Powder X-Ray Diffraction

Solving Larger Molecular Crystal Structures from Powder Diffraction Data by Exploiting Anisotropic Thermal Expansion**

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Powder diffraction is an important crystallographic tool when no single crystal of the substance of interest is available, or when the intrinsic nature of the material is polycrystalline. Crystal structures of ever increasing complexity are being solved and refined from good quality powder data because of recent improvements in data-analysis methods. However, the obscuring caused by the overlap of neighboring Bragg peaks reduces the information content of the diffraction data and consequently remains a barrier to the general application of this technique to complex systems. Herein, we report how a significant improvement in data quality can be obtained, and illustrate this with the routine direct-methods solution of a 48-atom fully organic structure. This improvement was achieved by exploiting anisotropic thermal expansion by using high-resolution synchrotron X-ray powder diffraction.

To solve unknown crystal structures where there is no prior structural model, two modern methods[1] are generally employed, these are the direct-methods solution of the crystallographic phase problem and the global optimization of known structural fragments within the unit cell. The number of degrees of freedom to be explored essentially limits the complexity of the structures that can be solved by the global optimization approach. Without a suitable fragment, direct methods must be employed, which require atomic-resolution data. The measured diffraction intensities represent the square moduli of the structure factors, $|F|^2$, which define the atomic structural information, so that the pattern decomposition to yield the intensity estimates is a crucial step in the structure-solution process. The adaptation of single-crystal methods to deal with powder diffraction data has been extensively discussed.[2]

There are, however, intrinsic difficulties associated with intensity extraction, which arise from the overlap of the Bragg reflections in the powder diffraction pattern. Overlap reduces the accuracy of the extracted intensities, and when overlap blurs into a continuum towards the smaller interplanar lattice spacings, it may become essentially impossible to have any clear indication of the individual peak intensities. If the accuracy of the integrated intensities is poor the phasing process by direct methods is not reliable and therefore fails more often when used with powder data than with single-crystal data. The number of atoms that can be located by this approach using powder data is usually limited to around 30 for equal-atom structures, such as organic molecules. A great deal of effort has been spent in developing new strategies for obtaining better estimates of the relative intensities of overlapping reflections,[3] or employing more sophisticated tools, for example, maximum entropy[4] or Bayesian statistics,[5] and correcting for other systematic problems, for example, trying to evaluate the contribution of preferred orientation.[6]

Novel approaches to data collection have also been devised.[7] Wessels and co-workers[7a] collected diffraction data from deliberately textured samples in which preferred orientation was particularly pronounced. Another way to reduce effective peak overlap is to exploit the anisotropy in thermal expansion that many low-symmetry materials naturally exhibit. At different temperatures the relative positions of Bragg reflections change, owing to the anisotropic changes in the lattice dimensions, but maintain approximately the same intensities. By collecting data at multiple temperatures it is possible to assess the individual contribution of reflections that are overlapping at one temperature, but are better resolved at another. In a pioneering paper Zachariasen and Ellinger[8] show the changes in the diffraction pattern of plutonium metal, even with fairly modest resolution. Shankland and co-workers[9] have emphasized the utility of this approach in their work on the solution of the crystal structure of the pharmaceutical organic molecule chlorathiazide.

Changes in the overlap of the reflections as the temperature is varied are best revealed with an intrinsically high-resolution instrument, so that the effects of small peak shifts are more readily discernable. Furthermore, high X-ray intensity is required, this leads to good counting statistics, so that subtle changes in the patterns are not fogged by statistical noise, and overall counting times are reasonable. The high-resolution powder diffraction beam line[10] at the European Synchrotron Radiation Facility (ESRF) has recently been upgraded, by being moved from a bending-magnet to an undulator source, where it receives a significantly more intense incident X-ray beam. The performance is now such that the systematic use of anisotropic thermal expansion to study more-complex crystal structures by powder diffraction can be envisaged.

During our continuing studies on the low-temperature structures of small globular organic molecules, we had been unable to solve the structure of 9-ethylbicyclo[3.3.1]nona-9-ol ($C_{11}H_{20}O$) despite having determined the unit cell and the space group.[11] Having 48 non-hydrogen atoms in the asymmetric unit (four independent molecules), this substance was

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selected as a promising candidate for the anisotropic thermal expansion approach. Previous successful applications of direct methods to relatively large organic structures include fluorescein diacetate with 31 carbon and oxygen atoms,[14] and sulfathiazole, 32 atoms, which has the benefit of containing the heavier sulfur atoms.[15] Thus, solving a structure containing 48 atoms would be a notable advance in the technique.

Five powder diffraction patterns at different temperatures (80, 120, 140, 160, and 180 K) were collected on the new ID31 beam line at the ESRF in a total time of about 12 h by using an incident X-ray wavelength of 0.80175(4) Å. Figure 1 illustrates the changes in the diffraction pattern arising from peak shift as a consequence of the anisotropic thermal expansion manifested between 80 and 180 K. Integrated intensities were extracted by a multipattern Pawley-style refinement procedure.[16] This method is similar to a Rietveld refinement in that a diffraction profile is calculated as a sum of overlapping reflections. However, in the Pawley case, the intensities are not defined by a structural model, but are variables in a least-squares procedure. For the patterns collected at different temperatures, a single set of peak intensities was fitted to the multiple data sets. During the data collection a first attempt to solve the structure was made with just two data sets (collected at 80 and 120 K). The extracted intensities were input to the single-crystal direct methods program SHELXS,[17] but did not lead to an interpretable structure. After adding the data collected at 140, 160, and 180 K to the refinement, a much improved set of diffracted intensities was produced,[18] using the same simultaneous-fitting approach and extracting peaks up to a maximum angle of $2\theta = 50°$ ($d_{\min} = 0.95$ Å). There was severe peak overlap at high angles, where approximately 250 peaks are present per degree of the pattern. With a refined peak width of approximately 0.015 degrees this corresponds to an average of four contributions for each resolvable peak in a single pattern.

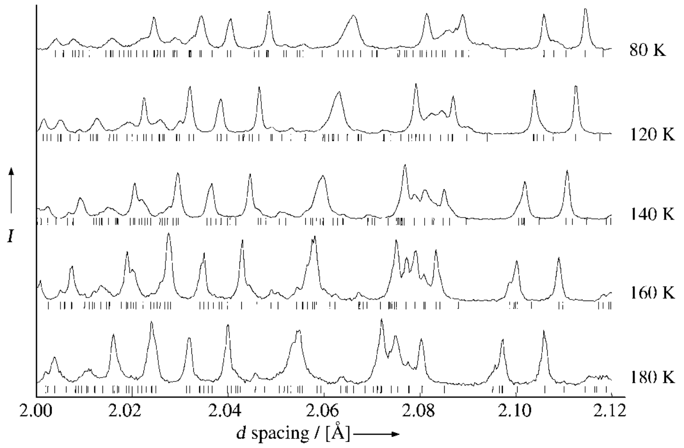

Figure 1. An example of selected regions of the diffraction patterns showing anisotropic thermal expansion: the five diffraction patterns are fitted simultaneously with a Pawley-style refinement with a single set of intensities. Vertical bars indicate Bragg peak positions.

Three whole molecules could be identified in the SHELXS solution and the fourth molecule was completed by Fourier recycling against the same set of extracted intensities, without returning to the powder diffraction pattern to improve the partitioning of overlapping peaks in the light of the partial model. The marked improvement upon adding the further data sets (140–180 K) can be explained by the anisotropy of the thermal expansion, as shown in Figure 2. The basis of this method is that the thermal expansion of the cell parameters must be different to change the relative positions of the peaks: up to 140 K peaks belonging to the *hk0* zone will show no relative change as the *a* and *b* axis expand at similar rate, whereas all the five data sets together will display anisotropic relative shifts of all the *hkl* peaks.

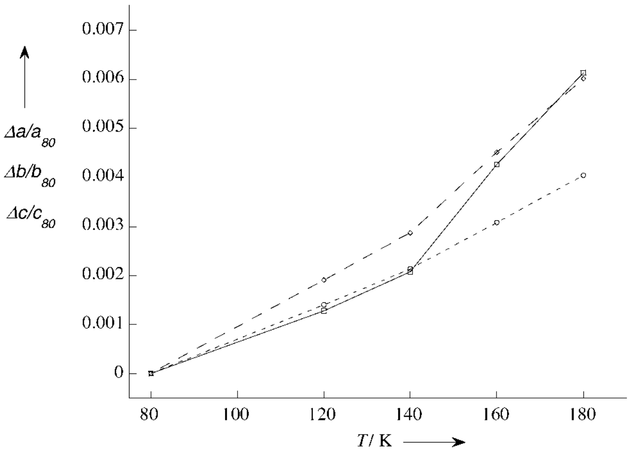

Figure 2. The measured relative variation of the cell parameters *a* (-----○), *b* (——□), and *c* (– – –◇) of 9-ethylbicyclo[3.3.1]nona-9-ol as a function of temperature, which shows the anisotropy in the thermal expansion of the unit cell. The error bars are smaller than the symbols.

The structure obtained is chemically reasonable in terms of interatomic and intermolecular distances. The arrangement of the four independent molecules is illustrated in Figure 3. They form a tetramer linked by an approximately square arrangement of O–H···O hydrogen bonds between hydroxide groups. Three of the hydroxide oxygen atoms lie in a plane essentially perpendicular to the crystallographic *c* direction, with the fourth oxygen, O(76) lying 1.3 Å out of this plane. The oxygen atoms are completely at the heart of the cluster, the outer surface of which is composed of hydrogen atoms. Interactions between adjacent clusters are therefore entirely of a van der Waals nature. The presence of the O–H···O hydrogen bonds explains why this molecule does not exhibit the disordered structures found for other related molecules,[19] for example, S-camphor or bicyclo[3.3.1]nonan-9-one which have weaker C–H···O networks.

An essentially complete structure could be derived from the extracted integrated intensities, without any need for recycling of partial structural models to improve the estimates of intensity partitioning under overlapped peaks. The addition of further diffraction profiles increases both the counting statistics for the weak peaks at high angles, as well as the

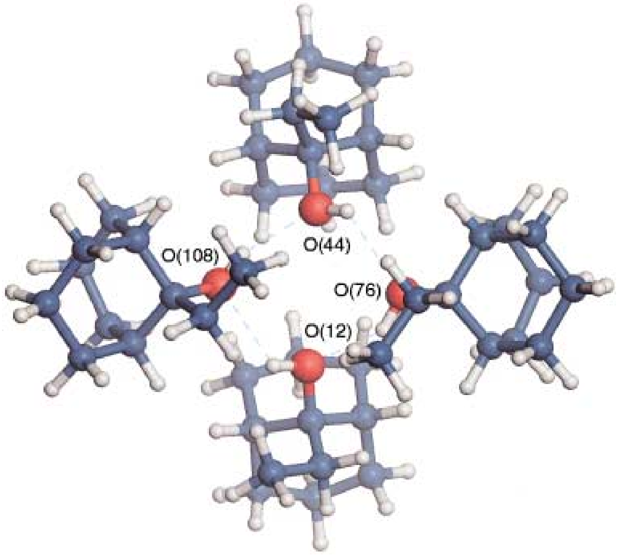

Figure 3. View of the arrangement of the four 9-ethylbicyclo[3.3.1]nona-9-ol molecules to form a hydrogen-bonded tetramer. The O–H⋯O hydrogen bonds are shown with dashed lines: O(12)-O(108) 2.825(4), O(44)-O(76) 2.761(4), O(76)-O(12) 2.804(4), O(108)-O(44) 2.869(4) Å. The crystallographic *c* direction is perpendicular to the plane of the Figure. O red, C blue, H gray.

estimates of individual intensities where peaks overlap, both of which are crucial to the success of direct methods. The solution of this structure illustrates a considerable advance in the quality of data: data collection was completed in about 12 h during the first day of scheduled-user experiments on the newly commissioned beam line, with the structural model being derived the very next day. The speed and simplicity of both the data collection and analysis strongly suggest that even larger structures will also be tractable with powder X-ray diffraction data.

Experimental Section

A specimen of 9-ethylbicyclo[3.3.1]nona-9-ol ($C_{11}H_{20}O$, Aldrich 99 %) was contained in a 1.5-mm diameter borosilicate glass capillary. The capillary was mounted on the diffractometer on the new ID31 beam line and spun at approximately 2 Hz to improve the powder average. The sample was cooled by a stream of cold nitrogen gas from a Cryostream cooler, oriented coaxially with the capillary. Powder diffraction patterns at five temperatures (80, 120, 140, 160, 180 K) were collected with an incident X-ray wavelength of 0.80175(4) Å.

The model obtained by direct methods (SHELXS combined with Fourier recycling) was refined against the diffraction profile collected at 140 K together with stereochemical restraints using the Rietveld software package GSAS.[20] Hydrogen atoms were added to the model in their expected positions. 144 atomic coordinates plus coordinates of the 80 hydrogen atoms, profile and background parameters were refined in each cycle. The bond length and angle restraints were set to values obtained from an ab initio molecular-orbital optimization of the molecular structure performed using the program Gaussian 94[21] with a 6-31+G(d) basis set. They were weighted, respectively, 0.001 Å and 0.1°. It was quickly realized that one ethyl group is disordered. The final refinement converged satisfactorily to $R_{wp} = 5.3\,\%$, $R_{F^2} = 7.5\,\%$, and $\chi^2 = 16.5$, with the highest peak and lowest hole in the final difference Fourier map being 0.2 and −0.2 electrons. The high χ^2 value reflects the extremely high counting statistics of the data which produced a $R_E = 1.3\,\%$. Final cell parameters at 140 K are: $a = 21.10871(4)$, $b = 23.14144(5)$, $c = 16.46364(3)$ Å, $V = 8042.26(3)$ Å^3, $Z = 32$. Lists of refined atomic coordinates and of bond lengths and angles of the 9-ethylbicyclo[3.3.1]nona-9-ol crystal structure are available as Supplementary Information in Tables S3 and S4. The observed, calculated, and difference profiles of the final fit at 140 K are shown in Figure 4. Further refinement of the crystal

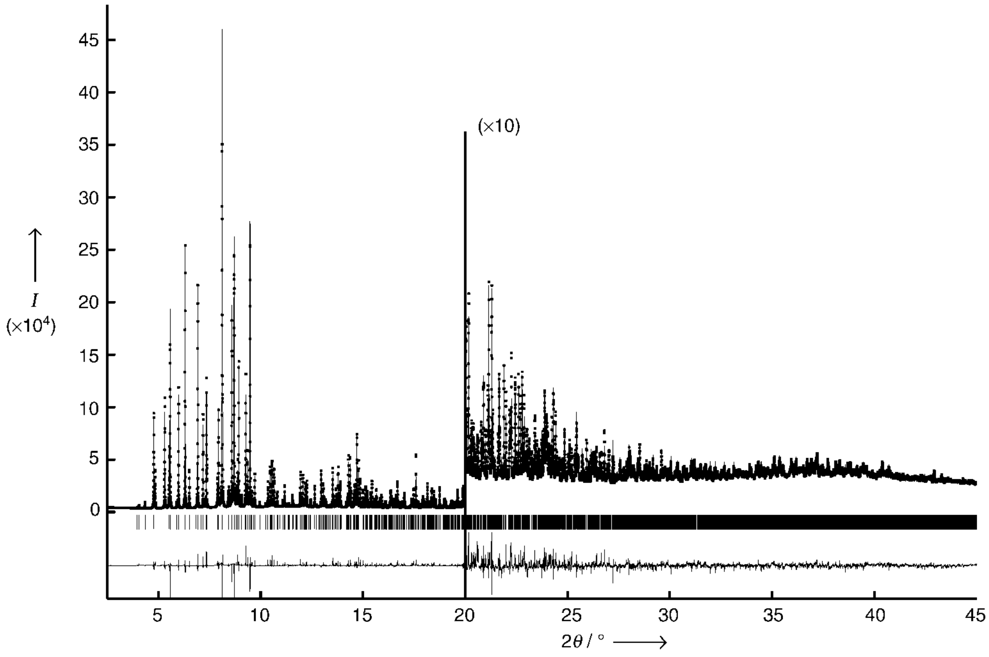

Figure 4. Observed (·), calculated (——), and difference plot of the final Rietveld refinement of 9-ethylbicyclo[3.3.1]nona-9-ol recorded at 140 K; reflection positions are shown as vertical lines.

structure at all five temperatures would allow the thermal evolution of the structure to be followed in detail.

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