MOLECULAR CRYSTAL STRUCTURES FROM POWDER DIFFRACTION DATA: APPLICATIONS TO PHARMACEUTICAL ANALYSIS AND TO THE CHEMISTRY OF DYES

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ABSTRACT

A number of molecular crystal structures of two families of organic compounds - pharmaceutically important heterocycles and dyes - successfully solved from various powder diffraction data are presented. The obtained results demonstrate the power and reliability of powder diffraction methods in their applications to characterization solid organic materials which can only be prepared in polycrystalline form.

INTRODUCTION

Powder diffraction methods play an important role in characterization of solid organic materials which can only be prepared in polycrystalline form. The number of molecular organic crystal structures solved \textit{ab initio} from powder data is increasing steadily [1]. In addition to the direct and Patterson methods, a number of new techniques for structure solution from powder data are now available. Among them are Patterson search methods on fragments [2], entropy maximization and likelihood ranking techniques [3], Monte Carlo methods [4], difference Patterson methods [5], pseudo-atom method [6], genetic algorithms [7, 8], simulated annealing [9], grid search techniques [10-13] and some others [1]. Having obvious progress in molecular crystal structure solution from powder data, we need to know more about the possible applications of the developed methods to the real problems. This paper presents the results of the application of powder diffraction methods to the investigation of two families of organic compounds, pharmaceutically important heterocycles P1-P6 and a number of dyes D1-D7 quoted in Table 1.

Table 1. Code name, crystal and experimental data for the investigated compounds.

<table>
<thead>
<tr>
<th>Code</th>
<th>Formula</th>
<th>Sp. gr.</th>
<th>Unit cell volume, Å\textsuperscript{3}</th>
<th>Z</th>
<th>Instrument*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>C\textsubscript{7}H\textsubscript{7}N\textsubscript{3}O\textsubscript{3}</td>
<td>P2\textsubscript{1}/n</td>
<td>832</td>
<td>4</td>
<td>XI, X2, N</td>
<td>[14]</td>
</tr>
<tr>
<td>P2</td>
<td>C\textsubscript{6}H\textsubscript{6}N\textsubscript{3}O\textsubscript{2}</td>
<td>P\text{I}</td>
<td>456</td>
<td>2</td>
<td>XI, X2</td>
<td>[14]</td>
</tr>
<tr>
<td>P3</td>
<td>C\textsubscript{8}H\textsubscript{11}N\textsubscript{2}O\textsubscript{2}</td>
<td>P2\textsubscript{1}/n</td>
<td>889</td>
<td>4</td>
<td>XI, S, N</td>
<td>[15]</td>
</tr>
<tr>
<td>P4</td>
<td>C\textsubscript{6}H\textsubscript{6}N\textsubscript{6}O\textsubscript{4}H\textsubscript{2}O</td>
<td>P2\textsubscript{1}/n</td>
<td>894</td>
<td>4</td>
<td>XI, S, N</td>
<td>[15]</td>
</tr>
<tr>
<td>P5</td>
<td>C\textsubscript{3}H\textsubscript{10}N\textsubscript{4}O\textsubscript{3}H\textsubscript{2}O</td>
<td>P2\textsubscript{1}/a</td>
<td>1074</td>
<td>4</td>
<td>XI</td>
<td>[16]</td>
</tr>
</tbody>
</table>
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**EXPERIMENTAL**

The unit cell dimensions of all compounds were determined from laboratory X-ray data by the indexing programs ITO [23], TREOR90 [24] and AUTOX [25], and were refined with the program LSPAID [26]. The possible space groups were determined on the basis of systematic extinction rules and confirmed later by the crystal structure solution. The raw data for crystal structure solution and refinement were collected at room temperature at four instruments. Guinier photographs were taken in transmission mode with an Enraf-Nonius Guinier-Johansson FR552 camera using quartz monochromated CuKα1 radiation (instrument X1, Table 1). Another laboratory instrument (X2) was a DRON3 vertical diffractometer, Bragg-Brentano mode, Ni-filtered Cu radiation. Kα1, Kα2 and Kβ wavelengths were taken into account during calculations. Synchrotron X-ray diffraction measurements were carried out at the powder diffraction beam line BM16 at the ESRF, Grenoble, France. Neutron powder diffraction measurements were carried out on the high resolution multi-counter powder diffractometer (HRMCPD, Petersburg Nuclear Physics Institute) situated at the Orphee reactor of the Leon Brillouin Laboratory, Saclay, France. The exhaustive experimental details are given in [14-22].

**STRUCTURE SOLUTION AND REFINEMENT**

The full-pattern-decomposition procedure and bond-restrained Rietveld refinement were performed with the updated MRIA program [27]. All patterns were fitted using a split-type pseudo-Voigt peak profile function [28]. The observed anisotropy in diffraction-line broadening was approximated by a quartic form in h, k, l [29]. March-Dollase [30] and symmetrized harmonics expansion [31, 32] texture formalisms were used while processing textured patterns. The background was approximated by a Chebyshev polynomial. All structures (Table 1) were originally solved with the grid search procedure [13] using a priori known information from NMR and mass-spectra about the possible geometry of the molecules. Using a set of |F|^2 values derived from the synchrotron patterns after the full-pattern-decomposition procedures, the structures P3 and P4 were confirmed by direct methods via SHELXS96 [33], SIRPOW.92 [34] and POWSIM (SIMPEL algorithm [35]) without any preliminary models of the molecules, and by Patterson search methods via DIRDIF96 [36] and PATSEE [37] with the use of rigid fragments from each of the molecules.
APPLICATIONS TO PHARMACEUTICAL ANALYSIS

The compounds P1-P5 have been investigated in the framework of the study of pyrazolo[1,5-α]pyrimidine derivatives which demonstrate a potent and selective activity against the influenza virus A and coxsackie virus B3 [38]. Compound P3 belongs to the family of Ranitidine-related compounds of imidazolidine type containing a methylene group. The investigation of their possible conformations allows the study of the properties of the H₁-receptor blocker. Compound P4 is a representative of 3-amino-4-nitro-7-oxopyrazolo[1,5-α]pyrimidine derivatives which demonstrate antiphlogistic and anti-inflammatory activity in α-hydrosteroid dehydrogenase (α-HSD) tests. Compound P6 is an important precursor of some anticancer agents, e.g. prospidine [39], acting as dihydrofolate reductase inhibitors [40]. Recently, derivatives of P6 were also found to exhibit antiviral properties [41]. Two main goals have been attained for compounds P1-P6 while solving their crystal structures from powder data. First, to determine the correct molecular structure, distinguishing between several possible isomers which are indistinguishable by spectroscopic and quantum chemical methods. Second, to determine the solid state packing, which helps to build structure-activity relationships. Without crystallographic information our understanding of how the bio-chemical properties of pharmaceutical materials are related to the solid state structure remains tentative.

An illustrative example, which demonstrates the power of powder diffraction methods, is the molecular structure determination of P4. Three possible molecular structures A, B and C (Fig. 1) were suggested from the preliminary study with equal probability.

Fig. 1. Chemical diagram for the initial models of the molecule of 2,6-diamino-5-hydroxy-3-nitro-4H-pyrazolo[1,5-α]pyrimidin-7-one.

The models A-C are qualitatively equivalent. The NMR and IR spectra as well as semi-empirical calculations on AM1 level [42] using the MOPAC 7.2 program [43] give no preference to any of isomers. The crystal structure of P4 was successfully solved from three different powder patterns. The solvent water was unexpectedly found in the unit cell, so the calculated volume per non-hydrogen atom became equal 13 Å³. As a consequence of the crystal structure solution of P4, the correct molecular structure A and a three-dimensional hydrogen-bond network were determined [15].

APPLICATIONS TO ORGANIC DYES

Upon transfer from solutions to the solid state, many organic dyes demonstrate considerable changes in their visible spectra, and hence, in their color. The dependence of color on crystal packing motif has been prominently illustrated by differently colored pairs of polymorphs [44, 45]. For these objects, the powder diffraction technique complements single-crystal methods very well, because single crystals of many interesting compounds (i.e. those demonstrating the largest spectral changes) are not available, whereas powder diffraction allows the unambiguous
determination of crystal structures even with laboratory data. Because the molecular structures
of the majority of organic dyes are predictable a priori (except of few intramolecular degrees
of freedom), their models can be efficiently used in the grid search procedure. In the course of
the study of the relationship between the crystal packing motif and the reflection spectra, we
determined seven crystal structures of organic dyes from powder diffraction data. The details
are given below (see also Fig. 2):
D1: 2-aminophenalenone. The derivatives of phenalenone demonstrate high yields of
fluorescence and therefore are applied as laser dyes [46].
D2: 3-methoxybenzanthrone, Disperse Yellow 13, also used as a laser dye.
D3: 1,4-dihydroxy-3,8-bis(p-tolylamino)-anthraquinone, non-sulfonated base of Acid Green
41.
D4: 2-hydroxy-5-phenylazo-benzoic acid, used as pH indicator.
D5: 1,2,4-trihydroxyanthraquinone (purpurin) monohydrate. Position of the water oxygen
atom found from the difference Fourier synthesis.
D6: 2-hydroxy-5-[(4-nitrophenylazo)-benzoic acid, Mordant Orange 1.
D7: 4-phenylazo-benzenamine monohydrochloride, Solvent Yellow 1. The structure was
determined in two steps: first, chloride anion was localized from the Patterson map, and
second, the cation was positioned by the grid search procedure.

Fig. 2. Chemical diagrams for the dye molecules studied.

The molecular models of D1-D7 were built with semi-empirical methods (AM1, PM3), or
were constructed using structural fragments retrieved from the Cambridge Crystallographic
CONCLUSION

The examples presented, of successful molecular crystal structure solution of several representatives of two families of organic compounds from powder patterns measured at the X-ray, synchrotron and neutron devices, demonstrate the extended area of applications of powder diffraction methods to characterization of molecular compounds.

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[47] Cambridge Structural Database, Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 2EW.