COMMISSION ON POWDER DIFFRACTION

INTERNATIONAL UNION OF CRYSTALLOGRAPHY

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IN THIS ISSUE

Structure Determination from Powder Diffraction Data

(Bill David, Editor)

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CPD Chairman's Message

The CPD Newsletter is a very popular publication – more than 2000 people have now asked to receive a copy. This has motivated us to make a number of improvements. As from the present issue, the CPD newsletter will be registered as an official publication with an ISSN number (1591-9552). One of the reasons for this is to facilitate reference to articles and news reported by the newsletter and to provide a permanent forum for powder diffractionists, where new ideas and findings can be reported and disseminated to a large audience of more than 2000 recipients around the world. Following the same principle, the Newsletter is also available on the web pages of the CPD (http://www.iucr.org/iucr-top/comm/cpd/Newsletters/) from where recent issues can be downloaded. We intend to make available all the Newsletters since the first issue of 1989 and have recently started a new project that should lead to the publication of a CD-ROM with the entire collection in a few months.

A recent achievement, which is also one of the themes of the present Newsletter, is the publication of the paper resulting from the CPD Round Robin on the Quantitative Phase Analysis (QPA), carried out by Ian Madsen and colleagues. We thank Ian and his colleagues for all the effort that they put into organising the Round Robin and for producing an excellent summary article. We would also like to thank the IUCr Editorial Office for giving us permission to include the reprint from the Journal of Applied Crystallography (JAC) as an annex to the present issue. Copies of the article can also be freely downloaded from the JAC web site and will also be made available through the CPD web site.

The recently concluded congress on Accuracy in Powder Diffraction III (APD3, Gaithersburg, MD, USA, 22-25.4.2001) was the main event of the season in the field of powder diffraction. The conference provided a comprehensive review of the most relevant and recent results in a dense and well-conducted programme. We can expect that APD3 proceedings, to be published in the next months, will provide a useful reference to the current status of powder diffraction worldwide in the same way that the previous two conferences charted the state-of-the art ten and twenty years ago.

Forthcoming dates for your diaries in powder diffraction this year include the annual Denver conference (August 2001) and the third Size-Strain conference in Trento (December 2001). Important events next year include EPDIC 8 (Spring 2002) in Sweden and the IUCr World Congress (now moved from Israel to Geneva, August 2002) where eight microsymposia will be dedicated to powder diffraction and related topics.

Structure solution and refinement are two central themes of powder diffraction. These are the main topics of the present (structure solution) and next (structure refinement) issues (No.26). The next issue will be edited by Robert Dinnebier and should be printed just before Christmas. Contributions on the subject of structure refinement should be sent to Robert. News concerning powder diffraction, new software and information and reports on schools, workshops and conferences will be appreciated.

Paolo Scardi

From the Editor of Newsletter 25

This newsletter focuses on structure determination from powder diffraction data. Most of us are familiar with the more common process of structure refinement by the Rietveld method. Structure refinement, which requires an approximate structural model, has been phenomenally successful in areas as diverse as high temperature superconductivity, zeolite chemistry, fullerenes and mineralogy. Structure determination is a rather more complicated process than structure refinement, because initially we have no idea where the atoms are in the crystal structure. However, this emerging field has developed rapidly over the recent years and a diverse set of crystallographic tools have been developed to enable us to solve structures ab-initio from powder diffraction data alone.

As with all emerging fields, structure determination from powder diffraction data is not without its controversial aspects. The first article in this newsletter considers the situation in 1998 when novel global optimisation strategies were still viewed with scepticism by some and structure determination from powder data was far from routine for the majority. The challenge described in this article (which was to solve two crystal structures directly from supplied diffraction data alone) was risen to by few and met by even fewer; there was a resounding silence from the majority of the powder diffraction community. However, things have moved on some way since then. Global optimisation has proven to be competitive with direct methods and the increasing availability of software for structure solution means that many more people can now participate in successful structure determinations from both laboratory X-ray, synchrotron X-ray and neutron data. Whilst not yet routine in the sense of single crystal determinations, the application of structure determination from powder diffraction methods can be routine in many circumstances. We are now in the fortunate position where modern SDPD methods can be applied to substantial and significant problems, some excellent examples of which are described in this newsletter.

It is reassuring for us to see that it is not simply increased computing power that has underpinned recent successes, though there is no doubt that it has catalysed many developments, especially in the area of global optimisation. Rather, algorithmic developments, experimental ingenuity, chemical intuition and a refusal to accept that certain things are "just not done using powder diffraction" have all had a role to play. The articles in this newsletter serve to illustrate these points and give some idea of the breadth of the field. I hope that you will enjoy reading them as much as I have enjoyed pulling them together.

Bill David

CPD projects

QUANTITATIVE PHASE ANALYSIS ROUND ROBIN

The International Union of Crystallography (IUCr) Commission on Powder Diffraction (CPD) has sponsored a Round Robin on the determination of quantitative phase abundance from diffraction data. Specifically, the aims of the Round Robin were

(i) to document the methods and strategies commonly employed in quantitative phase analysis (QPA), especially those involving powder diffraction,
(ii) to assess levels of accuracy, precision and lower limits of detection,
(iii) to identify specific problem areas and develop practical solutions,
(iv) to formulate recommended procedures for QPAusing diffraction data,
(v) to create a standard set of samples for future reference.

Some of the analytical issues which have been addressed include (a) the type of analysis (integrated intensities or full-profile, Rietveld or full-profile, database of observed patterns) and (b) the type of instrument used, including geometry and radiation (X-ray, neutron or synchrotron). While the samples used in the Round Robin covered a wide range of analytical complexity, this paper reports the results for only the sample 1 mixtures. Sample 1 is a simple three-phase system prepared with eight different compositions covering a wide range of abundance for each phase. The component phases were chosen to minimize sample-related problems, such as the degree of crystallinity, preferred orientation and microabsorption. However, these were still issues that needed to be addressed by the analysts. The results returned indicate a great deal of variation in the ability of the participating laboratories to perform QPA of this simple three- component system. These differences result from such problems as (i) use of unsuitable reference intensity ratios, (ii) errors in whole-pattern refinement software operation and in interpretation of results, (iii) operator errors in the use of the Rietveld method, often arising from a lack of crystallographic understanding, and (iv) application of excessive microabsorption correction. Another major area for concern is the calculation of errors in phase abundance determination, with wide variations in reported values between participants. Few details of methodology used to derive these errors were supplied and many participants provided no measure of error at all.

SIZE-STRAIN ROUND ROBIN

The first round-robin phase on methods of line-broadening analysis was concluded in March after the last results were received from round-robin participants.

The preliminary report and analysis of results are available at http://www.boulder.nist.gov/div853/balzar , CPD and CCP14 Web sites. More details about specimen preparation and new developments will follow in future Newsletter issues.

WWW sites related to powder diffraction

The Commission on Powder Diffraction (CPD): http://www.iucr.org/iucr-top/comm/cpd/
The International Union of Crystallography (IUCr): http://www.iucr.org
The International Centre for Diffraction Data (ICDD): http://www.icdd.com
The International X-ray Analysis Society (IXAS): http://www.ixas.org
CCP 14: http://www.ccp14.ac.uk/index.html

Submitting a proposal for neutron diffraction or Synchrotron Radiation X-ray Diffraction is possible at many Large Scale Facilities (LSF) in the world. It represents an important and frequently unique opportunity for powder diffraction experiments. A useful guide and information can be accessed through the following web-sites, maintained by R.Dinnebier*:*
http://www.pulverdiffraktometrie.de

This list is far from being complete and needs input from users and readers of the Newsletter. Please, send comments directly to *R. **Dinnebier*** (r.dinnebier@fkf.mpg.de)

Corrigendum in CPD Newsletter (No 25)

In the previous issue of the CPD Newsletter, there was a small typographical error in the ordering of the figures in the article by Paul Fewster entitled *"Insight into polycrystalline materials with ultrahigh resolution and reciprocal space mapping"*. To make full sense of this excellent article, Figures 2 and 3 should be switched round. (*Ed*.)

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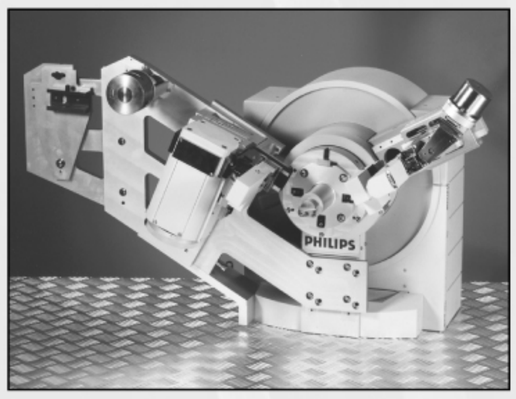
X-ray diffraction for today and tomorrow



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No Internet access? No problem

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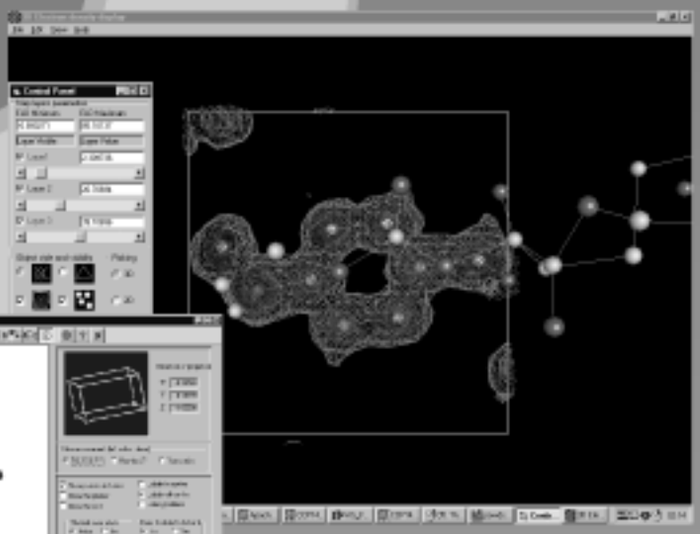
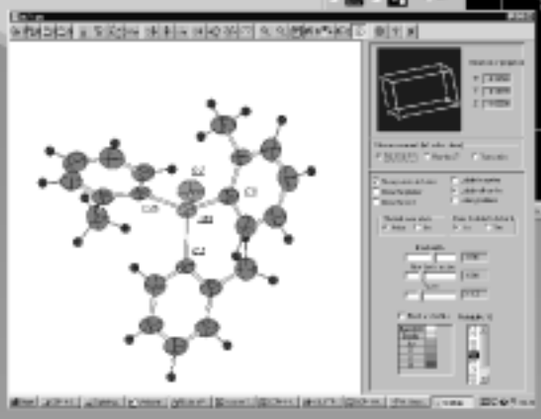


Packed with a host of crystallographic software packages and resources, these virtual Internet CD-ROMs have been produced with the permission of software and website custodians. The organizer of the NeXus project, the IUCr Committee on Electronic Publishing, Dissemination and Storage of Information, invites academics and students in crystallography working in laboratories in developing countries that are isolated from the Internet to register their interest. The CD-ROMs are free of charge and available while stocks last.



Contents

Multiple software packages and suites relevant to single-crystal, powder diffraction, crystallographic structure validation and crystallographic teaching, including

- single-crystal structure solution and refinement suites for PC
- crystallographic structure visualization programs
- powder diffraction pattern visualization, peak profiling and indexing software
- powder diffraction structure solution
- classic and modern crystallographic program source code
- Rietveld refinement packages
- structure validation and checking software
- powder pattern simulation and journal-quality structure plotting and photorealistic rendering programs
- educational websites dealing with crystallographic teaching
- webpage-based tutorials on how to use many of the programs within the CD-ROM
- part of the IUCr website including IUCr Commissions.

The CD-ROM is sponsored by the International Council for Science, the IUCr and the Collaborative Computational Project No. 14 (CCP14) for Single Crystal and Powder Diffraction.

Send your request for a free Crystallographic NeXus CD-ROM (preferably via e-mail or by conventional mail) to

Lachlan M.D. Cranswick
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E-mail: L.Cranswick@dl.ac.uk
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Fax: +44 1925 603124
WWW: http://www.ccp14.ac.uk

The CD-ROMs, and regular updates, will be sent by airmail.

Revisiting the 1998 SDPD Round Robin

Armel Le Bail [(1)] *and Lachlan M.D. Cranswick* [(2)]

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INTRODUCTION

In the middle of 1998, the number of structure determinations by powder diffractometry (SDPD) was close to 300 of which 250 were published in the period 1992-1997 [1]. At that time, a huge number of methods and computer programs had already proven, at least once, their efficiency in succeeding in the various steps of the process of solving structures from powder diffraction data. The word "routine" was pronounced more and more frequently, so that it was considered timely to organize a Round Robin, in order to try to clarify the various claims about the ease or otherwise in performing SDPDs. Data and questionnaires were made available from a Web site starting from May 18, 1998 and the deadline was the last day of June. The competition was spammingly announced at many Newsgroups and Mailing lists related to crystallography and material science. Mails were sent also to some chemistry lists (Chemweb and CCL), trying to interest structure predictors to undertake first principles or semi-empirical calculations. Moreover, personal e-mails were sent to a number of well-known experts. As a consequence of this campaign, more than 800 visitors had a link to the homepage, which is still available [2]. 70 of the 800 visitors downloaded the data.

SELECTION OF SAMPLES FOR ANALYSIS

There is a clear distinction between compounds for which prior knowledge is available (molecular formula) or not. This difference may lead to one choosing quite different methods for solving the crystal structures. It was thus decided to propose two samples that fulfilled these conditions. We restricted the scope of this Round Robin to the structure solution part by providing the cell and space group information. The first sample was inorganic, a carbonatocobalt(III)pentamine nitrate hydrate; the second sample was organic, the pharmaceutical compound tetracycline hydrochloride. A medium resolution synchrotron pattern was provided for the latter, as well as a conventional X-ray powder pattern with similar resolution. The organic sample was especially selected for model location methods; the molecular shape, however, was not given. We considered that the shape could have been very easily obtained from various sources. During the Round Robin course, one of the participants gave a very accurate structure for tetracycline hydrochloride that even included hydrogen positions. Thus for validation purposes, it was found necessary to record a data set from a very small single crystal (40x30x20µ) selected in the powder, using the Daresbury 9.8 station equipped with the SMART Siemens system [3]. The subsequent structure was determined easily (*SHELXS*) and refined without any constraint, including the hydrogen atoms [4]. This raises the question of what constitutes a powder and what a single crystal sample. The inorganic structure is also published now proving that a solution was obtainable from powder data [5].

PARTICIPANTS

The 70 people who downloaded data may be considered to be subscribers to this Round Robin. The possibility was given for either anonymous download or filling a Web form asking for details about which methods and software will be used for 3 main steps : structure factors extraction, structure solution and structure completion and refinement. 31 subscribers filled in the Web form, more or less completely, indicating that they intended to use some of the best known programs such as *GSAS*, *FULLPROF*, *SHELX* and *SIRPOW*. 11 participants gave explicit answers to all the 3 main steps, simultaneously. One expert indicated after the deadline that he would have participated if the molecular shape had been given for sample 2.

RESULTS AND DISCUSSION

In the end, we received 5 full questionnaires from 4 final participants; one questionnaire for sample 1 and four for sample 2. Participant 1 made a very rapid reply but was unable to provide coordinates. By a search in the Cambridge Structural Database, he easily found the reference for the pharmaceutical compound as being the tetracycline (alias achromycin) hydrochloride. He then suggested that the coordinates should be found in this reference. Unfortunately, however, the coordinates were not available in this paper or in the Cambridge Structural Database. Only the molecular formula was available. Participant 2 was the only regular subscriber to have sent a successful questionnaire. He focused his attention exclusively on sample 2 and solved its structure, including the hydrogen atom positions by the global optimization method. A model for the molecule was taken from the tetracycline hydrate in the Cambridge Structural Database (TETCYH10 entry) and the water was removed. The tetracycline fragment and the Cl atom were positioned at random in the unit cell and an optimum position was searched (Fig. 1) by simulated annealing using the DRUID program against the 100 first structure factors extracted by the Pawley method from the synchrotron data. The final Rietveld refinement plot is shown on the Figure 2. There is something curious between the starting and final model. The main move is that O2 and N1 in the TETCYH10 model have rotated by 180° along the C2-C3 axis. The H

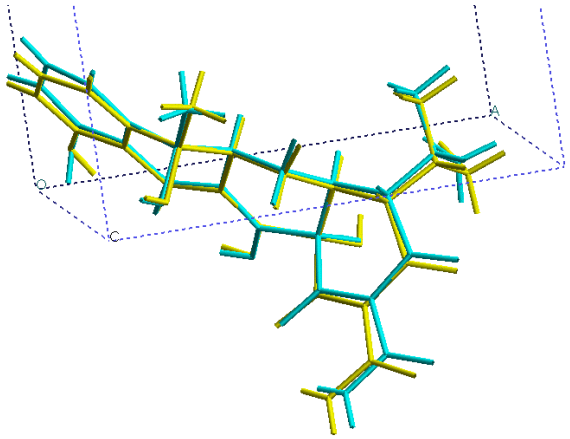

Fig. 1 Comparison of the molecular structures of tetracycline hydrochloride obtained from global optimization and from the final Rietveld refinement (Participant 2)

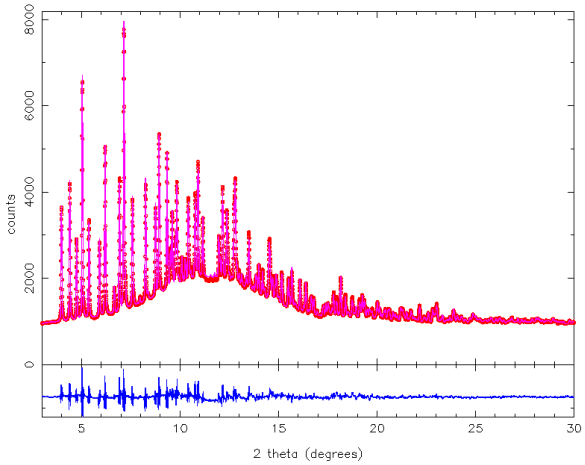

Fig. 2 Final synchrotron X-ray diffraction Rietveld plot for tetracycline hydrochloride.

atoms did not moved much between the initial and final model. An additional hydrogen atom should have been found for building the complete sample 2 structure, O2 in the hydrate becoming an OH. This hydrogen was not included by participant 2. Interviewed on this question, participant 2 commented that the exclusion of the hydrogen atom was an oversight caused by no sleep on the previous night. The diffraction pattern had been downloaded and the structure solved the day after a trans-Atlantic flight. The total time for solution was two hours.

Participant 3 did not have easy Web access and obtained the data by e-mail. He thought that sample 2 would be unsolvable without the molecule connectivity and asked for it. We had anticipated that we would reply positively to such a request, as the connectivity could normally be independently determined by a chemist using other methods such as magnetic resonance. Participant 3 sent filled questionnaires for samples 1 and 2, estimating finally that both of them were unsolvable. We are forced to conclude that the remaining participants found the structures either non-routine, non-solvable or too uninteresting.

Participant 4 downloaded the data anonymously and solved the sample 2 structure from the conventional X-ray data by using the CSD package. 158 structure factors were extracted by using the CSD-PROFAN program. Using the CSD-MAIN program, the chlorine atom was located by Patterson methods. The first Fourier map produced the coordinates of ten of the other atoms. Several cycles of Rietveld and Fourier syntheses were required to complete the structure (Figs. 3 and 4). According to participant 4, the full time needed for solution and refinement was only 3 hours, 2 cups of coffee and 5 cigarettes by using a low-end Intel PC. Participant 4 wrote also that "the structure of the inorganic complex is very simple and that is why it is not interesting."

It should be stated that participant 2 had provided the most accurate results with mean displacements relative to the single crystal data lower by a factor 2 than those from participant 4 and from the organisers [2]. Even the hydrogen atom positions were well located with a mean error of 0.2 angstroms.

COMMENTS

If the structure was in fact quite simple to solve using Patterson - doesn't it say something t hat there was not a

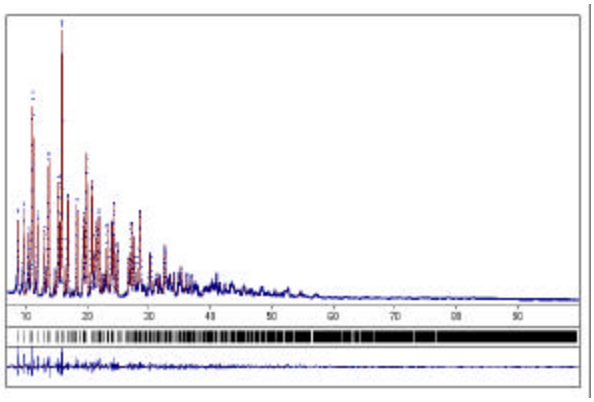

Fig. 3 Final conventional X-ray diffraction Rietveld plot for tetracycline hydrochloride.

flood of results? The solving of sample 2 structure from Patterson is not really the way that most crystallographers would have expected. Preconceived ideas would have prevailed that the unique Cl atom would not have been so heavy that a Patterson would have easily disclosed it.

Participant 4 obtained R_F=0.57 with the Cl atom. Remember that putting anything at any place gives you already R_F=0.5 or 0.6. In fact, the structure solution as described by participant 4 appears disarmingly simple, but it is not that straightforward. Here is why. Let us examine the Fourier difference as Participant 4 provided it. The 2 main first peaks are not atoms, neither is the fourth, the seventh nor the ninth. Many standard crystallographers would have given up at this stage, but not Participant 4. He was able to recognize a connected chain of 6 atoms. Here is the importance of skill, and experience. Most people would have stopped, rejecting this Fourier synthesis because of the two first intense peaks do not correspond to anything, or perhaps would have attempted a refinement of the coordinates, which would have failed. Many would not even have believed that a Fourier synthesis with only the Cl atom would have a chance to be successful. The organizers did not try the Patterson method because they had the preconceived idea that it was impossible (in fact we continue to think that way). Because the SDPDRR is mainly a YES/NO Round Robin (i.e. you win or not), we should take all those lacking questionnaires for 68x2 as a failure to solve. Perhaps, we should not count the 70 data downloaded but only the 31 regular subscribers. Anonymous downloaders never formally declared their intention to solve the problems. However, it should be noted that if single crystal data had have been provided, structure solving would have been “routine” using all freely and commonly available single crystal structure

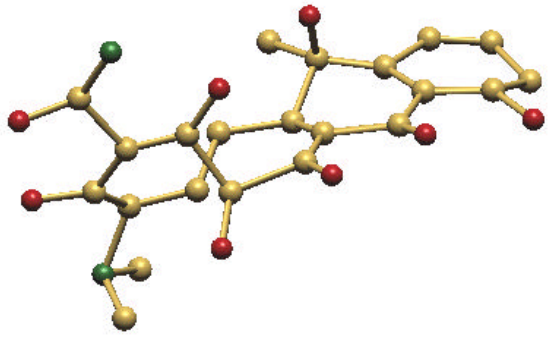

Fig. 4 Tetracycline hydrochloride model built from Patterson and Fourier recycling (Participant 4).

solution packages; e.g.; *SHELXS*, *SIR*, *DIRDIF*, *CRUNCH*.

CONCLUDING REMARKS AND RECOMMENDATIONS

The conclusion from this 1998 Round Robin is that solving structures "on demand" from powder diffraction is non-routine and non-trivial, requiring much skill and tenacity on the part of practitioners (though this should be tempered by the fact that no molecule location program was easily available for free from any website in 1998). Publications stating that structure solution using powder diffraction data is now "routine" (especially from the perspective of single crystal practitioners attempting powder diffraction based structure solution) could be considered misleading. Providing inaccurate, rosy reviews can be counter productive with respect to bringing the field into disrepute as being one populated by the crystallographic equivalent of snake-oil salesmen. The crystallographic definition of "routine" structure solution is presently based on the single crystal experience, of one where structures literally solve to near completion at the click of a button. At present much work can be done to enhance powder diffraction based software to give them single crystal quality automation and robustness to help make structure solution from powder diffraction more an attractive method than it is at present.

TODAY

A report on the SDPD Round Robin delivered at the ECM-18 congress is still available [6], as well as one written by a scientific journalist, David Bradley [7]. The number of determined structures using powder diffraction data is now approaching 500, and the proportion of organic compounds slightly increases, but remains lower than 20%. New programs for molecule location have been made available [8]: *POWDERSOLVE* (having proposed a post-deadline contribution [9]), *PSSP*, *ENDEAVOUR*, *TOPAS*, *ESPOIR*, etc, or new options of old programs (the upcoming version of *EXPO2000* and the renamed *DASH*, which was formally *DRUID*. Alas a good number of these programs are commercial. Moreover, the use of the Internet has grown since 1998 so that if the Round Robin had been proposed in 2001, more participants would have had a chance to succeed with both samples. Nevertheless, confirming this hypothesis needs a new Round Robin to be organized. Perhaps now is a good time.

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A 117-Atom Structure from Powder Diffraction Data

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INTRODUCTION

This is the story of how the structure of the very complex zeolite UTD-1F, with 117 atoms in the asymmetric unit, could be solved from powder diffraction data[1]. The structure solution was the culmination of a long period of method development that required not only new data analysis software, but also a new way of collecting data [2]. But let us begin at the beginning.

Our research group has a long-standing interest in zeolite structure analysis, and, because zeolites are rarely available in the form of single crystals, this has always included development of powder diffraction methodology. In our search for more powerful approaches to zeolite structure solution, model calculations reported by Hedel et al.[3] prompted us to consider the possibility of exploiting texture (preferred orientation of the crystallites). Usually, powder diffractionists go to great lengths to avoid any preferred orientation in their samples, because it can severely distort the intensities in the measured diffraction pattern. However, if the data are collected appropriately, this distortion, which is a function function of the orientation of the crystallites in the sample and of the sample in the X-ray beam, can provide additional information about the relative intensities of reflections that overlap in 2θ.

CONCEPT

Consider the three types of samples (single crystal, "ideal" powder and textured powder) sketched in two dimensions in Fig. 1a-c. The textured sample is intuitively intermediate between a perfectly oriented single crystal, and a powder with crystallites oriented in all directions, and the corresponding two-dimensional diffraction patterns support this view. The three reflections highlighted in (a),

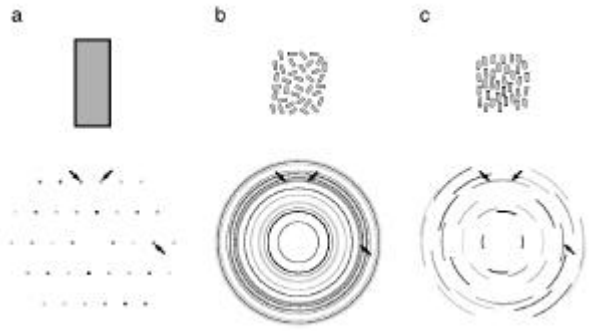

Fig 1 Two-dimensional schematic drawings of a specimen and its diffraction pattern for (a) a single crystal, (b) a powder with randomly oriented crystallites, and (c) a textured powder. The arrows highlight three reflections with similar diffraction angles that are separated in the single-crystal pattern, but overlap in the normal powder pattern. The diffraction angle 2θ increases radially from the center of each diffraction pattern.

overlap in the powder pattern in (b), but can be distinguished in (c).

By collecting data along several different radial directions (i.e. by orienting the sample appropriately in the X-ray beam), information about the relative intensities of reflections that overlap in a standard powder diffraction pattern can be obtained. This was the basic idea behind the subsequent method development.

Experimental Setup

To collect the necessary data on a flat-plate sample in which a preferred orientation of the crystallites has been induced, a controlled way of orienting (tilting and rotating) the sample in an X-ray beam is required. This is easily done by adding two more circles (χ for tilting and ϕ for rotating) to a Bragg-Brentano diffractometer, so that the instrument resembles a standard 4-circle single-crystal diffractometer. However, problems arise as soon as the sample is tilted, because parts of the sample are moved off the focusing circle and the parafocusing condition is violated. The result is that the peaks in the diffraction pattern become very broad as the tilt angle increases. To circumvent this problem, a parallel beam geometry with a pre-detector analyzer crystal was used. This setup (Figure 2) was installed on the powder diffractometer on the Swiss-Norwegian Beamline (SNBL) at the European Synchrotron Radiation Facility (ESRF) in Grenoble, and early experiments showed that high-resolution patterns could indeed be obtained at any tilt angle.

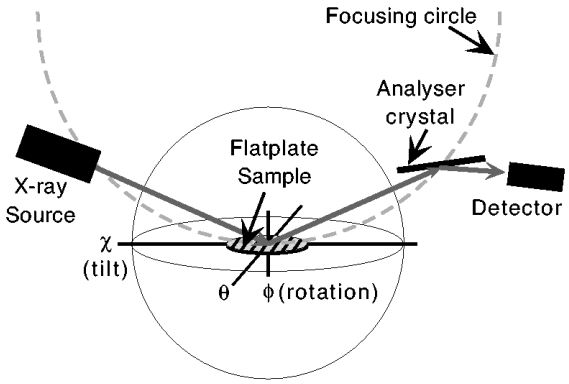

Fig. 2 Experimental setup

Data Collection

Before any data collection can be done sensibly, the intensity fall off as a function of 2θ and tilt (the X-ray beam overshoots the sample at higher tilt angles) must be calibrated with an untextured sample that has an absorption similar to that of the sample of interest. We used a sample of the cubic Zeolite A with very small crystallites for this purpose. The next step is to determine how the crystallites are oriented in the sample, and that is done by measuring pole-figure data on several (number depends upon the symmetry) non-overlapping reflections. That is, the variation of the intensity of a single reflection is measured as a function of sample orientation (5° steps in both rotation and tilt, for a total of 1081 measurements (72×15+1) for a maximum tilt of 80°). Finally, those sample orientations that are likely to give the largest intensity contrasts are selected for the collection of full diffraction patterns.

Data Analysis

Data analysis is based on the equation

$$y(2\theta,\chi,\phi) = \sum_{hkl} I_{hkl} P_{hkl}(\chi,\phi) G(2\theta - 2\theta_{hkl})$$

where y is the intensity of the powder diffraction pattern measured at step 2θ for the sample orientation (χ,ϕ), the summation is over all reflections contributing to the intensity at that step, I_{hkl} is the true integrated intensity of reflection hkl (single-crystal value), $P_{hkl}(\chi,\phi)$ is its pole-figure value for the sample orientation (χ,ϕ), and $G(2\theta - 2\theta_{hkl})$ is the peak profile function.

First the texture of the sample is determined from the pole-figure data. Once this has been done, the orientation of the crystallites is known, and the values of $P_{hkl}(\chi,\phi)$ (measure of how much of the total intensity of reflection hkl will be measured at a specific sample orientation) can be calculated for any sample orientation. A single set of single-crystal-like intensities can then be extracted simultaneously from the full diffraction patterns measured at different sample orientations. Although the uncertainties in these reflection intensities will be larger than those obtained from a single crystal, they will be much more realistic than those obtained from a standard powder diffraction pattern.

The High-Silica Zeolite UTD-1F

As the method development was approaching completion, we received a highly crystalline sample (i.e. the peaks in its powder diffraction pattern were very sharp) of the zeolite UTD-1F from Dr E.J.Creyghton, Shell, Amsterdam. Preliminary indexing of the pattern gave a monoclinic unit cell (a = 14.963 Å, b = 8.470 Å, c = 30.010 Å, β = 102.7°, V = 17,616 Å^3), and the systematic absences were consistent with the space group $P2_1/c$. Because of the size

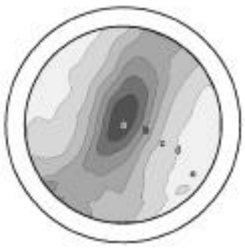

Fig. 3a The pole figure for the $10\bar{2}$ reflection of the textured UTD-1F sample.

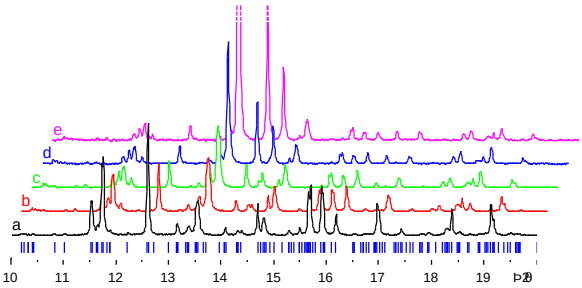

Fig. 3b Small sections of the five diffraction patterns collected at the sample orientations indicated in the pole figure.

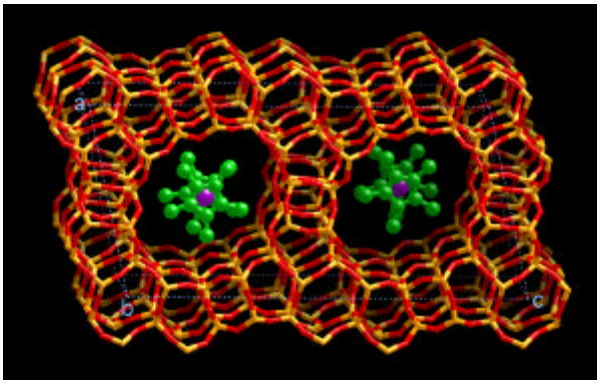

Fig.4 The structure of the high-silica zeolite UTD-1F showing the framework structure and the ordering of the $Co(Cp^*)_2^+$ complexes in the 14-ring channels.

and symmetry of the unit cell, the reflection overlap is considerable, and attempts to solve the structure using standard techniques did not succeed. The unit cell appeared to be substantially different from that reported for a similar material UTD-1 (orthorhombic, a = 18.98, b = 8.41, c = 23.04 Å), which had been shown to be disordered [4].

Fortunately, the crystallites in the sample were very long fine needles (ca. 0.5 × 0.5 × 40 μm^3) and appeared to be particularly well-suited for the application of the new method. To orient the crystallites, the polycrystalline powder was mixed with a small amount of a viscous polystyrene / tetrahydrofuran solution and then smeared on a glass slide using a single motion. The slurry was allowed to dry and then a second coat was applied by smearing in the same direction. This process was repeated until the specimen was suitably thick.

Pole-figure data were collected for 7 non-overlapping reflections, and then full diffraction patterns were collected for five different sample orientations (Fig. 3). A full texture analysis of the pole-figure data was performed using the program package BEARTEX[5] to determine the $P_{hkl}(\chi,\phi)$ values, and then using these values, a single set of reflection intensities was extracted from the five diffraction patterns. These data were used as input to the direct methods programs in the single-crystal program package Xtal3.2 [6] running in default mode.

In the top 40 peaks of the initial *E*-map, 16 Si, which described a complete 3-dimensional, 4-connected framework with 14-ring pores (Fig. 4), and even 17 of the bridging oxygens were found. Subsequent difference electron density maps generated using the *pseudo* single-crystal data allowed the remaining 15 oxygens and the (non-framework) Co to be located. The electron density map generated using this structural model and the powder diffraction data collected with synchrotron radiation on a non-textured sample, immediately revealed the location of the C atoms of the pentamethylcyclopentadienyl (Cp*) rings coordinated to the Co, to yield a structure with 69 atoms (16Si + 32O + 1Co + 20C) in the asymmetric unit. However, the short distances between symmetry-related $Co(Cp^*)_2^+$ complexes required that a disordered model be assumed.

Refinement of this structure, particularly the atoms of the Co complex, was not stable, and small but significant intensity differences between the observed and calculated diffraction patterns remained (R_F = 0.118 and R_{wp} = 0.309). Consequently, a reduction of the symmetry to *Pc* was attempted, even though the concommitant increase in the number of positional parameters (from 207 to 349) was understood to be problematical. Much to our surprise and delight, the refinement then proceeded smoothly and eventually converged with R_F = 0.041 and R_{wp} = 0.134 (R_{exp} = 0.101). The weight of the geometric restraints on the atoms of the framework and the Co complex could be reduced to 1.0 (i.e. each restraint has the same weight as a single point in the diffraction pattern) and the atomic positions remained stable and chemically sensible. In the final structure, with 117 atoms (32Si, 64O, 1Co and 20C) in the asymmetric unit, the Co complex is found to be completely ordered in the 14-ring channels (Figure 4).

CONCLUSION

And so a 117-atom structure was solved from powder diffraction data alone. The power of the texture approach lies in the fact that reflection intensities much closer to the true single-crystal values are obtained, so subsequent structure analysis is more likely to be successful. Although a zeolite structure solution has been described here, the method is by no means restricted to zeolites. It can be applied to any kind of polycrystalline material as long as a sample with a homogeneous texture can be prepared (not as difficult as it sounds). The data collection for UTD-1F took 3 days of synchrotron beamtime, but a recent adaptation of the method to transmission mode using an area detector has allowed the beamtime required to be reduced to as little as 3 hours. This makes it a much more attractive option when standard approaches to structure solution do not work. Data analysis is admittedly less straightforward than a normal intensity extraction, but the software (*expol*) has been written[7], and will be made available once the testing phase is complete. While this is not the method of choice for straightforward problems, it is clearly a very powerful one for more complex ones.

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Drug polymorphism and powder diffraction

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INTRODUCTION

Polymorphism, the occurrence of different structural forms of the same compound, is a very common phenomenon in pharmaceutical compounds. This is not hard to understand since the internal torsional flexibility of most drug compounds results in energetically similar molecular conformations and consequently different crystal structures. Clearly of scientific interest, this is also important commercially, since the occurrence of polymorphism poses problems in the processing and manufacture of drug products.

Anecdotal evidence amongst pharmaceutical scientists would suggest that polymorphism in drug compounds is the rule rather than the exception. Indeed, McCrone has stated that "the number of polymorphs found for a chemical substance is proportional to the time and effort spent researching it."

In contrast to this assertion, the Cambridge Structural Database, which contains a quarter of a million organic and organometallic crystal structures, is not a reliable indicator of the prevalence of polymorphism in these systems. One reason is that many polymorphs are only easily obtained as polycrystalline powders rather than single crystals. Moreover, it is often difficult to isolate phase-pure samples of individual polymorphs. It takes substantially more effort to extract these structures from powders and particularly from multiphase samples. Fortunately, the global optimisation methods that are ideally suited to these problems are now more generally available and the number of polymorphic samples solved from powder data alone is growing.

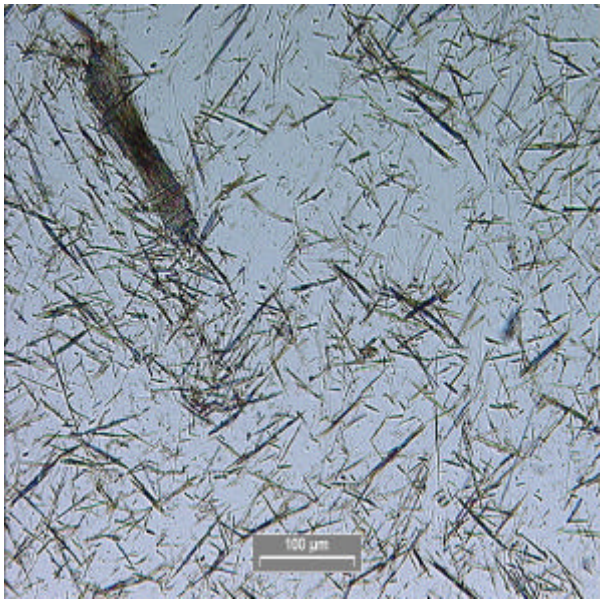

Fig. 1a Photograph of form A of Telmisartan: (long needle-like crystals)

The potential rewards for solving multiple polymorphs are substantial and not merely from the financial viewpoint of patent protection. The structural description of a complete range of polymorphs can lead to a much deeper understanding of the structure and properties of the drug in question.

STRUCTURE SOLUTION OF TELMISARTAN

In this article, we discuss a new orally active non-peptide angiotensin II receptor antagonist that is used in the indication of hypertension and congestive heart failure. Telmisartan is now known to exist in different crystalline modifications, but this polymorphism was only encountered very late in the compound's development cycle; i.e a small change in the last purification step induced the appearance of new polymorphs. At least three different forms, the two anhydrous forms A and B, which are described in this paper, and a solvated form C, are thus far known. The structure of the solvated form C was determined from single crystal X-ray diffraction data. All attempts to grow single crystals of the two solvent free polymorphs A and B suitable for single crystal diffraction failed. Form A crystallizes in extremely long needles (see Fig 1a), while form B (Fig. 1b) is obtained by subsequent drying from the solvated form C. Polymorph B could not be obtained as a single phase, which made successful structure determination of this form even more challenging. Furthermore, during the drying process of the solvated form C traces of another so far unknown crystalline form of Telmisartan were formed as a contaminant alongside form B. Although the morphology of the single crystals of the solvated form C is preserved upon drying, the single crystals themselves disintegrate. The crystal structures of both anhydrous forms A and B could, therefore, only be solved by *ab initio* structure determination from high resolution X-ray powder diffraction patterns. The structures were finally solved using the global optimisation program DASH largely because this approach makes good use of the already known molecular topology. All the compounds were characterized by microscopy, infra-red spectroscopy, solid state ^{13}C-MAS NMR spectroscopy and thermal analysis (DSC and TG).

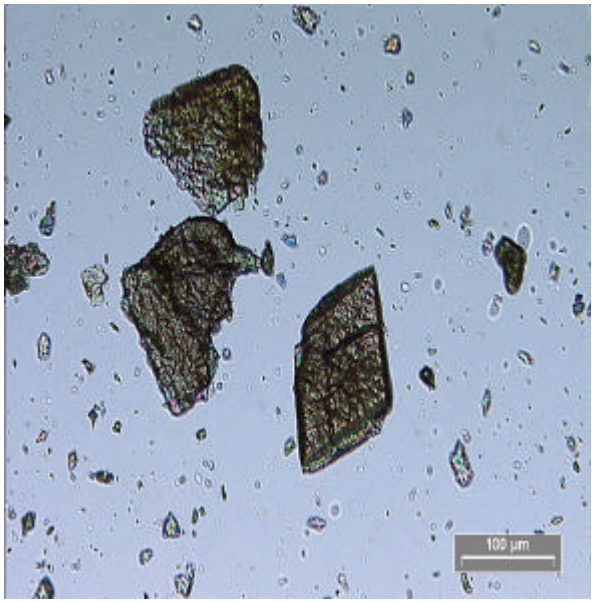

Fig 1b Photograph of form B of Telmisartan: (platelet-like crystals with prismatic shape).

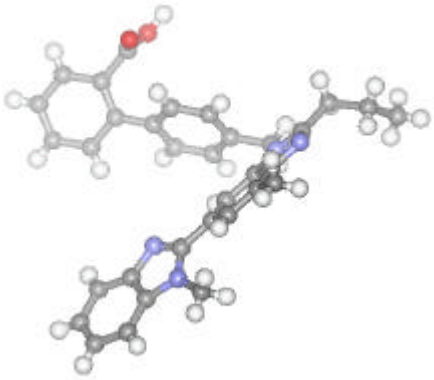

Fig 2a The molecular conformation of Form A

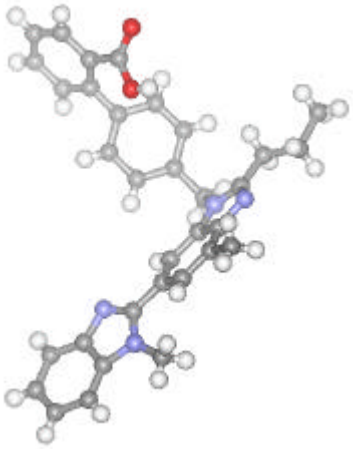

Fig 2b The molecular conformation of Form B

EXPERIMENTAL

The samples were sealed in quartz glass capillaries for the high-resolution X-ray powder diffraction experiments. Data were collected at room temperature at beamline X3B1 at the National Synchrotron Light Source, Brookhaven National Laboratory. For polymorph A (λ = 1.14981(2) Å), X-ray scattering intensities were recorded for 2.8 seconds at each 2 θ in steps of 0.004° from 2.0° to approx. 40°. For form B (λ = 1.14911(2) Å), each point was measured for 2.2 seconds at a 2 θ interval of 0.01° from 2.0° to approx. 30°. Samples were spun around θ during measurement to reduce preferred orientation effects. Both powder patterns are characterized by a rapid fall off of intensity beyond $\sin\theta/\lambda \approx 0.17$ Å^{-1}. In general, the crystallinity of polymorph A was superior to that of polymorph B.

Data reduction was performed using the program GUFI 5.0. Indexing of the powder patterns of polymorphs A and B using the program ITO led to primitive monoclinic unit cells of volumes of ~2700 Å^3. Due to the contamination of the sample representing polymorph B, the correct indexing of the powder pattern was very challenging. The space groups could, however, be determined unambiguously as $P2_1/c$ for polymorph A and a metrically distinct space group $P2_1/a$ for polymorph B from the observed extinction rules. The number of formula units per unit cell could be determined to Z= 4 from packing considerations.

Structure solution of polymorphs A and B was attempted using direct methods but all efforts failed. This can be understood in view of massive accidental overlap of peaks, typical for a unit cell of that size with low space group symmetry. Since the connectivity of the atoms was known from the single crystal study of the solvated form C, structure determination for polymorphs A and B was carried out by means of a simulated annealing technique, using the program DASH. For the definition of the connectivity between the atoms within the molecule, the Z-matrix notation was used, which the program package DASH calculated automatically from the structure PDB-file obtained from the single crystal study of the solvated form C. This notation allows a description of the entire molecule and its intramolecular degrees of freedom by using interatomic distances, angles and dihedral angles. All intramolecular angles and distances were kept fixed at the values of the single crystal data of the solvated form C, allowing only the 7 torsion angles to vary. The diffraction intensities were extracted from a Pawley type refinement, also part of the DASH program. A total of 14 parameters was varied during the simulated annealing runs (7 torsion angles, 3 fractional parameters for the position of the molecule and 4 quaternions describing the orientation of the molecule within the unit cell). The crystal structures of forms A and B were solved fully without any use of intervention by the simulated annealing procedure on a personal computer (Pentium III 733 MHz) in approximately one hour, needing approx. 4 million moves in the simulated annealing. Final Rietveld refinements were carried out using the program GSAS, in which only the scale and overall temperature factors were refined. The excellent agreement between the measured and the calculated profile for polymorph A indicates that further refinement probably not reveal any more significant structural details. Misfits between the measured and the calculated profile for polymorph B mainly arise from the contamination with an impurity phase as discussed previously.

CONCLUSIONS

It was indisputably possible to determine the molecular conformations with high precision of both polymorphs showing that moderately complex molecular crystal structures can nowadays be solved quickly and routinely from X-ray powder diffraction data. It was not possible to determine individual bond lengths and angles within the molecules. However, this was not the goal of this study, because the interatomic distances and angles of the molecule were already known from the single crystal study of the solvated form C. Of much more interest was to get some idea of why different polymorphs of Telmisartan can be formed. This question could be clearly answered by solving the structures of the polymorphs A and B from X-ray powder diffraction data. It is quite obvious from this study that the molecular conformations of the three crystalline modifications (including also the solvated form C) differ significantly. It was very interesting to learn that the small changes in the molecular conformation have a strong impact on the packing of the molecules, resulting in completely different structures with completely different intermolecular binding forces thus resulting in completely different physicochemical characteristics (e.g. melting or solubility behaviour) within one and the same compound.

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Malaria, Synchrotron Radiation and Monte Carlo

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INTRODUCTION

Malaria presents a terrible health problem. As many as half a billion people are sick with the disease and several million die of it each year. Most of these are young children in Africa. The problem is exacerbated by the fact that the *Plasmodium* parasite, which causes malaria, is developing resistance to the drugs in wide use today.

The plasmodium parasite has a complicated life cycle with several developmental stages in mosquitoes and also in its human victims. The most damaging phase of *Plasmodium* is the late trophozoite, where it infests the red blood cells, digesting the oxygen-carrying enzyme hemoglobin. In a massive infection, 80% of the victim's hemoglobin may be consumed. To any parasite, this is a dangerously spicy dish. Its active site for oxygen absorption, the iron porphyrin ring, is a potent oxidizing agent in solution and would prove fatal to the trophozoites if present in significant concentration in the digestive vacuole of the microorganism. Just as a diner in a Szechwan restaurant piles the hot peppers on the side of the plate, *Plasmodia* immobilize the heme groups liberated by proteolysis into an insoluble crystalline material called hemozoin. The process by which hemozoin is formed is not known and until our recent work at NSLS neither was its structure.

Approaches to controlling the disease may be made at many stages of its life cycle from controlling the mosquito vectors to current efforts to develop a vaccine against the early infestation. In the 17th century, Jesuit missionaries observed indigenous peoples of Peru using the bark of the cinchona tree to treat fevers and noted that it had the ability to cure malaria and brought the material to Europe. The active ingredient, quinine, is arguably the first drug known to treat any disease. However, it has limited effectiveness and is somewhat toxic in therapeutic does. Synthetic drugs have been developed since the mid-20th century and have largely replaced quinine.

Chloroquine has been the most successful antimalarial drug. There is a long history of models for the action of chloroquine and related drugs, many of them subsequently disproved. Various experiments, such as autoradiography of trophozoites growing in the presence if labelled chloroquine, show that it is associated with the crystallization of hemozoin. This suggests that the drug acts by interfering with the growth of the solid phase and suggest avenues for the possible development of new drugs, especially ones that might sidestep the resistance of some Plasmodium strains to chloroquine. Progress toward these goals depends on understanding the precise nature of hemozoin. For a long time, it has been widely assumed that hemozoin is a polymer, consisting of covalently bonded chains of heme groups. Evidence for this has been the observation that iron-carboxyl bonds via infrared absorption in hemozoin and the low solubility of hemozoin. However, neither of these observations proves the polymer model. Nevertheless, the idea has been reinforced in the literature so that most biochemical papers refer to it as heme polymer. Unfortunately, crystals of natural hemozoin, as well as synthetically produced materials are too small for single crystal analysis, even though microscopy shows that they are needles with well-defined facets (Fig. 1).

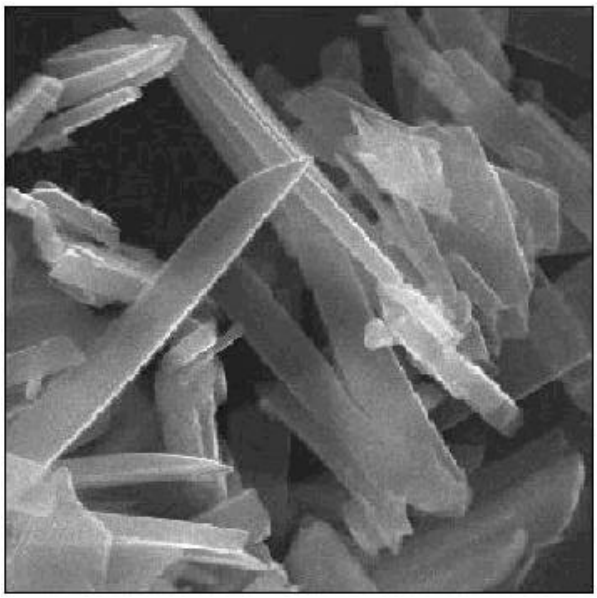

Fig. 1 Scanning electron micrograph of synthetic hemozoin crystallites. The width of the image is about 50 microns.

INITIAL RESULTS

In our first powder diffraction measurements, in collaboration with David Cox and Robert Dinnebier, we used the powder diffraction peak positions alone to identify the dimensions of the unit cell. We readily found that the hemozoin unit cell is triclinic, with a volume of 1416 Å^3.

From the density, we inferred that there must be two molecules in the unit cell, and since the material is a racemate, we knew that they would be related by inversion, so that only one molecule must be placed in the unit cell and the resulting space group is $P\bar{1}$. In that initial work, we also showed that synthetic hemozoin (known as β-hematin) had a powder diffraction pattern identical to the crystalline component found in whole dried blood cells which had been infected with malaria.

THE PSSP COMPUTER PROGRAM

The nature of the crystal structure solution problem, especially from powders, is that it is easy to see if given a candidate solution is compatible with experimental data, and to refine the details of a given model if it is essentially correct. When no model exists, the problem is far more complicated. However, for organic molecular solids, a large amount of structural information, such as bond lengths and angles, is known with good accuracy. Thus, the crystal structure of a molecular solid can be described by specifying the location and orientation of the molecule in the unit cell and any remaining internal degrees of freedom. As long as this prior information is sufficiently accurate, all chemically allowed structures can be summarised in a few parameters. Fig. 2 shows the molecular structure of the iron porphyrin molecule, which comprises hemozoin, known from biochemical studies, including the aforementioned synthesis.

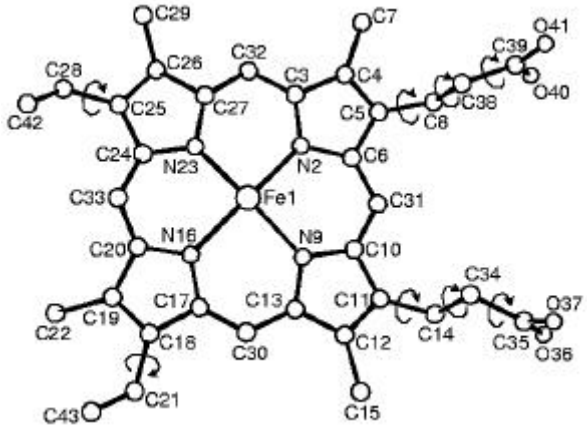

Fig.2 Representation of the Fe^{III}-protoporphyrin-IX molecule which crystallizes to form hemozoin. The arrows indicate torsional degrees of freedom which must be determined in order to obtain the intermolecular linkages.

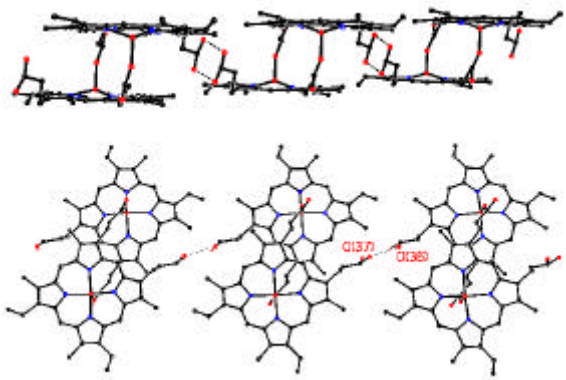

Fig. 3. Drawings of the structure of hemozoin, determined from powder diffraction. Note that the molecules shown in Fig. 1 are dimerized by reciprocal iron-carboxyl linkages at the end of the propionic acids, and that these dimers are assembled into the lattice by hydrogen and van der Waals bonds.

Since the molecule does not have any of the symmetry elements of the lattice (in this case, only inversion), it must occupy a general position and orientation in the cell. Accordingly, six parameters give its position and orientation, and the eight bond torsion angles shown in Fig. 2 specify the internal degrees of freedom. The correct structure can be determined by searching that fourteen dimensional parameter space and finding the values that give the best agreement between experimental data and calculated diffraction pattern. While much simpler than finding each atom individually, this is still too large a task to solve by an exhaustive search.

The simulated annealing method is a general technique for obtaining approximate solutions to optimisation problems, based on the analogy with finding a low-energy state of a physical system by annealing it: heating it to a high temperature and cooling it slowly. Several groups have independently applied this idea to the solution of crystal structures from powder data. Generally, one regards the parameter which is to be minimised, such as the familiar crystallographic weighted profile R-factor, as an energy, and performs Monte Carlo searches to sample the configuration space, initially at some high "temperature." This process is repeated as the temperature parameter is lowered, and eventually, the system should condense into a low energy state, i.e., a satisfactory solution. There are different approaches in practice, based on the choice of energy parameter, form of the Monte Carlo moves, tricks for accelerating the algorithm, etc. Our own program, PSSP (for Powder Structure Solution Program) has been used for several other problems, and is distributed, with several examples and tutorials, on the web at http://powder.physics.sunysb.edu/programPSSP/pssp.html.

A run of PSSP on one of our β-hematin data sets proceeds as follows. Initially, the temperature parameter is so high that essentially every Monte-Carlo step is accepted. The value of the goodness-of-fit *S* parameter is large enough to indicate that the candidate structures probed are no better than randomly placed atoms. In this simulation, the algorithm computes 100,000 structures before lowering the temperature by 20%. The fit between experimental data and model structures gradually improves until it condenses into reasonable agreement. We typically repeat this procedure many times, and take seriously a structure only if it recurs frequently, and if it makes chemical sense. In the present case, the only solution that emerges is the one illustrated in Fig. 3, in which the hematin molecules are dimerized. Besides the excellent agreement in the refinements of the diffraction data, the supporting evidence for this structure is that the solution has produced the iron-carboxyl bond observed in the infrared, which was not built into the individual molecule from the start.

CONCLUSIONS

What is surprising about this structure is that the iron-carboxyl bonds do not form the anticipated polymer chains, but instead dimerize the hemes, so that the crystal is held together only by hydrogen bonds and the van der Waals attraction between dimers. What are the consequences of this structure for understanding, and perhaps interfering with the sequestration of heme? Our work supports the hypothesis, originally voiced by Ridley and Goldberg, that the quinoline antimalarial drug action is due to its binding to high affinity sites on the surface of the hemozoin crystallites. It further suggests that appropriate studies of the morphology of the hemozoin crystallites will lead to improved understanding of the biological control of their formation, analogous to the current status of understanding of biomineralization. More broadly, it should call attention to the growing power of powder X-ray diffraction to research communities who might find other interesting applications for these techniques.

ACKNOWLEDGEMENT

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A Case of Mistaken Identity: Metastable "dimethyl sulfide dibromide"

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INTRODUCTION

Synthetic chemistry is not always straightforward and we are often confronted with surprises. This is particularly true when the synthesis route does not lead to the thermodynamically stable phase. In this article, we will discuss a particularly unusual case that we have studied recently - the example of dimethyl sulfide bromide. When bromine is added to dimethyl sulfide, Me_2S, in equimolar quantities, a yellow solid forms[1]. IR and Raman spectroscopy indicate that this is a charge-transfer complex, $Me_2S \rightarrow Br_2$ with a nearly linear S-Br-Br arrangement. So far, so good.

However, as all crystallographers know, the only way to be sure about the structure of a material is to go ahead and solve it from diffraction data. Unfortunately, no single crystals were readily available and so we had to resort to structure solution from powder diffraction data alone. This turned out to be straightforward and the structure was solved, via standard powder procedures and direct methods using SIRPOW, from high-resolution powder synchrotron X-ray diffraction data, collected at the Swiss-Norwegian beam line at ESRF.

ANALYSING METASTABLE PHASES

Now comes the twist to the story. If the synthesis is modified and the reagents are added in the reverse order, i.e. Me_2S is added to bromine in dichloromethane at -30°C, then an orange solid forms. This material is metastable; over a number of weeks, it transforms back to the yellow form. The spectroscopic and chemical analyses suggested that the material was ionic, i.e. $(Me_2SBr)^+Br?$. The powder diffraction pattern contained a large number of clearly resolved peaks, indicating an excellent degree of crystallinity for the metastable material (see Fig. 1). However, attempts to index the pattern were unsuccessful, even though several different indexing programs were used. No remotely acceptable figure of merit was obtained. This was a disappointment and a puzzle as a pattern of such high quality is usually indexed as a matter of routine.

In such conditions, the most likely cause for failing to index the pattern is the presence of more than one crystalline phase. Now came the next problem. How many phases were there? Matters would have been relatively straightforward if the pattern contained the original stable phase and one new unknown metastable phase. However, there were no peaks discernable in the pattern from the stable phase and, to make matters worse, no apparent differences in the shapes or widths of any of the peaks that might betray the presence of a second phase.

INDEXING THE DIFFRACTION PATTERN

The only way to proceed was to make the next simplest

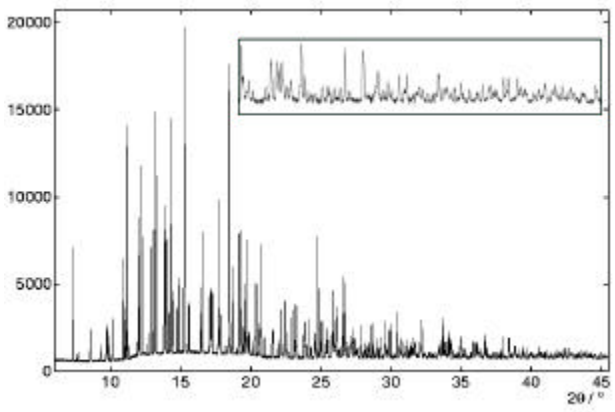

Fig. 1 The powder diffraction pattern of the metastable compound, collected with λ = 0.94718(1)Å

assumption – that there were two unknown phases. We thus attempted to index the pattern from the positions of around 50 diffraction peaks. With two phases and 50 peaks, at least 25 peaks must come from one of the phases. We used the indexing program TREOR, running it cyclically via a Unix shell script and gradually increased the maximum cell volume and edge and the number of unindexed peaks allowed (up to NIX = 30). Crucially, we also enforced a very high degree of agreement between observed and predicted peak positions. This constraint limits the number of trial solutions and excludes misindexed peaks from corrupting the trial cells. It does, however, require the peak positions to be determined to very high angular accuracy for this approach to be effective. Fortunately, this is generally the case the synchrotron data. A monoclinic solution with an M_{20} of 122 was eventually found which could account for about half of the peaks. The unindexed peaks were then processed separately, and a second monoclinic cell with an M_{20} of 198 was found, corresponding to a C-centred orthorhombic lattice. Systematic absences indicated the space groups $P2_1/n$ and *Cmca*. Multi-pattern LeBail decomposition was used to obtain the peak intensities. For the monoclinic phase, the extracted intensities were used directly and the structure was successfully solved using SIRPOW. For the orthorhombic phase, the partially refined model of the monoclinic structure was used to describe the intensities of the peaks belonging to this phase whilst those of the orthorhombic phase were extracted. Again, the structure of the orthorhombic phase was successfully solved using SIRPOW.

DETERMINING THE CORRECT STRUCTURE AND STOICHIOMETRY

In both structure solutions, extra peaks were found in the E-maps; these were due to extra bromine in the structures. After refinement, it was apparent that the stoichiometries of the monoclinic and orthorhombic phases were Me_2SBr_4 and $Me_2SBr_{2.5}$, respectively - these values were different from the reported chemical analysis. The composition of the two-phase mixture was refined to be 60.6(2)% monoclinic and 39.4(2)% orthorhombic form, implying a mass fraction for Br in the sample of 80.7%, in contrast to 72.0% from the assignment as a form of Me_2SBr_2.

In agreement with the spectroscopic analysis, the orthorhombic phase, $Me_2SBr_{2.5}$, is clearly ionic and has a Br? ion coordinated by two $(Me_2SBr)^+$ species in a layer-like arrangement. Between the layers, additional Br is incorporated into near-linear Br_4^{2-}? ions.

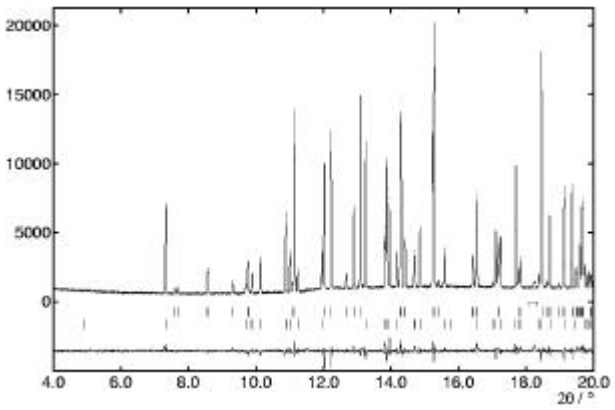

Fig. 2 The low-angle part of powder diffraction pattern of the metastable compound (λ = 0.94718(1)Å). Peak positions for the 2 phases are shown: top Me_2SBr_4, *a* = 9.03811(7)Å, *b* = 11.65889(9)Å, *c* = 8.88592(7)Å, β = 90.1338(5)°; and bottom: $Me_2SBr_{2.5}$, *a* = 21.9676(2)Å, *b* = 11.1972(1)Å, *c* = 11.05307(8)Å.

In terms of the complex ions present, the composition per unit cell is $(Me_2SBr^+)_{16}(Br?)_8(Br_4^{2-}?)_2$. The monoclinic structure, Me_2SBr_4, is more complicated and looks less ionic than $Me_2SBr_{2.5}$, and indeed has structural features that resemble those found in the simple charge-transfer complex Me_2SBr_2 and in $Me_2SBr_{2.5}$. In terms of an ionic formulation, the contents of the unit cell are $(Me_2SBr^+)_4(Br?)_4(Br_2)_4$.

How might changing the order of adding the reactants cause different products to form? It is clear from the results of this study that a single Me_2S molecule can interact with more than one molecule of bromine. When bromine is added to Me_2S, there is only a limited amount of bromine available at any instant. It is evenly taken up by the waiting Me_2S molecules. When Me_2S is added to bromine, there is initially a large excess of bromine. The first Me_2S molecules added saturate themselves forming Me_2SBr_4. Later molecules form $Me_2SBr_{2.5}$. Presumably the last Me_2S molecules find nothing left for them, (c.f. the perennial situation at a conference buffet), and are lost during removal of the solvent. The most stable product of reaction is Me_2SBr_2 and the metastable compounds convert to this by loss of bromine over a period of weeks.

SUMMARY

The story therefore has a happy ending. High-resolution powder diffraction data has been used to solve the structures of two previously unknown compounds, without prior knowledge of either their individual stoichiometry or the fact that there were two compounds present in the sample. Interestingly, there was a clear problem with the ancillary chemical analysis, which probably occurred because of the metastable nature of the two phases. Crystallography gave the definitive answer.

Perhaps the crucial step in solving the structures was the indexing of the two individual diffraction patterns. This was only possible because of the very high angular accuracy of the data. The peaks were essentially in exactly the correct positions, allowing the stringent requirement for agreement between observed and predicted peak positions to be imposed in the indexing program. Another important factor in the structure solution was the reliable extraction of a large number of non-overlapping reflections. The high angular resolution available on the Swiss-Norwegian beam-line at the ESRF facilitates this but also allows the identification of the small monoclinic distortion since β is very close to 90° (β = 90.1338(5)°). Figure 2 shows the positions of the peaks from the two phases at low angle showing that the two patterns are comprehensively entwined. In the end, despite misleading evidence from the chemical analysis, the nature of the metastable compound was solved and the case of mistaken identity was tracked down to two materials not one.

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Combined Rietveld- and Stereochemical-Restraint Refinement with High Resolution Powder Diffraction Data Offers a New Approach for Obtaining Protein-Drug Structures

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INTRODUCTION

With the decoding of the human genome, the paradigm of drug discovery will change to one that is focused on the creation and characterization of compounds that interact with specific proteins under a wide variety of conditions. Current techniques require either the formation of protein-ligand single crystals of sufficient quality for x-ray diffraction work or the interpretation of nuclear magnetic resonance (NMR) spectra. Growing single crystals of proteins is an arduous process, requiring careful selection of conditions to achieve success. A protein-structure study would be completely halted by the inability to produce a single crystal. Furthermore, single-crystal growth of a protein-ligand complex often presents completely new challenges compared with growing crystals of the protein alone. NMR, meanwhile, is limited by spectrometer resolution to studies of proteins with a molecular weight of no more than 25 kDa. The difficulties of studying protein-ligand complexes are best seen through a cursory examination of the Protein DataBase, which shows that only about 10% of the entries involve these complexes - see http://www.rcsb.org/pdb/

PROTEIN POWDER DIFFRACTION

A new method for obtaining the structure of protein-drug complexes is suggested by the fact that the most easily prepared form of these materials is a polycrystalline powder consisting of many small crystals. This powder can be formed over a wide range of conditions and time scales quite unlike the restricted circumstances required for producing large, single crystals. In many cases, polycrystalline powders can be readily made, but large, single crystals prove impossible to grow. High-resolution diffraction patterns from this polycrystalline material can display considerable sensitivity to subtle structural changes typified by shifts in the diffraction peak positions and by changes in intensity. This sensitivity has been long recognized by materials scientists, and over the past 30

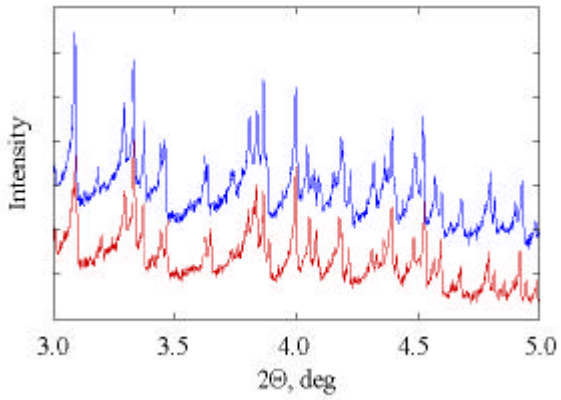

Fig. 1 A small segment of high-resolution, x-ray powder-diffraction patterns of lysozyme (bottom) and N-acetylglucosamine–lysozyme complex (top) both prepared from 0.5M NaCl 0.05M pH 6.0 buffer. The two patterns have been offset for clarity.

years considerable progress has been made in extracting structural information from powders. For example, virtually all our structural knowledge for high-temperature superconductors comes from x-ray and neutron-powder-diffraction experiments. Superconducting materials readily form powders but are not amenable to growth as large, single crystals. Many of them are also subject to phase changes that would render single crystals useless for diffraction experiments. Powder-diffraction experiments and Rietveld refinement[1, 2] have elucidated the nature of these phase changes and the very subtle structural changes that accompany changes in their superconducting properties with, for example, composition.

Until recently, protein crystal structures were considered far too complex for powder-diffraction experiments to give any useful information. However, our recent work at the Brookhaven National Laboratory's National Synchrotron Light Source has shown that proteins give extremely sharp x-ray powder-diffraction patterns that can be analyzed by a combined Rietveld and stereochemical restraint refinement to give structures of moderate resolution and, in one case, has led to the first solution of a protein structure from powder-diffraction data.[3,4] Protein lattice parameters determined from this powder data are perhaps two orders of magnitude more precise than those obtained from typical single-crystal experiments.

For the study of protein-ligand complexes, powder diffraction offers a distinct advantage over single-crystal work in its complete immunity to crystal fracture and to any phase change that may accompany complex formation. The extreme sensitivity of diffraction patterns to changes in lattice parameters makes powder diffraction sensitive to complex formation. Furthermore, rapid formation of a polycrystalline precipitate allows possible exploration of initial complex formation under a wide variety of conditions not accessible in slow-soaking or single-crystal growth experiments.

We recently explored this possibility in a study of the binding of N-acetylglucosamine (NAG) to chicken egg lysozyme.[5] In this experiment a high-resolution powder diffraction pattern of the protein alone was compared to that of the complex, both obtained from identical solvent mixtures (0.5M NaCl in pH 6.0/0.05M phosphate buffer).

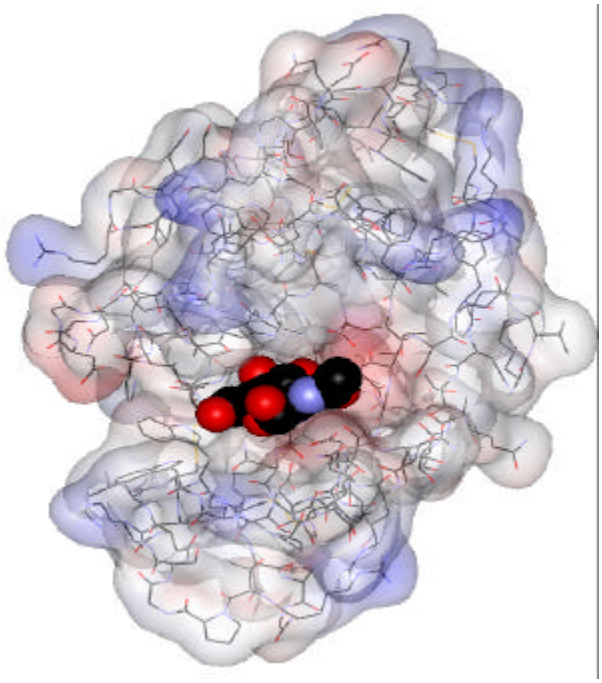

Fig. 2 View of the molecular surface of lysozyme with a space-filling model of the bound N-acetylglucosamine.

The patterns showed a clear indication (Fig.1) of a structural change upon formation of the complex. Subsequent combined Rietveld and stereochemical restraint refinement revealed the position and orientation of the NAG ligand in the C-ligand binding site of lysozyme (Fig. 2). Interestingly, a similar comparison of materials prepared from a pH 5.0 buffer showed no indication of complex formation. This finding clearly demonstrates the usefulness of preparing polycrystalline protein/ligand mixtures under a wide range of conditions.

FUTURE DEVELOPMENTS

High-resolution powder diffraction of proteins is still in its infancy, and the current molecular weight limit of perhaps 50 kDa is largely due to the density of reflection overlaps in the diffraction pattern. These limits are stricter than those of single-crystal diffraction, and there is no present way of solving protein structures *ab initio* from powder data; but model building and molecular replacement work quite well. Nonetheless, we can easily see future developments of the method that will allow examination of protein structures that exceed 100 kDa.

In particular, current data-collection technology scans the powder-diffraction pattern a few points at a time over a narrow field of view. Consequently, data-collection times at a synchrotron source are on the order of half a day. The use of high-resolution imaging technology and x-ray focusing optics should improve this by a thousand-fold or more, making it possible to use powder diffraction on a laboratory x-ray source to screen for the formation of protein-drug complexes and to determine their structures.

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On the reliability of R_{wp} in structure prediction

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INTRODUCTION

The determination of medium-sized molecular (~40 atoms) crystal structures from powder data still remains a challenge [1,2]. The reduced amount of information that may be extracted from a powder pattern in the form of traditional structure factors often makes the process of crystal structure solution rather difficult and ambiguous. An another method that can be used for crystal structure determination is structure prediction by potential energy minimisation. Various techniques have been suggested [3], but in general, structure prediction can be divided into four steps:

(i) building of the molecular model

(ii) generation of possible crystal structures by energy minimisation

(iii) ranking the structures using a suitable criterion and optionally

(iv) structure refinement via the Rietveld method.

Recently we have succeeded in predicting the crystal structures of three monosaccharides (all around ~38 atoms per molecule) [4,5]. Two of the compounds were test studies (the structures were already known from single crystal data) in which the behaviour of different force fields and atomic charges were tested. However, the structure of the third was not known in advance. In all our studies, we have applied criteria of fit based on both potential energy evaluation and on R_{wp} from subsequent Rietveld refinements (R_{wp}).

RESULTS AND DISCUSSION

In all test studies it was found that the correct structures always gave the lowest potential energy, *E*. Though the R_{wp} values have in general reflected the trends in energies, some low values corresponding to unrealistic energies have also been observed. However, due to empirical nature of the force fields and a certain arbitrariness in the calculation of atomic charges, the *E* values could not be taken to be definitively accurate. Some predicted structures were, herefore, cross-checked by refinements of the predicted models against the observed single crystal data. Fig.1 shows a typical variation of R_{wp} value against calculated energy.

The bullet positioned near the intersecting dashed lines in Fig. 1 represents the correct structure. The arrowed point, on the other hand, highlights a controversial result. The R_{wp} value is quite acceptable but the energy is too high (though it must be noted that neither the cell nor the atomic parameters were refined). To rationalise this situation, all trial structures were input into SHELXL97 [6] and refined against the corresponding single crystal data set. The atomic coordinates were, of course, fixed. The results of such a cross-check are shown in Fig. 2.

It is seen that the lowest R_{wp} values always correspond to the lowest *R*1 factors (as defined in SHELX97), while the second best R_{wp} has a misleadingly low value. In other words, despite the approximate nature of the energy evaluation, it has clearly revealed an inaccurate structure [7].

Another set of predicted structures [5] were used as starting models for rigid-body Rietveld refinements to see if powder data alone could be used to enable the predicted model to jump out of a supposed local minimum. Simulated structures were divided into six sets, which covered the crystal structures with identical or very similar R_{wp} values. A representative structure of each set was then refined using rigid body Rietveld technique [8]. The general strategy was such that in the first step, only the profile width parameter, *W*, the scale factor and zero-point were refined. When a refinement of profile parameters converged, two translation parameters (t_x and t_y) were also allowed to vary. In the last step also three rotational parameters were included in the refinement.

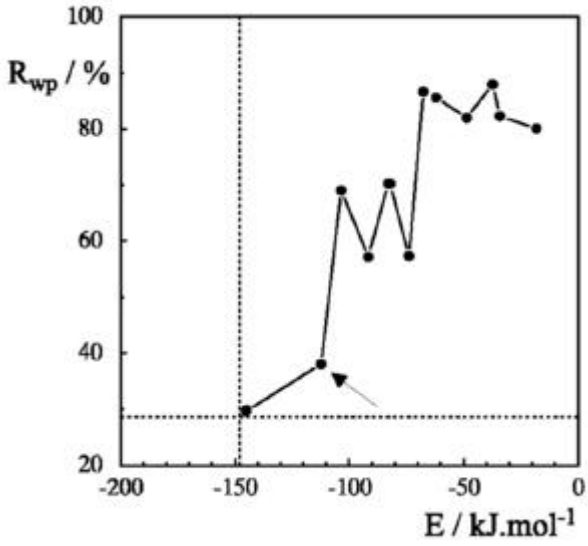

Fig. 1 R_{wp} vs. *E* for charge type/force field pair W/E for a monoclinic monosaccharide RKSA1 [4]. The dashed lines indicate the expected values of *E* and R_{wp} calculated using the atomic coordinates from single crystal data. Bullets represents individual structures (or their groups in the case of having similar *E*/ R_{wp} values) are connected by a line for sake of clarity.

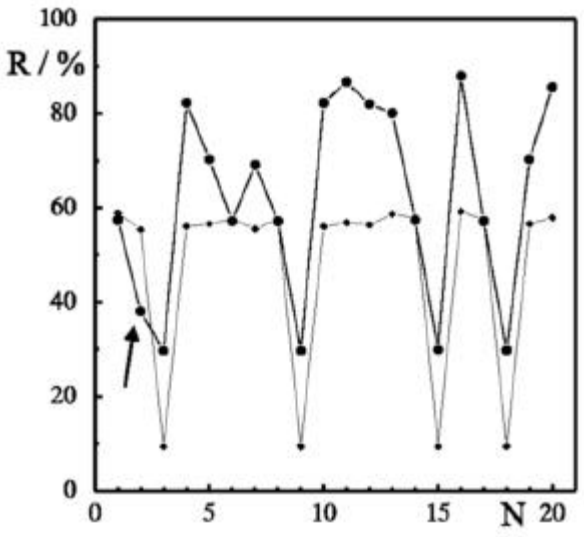

Fig. 2 A comparison of the values of R_{wp} (filled circles) and *R*1 (small diamonds) calculated by SHELXL97 for trial structures of RKSA1. *N* – structure's sequential number within the set. Crystal structure giving the second best R_{wp} is arrowed.

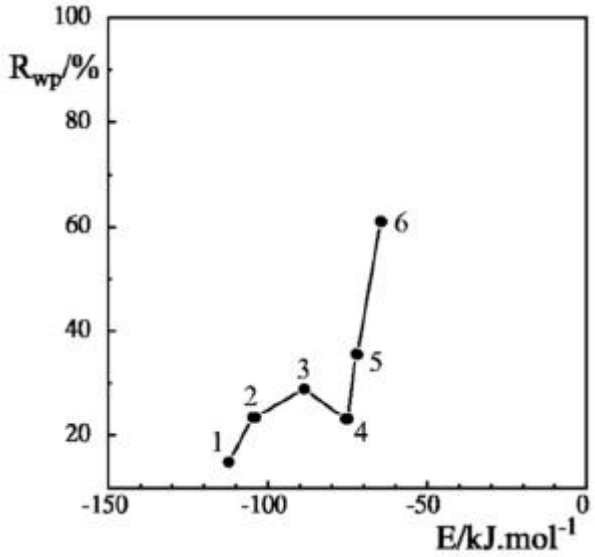

Fig. 3 R_{wp} on E dependence for charge type/force field pair W/M for six sets of trial structures of monosaccharide RKS2 [5].

The results can be summarized as follows. The weighted profile R-factor values of crystal structures belonging to set one (those with the lowest values of R_{wp} and E) remained almost constant during refinement at ~15 %. On the other hand, the values of R_{wp} of crystal structures of the other sets changed much more. After relaxation of the translation parameters R_{wp} decreased remarkably, but never below 15%. However, when rotation of molecule described by Euler angles was refined, value of R_{wp} increased dramatically and the final R_{wp} had in one case (set five) extremely high values of greater than 100%. Interesting results were obtained during refinement of crystal structure belonging to the set six.

R_{wp} value first dropped after refinement of translation parameters from 61 % to ~16% and after relaxation of the rotation parameters increased to a very encouraging ~17%. Unfortunately, the decrease of R_{wp} was accompanied by an increase in energy from an initial value of –37 kJ/mol^{-1} to +284 kJ/mol^{-1}. Inspection of the molecular packing revealed very short intermolecular distances.

REMARK

We have documented that R_{wp} and most probably all R_{wp} based criteria may in some situations lead to erroneous conclusions. A possible remedy for this problem is the simultaneous calculation of molecular and/or crystal energies. Unfortunately, such a calculation even using a simple procedure is much more time consuming than structure simulations based on diffraction data alone. However, these simulations need not be very sensitive to subtle details such as a wrong dihedral angle, which leads, or example, to a collision of hydrogen atoms. On the other hand, such a "misunderstanding" can be easily detected by any coulombic term included in the energy calculation.

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Ab initio structure determination of oligopeptides from powder diffraction data

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INTRODUCTION

An intrinsic limitation of single crystal X-ray diffraction is the requirement to prepare a crystal of sufficient size, quality and stability. When appropriate single crystals cannot be obtained, it is necessary to tackle structure determination using powder diffraction data[1]. For these reasons, we are focusing on the development, implementation and optimization of new techniques for structure solution from powder diffraction data, with emphasis on tackling the specific challenges encountered for molecular solids. Our methods are based on a direct-space strategy[2,3] in which a hypersurface defined by the profile R-factor (R_{wp}) is searched using Monte Carlo[3] or Genetic Algorithm (GA)[4–7] techniques. In this paper, we describe recent progress in the application of our GA technique in the structure determination of oligopeptides.

Clearly, knowledge of the structural properties and interactions in model oligopeptide systems can yield fundamental insights concerning structural properties of polypeptide sequences in proteins.

In the direct-space strategy, a large number of trial structures are generated in direct space, and the "quality" of each structure is assessed by comparing the powder diffraction pattern calculated for the structure and the experimental powder diffraction pattern (in our work, this comparison is made using the weighted profile R-factor R_{wp}). In effect, the direct-space strategy involves searching the R_{wp}(G) hypersurface to find the structure of lowest R_{wp}, where G represents the set of variables that define the structure. In the GA method[4–9], a population of trial structures 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. For the case with one molecule in the asymmetric unit, each structure is specified by the position $\{x, y, z\}$ and orientation $\{q, f, y\}$ of the molecule in the unit cell, and the molecular geometry is specified by a set of variable torsion angles $\{t_1, t_2, ..., t_n\}$. These variables

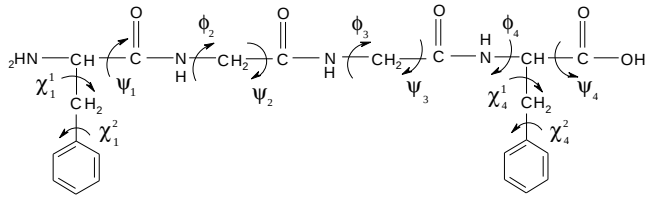

Fig. 1 Molecular structure of Phe–Gly–Gly–Phe, showing the variable torsion angles in the GA structure solution calculation.

represent the "genetic code" (G) that uniquely characterizes each member of the population. The 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. After a sufficient number of generations, the structure in the population with lowest R_{wp} should be close to the correct crystal structure. In our most recent implementation[8], each new structure generated in the GA calculation is subjected to local minimization of R_{wp} with respect to the variables in G, and only these minimized structures are used subsequently.

EXAMPLES

Here we give two examples of structure solution of oligopeptides, Phe–Gly–Gly–Phe and Piv–Pro–Gly–NHMe. Powder X-ray diffraction data were recorded at ambient temperature on a laboratory diffractometer (Siemens D5000; $CuK_{\alpha 1}$; transmission). The unit cells and space groups were determined directly from the powder diffraction data. The GA structure solution calculations were carried out using our program EAGER[10], and Rietveld refinement was carried out using GSAS[11]. The GA structure solutions for Phe–Gly–Gly–Phe[12] (Fig. 1) and Piv–Pro–Gly–NHMe[13] involved 11 and 6 variable torsion angles respectively, with all peptide groups fixed as planar units with O–C–N–H torsion angle of 180°. The molecules were constructed using standard bond lengths and angles.

The structure of Phe–Gly–Gly–Phe (space group $P4_1$) comprises ribbons that run along the ***c***-axis. Adjacent molecules in these ribbons interact through three N–H···O hydrogen bonds (Fig. 2), forming a direct analogue of an anti-parallel β-sheet. Intermolecular N–H···O hydrogen bonds involving the end-groups of the oligopeptide chains give rise to two inter-twined helical chains running along the 4_1 screw axis. In the structure of Piv–Pro–Gly–NHMe (space group P1), the molecule is found to adopt a Type II β-turn conformation stabilized by an intramolecular hydrogen bond between the C=O group of Piv and the N–H group of NHMe (Fig. 3). Adjacent molecules along the ***c***-axis form chains through intermolecular N–H···O bonds.

Our successful determination of the crystal structures of the oligopeptides Phe–Gly–Gly–Phe and Piv–Pro–Gly–NHMe illustrates the current scope and potential of techniques for the determination of molecular crystal structures from powder diffraction data, and provides

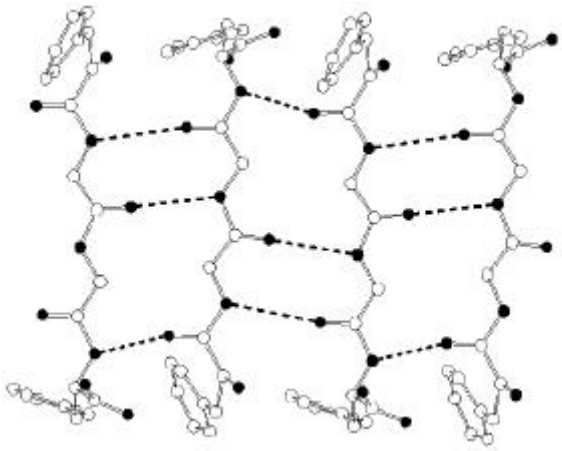

Fig. 2 Interactions between adjacent molecules in the crystal structure of Phe–Gly–Gly–Phe (viewed ⊥ to the ***c***-axis) illustrating the formation of an anti-parallel β-sheet arrangement. H atoms are omitted for clarity.

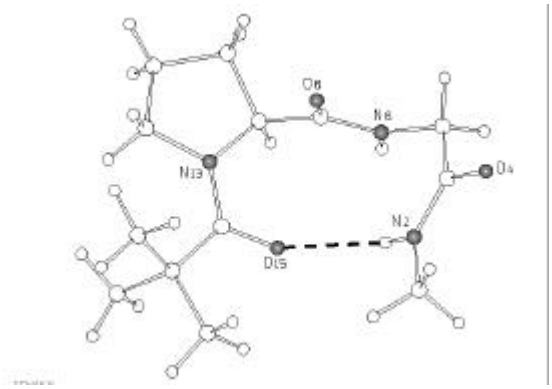

Fig. 3 Molecular geometry of Piv–Pro–Gly–NHMe in the crystal structure, with the intramolecular hydrogen bond shown as the dashed line.

promise for the future application of these techniques to solve structures of increasing complexity in this field.

ACKNOWLEDGEMENTS

We are grateful to EPSRC, the University of Birmingham, Wyeth-Ayerst plc and Ciba Specialty Chemicals for financial support, and to Professor P Balaram for valuable discussions and for supplying the sample of Piv–Pro–Gly–NHMe.

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Correlating crystal structure with the physical properties of pharmaceutical compounds

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INTRODUCTION

The active ingredients that are used in the formulation of medicinal products are widely manufactured in the form of polycrystalline powders. The existence of different crystalline (both polymorphs and solvates) and amorphous forms of these materials can have significant effects upon the processing, manufacture and stability of medicinal products. Moreover, new forms can often appear unpredictably in batches of raw materials. Clearly, the physical and chemical properties of a pharmaceutical compound are correlated with its crystal structure and so a detailed crystallographic understanding of these materials is important. One topic of particular interest is the reversible transformation between hydrated and anhydrous forms, especially where the transformation is associated with unwanted changes in chemical and physical properties.

The starting point for this study is a dihydrate of zopiclone (Fig. 1), a non-benzodiazepine hypnotic drug used in the treatment of insomnia. The stimulus for our investigation was this: knowing that the compound exists in more than one crystalline modification, one of which is a dihydrate, could we determine the crystal structure of the anhydrous material produced on heating the dihydrate? If so, might we be able to observe a relationship between the two structures and thus gain some insight into the structural mechanism of the transformation?

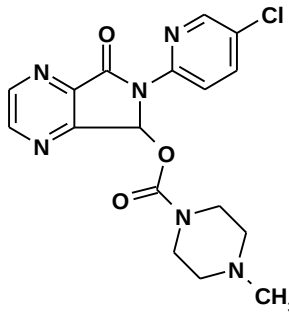

Fig. 1 Zopiclone

TRANSFORMATIONS OF ZOPICLONE

The design of this particular experiment was based on earlier 'pathfinding' explorations of the zopiclone system that suggested a reversible solid-state dihydrate ↔ anhydrous transformation. This transformation was observed using a laboratory X-ray diffractometer with a flat-plate powder sample being subjected to: (i) temperatures in the range 25-175°C; (ii) high and low humidity environments.

While we knew the structure of the "ubiquitous dihydrate" from single crystal data, we were unable to obtain single crystals of the anhydrous form. The key experimental issue, therefore, centred on maximising our chances of solving the crystal structure of the anhydrous form from a sharply diffracting polycrystalline sample produced simply by heating the dihydrate. With a combination of high beam intensity at short wavelength, multicrystal detector and ease of variable-temperature work, BM16 at the ESRF is an ideal choice for such an experiment.

EXPERIMENTAL

A 1 mm capillary was filled with a sample of zopiclone dihydrate, mounted on the BM16 diffractometer and a diffraction pattern recorded (λ = 0.8Å) for the purpose of structure identification. The pattern indexed to a monoclinic unit cell with dimensions a = 16.482 Å, b = 7.146 Å, c = 17.401 Å, β = 109.805°, V =1928 Å^3 at 298 K, confirming the identity of the sample to be essentially 'pure' zopiclone dihydrate.

Although the structure of the dihydrate had been determined previously from single-crystal data, we decided to collect around one hour of diffraction data and thence attempt to solve the structure using DASH, as part of our on-going testing of the program. Using an internal

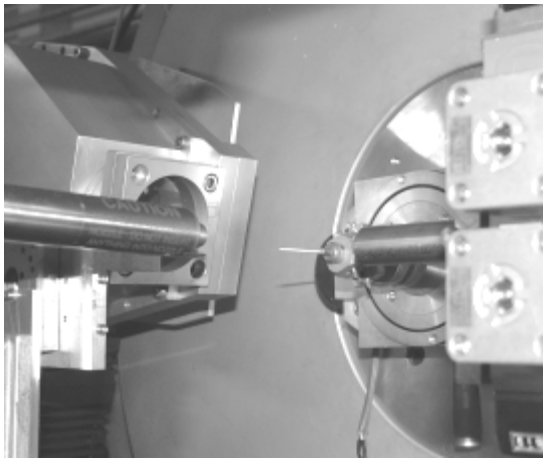

Fig. 2. Heating a capillary packed with zopiclone dihydrate transforms the structure to monoclinic anhydrous zopiclone

coordinate description of the zopiclone molecule (non H-atoms only) derived from the published structure of the orthorhombic form, and approximating the water molecules by inputting two independent O-atoms, it proved straightforward to solve the crystal structure. An overlay of the structures obtained from the powder and the single-

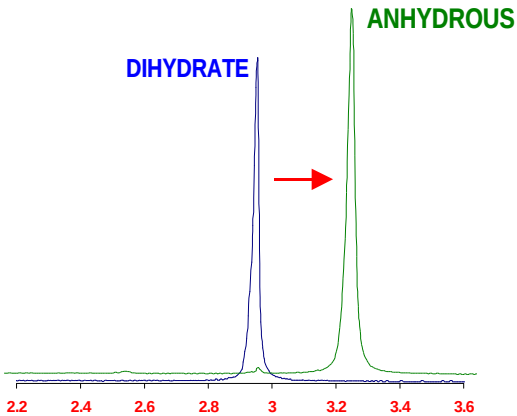

Fig 3. The transformation of zopiclone dihydrate to monoclinic anhydrous zopiclone on heating

crystal data confirmed the accuracy of DASH solution.

Next, the end of the capillary containing the dihydrate sample was carefully broken off to expose the powder to the stream of warm nitrogen from a Cryostream mounted along the axis of the capillary (Fig. 2.). The temperature of the gas stream was slowly raised from ambient to 370 K whilst the diagnostic region of the diffraction pattern (2 - 4.5° 2θ) was scanned repeatedly.

The conversion of the dihydrate to an anhydrous form was easily monitored by observing the gradual decrease in intensity of the dihydrate reflection at ~2.95°, and the steady increase in intensity of a reflection at ~3.25°, attributable to the anhydrous form (Fig. 3).

At the point where there was practically no observable dihydrate, the temperature was decreased to 325 K, and data collected for around three hours. The choice of temperatures in this particular experiment was based on the 'pathfinding' exploration of the zopiclone system mentioned earlier in the Introduction.

The pattern indexed to a monoclinic unit cell with dimensions a = 15.199 Å, b = 7.150 Å, c = 17.651 Å, β = 111.21°, V = 1788 Å^3 at 325 K. The crystal structure of this monoclinic anhydrous structure was then solved using DASH, inputting the same internal coordinate description that had been used to solve the dihydrate structure. The solved crystal structure gave a good fit to the diffraction data, and confidence in the result was increased by the fact that no unfavourable contacts were visible within the structure after addition of hydrogens.

Armed with both the dihydrate and anhydrous crystal structures, it is possible to develop a clear insight into the nature of hydration and dehydration in this material. The first thing that we noticed was that the molecular conformations for both materials were essentially identical. This was surprising since the dihydrate structure showed a substantial amount of hydrogen bonding between the water and zopiclone molecules. In the anhydrous form, the hydrogen bonding is absent and the lattice is held together by van der Waals forces. Accordingly, one might expect relaxation of the molecular shape to accommodate these fundamental changes in bonding. A closer look at the two crystal structures revealed further, more profound structural similarities. The zopiclone molecules arrange themselves in bilayer sheets in both materials (with the water molecules in the dihydrate sandwiched between) and these sheets of zopiclone molecules are effectively unchanged in the dehydration process. This close structural relationship is shown in Fig. 4, where we have overlaid the bilayers of both structures – the register is almost exact, not only in projection. This gives a clear insight into the dehydration process. Whole sheets of the zopiclone structure remain unchanged as the water molecules are co-operatively removed from the crystal structure. The process is facile and thus energetically straightforward; the principal structural change in the dehydration process (apart from the loss on water) is the slipping of each bilayer by approximately half a unit cell perpendicular to the bilayer.

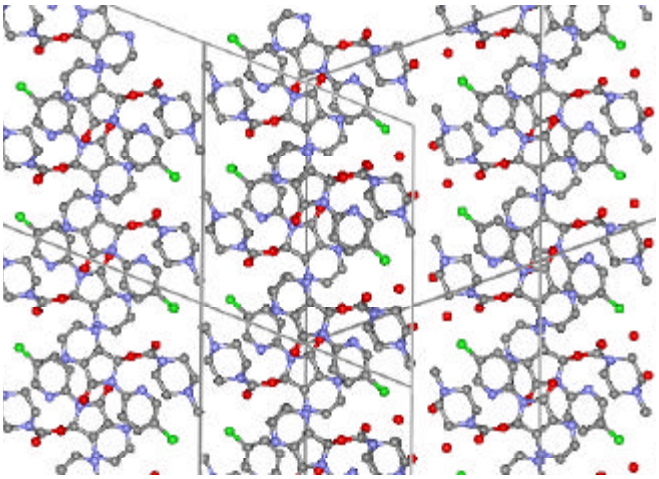

Fig. 4 Overlaid structures of the anhydrous zopiclone (left) and zopiclone dihydrate (right). The zopiclone bilayer in both structures is essentially identical.

We have thus established directly from these experiments that the reversible transformation between the two structures involves relatively minor shifts between the respective crystal packing arrangements. This is certainly consistent with the ease of water loss from the dihydrate, and the highly hygroscopic nature of the resultant anhydrous structure. Hygroscopicity can lead to problems of tablet weight gain and softening, and the work presented here demonstrates the power of structure elucidation in 'troubleshooting' such processing problems.

EXPO: New developments

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INTRODUCTION

Ab-initio crystal structure solution from powder diffraction data is not a straightforward process. Peak overlap, background noise and preferred orientation can all contribute to the low accuracy of integrated intensity estimates extracted from the powder diffraction pattern. As a result, the straightforward application of Direct Methods for carrying out the phasing process may fail. EXPO [1] is a program that aims to overcome these problems and is based upon the Le Bail[2] extraction of integrated intensities (first stage) followed by Direct Methods structure solution (second stage). It is based on a revised *two-stage* approach: information becoming available during the structure solution stage can be exploited in the extraction step for improving the structure factor moduli estimates and, consequently, the solution process itself. The following information can be exploited:

- the presence of pseudo translational symmetry [3];
- the positivity condition of the electron density map in the direct space [4];

- the positivity condition of the electron density map in the reciprocal space [5];
- a located partial fragment [6].

NEW STRATEGIES

New strategies for overcoming the difficulties in the structure solution process and for providing a complete model have been developed and introduced in EXPO. They will be available for the crystallographic community in future versions of the program. In this article, we give a brief description of our developments.

A critical preliminary step for the crystal structure solution is the indexing of the powder pattern. The program TREOR90 [7] has been combined with an efficient peak search algorithm and optimised [8] in such a way that: a) the coded crystallographic decisions are more suitable to the practical cases; b) the graphical interface makes the program very user friendly; c) the refinement of the selected unit cell is automatically executed. The modified version, called N-TREOR, has been integrated into EXPO, which is therefore able to carry out the structure solution by using as minimal information only the observed diffraction pattern.

Frequently the structure model provided by Direct Methods is incomplete. This is particularly true in case of a heavy atom structure for which the location of the heavy atoms is immediate but the light atom positions are hardly recognised. If the information about the located cations and the relative polyhedra is available, the new POLPO procedure exploits it for building the missing anions [9]. POLPO needs the information about the type of coordination (tetrahedral or octahedral) and the expected bond distances (a tolerance parameter is required also). The automatic analysis of the connectivity of the located cations is carried out. The procedure, based on the Monte Carlo technique, generates different feasible models, all obeying the prior information. The model corresponding to the best fit between the observed and calculated profiles is selected. POLPO is able to provide the complete solution also in case of complicated structures like zeolites.

The tendency of the Le Bail formula at equipartioning the intensity of a group of reflections strongly overlapped produces a bias in the integrated intensity estimate. The intensities of overlapping reflections are affected by errors so compromising the phasing process by Direct Methods. A very recent procedure aimed at breaking the equipartition tendency of the Le Bail technique and at modifying the intensity of both the strictly and the loosely overlapping reflections has been developed [10]. Several attempts of random partition of the intensity of each cluster of overlapping reflections are generated. The trial corresponding to the best profile fit in the range of the cluster is selected and subjected to the Le Bail algorithm for obtaining a feasible set of intensity estimates. The use of the intensities extracted by the random procedure in the Direct Methods lowers the phase error and increases the probability of solving the crystal structure.

The quality of the electron density map obtained at the end of the Direct Methods procedure depends on several factors: the uncertainty about the structure factor moduli, the phase error and the amplitude truncation effect. Consequently, the values of the peak intensities are often distorted and peaks themselves misplaced with respect to the correct positions. The technique of peak labelling interms of atomic species according to the peak intensity may fail. On the other hand, the peak labelling is a necessary requirement both in the structure refinement and in those procedures (e.g. POLPO) exploiting the location of some atoms. A new algorithm has been developed [11] in order to improve the labelling by using the following prior information: 1) the heavy atomic species present in the unit cell; 2) for each heavy atomic species, the number of atoms in the asymmetric unit; 3) the expected heavy-heavy atom distance and the expected number of heavy atoms surrounding a given heavy atom; 4) the expected heavy-light atom distance.

In spite of the progress in experimental techniques and in the strategies for optimising the estimates of the powder integrated intensities, the phasing process by Direct Methods may be characterised by large errors. A procedure has been recently introduced in EXPO devoted to improving the structure factor phase estimate and providing a more reliable solution [12]. It is based on the cyclic combination of an Electron Density Modification procedure and Fourier map calculations in such a way that the phase information is improved and extended to a sufficiently large number of reflections, so facilitating the structure recovery.

The new EXPO developments described in the article have been successfully tested on a large number of structures. They represent efficient tools when the traditional *two-stage* approach fails and an important set of methodologies for improving crystal structure solution from powder data.

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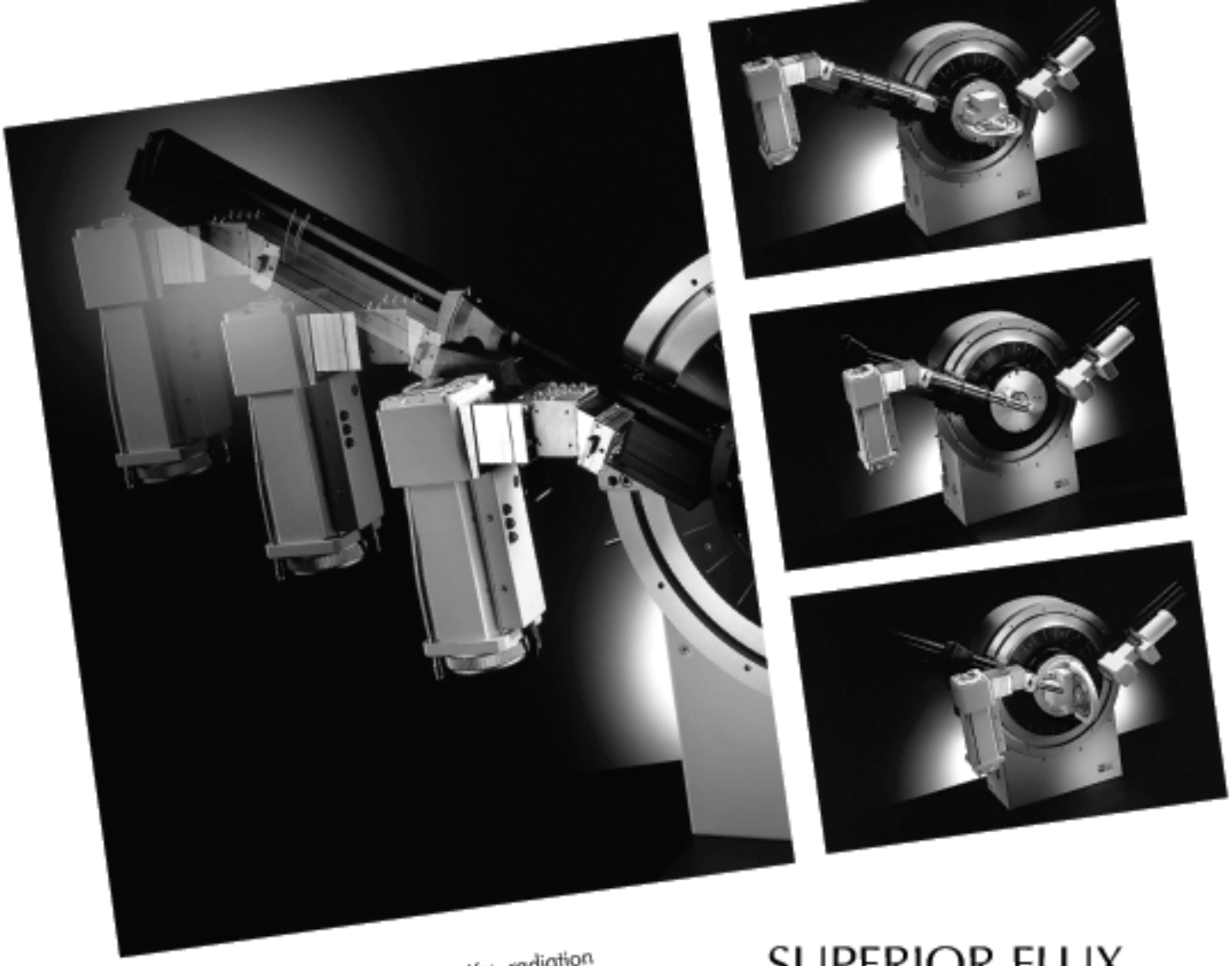

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News from the International Centre for Diffraction Data (ICDD)

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Dr. Ron Jenkins Announces His Retirement

Dr. Ron Jenkins, Executive Director of the ICDD, announced his retirement after sixteen years of service with the International Centre for Diffraction Data (ICDD). Dr. Jenkins held the position of Executive Director for the past five years.

Dr. Jenkins has served the ICDD in many capacities. He was a member of the Board of Directors in 1984, served as Principal Scientist from 1985 to 1996, and from 1996 to 2001 acted as the Secretary and Executive Director of the ICDD. As Principal Scientist, he directed the effort to convert the Powder Diffraction File to state of the art CD-ROM technology. He is recognized for the establishment of the ICDD educational programs, which over a period of ten years have provided basic instruction on powder diffraction and X-ray fluorescence to over 2000 students throughout the world.

Along with Deane K. Smith and Ron Anderson, Dr. Jenkins created the journal, *Powder Diffraction*, and served as the first editor. In 1992, he organized the initial meeting of the Pacific International Conference on X-ray Analytical Methods that brought together scientists from all parts of the world. Under his direction, the membership of the ICDD has increased significantly, making the ICDD a truly international organization. The ICDD's Grant-in-Aid Program has also been a benefactor of Dr. Jenkins' leadership. Today, the ICDD awards over 50 grants-in-aid to colleges and universities worldwide. Dr. Jenkins is also well known for his long and dedicated association with the Denver X-ray Conference, a program that the ICDD has administered since 1998.

Julian Messick, Secretary and General Manager of the ICDD from 1983 to 1994, is serving as interim Executive Director.

ICDD Annual Meetings Held

The ICDD Annual Meetings were held during the week of 12–16 March 2001.

The following Committees and Subcommittees met:

Committees:

- ❖Awards
- ❖Finance
- ❖Grant-in-Aid
- ❖Technical
- ❖Long Range Planning

Subcommittees:

- ❖Ceramics
- ❖Database
- ❖Education
- ❖Electron Diffraction
- ❖High Pressure/Temperature Diffraction
- ❖Marketing
- ❖Metals & Alloys
- ❖Minerals
- ❖Organic & Pharmaceutical
- ❖PDF Editorial Staff
- ❖Polymers
- ❖X-ray Diffraction Methods
- ❖X-ray Fluorescence

Minutes of the various committee and subcommittee meetings are posted on the ICDD web site as they become available.

Regional Co-chairs were recognized for their service to the ICDD during their recent terms, expiring in March. Regional Co-chairs, serving the term 2001–2003, are as follows:

Region	Co-chair
China	Shao-Fan Lin
Eastern Pacific Rim	Nubuo Ishizawa
England	David Taylor
European Community	David Rafaja
North America	James A. Kaduk
Russia	Evgueni Antipov
South America	José Miguel Delgado
Southeast Asia	Brian H. O'Connor

Ludo Frevel Crystallography Scholarship Recipients Announced

In the fall of 2000, applications arrived at the ICDD from all over the world for the 2001 Ludo Frevel Crystallography Scholarships. Six outstanding applicants were selected by the Scholarship Committee to receive this award designed to honor graduate students with major interest in crystallography. The ICDD congratulates the following award recipients:

Christina DeWitt, Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma, U.S.A.
Research title – "Determining the Structures of an Fc Derived from a Human IgG1 (κ) Antibody"

James Lettieri, The Pennsylvania State University, University Park, Pennsylvania, U.S.A.
Research title – "Ferroelectric Anisotropy and Integration of $SrBi_2Ta_2O_9$"

Maxim V. Lobanov, Moscow State University, Moscow, Russia
Research title – "Structural Studies of Low-Dimensional Magnetic Mn Oxides as Possible CMR Materials"

Christine McCracken, University of Manitoba, Winnipeg, Manitoba, Canada
Research title – "The Crystallography and Chemistry of Tourmaline"

Jennifer Stone, Oregon State University, Corvallis, Oregon, U.S.A.
Research title – "Structural Studies of High-Power Optical Materials"

Meitian Wang, University of Alberta, Edmonton, Alberta, Canada
Research title – "Developing Structural Principles for New Ternary Metal-Rich Pnictides"

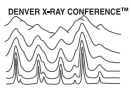
2001 XRF & XRD Clinics are a Success!

The ICDD hosted another successful season of clinics. The XRF clinics were held in April/May while the XRD clinics were held in June. The clinics offer both novices and professionals in the field of X-ray analysis an opportunity to learn techniques from the experts as well as the opportunity to discuss field experiences with peers.

The XRF faculty included: John Anzelmo and Larry Arias of Bruker AXS, Inc.; Richard Bostwick of Spex CertiPrep; John Croke (Emeritus), Philips Analytical; Mary Ann Zaitz of IBM Microelectronics; and Ron Jenkins (Emeritus), ICDD. In 2001, we welcomed Larry Creasy of Titanium Metals Corp. and Stephen Williams of Philips Analytical to the XRF team of instructors.

The instructors for the XRD clinics were: Tom Blanton of Eastman Kodak Co.; Harlan Clark, John Faber, Ron Jenkins (Emeritus), Suri Kabekkodu, W. Frank McClune, Fangling Needham, and Charles Weth of the ICDD; and Gerald G. Johnson, Jr. (Emeritus), Earle Ryba and Susan Quick of The Pennsylvania State University. New to the faculty in 2001 were Mark Rodriguez of Sandia National Laboratories and Bernie Squires of Rigaku/USA, Inc.

50th Anniversary of the Denver X-ray Conference



Steamboat Springs, Colorado will be the site of the 50th Anniversary celebration of the Denver X-ray Conference, 30 July through 3 August 2001. The program will highlight the historical aspects of X-ray analysis and the Conference over the last five decades.

IXAS News

The ICDD, the International X-ray Analysis Society (IXAS), and the Denver X-ray Conference Organizing Committee recently signed a *Memorandum of Understanding*. This memorandum sets forth the guidelines for the cooperation among the three groups to serve the X-ray analysis community by successfully conducting the Denver X-ray Conference on an annual basis.

The ICDD will also provide web site services to the IXAS, namely developing, managing, and maintaining the IXAS web site.

ISO 9001 Certification

The ICDD is proud to announce its recent ISO 9001 Certification. This certification assures satisfaction to our customers through quality planning, internal consistency, process control, and self-assessment. The scope of the ICDD's registration is centralized assembling, recording and publication of X-ray diffraction data for the use by scientific institutions worldwide and to provide technical forums for promoting X-ray diffraction techniques.

Computer Corner

Updates on Freely Available Crystallographic and Powder Diffraction Software
(Suggestions, corrections, comments appreciated; especially if you know of new program features, program updates and announcements that should be mentioned here).

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PULWIN PXRD ANALYSIS FOR WINDOWS BY SERGIO BRUCKNER

A new program for the analysis of powder patterns is PULWIN for Windows which can perform DFT (discrete Fourier filtering), background determination using a Robust smoothing procedure, unit cell refinement, Calibration of INEL PSD data, etc. Pulwin can be downloaded from ftp://ftp.cc.uniud.it/DEBVIN/ and CCP14 mirrors.

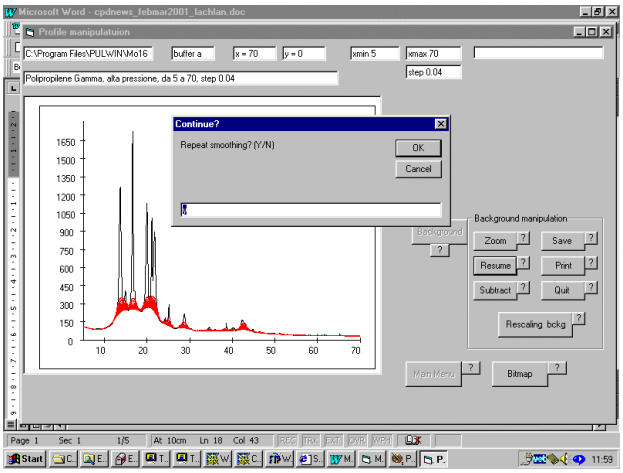


Fig 1: *PULWIN performing background determination using a Robust smoothing procedure.*

NIST TEXTURE PLUS FOR WINDOWS BY MARK VAUDIN

NIST Texture Plus for Windows has a variety of functionality relevant to texture analysis. It calculates the texture profile of a specimen using two x-ray scans obtained from the specimen using a powder x-ray diffractometer by obtaining a scan of a Bragg peak from the textured planes and a second rocking curve scan, with the diffractometer set at the angle of the Bragg peak. It can be downloaded from

http://www.ceramics.nist.gov/webbook/TexturePlus/texture.htm and the CCP14 UK web mirror.

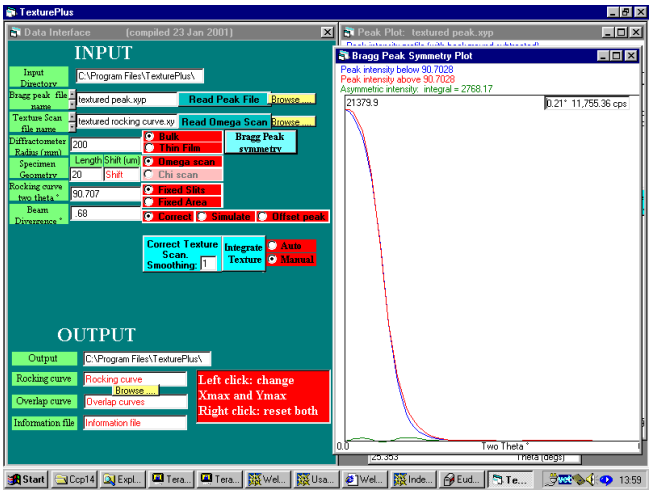


Fig 2: *NIST Texture Plus Interface.*

WEB BASED TUTORIALS ON MAUD FOR JAVA MATERIALS ANALYSIS RIETVELD BY LUCA LUTTEROTTI (MAC, WINDOWS AND UNIX)

Web based tutorials are viewable for using the MAUD for Java materials analysis Rietveld software. Tutorials including such topics as "Performing an X-ray quantitative analysis in seven easy steps!" and “Using Maud to Integrate Debye-Scherrer (or Guinier) film and Image Plate Data”. These can be accessed via CCP14 mirrors and http://www.ing.unitn.it/~luttero/maud/tutorial/index.html.

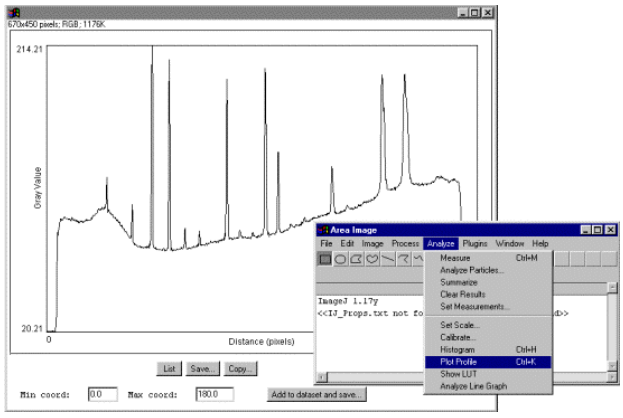


Fig 3: *A screen dump from one of the on-line MAUD tutorials. In this case using MAUD to integrate film data.*

UPDATED CRYSFIRE FOR DOS/WINDOWS POWDER INDEXING SUITE BY ROBIN SHIRLEY

As has been mentioned in previous articles, Crysfire is an indexing suite that links into 8 different indexing programs: ito, treor, dicvol, taup, kohl, lzon, fjzn and losh. A new feature in Crysfire is the rescale/unscale feature that allows the user to easily rescale the peak data into an expected cell volume range most likely to solve from indexing programs that work best solving cells around 500 - 1500 A**3 (rescaling is achieved by changing the wavelength). After indexing, the “unscale” program can be applied to the Crysfire summary file to convert found trial cells back to their correct unscaled values.

Rescaling was the method used by Bob von Dreele and co-workers to recently index a protein structure from powder diffraction data; which was then also solved and refined. *(R. B. Von Dreele, P. W. Stephens, G. D. Smith and*

R. H. Blessing, "The first protein crystal structure determined from high-resolution X-ray powder diffraction data: a variant of T3R3 human insulin-zinc complex produced by grinding", Acta Cryst. (2000). D56, 1549-1553. Synopsis: High-resolution synchrotron X-ray powder diffraction data have been used to solve the crystal structure of a new variant T3R3 human insulin-zinc complex produced by mechanical grinding of a polycrystalline sample.)

Crysfire download information as well as tutorials on installing and running Crysfire are available at http://www.ccp14.ac.uk/tutorial/crys/ with Internet download areas existing in the UK, Canada and Australia.

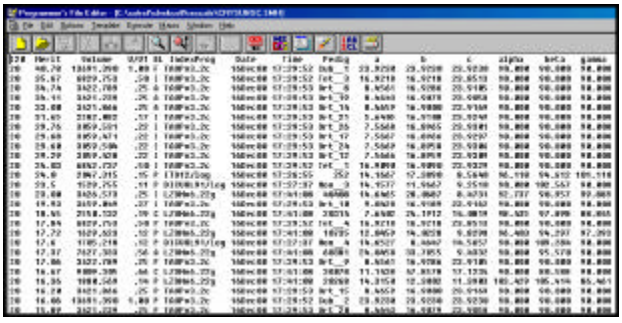


Fig 4: *Summary output from a Crysfire run using rescaling/unscaling. This shows the successfully indexing of a large celled inorganic cubic phase from standard laboratory powder X-ray diffraction data. TAUP was the indexing program to find the correct cell (confirmed from single crystal data).*

CHEKCELL FOR WINDOWS NOW COMES WITH LEPAGE FOR WINDOWS, SOLUTION SORTING AND GUI CELL TRANSFORMATION.

Chekcel, as has been mentioned in previous newsletters, is a graphical powder indexing helper tool by Jean Laugier and Bernard Bouchu that links into Robin Shirley's Crysfire (http://www.ccp14.ac.uk/tutorial/crys/) to aid in identification of good cell/spacegroup combinations from Crysfire format summary lists. This can be performed manually or automatically using a Best Solution mode based on "parsimony of extra reflections" for selecting interesting cells.

The latest Chekcell (presently a beta version) now includes: LePage; GUI Cell transformation; sorting and filtering of Crysfire summary files and auto-optimisation of angular tolerance for matching reflections to HKLs. To elaborate on one of the above. LePage for Windows (ported from fortran code written by Ton Spek and A. Meetsma) not only gives the "reduced cell", but can also can look for sub-cells and super-cells. LePage results link into a "best solution" routine such that cells can be checked if they are superior to the starting cell (using the criteria of "parsimony of extra reflections"). Thus LePage adds another feature into Chekcell for effective getting around the many and varied nuances of the available indexing programs; especially as many of these indexing programs favour low volume low symmetry cells when high volume, high symmetry cells can be the true solution.

Available indexing programs can have many nuances and foibles. A recent example of Chekcell's effectiveness to counter these nuances was of a summary list generated via the Crysfire suite. A cell obtained from poor resolution organic pharmaceutical data was reported by one particular indexing program that reported 18 out of 20 matched reflections. On being displayed in Chekcell, this cell actually matched all peaks to give the best visual solution. This solution was confirmed later by single crystal results to be the most likely cell.

Information and tutorials on using Chekcell are available at http://www.ccp14.ac.uk/tutorial/lmgp/#chekcell with internet download areas existing in the UK, Canada and Australia. Any new beta test versions of LMGP suite software are now placed in the subdirectory "bleeding_edge_beta_versions" of the main download directory.

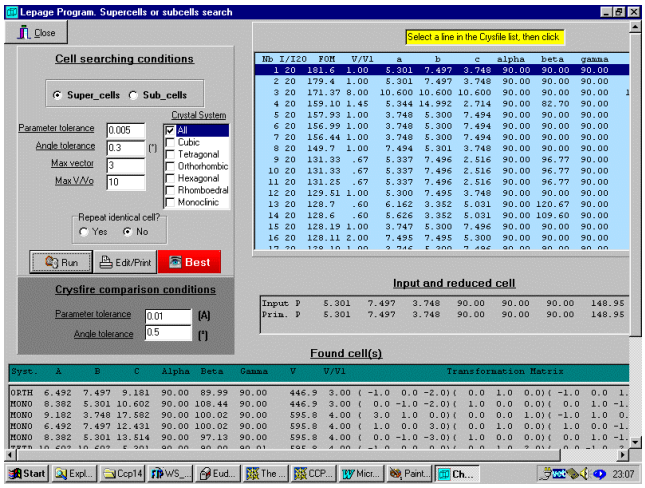


Fig 5a: *Chekcell powder indexing helper tool with LePage for Windows for both finding the "reduced cell" and looking for subcells and supercells.*

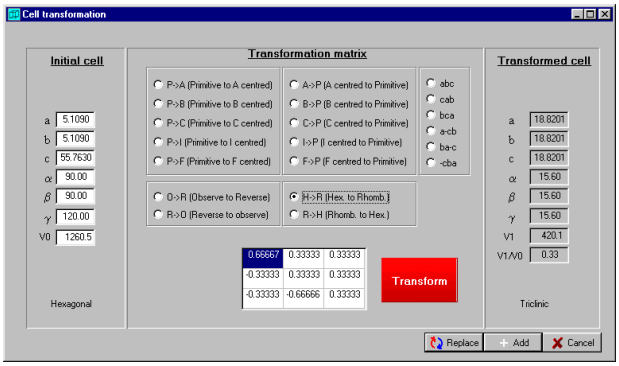


Fig 5b: *Graphical Cell Transformation within the latest Chekcell for Window making it easy to perform required changes to trial cells when looking manually for subcell/supercells effects and going from different cell settings.*

NEW ENHANCEMENTS IN BOB VON DREELE AND ALAN LARSEN'S GSAS RIETVELD SUITE

The latest features introduced into GSAS (ftp://ftp.lanl.gov/public/gsas/) include the ability to change the weighting of individual histograms (powder patterns); viewing of larger Fourier maps in Forplot, larger numbers of constraints; and an increase in the number of allowed total chemistry restraints (which can also be applied to restraint charge balance within the structure). These enhancements make possible the restrained refinement of more complex inorganic structures from medium resolution laboratory powder X-ray diffraction data and constant

wavelength neutron data (> 300 atoms, > 1500 bond restraints, 100's of constraints). The GSAS for Windows graphics are now drawn in MS-Windows boxes allowing MS-Windows Edit Copy, zooming and other standard Windows options to be performed.

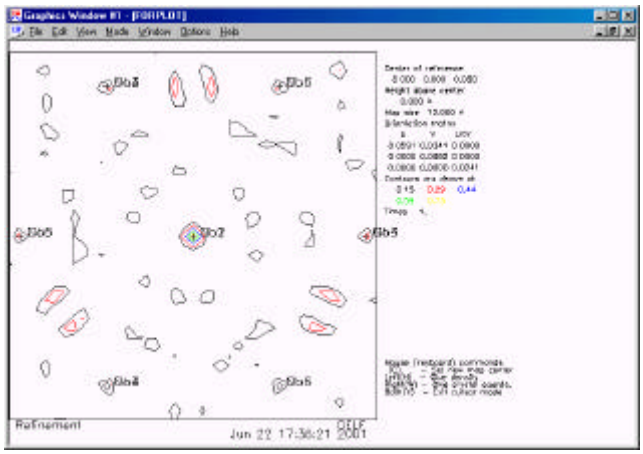


Fig 6: *Forplot display in the latest GSAS for Windows.*

BUGFIX VERSION OF EXPGUI FOR WINDOWS AND LINUX GRAPHICAL USER INTERFACE TO GSAS BY BRIAN TOBY

The latest version of EXPGUI fixes various issues users may have encountered when running Liveplot while running GENLES and other GSAS utilities. The latest version of EXPGUI fixes these problems and can be downloaded via

http://www.ncnr.nist.gov/programs/crystallography/software/expgui/expgui_intro.html and CCP14 mirrors.

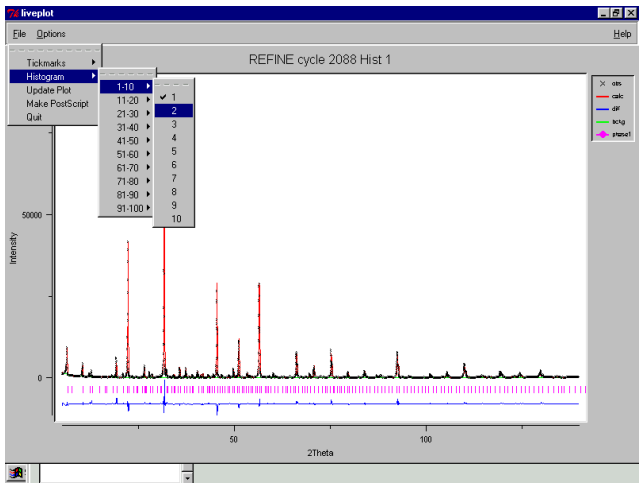


Fig 7: *Liveplot: included with EXPGUI for viewing GSAS Rietveld plots.*

CELREF FOR WINDOWS UNITCELL REFINEMENT SOFTWARE NOW INCORPORATES U.D.ALTERMATT AND I.D.BROWN'S GETSPEC SPACEGROUP SOFTWARE.

The latest Celref for Windows by Jean Laugier and Bernard Bochu (graphical unitcell refinement program; http://www.ccp14.ac.uk/tutorial/lmgp/) now incorporates U.D.Altermatt and I.D.Brown's Getspec space group code (http://www.ccp14.ac.uk/ccp/web-mirrors/valence/getspec/) . This means that Celref can handle almost any space group and setting that a user may want use.

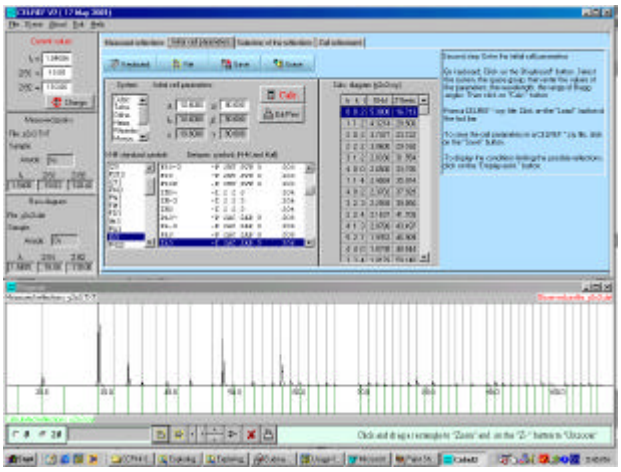


Fig 8: *Screen image of the new Celref interface into the GETSPEC spacegroup program.*

NEW FEATURES IN GRETEP (GRENOBLE THERMAL ELLIPSOIDS PLOT PROGRAM) FOR WINDOWS BY JEAN LAUGIER AND BERNARD BOCHU

The latest version of Gretep has a variety of new features including the improved importing of CIF and Shelx files and atom. Structures with atom labels and fonts can be saved in GRE Gretep format and can display each separate molecule as a separate colour. A Windows port of U.D.Altermatt and I.D.Brown's Getspec spacegroup software is included and Gretep can now render Povray files for photo-realistic rendering of structures. An SEM style Angstrom Bar is now displayed at the bottom left hand corner of the plot screen to give users an appreciation of the scale of the structure being investigated.

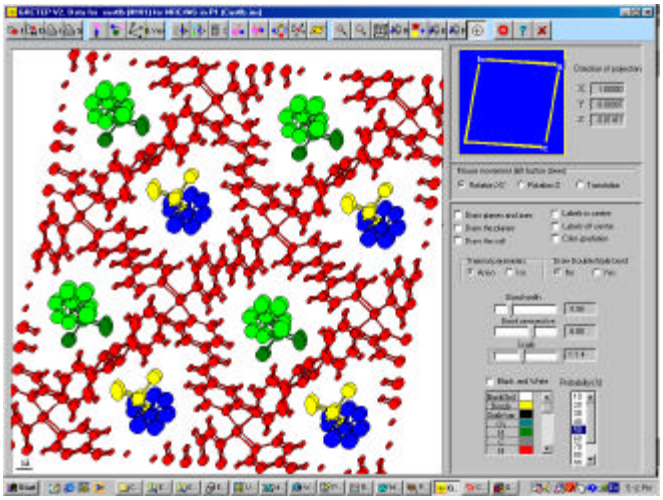


Fig 9: *Gretep: using the "fragment search mode" where each distinct molecule is coloured differently for ease of recognition. This can also be useful for graphically working with interpenetrating molecules of an elaborate complexity not necessarily evident when just looking at the asymmetric unit.*

PLATON BY TON SPEK (> NOV 2000 VERSION): YOU CAN'T HAVE TOO MANY ADDSYM DEMONSTRATIONS TO FIND MISSING SYMMETRY IN CRYSTAL STRUCTURES.

The Addsym subroutine within Platon uses a highly enhanced version of Yvon LePage's original algorithm for finding missing symmetry in crystal structures. This has been further enhanced in the November 2000 to February

2001 versions of Platon and can render valuable assistance to anyone involved in solving and refining structures from diffraction data (both single crystal and powder), model built structures guided by crystal chemical arguments as well as ab-initio crystal structure calculations. The effects of recent enhancements in Platon's Addsym with respect to subcells is shown by the following example of a triclinic structure with 96 independent carbon atoms. Running the latest > November 2000 version of Platon shows it to be monoclinic 1/8th sub-cell having only 3 independent carbon atoms. This is also an example of why it is important to make sure you keep up to date with new versions of freely available crystallographic software.

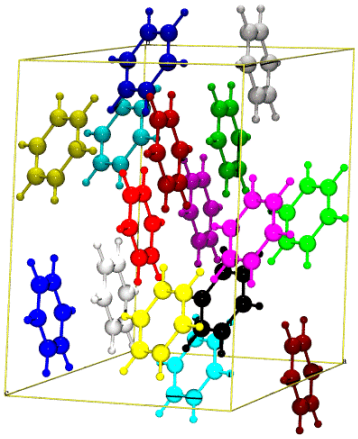


Fig 10a: *Original Triclinic P1 structure (96 Carbons in the asymmetric unit).*

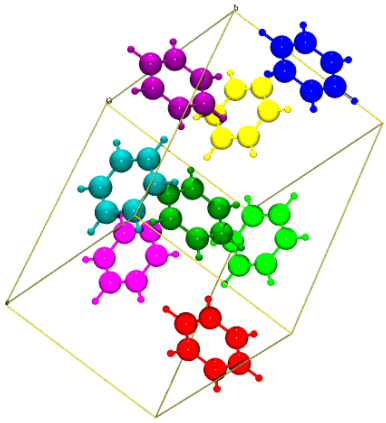


Fig 10b: *Triclinic P-1 half subcell using obtained pre-November 2000 version of Platon's Addsym subroutine (24 Carbon in the asymmetric unit).*

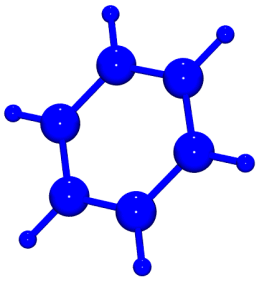


Fig 10c: *Monoclinic P 21/C 1/8th subcell obtained using post-November 2000 version of Platon's Addsym subroutine (3 Carbon atoms in the asymmetric unit).*

It is trivial to do run Addsym within Platon by opening a CIF, Shelx or Platon file. There is also the option to output a new Shelx coordinate file in the updated spacegroup found by Addsym

Platon can be obtained via http://www.cryst.chem.uu.nl/platon/ or CCP14 mirrors and tutorials area at http://www.ccp14.ac.uk/tutorial/platon/

PLATON'S ADDSYM AND MINERALS, ZEOLITES AND OTHER INORGANIC STRUCTUES

Though optimised for organics and organometallics; Platon's Addsym can be effective on polymeric inorganic compounds (minerals, zeolites, ceramics, etc). A suggestion for those involved with inorganics, including those performing model building as part of the structure solution process are recommended to pass their starting models and refined models into Platon's Addsym to see if there could be higher symmetry present that not be visually obvious. It can also be useful to run Addsym only on the metals and/or framework atoms. Please note that there have been some late February 2001 enhancements to Platon's Addsym to assist with inorganics. This is mainly to do with optimising some of the default tolerances (presently based on organics) to recognise inorganic structures and set to more optimal tolerances. Other Addsym tricks for inorganic structures include running addsym on different atom types (e.g., Metals, Oxygens) to check whether these may have higher symmetry that could be a guide for understanding the structure.

PLATON FOR MS-WINDOWS: ERRATIC CRASHING BUG NOW FIXED!

Older versions of Platon for Windows had the habit crash on some PC computers in an erratic manner. This has been traced to a very subtle bug in the Fortan compiler used to port the original UNIX code; and has now been rectified in the most current versions of Platon for Windows ported by Louis Farrugia of Glasgow University.

(http://www.chem.gla.ac.uk/~louis/software/platon/).

CONVERTING SINGLE CRYSTAL HKL DATA INTO POWDER PATTERNS WITH EITHER PATRICK MCARDLES POWUTL FOR WINDOWS TON SPEK'S PLATON FOR UNIX/WINDOWS

There are two new enhanced options for academics and students requiring freely available software to convert single crystal HKL data into pseudo-powder patterns. Post 15th June 2001 versions of Patrick McArdle's Powutl/Ortex (http://www.ucg.ie/cryst/software.htm) and Ton Spek's Platon using the new HKL2Powder subroutine (http://www.cryst.chem.uu.nl/platon/) will now convert single crystal Shelx format HKL data into common powder diffraction file formats. Powutl produces ING, CPI, XY and Riet7 DAT files; Platon's HKL2Powder can produce CPI files as well as reporting the number of missing reflections with sin(theta)/lambda < 0.3.

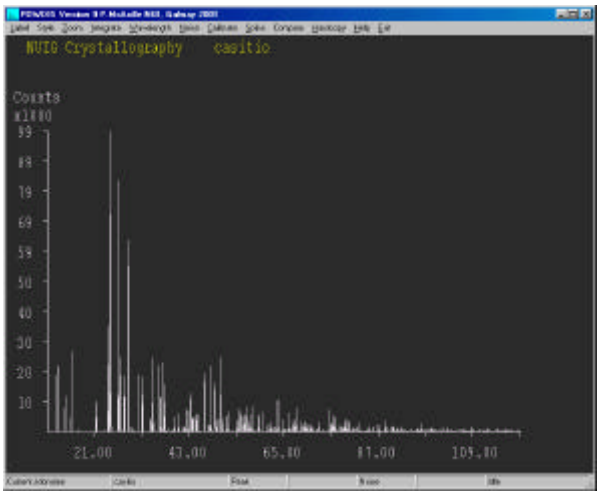


Fig 11a: Powdis displaying a pseudo-powder pattern generated from single crystal HKL data of Calcium Titanium Silicate using Powutl

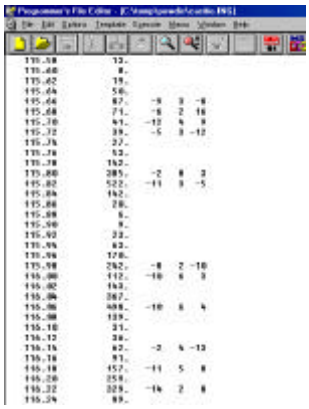


Fig 11b: Powutl generated pseudo-powder diffraction ING file with HKLs listed to the right of the powder diffraction counts

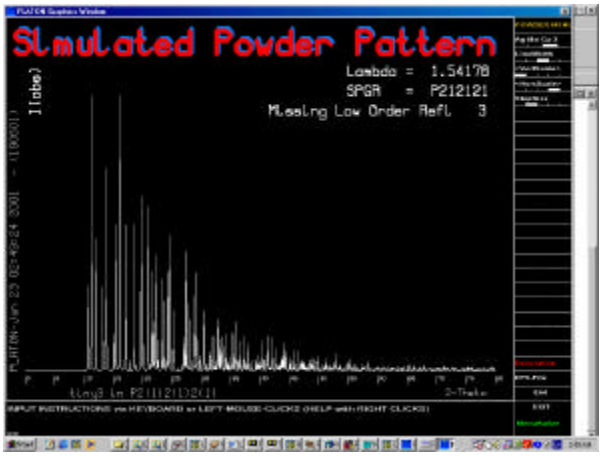


Fig 11c: Platon displaying a pseudo-powder pattern generated from single microcrystal HKL data of tetracycline hydrochloride.

RIETVELD SOFTWARE UPDATES (AS OF LATE JUNE 2001):

Hugo Rietveld website:
http://home.wxs.nl/~rietv025/

BGMN (11th June 2001)
http://www.bgmn.de/

DBWS (22nd February 2000)
http://www.physics.gatech.edu/downloads/young/download_dbws.html

Debvin (25th May 2001)
ftp://ftp.cc.uniud.it/DEBVIN/

GSAS (11th June 2000)
ftp://ftp.lanl.gov/public/gsas/

Jana (31st May 2001)
http://www-xray.fzu.cz/jana/jana.html

LHPM-Rietica (7th December 2000)
ftp://ftp.ansto.gov.au/pub/physics/neutron/rietveld/Rietica_LHPM95/

MAUD for Java (GPL'd) (26th December 2000)
http://www.ing.unitn.it/~luttero/maud/

Prodd (3rd April 2001)
http://www.ccp14.ac.uk/ccp/web-mirrors/prodd/~jpw22/

Rietan 2000 (GPL'd) (19th June 2001)
http://www.ccp14.ac.uk/ccp/web-mirrors/prodd/~jpw22/

Winplotr/Fullprof (5th June 2001)
http://www-llb.cea.fr/winplotr/winplotr.htm
ftp://bali.saclay.cea.fr/pub/divers/fullprof.2k/

Winmprof (21st June 2001)
http://lpec.univ-lemans.fr/WinMProf/

XND (31st May 2001)
http://www-cristallo.polycnrs-gre.fr/xnd/xnd.html
ftp://old-labs.polycnrs-gre.fr/pub/xnd/

All the above Rietveld programs are also available via the CCP14 based mirrors in UK, Australia and Canada (http://www.ccp14.ac.uk/mirror/).

Summary lists of some software available via the EPSRC funded CCP14 website:

Anharmonic Thermal Refinement Software
http://www.ccp14.ac.uk/solution/anharmonic/

Data Conversion for Powder Diffraction
http://www.ccp14.ac.uk/solution/powderdataconv/

Image Plate Software
http://www.ccp14.ac.uk/solution/image-plate/

Incommensurate Structure Software
http://www.ccp14.ac.uk/solution/incomm.htm

Indexing Software for Powders
http://www.ccp14.ac.uk/solution/indexing/

LeBail Method for Intensity Extraction
http://www.ccp14.ac.uk/solution/lebail/

Pawley Method for Intensity Extraction
http://www.ccp14.ac.uk/solution/pawley/

PDF, High Q Powder diffraction Analysis Software
http://www.ccp14.ac.uk/solution/high_q_pdf/

Peak Find/Profiling Software for Powder Diffraction
http://www.ccp14.ac.uk/solution/peakprofiling/

Pole Figure and Texture Analysis Software
http://www.ccp14.ac.uk/solution/pole_figure/

Powder Diffraction Data Visualisation
http://www.ccp14.ac.uk/solution/powder_data_visual/

Search-Match Phase Identification Software
http://www.ccp14.ac.uk/solution/search-match.htm

Single Crystal Structure Solution Software relevant to Chemical Crystallography
http://www.ccp14.ac.uk/solution/xtalsolution/

Single Crystal Structure Refinement Software relevant to Chemical Crystallography
http://www.ccp14.ac.uk/solution/xtalrefine/

Single Crystal Suites linking to multiple programs relevant to Chemical Crystallography
http://www.ccp14.ac.uk/solution/xtalsuites/

Spacegroup and Structure Transformation Software
http://www.ccp14.ac.uk/solution/transform/

Structure Conversion and Transformation
http://www.ccp14.ac.uk/solution/structconv/

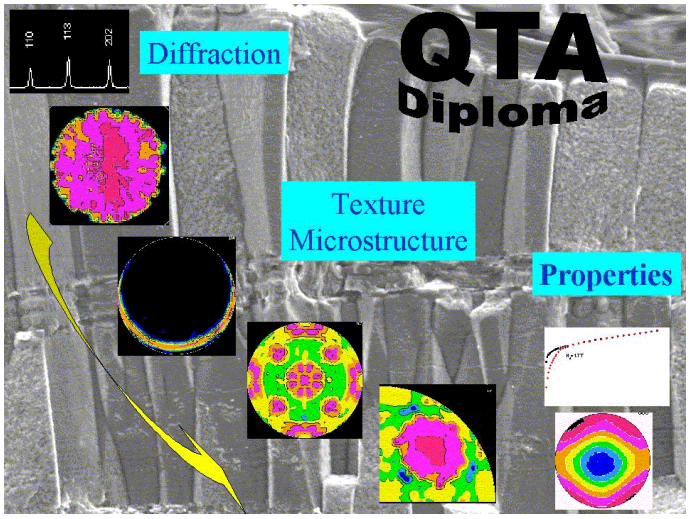
Structure Drawing and Visualisation
http://www.ccp14.ac.uk/solution/structuredrawing/

Unit Cell Refinement of Powder Diffraction Data
http://www.ccp14.ac.uk/solution/unitcellrefine/

Distant Learning In Crystallography

Université du Maine - France

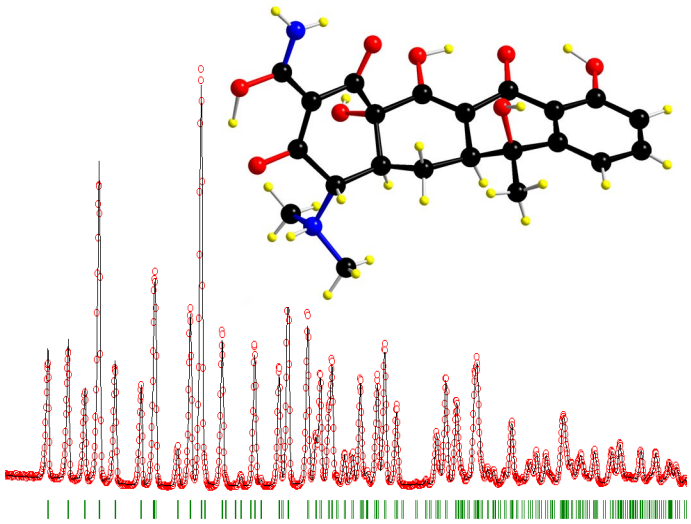
QTA Internet Course



From diffraction to quantitative texture-microstructure analysis to properties

http://lpec.univ-lemans.fr/qta
daniel.chateigner@univ-lemans.fr

SDPD Internet Course



Learn how to determine a crystal structure by powder diffractometry

http://sdpd.univ-lemans.fr/course
armel.le_bail@univ-lemans.fr

8th EUROPEAN POWDER DIFFRACTION CONFERENCE

Uppsala, Sweden 23 – 26 May 2002

Scientific Programme

The programme for the three-day conference will include invited plenary lectures, contributed talks and poster sessions. A commercial exhibition will also be organised.

The Scientific Programme will cover the topics:

1. Methods and techniques
2. Instrumental development
3. New or improved software
4. Databases
5. Materials research
6. Dynamic studies
7. Studies under non-ambient conditions
8. Industrial processes and applications
9. New research fields

Other contributions relevant or complementary to powder diffraction are welcome.

INFORMATION & CORRESPONDENCE

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Dept. of Materials Chemistry
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UPPSALA
UNIVERSITET

WHAT'S ON

The following web-site contains an up-to-date and semi-exhaustive list of conferences and workshops in crystallography and related areas
http://www.iucr.org/cww-top/mtg.date.html

30 July to 3 August 2001

THE 50TH ANNUAL DENVER X-RAY CONFERENCE
Fifty Years of the Denver X-ray Conference
Steamboat Springs, Colorado, U.S.A.

The Denver X-ray Conference is celebrating its 50th anniversary as one of the leading scientific events in the X-ray Analysis community. The celebration will include a history of the conference, and an overview of the monumental events in the field of X-ray analysis, as well as continuing the tradition of providing an international forum for discussions of state-of-the-art techniques and indications for future developments in X-ray analysis. The format consists of two days of tutorial workshops and poster sessions, followed by two and a half days of technical sessions. In addition to providing sponsorship, the ICDD publishes the conference proceedings in CD-ROM format through the series *Advances in X-ray Analysis.*

17 September 2001

PRACTICAL ASPECTS OF CRYSTAL STRUCTURE INVESTIGATIONS USING SYNCHROTRON- AND NEUTRON SOURCES
Stuttgart, Germany

A workshop sponsored by BMBF and MPG at the Max-Planck-Institute for Solid State Research (Stuttgart, Germany). For more information:
http://www.mpi-stuttgart.mpg.de/xray/seminar/

12 – 14 November 2001

SECOND ISPD--2001 AND ASCA 2001
Calcutta and Bangalore, India

Second International School on Powder Diffraction (ISPD--2001)will be held in Calcutta,India from 12-14 November, 2001. Lecture sessions include contemporary topics in powder diffraction by X-ray, electron, neutron and synchrotron radiation, given by experts with hands-on computer sessions for young and active researchers in institutes, universities, and companies. This will be a satellite meeting of AsCA (Asian Crystallography Association) to be held for the first time in India in Bangalore from18-21 November 2001. Participants may attend both meetings. Details will be announced shortly. The meetings are sponsored by IUCr, ICDD and other organizations.

For further information contact:
For ISPD 2001: Prof S P Sen Gupta,
E-mail:mssps g@mahendra.iacs.res.in,
Fax: 91-033-473 2805
For AsCA 2001: Prof M Vijayan , IISc, Bangalore,
E-mail: mv@mbu.iisc.ernet.in
Fax: 91-080-3600683,3600535.

2 – 6 December 2001

SIZE-STRAIN III - ANALYSIS OF MICROSTRUCTURE AND RESIDUAL STRESS BY DIFFRACTION METHODS
Trento, Italy

After the successful editions of Liptovski Mikulas (Slovak Rep.) in 1995 and Freiberg (Germany) in 1998, this conference will gather most of the specialists in Line Profile Analysis for the study of lattice defects and microstructure, as well as residual stresses by diffraction techniques.

For further information contact:
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29 April - 3 May 2002

PRACTICAL X-RAY FLUORESCENCE SPECTROMETRY
ICDD, Newtown Square, Pennsylvania, U.S.A.

Covering basics of X-ray spectra, instrumentation design, methods of qualitative and quantitative analysis, specimen preparation, review of mathematical matrix correction procedures, applications for both wavelength and energy dispersive spectrometry and new developments in XRF.

23 – 26 May 2002

EPDIC 8
Uppsala, Sweden

The *scientific* programme for the three-day conference will include invited plenary lectures, contributed talks and poster sessions. A commercial exhibition will also be organised.

The Programme will cover the topics:

1. Methods and techniques
2. .Instrumental development
3. New or improved software
4. Databases
5. Dynamic studies
6. Studies under non-ambient conditions
7. Industrial processes and applications
8. New research fields

Other contributions relevant or complementary to powder diffraction are welcome.

Internet: http://www.mkem.uu.se/epdic8
e-mail: epdic8@mkem.uu.se
Tel/Fax: 46-18-471 3733 / 46-18-513548
Surface mail: Attn. Gunilla Lindh
EPDIC-8**,** Dept. of Materials Chemistry,
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Box 538, SE-751 21 Uppsala, Sweden

3-7 June 2002

FUNDAMENTALS OF X-RAY POWDER DIFFRACTION
ICDD, Newtown Square, Pennsylvania, U.S.A.

Covering instrumentation, specimen preparation, data acquisition, and qualitative phase analysis.

10 – 14 June 2002

ADVANCED METHODS IN X-RAY POWDER DIFFRACTION
ICDD, Newtown Square, Pennsylvania, U.S.A.

Emphasizing computer-based methods of data collection and interpretation, both for qualitative and quantitative phase analysis.

For further information on all ICDD meetings contact:
Education Coordinator
International Centre for Diffraction Data
12 Campus Boulevard
Newtown Square, PA 19073-3273
Tel: +(610) 325-9814
Fax: +(610) 325-9823
E-mail: clinics@icdd.com
Web-site: www.icdd.com/education/clinics/

29 July to 2 August 2002

THE 51ST ANNUAL DENVER X-RAY CONFERENCE
Colorado Springs, Colorado, U.S.A.

The 51st Denver X-ray Conference will be held at the Adams Mark Hotel (formerly Antlers Doubletree Hotel) in Colorado Springs, Colorado. A tentative program will be available on the Denver X-ray Conference web site by September 2001, and the *Call for Papers* will be available in December 2001.

For further information contact:
Conference Coordinator
International Centre for Diffraction Data
12 Campus Boulevard
Newtown Square, PA 19073-3273
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Fax: +(610) 325-9823
E-mail: dxc@icdd.com

Web-site: www.dxcicdd.com

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Tel: +39 0461 882417/67
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How to receive the IUCr CPD Newsletter

If you wish to be added to the mailing list for the Newsletter of the IUCr Commission on Powder Diffraction or have changed address, please contact the Chairman or simply send an e-mail to CPD@ing.unitn.it

Call for contributions to the next CPD Newsletter (No 26)

The next issue of the CPD Newsletter will be edited by *Robert Dinnebier*, to appear in autumn of 2001. Robert will greatly appreciate contributions from readers on matters of interest to the powder diffraction community, e.g. meeting reports, future meetings, developments in instruments, techniques, and news of general interest. Please contact him for sending articles and suggestions. Software developments can be directly addressed to *Lachlan Cranswick* or to the Editor of Newsletter No 26 (addresses are given below)

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http://www.pulverdiffraktometrie.de

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