to Industrial Polymorphism

4.1. A Pharmaceutical Material with Applications in Asthma Treatment. Fluticasone propionate (Scheme 1; abbreviated FP) is a steroid of pharmaceutical importance as an antiinflammatory agent which suppresses inflammation of the bronchial passages in the lungs. When formulated as an inhaled product, the antiinflammatory action of FP treats the underlying inflammatory component of asthma. The FP molecule can exist in two different polymorphic forms. Form 1 is readily obtained by recrystallization from a variety of solvents, and the crystal structure of this polymorph was determined previously from single-crystal diffraction studies.[45] On the other hand, attempts to control the size and shape of the crystals by crystallization in a supercritical fluid medium was found to result in a new polymorph (Form 2).[31] Given that Form 2 could be prepared only as a microcrystalline powder, structure determination of Form 2 was carried out directly from powder X-ray diffraction data using the genetic algorithm method for structure solution[31] followed by Rietveld refinement. The good agreement between calculated and experimental powder diffraction patterns in the final Rietveld refinement (Figure 3) vindicates the correctness of the structure.

Scheme 1



FP

There are interesting similarities and contrasts between the crystal structures of Forms 1 and 2 of FP. Both structures contain similar hydrogen-bonded chains, but differ in the structural relationship between adjacent chains. In Form 2 (Figure 4; $P2_12_12_1$; $a = 23.24$ Å, $b = 13.98$ Å, $c = 7.65$ Å), molecules of FP are arranged in stacks along the *c*-axis with adjacent molecules related by translation. Zigzag chains of molecules related by the 2_1 screw operation run along the *b*-axis, and are linked by O−H···O═C hydrogen bonds involving the hydroxyl group and a carbonyl group of adjacent molecules. Form 1 also contains hydrogen-bonded chains (analogous to those along the *b*-axis in Form 2) but differs in the structural relationship between adjacent chains of this type. In Form 2, adjacent chains are antiparallel (related by a 2_1 screw axis), whereas in Form 1, adjacent chains are parallel to each other (related by translation).

4.2. A Latent Pigment Material. By definition, pigments are coloured solid particles that are insoluble in the medium in which the pigment is applied (for example, in paints, plastics, and printing inks).[46] To obtain good dispersion and optimization of other pigment properties (such as homogeneous colouration), pigment particles are generally microcrystalline, and as such, structural characterization of pigments in the form used in applications may be impossible using conventional single-crystal X-ray diffraction methods. Furthermore, poor solubility (another desirable characteristic of pigment materials) often prevents the growth of good-quality single crystals, and thus many pigments have eluded crystal structure determination by single-crystal diffraction techniques. For these reasons, structural characterization of

(45) Glaxo Smith Kline plc, unpublished results.

(46) Zollinger, H. *Color Chemistry*, 2; VCH: Weinheim, 1991.

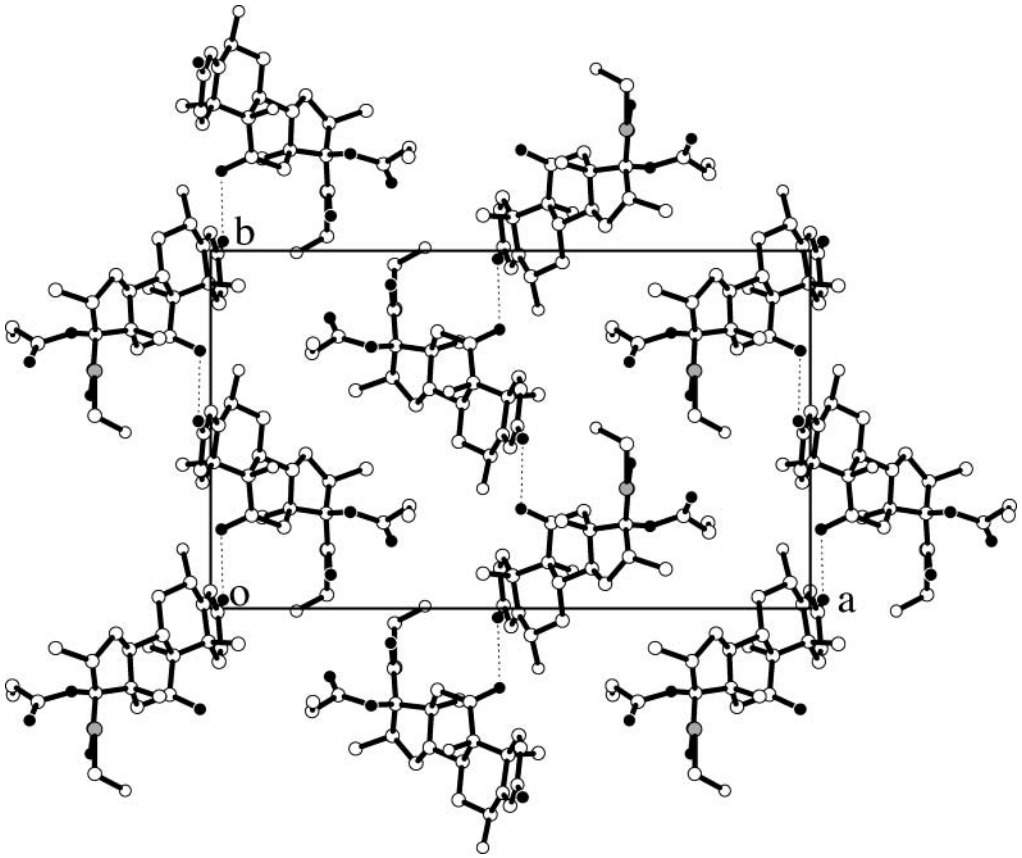
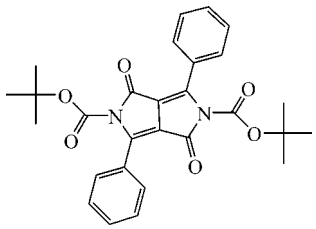


Figure 4. **Crystal structure of Form 2 of fluticasone propionate determined directly from powder diffraction data.**

pigment materials falls directly within the scope of powder structure determination techniques.

An important derivative of the commercial red pigment 1,4-diketo-3,6-diphenyl-pyrrolo[3,4-*c*]pyrrole (DPP) is 1,4-diketo-2,5-di-*tert*-butoxycarbonyl-3,6-diphenyl-pyrrolo[3,4-*c*]pyrrole (Scheme 2; abbreviated DPP-Boc). DPP-Boc is an

Scheme 2



DPP-Boc

example of a "latent pigment", which is utilized during the application process to achieve good dispersion of the pigment chromophore. Thus, DPP-Boc is readily soluble in the application medium, ensuring homogeneous dispersion; subsequently, solid particles of the DPP pigment can be generated in situ through a thermal decomposition reaction of DPP-Boc. This chemical transformation also occurs in crystalline DPP-Boc. Powder X-ray diffraction studies of DPP-Boc[24] revealed the existence of a new polymorph (β phase) in addition to a previously known polymorph (α phase).

The crystal structure of the β phase of DPP-Boc (Figure 5; $P2_1/c$; $a = 6.23$ Å, $b = 10.30$ Å, $c = 19.47$ Å, $\beta = 90.41°$) was determined[24] directly from powder X-ray diffraction data using the Monte Carlo method for structure solution. The asymmetric unit comprises half of the DPP-Boc molecule, whereas the crystal structure of the α phase ($P2_1/n$; $a = 10.49$ Å, $b = 21.46$ Å, $c = 17.13$ Å, $\beta = 95.25°$) has the somewhat unusual feature of containing three independent half molecules in the asymmetric unit.

In both polymorphs, molecules of DPP-Boc are stacked to form columns, although there are significant structural differences between the α and β phases in terms of the relative packing of molecules between these columns. In the α phase, the molecules in adjacent columns are packed relative to each other in a herringbone-type arrangement, whereas in the β phase, the molecules in adjacent columns are packed relative to each other in a nearly parallel fashion. Furthermore, there are differences in the details of the packing of molecules within a given column in the α and β phases. The kinetics of the chemical transformation from DPP-Boc to DPP are substantially different in the two polymorphs of DPP-Boc, and the structure of the β phase determined from powder diffraction data provides the opportunity to establish an understanding of the relationship between structure and reactivity in this polymorphic system.

4.3. A Pharmaceutical Material with Anticonvulsant Applications. 2-{[4-(4-Fluorophenoxy)phenyl]methylene}-hydrazinecarboxamide (Scheme 3; FPMHC) has been shown to have potential therapeutic use in anticonvulsant applications[47−49] and has been found to exist in two polymorphic forms (denoted A and B). Form A of FPMHC was discovered after polymorphic screening experiments in which the

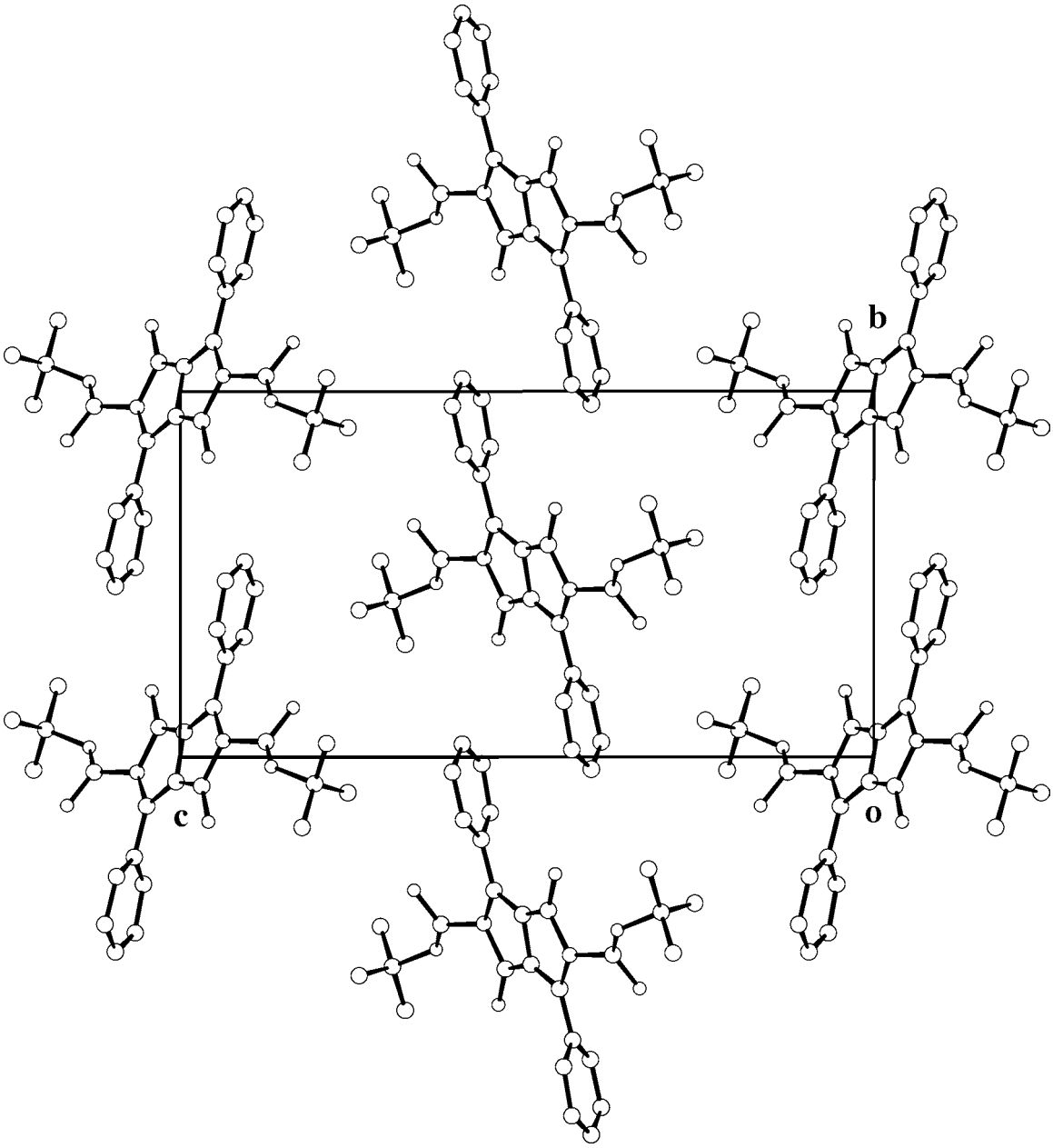
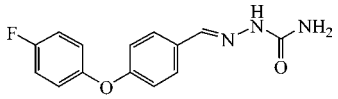


Figure 5. **Crystal structure of the β polymorph of DPP-Boc determined directly from powder diffraction data.**

Scheme 3



FPMHC

compound was recrystallized under a variety of different conditions, and the resulting solids were analyzed using thermal and spectroscopic techniques and powder X-ray diffraction. It was clear from this screening process that Form B is much more readily obtained and that the crystals of this polymorph are larger and of higher quality than those of Form A. The crystal structure of Form B ($P2_1/c$; $a = 12.71$ Å, $b = 7.74$ Å, $c = 13.28$ Å, $\beta = 104.0°$) was determined previously from single-crystal X-ray diffraction.[49] Form A is only obtained as a microcrystalline powder, which gives rise to a powder X-ray diffraction pattern that comprises a relatively small number of broad peaks, with appreciable peak overlap. Nevertheless, structure determination of Form A (Figure 6; $P2_1/c$; $a = 21.90$ Å, $b = 5.28$ Å, $c = 13.00$ Å, $\beta = 119.0°$) was carried out successfully from the powder X-ray diffraction data using the genetic algorithm technique for structure solution.[34]

In the crystal structure of Form B[34,49] (not shown here), both the NH_2 and NH groups act as hydrogen bond donors to neighbouring C═O hydrogen bond acceptor groups.

(47) Dimmock, J. R.; Puthucode, R. N.; Tuchek, J.; Baker, G. B.; Hinko, C. N.; Steinmiller, C. N.; Stables, J. P. *Drug. Dev. Res.* **1999**, *46*, 112.
(48) Puthucode, R. M.; Quail, J. W.; Stables, J. P.; Dimmock, J. R. *Eur. J. Med. Chem.* **1998**, *33*, 595.
(49) Dimmock, J. R.; Puthucode, R. M.; Smith, J. M.; Hetherington, M.; Quail, J. W.; Pugazhenthi, U.; Lechler, T.; Stables, J. P. *J. Med. Chem.* **1996**, *39*, 3984.

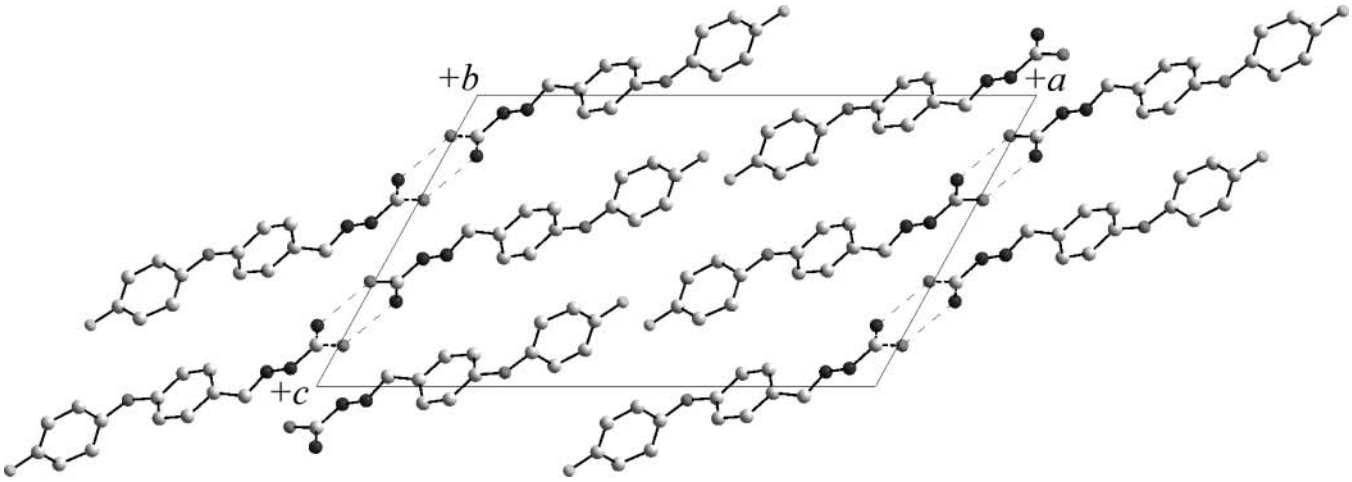


Figure 6. **Crystal structure of Form A of FPMHC, determined directly from powder diffraction data. Hydrogen-bonding interactions are indicated by dashed lines. Hydrogen atoms are omitted for clarity.**

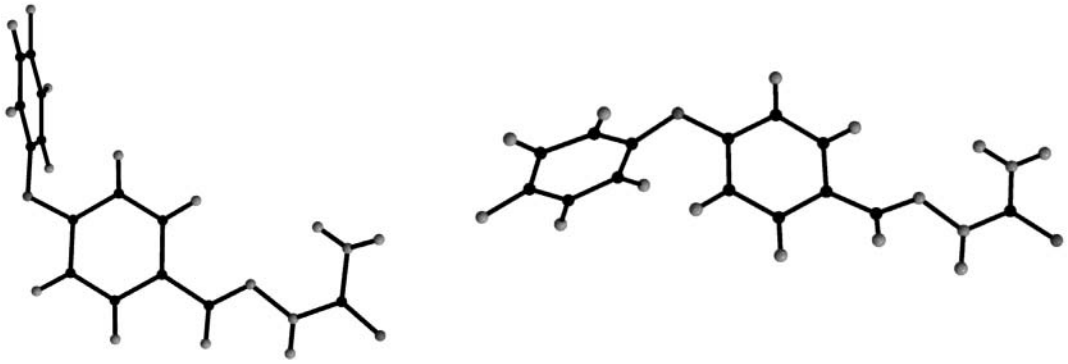


Figure 7. **The conformations of the FPMHC molecule in the crystal structures of Form B (left) and Form A (right).**

Molecules are grouped in pairs by N−H···O═C interactions involving the NH and C═O groups of both molecules in the type of eight-membered ring hydrogen-bonded "dimer" structure that is often found for amides. Each pair of this type is then linked to two other pairs via N−H···O hydrogen bonds involving the NH_2 and C═O groups of the molecules. In the crystal structure of Form A (Figure 6), only the NH_2 group is involved in hydrogen bonding interactions, and a zigzag hydrogen-bonded chain is formed along the *b*-axis involving N−H···O═C interactions.[34] In addition to the different packing arrangements in Forms A and B, the molecular conformation is also different, thus representing a case of conformational polymorphism. In both polymorphs the side chain containing the hydrogen bonding functionality is essentially planar, and coplanar with the central aryl ring, but the orientation of the *p*-fluorophenyl ring relative to the rest of the molecule differs substantially (Figure 7).

5. Concluding Remarks

Full characterization of polymorphic systems is now an important stage within the discovery and development process in industrial research, and powder diffraction represents one of the most important techniques for this purpose. In addition to its routine and well-established use as a qualitative tool for polymorph identification, powder diffraction data are a source of quantitative structural information when coupled with recently developed computational methods. As highlighted in this article for a number of structures of moderate complexity, this approach represents a powerful alternative to single-crystal diffraction for carrying out complete structure determination. Given the importance of understanding the relationships between structure and properties of polymorphic materials, access to reliable structural information is clearly essential and should not be restricted simply to those polymorphs for which single crystals of suitable size and quality for single-crystal X-ray diffraction experiments can be prepared. The application of recently developed techniques for carrying out structure determination from powder diffraction data clearly has a vital role to play in such cases.

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