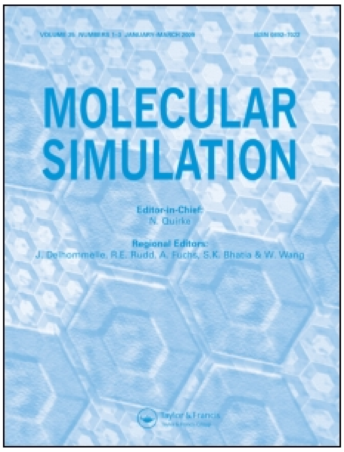

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A general purpose package (MADFOMS) for predicting the morphologies and powder X-ray diffraction patterns of molecular crystals

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A general purpose package (MADFOMS) for predicting the morphologies and powder X-ray diffraction patterns of molecular crystals

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We present a generalised procedure for predicting the morphologies and diffraction patterns of molecular crystals. The general purpose program MADFOMSs (Morphologies and Diffraction For Organic Molecular Solids) is described. The success of the approach is illustrated by application to the polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile.

Keywords: molecular crystal; morphology; diffraction; prediction

1. Introduction

Morphology prediction is an important area of study, particularly in relation to the pharmaceutical industry, since many properties of crystals, such as bio-availability and solubility are dependent upon their shape. The morphologies of crystals can have a major impact on their suitability as potential drugs both at the processing and post-processing stage. For example, in the production stage, there can be major problems if the morphology changes due to impurities or changes of solvent. Crystal morphology ultimately depends on the internal structure of crystals (molecular packing, etc.) and is thus becoming of major importance in the area of crystal structure prediction, since different polymorphs often produce differently shaped crystals. A polymorph which produces crystals which have a platy morphology is unlikely to be formed in preference to a crystal which has a prismatic shape [1].

Methods of systematically investigating the morphology of crystals were developed only comparatively recently, as compared to when their structures could be elucidated by experimental means [2]. The earliest approach to predicting crystal morphology was the Bravais Friedel Donnay Harker (BFDH) method [3–5], where the relative growth rate of a face is inversely proportional to the interplanar spacing d_{hkl} (i.e. the faces with the largest interplanar spacing have the slowest growth rates and are thus the most morphologically important). This method, however, takes no account of the molecular structure or intermolecular forces. In 1955, Hartman and Perdok introduced the concept of attachment energy and periodic bond chain (PBC) theory [6]. They classified faces into three groups according to the number of PBCs in the growth slice. A PBC is a chain of strong bonds, such as hydrogen bonds. A slice with two or more PBCs is an F (flat) face; those with two or more are S (stepped) faces and the rest are K (kinked) faces. The authors suggested that only F faces could grow according to a layer mechanism, with the S and K faces having a continuous growth mode. Hence, F faces will be slow growing and they will dominate morphologically. A more sophisticated method to model the growth rates of faces was provided by the concept of the attachment energy E_{att} (i.e. the energy released per molecule when a new slice of depth d_{hkl} is attached to the crystal face), which it is argued is proportional to the growth rate and hence inversely proportional to the morphological importance of the face. Hartman and Bennema later showed that this assumption is valid for F-faces below the roughening temperature [7]. The morphology determined in this way is known as the growth morphology as it is based on the idea of layers attaching themselves to a growing crystal.

An alternative approach to modelling morphology is to calculate the surface energy, which is the difference in energy of the atoms at the surface compared to those in the bulk per unit surface area. For a crystal in equilibrium with its surroundings, the surface energy must be a minimum for a given volume and hence the morphological importance of a face is inversely proportional to the surface energy. This approach is not generally appropriate for molecular crystals, since the resulting predicted morphologies generally contain many more faces than those that are observed experimentally.

In this paper, we describe an automated approach coded within the morphologies and diffraction for organic molecular solids (MADFOMS) program, for calculating the morphologies of molecular crystals using an automated method. The predicted morphologies can be visualised using a Wulff plot [8], which gives an indication

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of the growth rates and relative sizes of each of the observed faces. The utility of the new code is demonstrated by application to the polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile for which experimental morphology data are available.

2. Methodology

In order to calculate the morphologies and powder X-ray diffraction patterns of molecular crystals, we used the methods outlined in Figure 1. In the following section, we present first the theory behind the calculation of morphology. We describe both calculation of attachment energy and surface energy (although, as argued, the latter is not used here as it is not generally appropriate for organic molecular crystals). Second, we summarise the procedure used to obtain predicted morphologies of molecular crystals starting from the lattice vectors and fractional coordinates. Finally, the use of the Objcryst++ program library to calculate powder X-ray diffraction patterns is described.

2.1 Calculation of attachment energy

As discussed above, the attachment energy model [2] for the growth morphology of a crystal is based on the assumption that the growth rate of a face is proportional to the absolute value of the attachment energy.

The attachment energy E_{att} is defined as

$$E_{\mathrm{att}} = \sum_{i=1}^{\infty} E_{\mathrm{i}}(hkl), \tag{1}$$

where $E_{\mathrm{i}}(hkl)$ is the interaction energy per molecule between a slice of thickness d_{hkl} and the ith underlying slice. The relationship between the attachment energy and the slice energy is given by

$$E_{\mathrm{crys}} = E_{\mathrm{att}} + E_{\mathrm{slice}}, \tag{2}$$

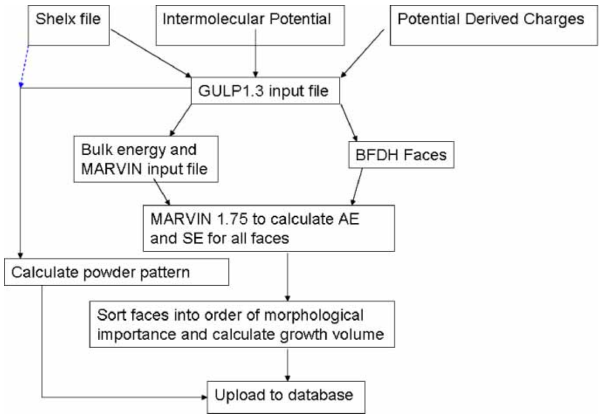

Figure 1. Scheme for prediction of properties.

where E_{crys} is the energy of the crystal, E_{att} is the attachment energy and E_{slice} is the energy of a slice of depth d_{hkl}.

The growth rate of a crystal face is assumed to be proportional to the absolute value of the attachment energy, i.e. faces with low absolute attachment energies grow most slowly and thus have the most morphological importance. Since, E_{crys} is constant for a given crystal structure, a large slice energy implies a low absolute attachment energy and so the face will be morphologically important [7].

2.2 Calculation of surface energy

As noted, an alternative approach to calculating crystal morphology is to calculate the surface energy, which is the difference in energy of the surface ions compared with those in the bulk per unit surface area. The surface energy $\gamma(hkl)$ is defined as

$$\gamma(hkl) = [E_{\mathrm{total}}(hkl) - E_{\mathrm{boundary}}(hkl) - nE_{\mathrm{cr}}]/A(hkl),$$

where n is the number of unit cells on the surface and $A(hkl)$ is the surface area of the simulation cell. E_{total} is the total energy of the system, E_{boundary} is the difference in energy between the surface atoms and the bulk atoms and E_{cr} is the energy of the crystal. The surface free energy (which we approximate by the internal energy at 0 K) must be a minimum for a crystal of given volume in equilibrium with its surroundings. Thus, the morphological importance of a face is inversely proportional to the surface energy.

2.3 Choice of intermolecular potential

To model the intermolecular forces between the molecules, we use a simple repulsion dispersion potential together with a set of point charges. Our method was originally developed to aid in the analysis of predicted crystals, where the MOLPAK-DMAREL method is used to generate a large number of hypothetical crystal structures [1,9–12]. Thus, in general we use the same isotropic *exp-6* potential as employed in the crystal structure prediction. Where an anisotropic intermolecular potential was employed (as in [12]), we use an equivalent isotropic potential for the morphology calculations.

The electrostatic interactions are modelled with a set of potential derived charges obtained using the ChelpG [13] algorithm within the program GAUSSIAN98 [14] from the same wave function as was used to obtain the distributed multipole moments [15–17] for the structure prediction. Potential derived charges give the most accurate reproduction of the electrostatic potential around the molecules within the atomic charge model [18]. Alternatively, the intermolecular potential parameters and charges from a molecular mechanics force-field such as CVFF [19] can be used.

2.4 Calculation of powder X-ray diffraction pattern

In order to simulate the powder X-ray diffraction of observed and predicted structures, we use a command-line driven program. This employs the Objcryst++ routines, which have been used in the program FOX [20,21] as a method for *ab initio* structure determination from powder diffraction. We routinely calculate powder diffraction patterns using an X-ray wavelength of 1.54056 Å for a range of 2θ from 5° to 60°, although this can be easily altered, as demonstrated in the examples below. With the program GNUPLOT, the calculated diffraction pattern is then plotted and the data is uploaded to a database.

2.5 Programs used

Our procedure uses a combination of scripts for program control together with existing programs for morphology (GULP, GDIS and MARVIN's) and powder diffraction pattern calculation (FOX/Objcryst++).

2.6 Procedure

The procedure we use to calculate morphologies is outlined in Figure 1. It involves the following steps:

(1) The atomic coordinates are assigned a potential type and charge.
(2) The program GULP [22,23] calculates the internal energy of the bulk crystal structure and generates an input file for the program MARVIN's.
(3) GDIS [24] is used to generate the faces of interest using the BFDH methodology. For each face, there will be a number of suitable cuts of the crystal face, which are also calculated by GDIS.
(4) The program MARVIN's [25] then calculates the attachment energies and surface energy for each of the faces and associated cuts in (3) above.
(5) For each face, the cut with the lowest absolute attachment and/or surface energy is taken as that which will which be slowest growing. These faces are then uploaded (in order of morphological importance) to a database for future investigation. GDIS can also be used to visualise the predicted BFDH, attachment energy or surface energy morphologies using a Wulff plot. Employing a numerical integration technique, we are also able to calculate the growth volume [26] to assist in identifying the likelihood of predicted polymorphs being observed.
(6) Finally, the powder X-ray pattern is simulated using the Fox/Obcryst++ package.

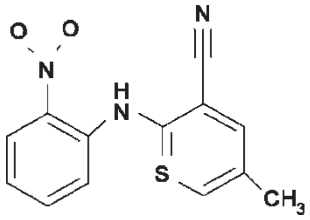

Figure 2. Molecular structure of ROY.

The resulting MADFOMS package is available from the authors.

2.7 Case study: The known polymorphs of ROY

2.7.1 Morphology prediction using the attachment energy model

As an example, we demonstrate how our procedure can be used to model the morphologies of the polymorphs of 5-methyl-2-[(2-nitrophenyl)amino]-3-thiophenecarbonitrile (Figure 2), which is known as ROY because of the red, orange and yellow colours of the crystals. This molecule

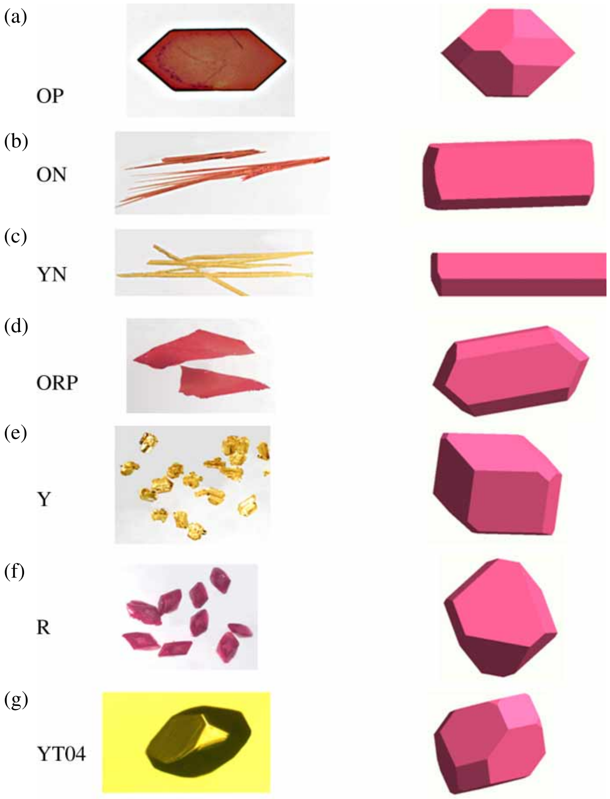

Figure 3. Comparison of observed (left) and predicted (right) growth morphologies of the seven characterized polymorphs of ROY: (a) OP; (b) ON; (c) YN; (d) ORP; (e) Y; (f) R and (g) YT04. Experimental morphologies reproduced with permission. (a)–(f) from [29] (copyright 2000 American Chemical Society). (g) from [27] (copyright 2005 American Chemical Society).

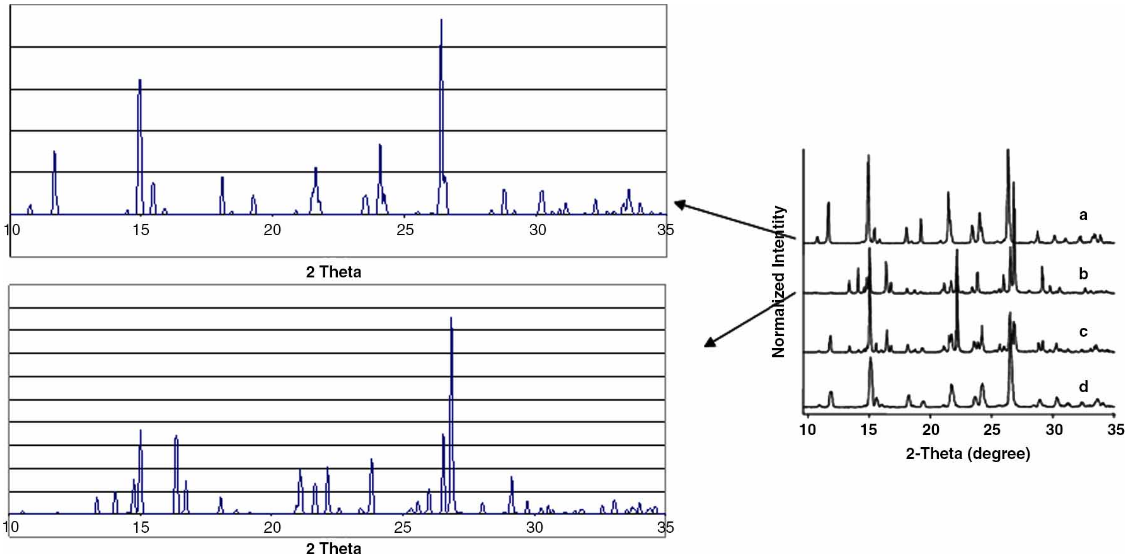

Figure 4. Predicted (left) and observed (right) powder patterns of two polymorphs of ROY:Y (top) and YT04 (bottom). Reproduced with permission from [27]. Copyright 2005 American Chemical Society.

is known to crystallise in at least ten polymorphs [27–29], which differ in the mode of packing and molecular conformation (which results principally from the thiophene torsion relative to the *o*-nitroaniline fragment). Of these, seven have been fully solved. The crystal structures of six of the polymorphs were solved by Yu et al. [29] and one has been solved by Chen et al. [27].

The following potential was used for the calculation of the attachment energies. The charges were calculated using the ChelpG [13] algorithm for an MP2/6-31G** wave function using the program GAUSSIAN [14]. The other contributions to the intermolecular potential were modelled using an empirical isotropic *exp-6* atom–atom potential. The parameters for C, Hc and Hp (hydrogen bonded to nitrogen) were taken from the FIT potential [30], while the parameters for S, O and N were taken from the work of Scherega in the 2001 blind test of crystal structure prediction [31].

The predicted morphologies using the attachment energy model are show in Figure 3. These are in very good agreement with the observed shapes of the crystals [27]. It is particularly noteworthy that we are able to predicted needle like morphologies for polymorphs ON and YN.

2.7.2 Prediction of powder X-ray diffraction patterns

We have also predicted the powder patterns for two of the polymorphs (Y and YT04) using the wavelength of 1.54184 Å used in the experimental determination and these are shown in Figure 4. Again, they are in excellent agreement with the observed powder patterns, thus indicating that our method is able to reliably reproduce experimental data.

3. Conclusion

In this paper, we have demonstrated a method that is able to routinely calculate the morphologies and powder patterns of molecular crystals. The predicted shapes of the crystals, as well as the powder patterns are in good agreement with the experimental results. This facility will be of great value in studies of crystal structure prediction and in guiding the development of crystals of pharmaceutical importance.

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