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Disorder and Motion in Crystal Structures: Nuisance and Opportunities

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Abstract: Conventional structure analysis averages the structure of an entire crystal into a single unit cell. If there is disorder and thermal motion, this averaging obscures information on local structure, intermolecular interactions and molecular dynamics. Nonetheless structural detail at the molecular and supramolecular level can be retrieved even for heavily disordered molecular materials by analyzing their diffuse scattering. Molecular dynamics can be elucidated and distinguished from disorder on the basis of atomic displacement parameters (ADPs) determined over a range of temperatures from conventional structure analyses. Such studies are now becoming feasible for molecular crystals through improved experimental techniques, faster computers and new algorithms.

Keywords: Anisotropic displacement parameters · Diffuse scattering · Disorder · Molecular motion · Supramolecular chemistry

1. Introduction

What a nuisance! You finally get the results of that all-important crystal structure and your crystallographer just keeps mumbling about inconclusive evidence due to disorder, large thermal ellipsoids and distorted geometries. Although such annoyances may be infrequent, they do remind us of the fact that the textbook idea of the translationally symmetric crystal – the periodic repetition to infinity of identical, motionless building blocks in three dimensions – is always wrong to a smaller or larger extent. Crystals are finite and imperfect rather than infinite and perfect. Their natural beauty is due to their regular, shiny faces reflecting light into the eye of the observer. A magnifying glass may reveal small cracks and inclusions. An optical microscope can uncover different crystal domains. With an electron microscope the stacking of unit cells may be found at fault. At the atomic level X-rays or neutrons may 'see' statistical occupation of different positions in the unit cell, and multiple orientations or conformations of molecules [1].

'Errors' in the crystal architecture are unavoidable because a macroscopic crystal contains a very large number of unit cells, about 10^{18} in a $(100\ \mu m)^3$ specimen built from $(10\ Å)^3$ cells. The Boltzmann distribution requires that a fault, which costs 3 kcal mol^{-1} of strain energy will be present in a concentration of about one percent provided crystallization took place at room temperature under equilibrium conditions. Careful single crystal diffraction experiments can detect this concentration. Even a 'perfect' crystal could never be periodic at any instant of time because the atoms move about their mean positions even at the absolute zero of temperature. As such motions are much slower (10^{-12}-10^{-14}s) than the time it takes for an X-ray photon to be scattered (10^{-18}s), each photon sees a not quite regular atomic arrangement. Crystal structure analysis from Bragg reflections provides only a mean structure, an average over space and time. Depending on the type of disorder and the extent of motion such averages show split atoms indicating superimposed molecules in the average unit cell, or large and anisotropic atomic displacement parameters (ADPs) arising from a combination of disorder and motion, or both. It can be quite difficult to deconvolute such blurred averages into individual molecules and to extract from them the information on molecular motion. It is impossible to deduce from the averages which of the disordered positions are occupied in neighboring unit cells and thus what the preferred nearest neighbor interactions are.

The actual (as opposed to the averaged) arrangement of building blocks can be investigated experimentally because disorder and motion manifest themselves in the diffuse scattering of neutrons and X-rays. The tools available for measuring and interpreting such scattering are still relatively primitive compared to the highly automated procedures available for determining ordered crystal structures. As a consequence diffuse scattering studies in complex molecular materials are few and far between. ADPs are an alternative source of information on molecular motion. They decrease with decreasing temperature. Service crystallography takes advantage of this effect to improve resolution and accuracy. The temperature dependence can also be exploited systematically for analyzing motion in crystals as appropriate models and

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corresponding computer programs are now becoming available.

Our interest in a better understanding of motion and disorder derives from two sources. On one hand, crystal structure analysis is widely regarded as providing an essentially static picture of molecular structure. Maybe it is time to revise this prejudice. On the other hand, chemists synthesize larger and larger supramolecules with less and less ordered structures, or materials whose properties may even depend on the presence of disorder. Alloys are classical examples of the latter and high T_c cuprate superconductors are a more recent one. Molecular biologists plan high-throughput protein structure factories which will certainly produce structures for which detailed investigations of disordered, multiple conformations or of the motion of protein segments might contribute to a better understanding of their mode of action. In the following sections prototypical problems, ways of dealing with them, and opportunities they provide will be discussed: static disorder and diffuse scattering, dynamic disorder and chemical equilibria in crystals, vibrational motion and temperature dependence of ADPs. The essay ends with a few remarks on new tools and technologies.

2. Static Disorder

Tris(bicyclo[2.1.1]hexeno)benzene (**1**) was synthesized to probe the possibility of a cyclohexatriene-like groundstate geometry [2a]. Yields of the five-step synthesis were so poor that at the time the world's supply of this substance was about half a dozen small crystals. Several sets of diffraction data were measured in different laboratories. The results were more than just a nuisance for the synthetic chemists: none of the data sets led to a model accurate enough to differentiate the cyclohexatriene structure from the completely delocalized one. Precession photographs eventually revealed the problem: diffuse diffraction streaks in addition to the usual sharp spots (Fig. 1). Once this was recognized it was relatively easy to develop a model of the average structure – ordered layers tiled with threefold symmetric molecules and stacked nearly randomly. The model unambiguously revealed a cyclohexatriene geometry even though it did not explain the details of the diffuse scattering [2b].

The above example might suggest that taking into account diffuse scattering is just another tool for determining average crystal and molecular structures

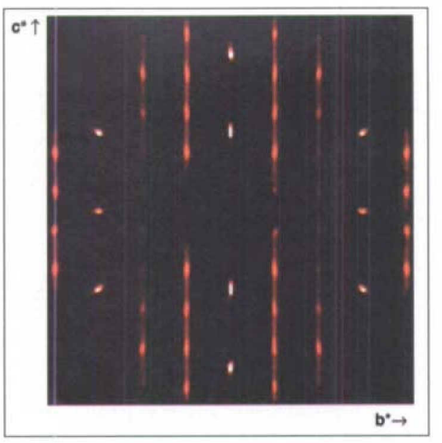
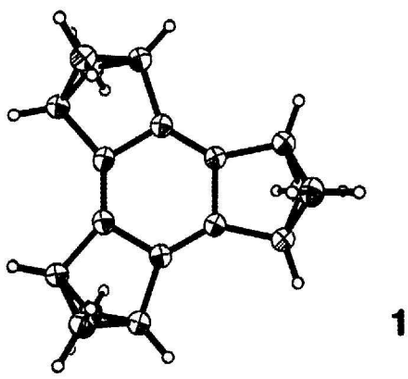


Fig 1. Observed 0kl layer of tris(bicyclo [2.1.1] hexeno) benzene (**1**). The diffuse streaks along **c*** indicate stacking disorder of layers tiled with **1**.

which do not yield with standard techniques. However, the study of diffuse scattering from disordered crystals is a worthwhile goal in itself as it may uncover supramolecular building principles of finite correlation length (as opposed to the infinite correlation length characteristic of the ideal crystal). Consider the hypothetical example of a one-dimensional crystal of molecular arrows (↑). Suppose that the *average* structure obtained from the Bragg intensities is ...↕↕↕↕↕↕..., *i.e.* the molecules in one half of the unit cells are oriented upwards, the ones in the other half downwards. Nothing can be said about the sequence of up and down molecules and thus on the self-recognition properties of this molecule. Several different *real* crystal structures are compatible with the *average* structure: *e.g.* (i) a random distribution of up and down molecules, ...↑↑↓↑↓↓↓↑↓↓↑↓↓↑↑..., (ii) preferred parallel orientation of neighboring molecules without long-range order ...↑↑↑↑↓↓↓↑↑↑↓↓↓↓↑↑... or (iii) preferred anti-parallel orientation without long-range order ...↑↓↑↓↓↑↓↑↓↓↑↓↑↑↓↑↓↑↓... From a chemical viewpoint model (i) implies that the molecules are equally happy with parallel and anti-parallel self-association. Models (ii) and (iii) imply a preference of one mode of association over the other. The three types of disorder are analogous to random orientation, partial ferromagnetic and partial antiferromagnetic ordering of spins, or to atactic, block isotactic and block syndiotactic stereochemistry of polymers. Although the three disordered structures show the same Bragg intensities, they may be easily distinguished on the basis of their diffuse intensities (Fig. 2).

The same problem is found in the macroscopically polar host-guest compound between racemic perhydrotriphenylene (PHTP) and nitrophenylpiperazine (NPP). The average structure is built from stacks of PHTP molecules arranged in a honeycomb pattern, which hosts the NPP guest molecules (Fig. 3). The arrangement of PHTP molecules shows racemic disorder with half an *R*-molecule superimposed on half an *S*-molecule in the averaged structure [3]. This disorder implies that nearest neighbor contacts in the crystal structure may be *R*/*R*, *S*/*S* or *R*/*S*. The average structure does not show which of these possibilities is preferred. In view of the polarity of this material, detailed knowledge on the supramolecular association properties of the host molecules is of some interest. Because the arrangement of the PHTP molecules is *centrosymmetric* only on average, polar host domains inducing or at least helping the formation of the *non-centrosymmetric* arrangement of the guest molecules cannot be excluded. Diffraction experiments reveal a complicated, highly modulated pattern of diffuse intensities (Fig.



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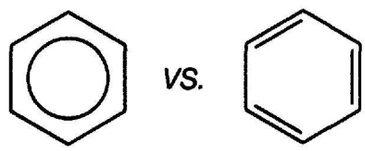


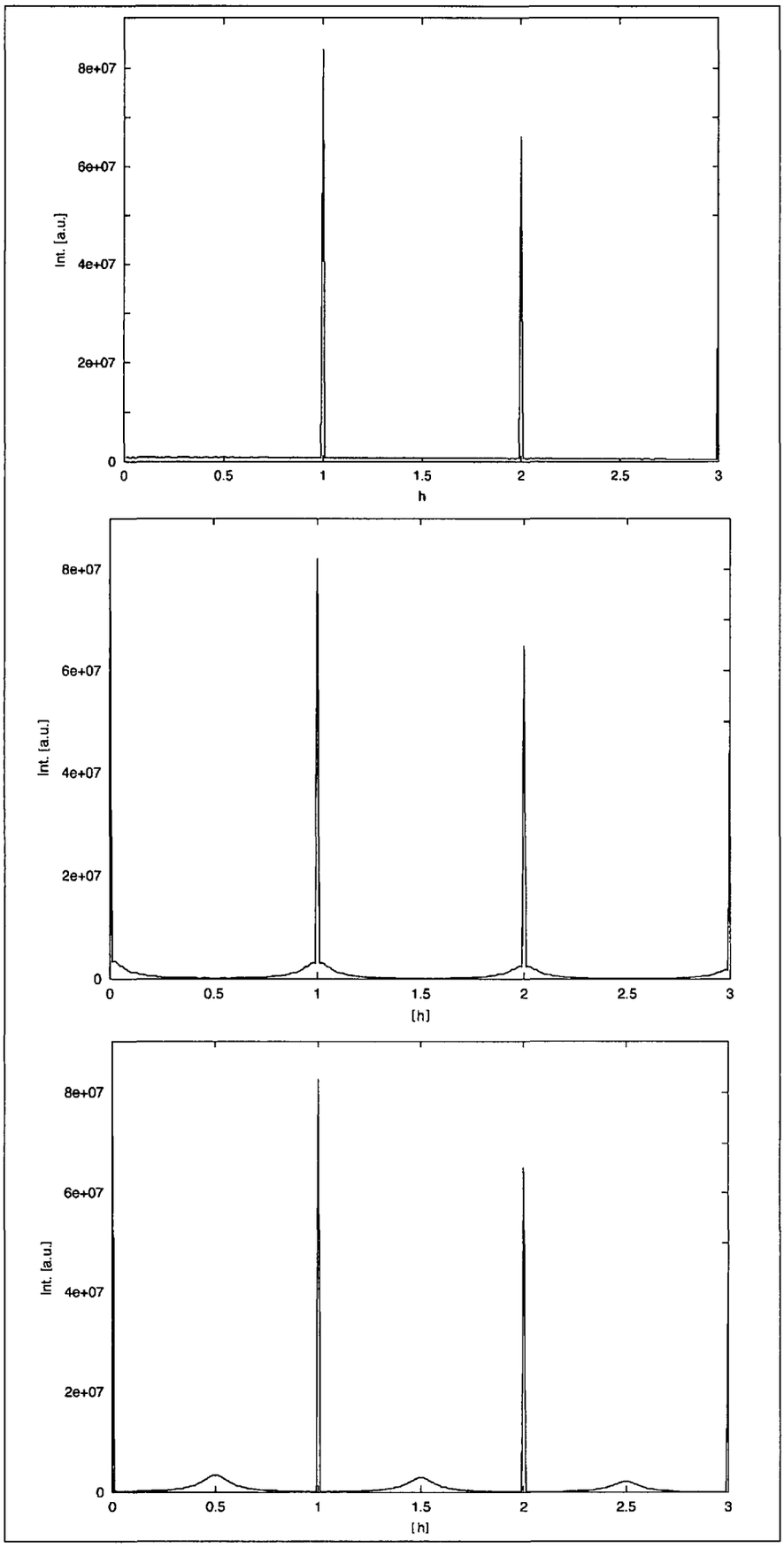


Fig. 2. X-ray scattering from disordered one-dimensional crystals. a) random distribution b) partial ferromagnetic ordering and c) partial antiferromagnetic ordering. (For ease of calculation the up and down arrows mentioned in the text have been replaced by carbon and hydrogen atoms, respectively).

4a shows a small portion of it). Well-defined parts of this pattern could be assigned exclusively and unambiguously as arising from the actual (rather than the average) distribution of the *R*- and *S*-host molecules [4a].

Much like conventional structure analysis, interpretation of diffuse scattering proceeds in two steps: defining a model of the disordered structure and determining the best values of its parameters. The PHTP host lattice was modeled with the assumption that the distribution of *R*- and *S*-molecules is fixed on the crystal surface during crystal growth because racemization and dynamic exchange between an *R*- and an *S*-molecule in the bulk are very improbable [4b]. Molecules are added to a layer of randomly distributed enantiomers. Their chirality and positions are determined from a Boltzmann distribution based on attachment energies (Monte Carlo algorithm). Calculating these energies from tabulated atom–atom potentials would be very time consuming. Simplifying the description of intermolecular interactions to four harmonic springs between the attaching molecule and every one of its prospective nearest neighbors, reduces the complexity of the simulation to a manageable size. The simplicity also has a drawback: the spring constants merely represent a parameterization of the problem and have no immediate physical or chemical significance.

There are many methods to find the best model parameters, *i.e.* the ones leading to a structure with optimal agreement between observed and calculated diffuse intensities. Least squares methods are one option [5]. The lack of direct physical significance makes it difficult to guess initial parameter values reliably. If they are not sufficiently close to the global optimum in refinement space, this method runs the risk of getting stuck in a local optimum. Evolutionary algorithms are more flexible in this respect and also more powerful than analytical or conventional trial-and-error methods [6]. In analogy to evolution in natural systems, a set of virtual individuals is defined, each with a different *genotype*. Initially the genes of an individual, *i.e.* the values of the model parameters, are chosen randomly from within a reasonable range. The *phenotype*, *i.e.* the actual crystal structure, is obtained with the Monte Carlo algorithm described above. The fitness of an individual is high if the calculated diffuse intensities agree well with the observed ones (low R-value). New individuals are obtained by mating within the initial population, *i.e.* by crossover and mu-

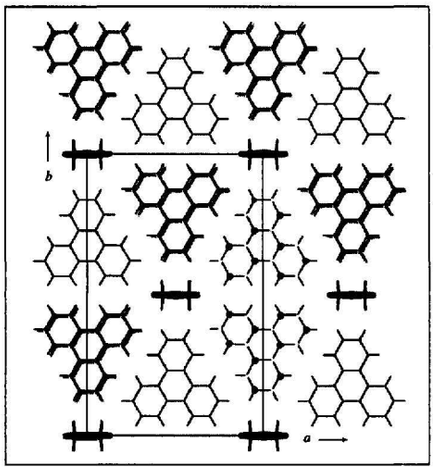


Fig 3. The structure of the $PHTP_5$•NPP inclusion compound viewed down the polar stacking axis of PHTP host and NPP guest molecules. A left- and a right-handed, D_3-symmetric PHTP molecule is indicated at the right boundary of the unit cell. The space-group of the average host structure is centrosymmetric, *Cmcm*; that of the average guest structure is polar, $Cmc2_1$.

tation of the parent genes. Only the fittest individuals in this enhanced population are allowed to propagate to the next generation. This procedure is repeated until the population has converged.

Refinement of the PHTP data using a variant of evolutionary algorithms called *Differential Evolution* [7] produced very good agreement between experimental and calculated diffraction patterns (R = 0.15, see Fig. 4a, b and [6c]). Statistical analyses of the resulting structure show the following: (i) sequences averaging ~15 homochiral molecules along ***c***; shorter contact distances for homochiral than for heterochiral contacts (4.71 *vs.* 4.83 Å, homochiral sequences match the protrusions from axial hydrogen atoms of one molecule into the hollows between hydrogen 'atoms in the next as may be seen from space filling models). (ii) there is a slight preference for nearest neighbors along ***b*** to be heterochiral ($P_{hetero} = 0.64$); the same holds along ***a***, although to a lesser extent ($P_{hetero} = 0.58$). This correlates with the intermolecular contact surfaces which are larger along ***c*** than in the ***a*** and ***b*** directions. (iii) heterochiral contacts along ***a*** are associated with a small, but highly significant displacement of the molecules parallel to the tunnel axis, away from their position in the average structure (~ 0.05 Å). The PHTP example nicely illustrates the type and amount of information obtainable from analyzing diffuse scattering.

3. Dynamic Disorder

A disordered crystal in which the barriers to atomic repositioning, molecular reorientation or conformational change are low compared to thermal energy, will adjust its concentration of faults to changes in temperature and pressure. This situation may be referred to as 'dynamic disorder'. With decreasing temperature the time scales for such processes increase until at sufficiently low temperature dynamic disorder becomes static.

The crystal structure of C_{60} below 250 K displays two molecular orientations unrelated by crystal symmetry and with different concentrations (Fig. 5). As the temperature is lowered the occupation of the major orientation increases at the expense of the minor one. The ratio of concentrations is found to be a linear function of 1/T. At about 90 K no further change is observed within the time constraints of the experiments. The crystal freezes into what has been called an 'orientational spin glass' [8a,b]. The minor molecular orientation was initially overlooked, because it had been largely accounted for by (somewhat unreasonable) ADPs of the major one [8c]. Once the disorder was discovered, *ln* K(T), ΔH and ΔS for the reorientation equilibrium could be determined and detailed insight into the energetic aspects of two different ways of packing C_{60} molecules could be gained.

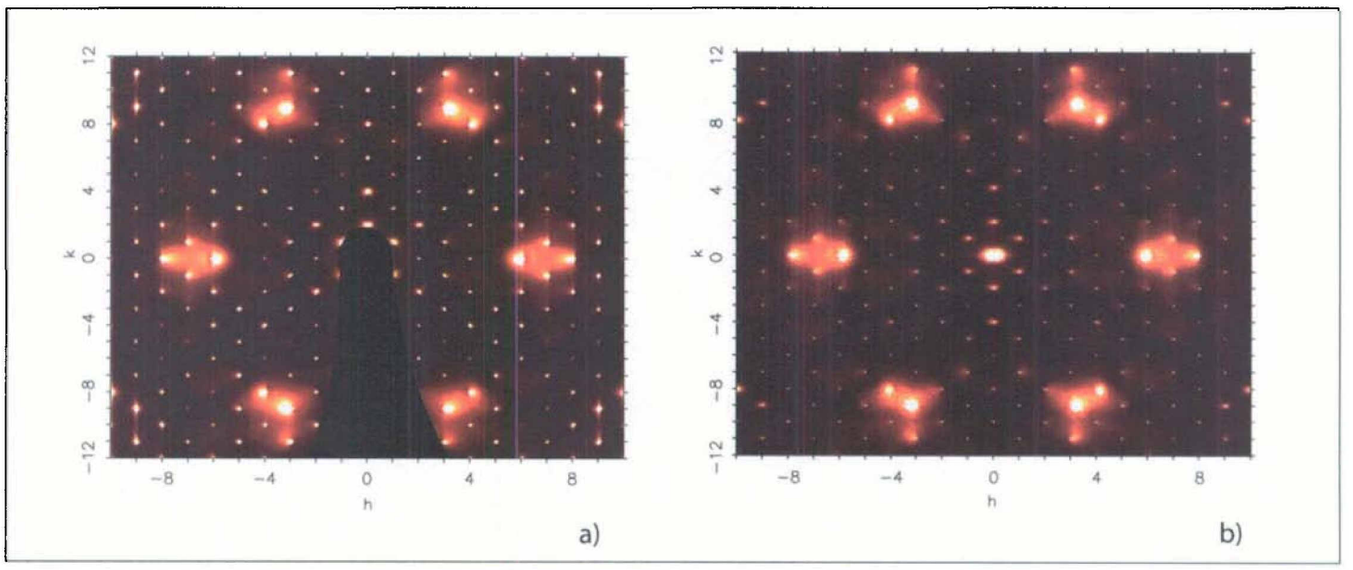


Fig. 4. Observed (left) and calculated (right) diffuse intensities in the hk2-layer of $PHTP_5$•NPP. Note the agreement with respect to the general distribution of diffuse intensities but also with respect to details such as the pronounced asymmetries in the neighborhood of Bragg reflections (*e.g.* 602 and 802). Contributions from the guest molecules were not included in the calculated intensities. In this case this does not affect the diffuse intensities, but is visible in the Bragg peaks.

The extra effort necessary to study equilibria in crystals is relatively modest: routine measurement and interpretation of the Bragg reflections at several temperatures. The example of C_{60} is prototypical. Several analogous equilibria have been reported: between tautomeric forms or different conformers, between species with different Jahn-Teller distortions, between different mixed-valence species, and others. [8c].

4. Atomic Mean Square Displacements (*alias* Anisotropic Displacement Parameters or ADPs)

In the limit of zero-barrier to atomic relocation, dynamic disorder becomes vibrational motion which persists down to the absolute zero of temperature. Even for a flawless crystal none of its instantaneous atomic configurations is periodic, only the time-averaged structure is. The nuisance here is with the ADPs. The uncertainty in atomic positions implied by typical values of ADPs is generally between 0.1 and 0.3 Å, much larger than typical standard uncertainties quoted for interatomic distances (0.001 to 0.01 Å). Adopting the smaller numbers to assess the accuracy of bond lengths and angles can only be justified if one can assume that ADPs reflect molecular translation, libration and deformation motions rather than disorder. Usually there is *indirect* evidence for this assumption from vibrational analyses and quantum chemical calculations. *Direct* evidence allowing to make the distinction between motion and disorder and thus to adopt the smaller uncertainties has become available only recently from analyses of the temperature evolution of ADPs as will be sketched below.

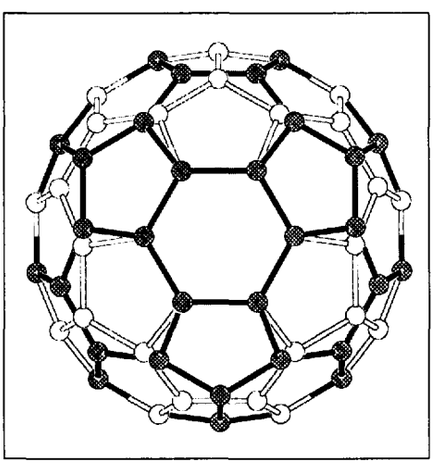


Fig. 5. Major and minor molecular orientations found in the average crystal structure of C_{60}.

Ermer has illustrated the problems associated with ADPs in an insightful note 'Concerning the Structure of Benzene' [9]. Contrary to widespread claims, the presence of a center of symmetry in the benzene molecule and thus the preference of the D_{6h}-symmetric, delocalized structure over the D_{3h}-symmetric cyclohexatriene alternative found for **1** above cannot be proven by standard X-ray or neutron crystallography. Ermer points out that 'the atomic positions originating from [...] diffraction analysis of crystalline benzene are *averaged* over time and space and are compatible not only with a crystallographically ordered D_{6h} model of benzene but also with a disordered D_{3h} model corresponding to a superposition of benzene molecules rotated with respect to each other by 60° around the threefold axis. [...] Assuming a difference of 0.10 Å between the C–C and C=C bond lengths in the D_{3h} model [...] the superimposed carbon atoms are only 0.058 Å apart [...] far below the resolving power of an X-ray diffraction experiment. [...] The C–C bond length difference [...] corresponds to a disorder contribution [to the ADPs of the C atoms] of only 0.0008 Å^2'. By comparison the values measured by neutron diffraction are ~0.023 Å^2 at 123 K and ~0.008 Å^2 at 15 K, at least an order of magnitude larger. All arguments about the presence or absence of disorder and thus of a molecular center of inversion must be inconclusive if based on diffraction evidence alone.

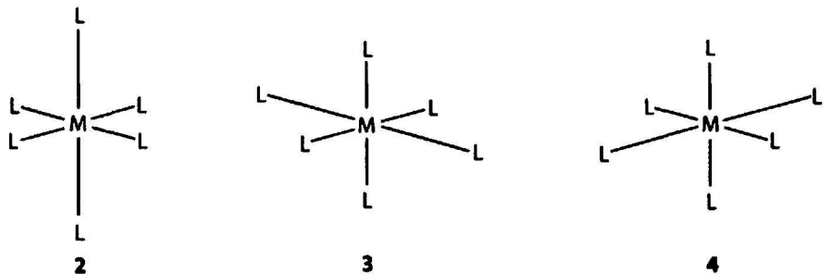
The problem of interpreting ADPs has been turned into a challenge: how can disorder be distinguished from motion and how can information on the cooperative dynamics of atoms be extracted from ADPs? In principle the study of thermal diffuse scattering could provide an answer. However, as indicated in Sections 2 and 5, the necessary experiments are not of a routine nature and the tools for interpretation poorly developed. A method that takes advantage of the ease of conventional structure analyses would be preferable. Meeting this challenge also implies solving another phase problem, because ADPs do not show whether neighboring atoms move in the same or in opposite directions, at least not directly. The problem was solved by developing a quantitative model of the temperature evolution of the ADPs over as large a range of temperatures as possible. The model considers molecules as moving in the average crystal field and makes the plausible assumption that the mean square displacement $\langle u^2 \rangle$ of a molecular normal mode follows the usual statistical thermodynamic expression for a harmonic oscillator with frequency ω: $\langle u^2 \rangle = h/(4\pi\omega) \coth(h\omega/4\pi kT)$. The model allows the separation of the large and strongly temperature dependent low frequency contributions to the ADPs from the temperature independent ones. In the case of benzene 90% of the ADPs at 15 K can be accounted for in terms of low-frequency librations and translations. The temperature independent residual is ~0.001 Å^2, a magnitude which may be interpreted either as a disordered arrangement of rigid cyclohexatriene molecules or as the zero-point motions of a D_{6h} symmetric benzene molecule, but not as both. Quantum theory requires zero-point motion, thus favoring the delocalized benzene structure in the crystalline state [10].

The situation where motion is insufficient to explain ADPs has also been described. Electronic structure theory predicts elongated tetragonal bipyramidal geometries for Cr(II), Mn(III) or Cu(II) ions coordinated to six chemically equivalent ligands (Jahn-Teller distortion). In crystals such complexes sometimes display six identical bond distances. If this observation is interpreted as a 1:1:1 superposition of the three bipyramids **2**, **3**, and **4** oriented along the three different metal–ligand directions, the ligand atoms must be disordered over two positions separated by ~0.2 Å, still well below the resolving power of the diffraction experiment.

The disorder contribution to the ligand ADPs of ~0.01 Å^2 has been observed, but only along the metal–ligand directions. In analogous Ni(II) or Zn(II) complexes which are expected to be regular, it is not seen [11]. Although analyses of ADPs cannot always completely

eliminate or fully confirm the kind of reservation expressed by Ermer, they substantially reduce the uncertainty of atomic positions associated with ADPs.

Variable temperature experiments also provide insight into dynamics other than libration and translation, *e.g.* molecular deformations [10][12]. An analysis of neutron diffraction data of urea shows that as far as the lowest energy motion is concerned (54 cm^{-1}) the urea molecule is not rigid. The mode combines translation perpendicular to the molecular plane (52%) with libration about the N...N vector (32%) and a significant amount of pyramidal distortion of the NH_2-groups (16%). It does this in such a way that the oxygen and hydrogen atoms are displaced very little compared to nitrogen and carbon atoms (Fig. 6, bottom right). A related mode much higher in energy (101 cm^{-1}) also combines translation (24%) with libration (67%) and nitrogen pyramidalization (9%), but such that the hydrogen and oxygen atoms move (Fig. 6, top left). The comparison indicates that it is easier to deform the molecule than to disrupt the hydrogen-bonding. To the extent the N–C bonds in urea are comparable to peptide bonds this mode of motion is relevant to the flexibility and deformability of proteins. The mixing of molecular deformations into a mode of low frequency also implies that at room temperature their contribution to the total molecular deformation is about the same as or larger than that from the usual high frequency deformation modes. The relevance of this phenomenon to the understanding of chemical reactivity remains to be explored. In the present case one could speculate that the ease of pyramidalizing the NH_2-group facilitates rotation about the C–N bond and subsequent nucleophilic attack at the carbon atom.



5. New Technology, New Tools

The studies of motion described above require measuring the sharp Bragg spots to high resolution and at multiple temperatures including, if possible, the low temperature, zero-point motion regime. With the help of CCD- or other large and fast area-detectors, experiments at five or six temperatures can be performed within a matter of days.

A suite of programs for analyzing the temperature evolution of ADPs has been developed. Program NKA (Normal Koordinaten Analyse) extracts a model of molecular motion from the temperature dependence of ADPs [12a,b]. It handles molecular translation, libration, as well as torsional, angle bending and bond stretching motions. The graphics program PEANUT plots thermal ellipsoids or mean-square displacement surfaces [12c,d]. The latter option is especially important for testing models of motion by inspecting differences between observed and calculated ADPs; such differences are usually hyperbolic rather than ellipsoidal. The program QMView provides for animation of normal coordinate motion [12e].

Studies of disorder phenomena require quantitative measurements of the diffuse scattering which is not only continuous, but also weaker than Bragg scattering. Complete and accurate data can be obtained in about a day with an area-detector and synchrotron radiation off a

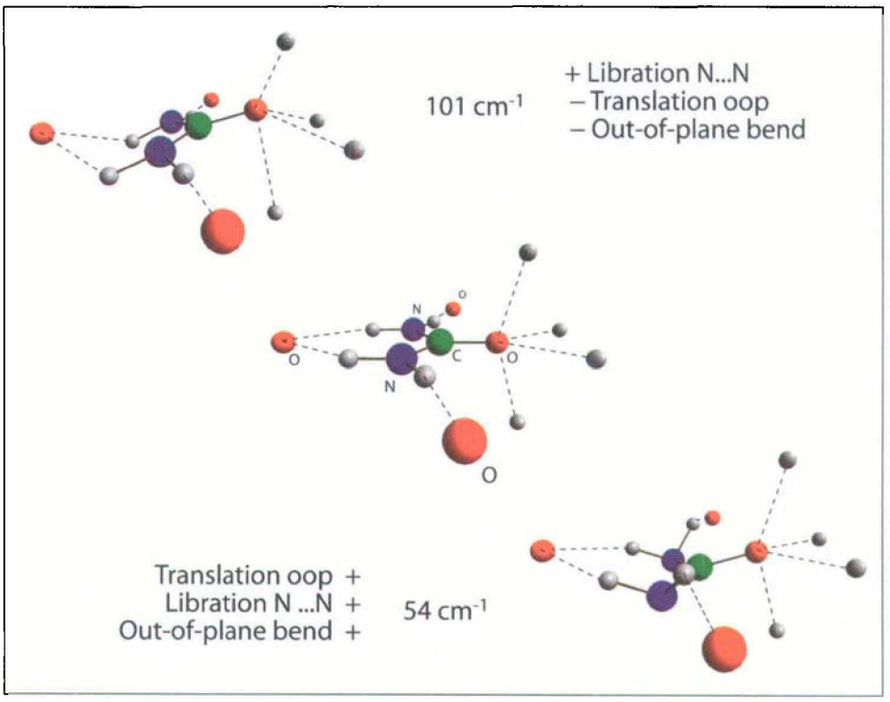


Fig. 6. Two modes of motion of a urea molecule in its crystal field showing that distorting the NH_2-groups from planarity takes less energy than distorting the hydrogen bonds. Bottom right: atomic displacements in lowest energy mode are large for N and C, smaller for H and O. Top left: atomic displacement in higher energy mode are large for H and O, smaller for C and N. Center: urea molecule surrounded by hydrogen- and oxygen-atoms of neighboring molecules, all in equilibrium positions.

bending magnet at the Swiss Norwegian Beam Lines (SNBL at ESRF). If the high intensity and narrow collimation of synchrotron radiation are not mandatory, the experiments may also be performed in the home laboratory. In order to be useful the diffuse data must be transformed from diffractometer coordinates into crystallographic reciprocal space. The processing, *e.g.* with program XCAVATE [13], is computationally demanding as the size of a typical raw data set is not negligible, about 1.5 Gbytes. With today's workstations data processing takes about the same time as the experiment itself. The combination of area-detectors and computers speed up measurement of complete diffraction patterns by one to two orders of magnitude and produce data in electronic form thus making X-ray cameras and photographic equipment obsolete.

Software for developing and refining models of disorder is available, but is not yet as versatile and user-friendly as that for conventional structure analysis. At present the package DISCUS [14] is the only general-purpose computer program, which supports various ways of simulating crystal structures and the subsequent computation of diffuse intensities. Standard programs incorporating advanced Patterson methods and analytic models of disordered systems are not yet available. This is due partly to the structural complexity of most disordered crystals and partly to a lack of the computational resources necessary to analyze such structures in a reasonable time. In the PHTP example described above, up to 10 CPUs of various workstations (SUN SPARC, SGI, Pentium PC) cooperated in a scheme of distributed computing for about a month to complete 220 generations of differential evolution. Given the continuing increase in computing power, it seems reasonable to expect that over the next couple of years coherent and practically useful programs for the 'determination of disordered crystal structures' (not just average structures!) will be developed.

6. Conclusions

Crystal structure analysis of organic and inorganic, small to medium sized molecules has been very successful. Its theory and practice are sufficiently well understood to mold into a highly automated, routine analytical technique. What is true today for small molecule structure determination may well hold in biological crystallography tomorrow. Crystallographers for their part have probably been too successful. They are now often replaced by machines and computer programs and have begun to disappear from listings of research faculty. This raises the question where research in structure determination might go.

Predicting the future is difficult, but making projections may be useful. This paper adds two lines of thought to the many other ideas collected in this issue of CHIMIA. One derives from the perception of most consumers of crystal structures that X-ray and neutron diffraction studies provide very detailed, but essentially static pictures of structures. Here it has been shown that studies at several temperatures provide insight into molecular motion and chemical equilibria in the crystalline state thus adding a dynamic dimension to diffraction studies. The second line is related to disorder. Materials scientists continue to produce substances with desirable and interesting properties but disordered structures. Biochemists crystallize larger and larger proteins with more and more disorder in the main chain, in side chain conformations, and in solvent distribution. To the extent that properties of substances and functions of molecules are tied to their structures, a better description and understanding of such disorder is desirable, at least in certain cases. Here it has been shown that studying the average structure at different temperatures allows disorder to be distinguished from motion and that studies of diffuse scattering can characterize the disorder structurally.

In summary, crystallographers might have to forget about past successes, take advantage of available technology, and develop new methods allowing real crystals to be probed for the static and dynamic departures from the regularity of their ideal relatives. Availability of such methods will enable chemists and biologists to address some of their unanswered questions thus transforming nuisance into opportunity.

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