PROGRESS IN INORGANIC CHEMISTRY

Edited by

KENNETH D. KARLIN

DEPARTMENT OF CHEMISTRY
THE JOHNS HOPKINS UNIVERSITY
BALTIMORE, MARYLAND

VOLUME 41

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Preface

I am especially pleased and honored to have been appointed the new Editor of *Progress in Inorganic Chemistry*. I welcome this opportunity to have some influence and aid in the dissemination of information concerning recent exciting developments in the field. Inorganic chemistry has become extremely broad and highly interdisciplinary, not only expanding the interests of traditional inorganic or coordination chemists, but also encompassing students and active researchers from other fields. As defined by the subdivisional organization of the Inorganic Division of the American Chemical Society, Inorganic Chemistry is comprised of organometallic, solid state, and bioinorganic chemistries, each of which influences contemporary aspects of all of chemistry, and science in general. I plan to continue presenting very current articles of interest in these areas, while also trying to solicit and emphasize works that cross these lines and/or represent interdisciplinary efforts impacting on fields outside traditional inorganic chemistry. Many aspects of the field greatly concern other areas, for example, materials science and engineering, organic synthesis, medicinal chemistry and pharmaceuticals, and biochemistry and molecular biology. As there is, perhaps, also a natural tendency for researchers to focus upon their own specialty subdivisional meetings and related journals as their discipline grows, it is important to provide a forum where communication across the subdivisions can exist and prosper.

In this, my first edited volume, nine articles are presented, representing a diverse array of topics. The use of X-ray crystallography in the characterization of molecular and material inorganics is of importance to most within the discipline. Thus, in the first chapter H. Hope presents a concise summary of the technique, with applications and hints for improved usage; students and senior researchers alike will find this to be an extremely valuable treatment. I plan, on occasion, to present other technique or application oriented review commentaries like this. In the second paper, N. S. Lewis and co-workers provide a comprehensive overview of semiconductor photoelectrochemistry, a treatment that should be of considerable pedagogical value. J. T. Spencer then details chemical vapor deposition techniques, using organometallic precursor compounds, an area of substantial current interest in materials chemistry and industry. Subsequently, A. L. Balch describes the systematic design, synthesis, and structures of a novel class of organometallic compounds with phosphine-based ligands, while C. G. Pierpont and C. W. Lange update the transition metal chemistry of catechol and semiquinone ligands, of interest as redox-active coordination complexes, with implications for certain biological phenomena. The

next two articles have clear bioinorganic connections. Macrocyclic polyamine zinc complexes have an elaborate coordination chemistry relevant to hydrolytic processes carried out by zinc containing enzymes, and E. Kimura details his own efforts in this area. This is followed by A. F. Kolodziej's presentation providing a comprehensive overview of both the chemistry and biochemistry of nickel-containing enzymes. In the next article, J. O. Edwards and R. C. Plumb describe properties of peroxonitrites, which are of importance in atmospheric, geological, and biological spheres of chemistry. Finally, I. G. Dance and K. Fisher provide a comprehensive review of the structural systematics of metal-chalcogenide clusters, compounds that are also of interest from a variety of perspectives.

I wish to thank the members of the Editorial Board for their current and impending assistance in the planning of this and future volumes. Special thanks go to Stephen J. Lippard, the previous Editor, whose high standards I will try to match.

KENNETH D. KARLIN

Baltimore, Maryland
September, 1993

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Volume 41

X-Ray Crystallography: A Fast, First-Resort Analytical Tool

HÅKON HOPE

Department of Chemistry
University of California, Davis
Davis, California

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I. INTRODUCTION

An important part of understanding a chemical process is the ability to visualize in three dimensions the processes and species involved. If we cannot describe the three-dimensional structures of reactants and products, our understanding of the chemistry is severely limited. Chemists expend major effort on the elucidation of structures. Although methods based on various spectroscopic techniques are most commonly used, diffraction-based crystallography is generally considered the ultimate in reliability. Crystallography is unique among the structure determination methods in that it provides the only mathematically direct path from primary observations to a three-dimensional chemical structure. Spectroscopic methods, however powerful, rely on interpretation, analogy, and model fitting. For truly unknown structures the interpretation of spectra can be very difficult and time consuming, if not impossible. A diffraction experiment is much less dependent on the inventiveness of the interpreter, and can normally be expected to yield a readily understood structure. Although relatively rare, there are of course exceptions. These exceptions can be related to disorder or to difficulty in distinguishing between elements of similar atomic number above about 35. Chemical or general structural knowledge can be a valuable adjunct to crystallographic data.

The formula for the electron density at a position x, y, z in the unit cell, $\rho(xyz) = V^{-1}\Sigma_{hkl}F(hkl)\exp\{-2\pi i(hx + ky + lz)\}$, illustrates the direct path from data to structure. The unit cell volume V and the indices hkl are obtained directly from measurement. The quantity $F(hkl)$ is derived from the measured diffraction intensity; the intensity is proportional to the product of F and its complex conjugate F^*. The only problem of consequence is the derivation of F from the intensity—the well-known phase problem in crystallography. For small-molecule data the problem is for all practical purposes solved. The work of Herbert Hauptman and Jerome Karle on the development of direct phase determination methods has been recognized through the award of the 1985 Nobel Prize for chemistry, because of the tremendous impact the results have had on the practice of chemistry. With the implementation of their methods in the form of working computer programs [e.g., Multan (1), SHELX family of programs (2)] structure solution is normally uneventful. Some small percentage (maybe 2%, certainly not $> 5\%$) of data sets may resist solution attempts, but with some persistence on the part of the crystallographer virtually all small-molecule structures can now be solved, with possible exceptions related to severe disorder. Molecules are considered "small" if they have fewer than about 200 atoms heavier than hydrogen.

For inorganic compounds with a small number of heavy atoms among a larger number of light atoms the situation has been less complex ever since the introduction of Patterson/heavy atom methods (3). In part, because of the rel-

ative ease of solution for many inorganic or metal-organic structures, and in part because of the greater difficulty in interpreting spectroscopic data, X-ray crystallography has long been part of the tool set of inorganic chemists. The unraveling of the structure of vitamin B_{12} (4) provides an early example of the power of the Patterson method.

In recent years there have been major developments in instrumentation, experimental methods, and computing methods related to X-ray crystallography. In this time, reliable rotating-anode systems with up to a 10-fold increase in intensity over conventional sealed-tube generators have become available, practical low-temperature equipment has been constructed, high-speed detectors to handle higher X-ray fluxes have been introduced, methods for higher speed data collection have been developed, the price of computing equipment has dropped drastically, and crystallographic software is becoming more and more user-friendly. A structure that would have taken 10 days to complete 15 years ago may now well be available in 10 h, or less, from receipt of the sample. The vitamin B_{12} (4) structure also gives us an historical perspective. This structure determination stretched over about 8 years. Determination of structures of similar complexity can now be finished in a few days, including data collection, with the solution performed by an automatic Patterson interpreter.

Unfortunately, the chemical community in general is not enjoying the full benefits of these advances. The majority of structures published today have been determined from data obtained in ways that are not much different from those in use 20 years ago. The result is that X-ray crystallography in many laboratories is still regarded as a time-consuming, expensive method of last resort, when in reality it can be a very fast, reliable, and inexpensive analytic tool. For reasons not explored, conservatism runs strong among small-molecule crystallographers. A passage in a widely used introductory text (5) is illuminating: "It is generally possible, as well as tempting, to mount a crystal in an arbitrary orientation, set it on the diffractometer, and return in a few hours to find that the machine appears to know all that is required to proceed to intensity measurements. . . . *This is a dangerous path to follow.*" The book then goes on to describe "strongly recommended" photographic methods that will ensure correctness, including the orientation of a crystal axis along the goniometer ϕ axis. There are several things wrong with both warning and advice. To begin with, a great many important compounds are not sufficiently stable to allow anything but fast transfer to a diffractometer, in whatever orientation happens to result. There is nothing in diffractometer theory to predict that orienting an axis along ϕ is superior. If anything, there are disadvantages. The implication seems to be that only stable, well-developed crystals with clean-looking diffraction patterns are worthy of diffractometer time. That view completely ignores the needs of the chemist. It also ignores the reality of thousands of correct structures from less than perfect crystals that have never seen a Weissenberg camera. The chem-

ist is concerned with identification of new compounds as quickly as possible, not with crystallographic cosmetics. The experience in this laboratory shows that even ugly crystals, with wide ω scans and evidence of numerous misaligned fragments in the sample readily lead to fully adequate structures. Experience with thousands of data sets also testify to the fact that if generally sound practices, including those recommended by the equipment manufacturer, are followed, problems of misindexing are virtually nonexistent. In my experience with many graduate students it has been much easier to teach crystallographically safe practices with a diffractometer than with Weissenberg or precession cameras. Besides, photographic work is generally time consuming and expensive. The most insidious part of the "advice" is the implied attitude toward the real needs of the chemist colleague. Although it may not have been the authors' intent, the message readers see appears to be "Stay away from modern methods. They will get you in trouble. No chemistry is worth the risk." A better message would be "You are right to want a crystal structure. I will do whatever is possible with your sample, as fast as possible." A final point: If there are no unusual difficulties, setup time is not a few hours, but less than 1 h.

This chapter emphasizes the methods and attitudes that can dramatically increase the productivity of an X-ray laboratory, thereby also increasing the productivity of the synthetic or natural product chemist, making the crystallographer a fully active participant in the chemical life of his/her research unit. Most of what will be discussed is based on observations and practices in the author's laboratory.

II. OVERVIEW OF THE EXPERIMENT

A. The Crystal

The main steps in a crystal structure determination are (a) prepare the compound in reasonably pure form, (b) grow crystals, (c) select and transfer a crystal to a diffractometer, (d) measure X-ray data, (e) solve and refine the structure, and (f) prepare drawings and tables of structural results.

A crystal is a regular stack obtained by repetition of a base motif, the unit cell, in three dimensions. The potential for an accurate structure increases with the accuracy of the reproduction of unit cells. Without a crystal there will be no crystallographic study.

There is a nearly boundless number of ways to prepare crystals, and there is no one "right" way to grow them. Whatever produces crystals is right. It all depends on what the compound is. With a sample obtained from a high-temperature melt you most likely will take what you find after cooling. We have found that if the compound is expected to have formed in solution in a Schlenk

tube, just placing the tube in a $-20°C$ freezer has resulted in hundreds of successful crystallizations. But if the compound is too soluble, this relatively mild cooling will not produce crystals. If a precipitating solvent is found, miscible with the original solvent, a liquid–liquid diffusion often produces crystals. This experiment can conveniently be done by layering the less dense of the solvents over the other in a long, narrow tube, such as a discarded NMR tube.

Once promising looking crystals have formed, the next task is to transfer one of them to the diffractometer with as little damage to the sample as possible. *A cardinal sin is to remove the crystals from their mother liquor before they are brought to the X-ray laboratory.* Many crystals contain solvent of crystallization. Removal from the mother liquor will then normally start a process of solvent loss, usually leading to collapse of the crystal structure. Even if there is only partial loss, this can result in much additional, nonproductive work spent on deciphering partial occupancy, and in other refinement problems. The urge to dry the sample is strong, and felt by many chemists, but it must be oppressed with firmness. It should be the crystallographer's responsibility to perform the final sample preparation. Crystal evaluation, selection, sizing, cleaning, and mounting require special training and insight. The final outcome of the structure determination depends critically on the choice of sample, and on the quality of mounting.

It is also common to worry about crystal purity, frequently leading to attempts at recrystallization. In general, the urge to recrystallize should also be resisted. It has happened far too often that the first batch of crystals, obtained from an impure product, also was the last. A good piece of advice is to save a portion of the initial crystals, before performing additional chemical or recrystallization experiments.

B. The Workspace

In an X-ray laboratory where reactive crystals are handled, it is important that crystal selection and mounting take place in the room where the diffractometer is located, only a few meters away from it. Work on the crystal should be done under a good binocular stereomicroscope equipped with a cool light source, preferably a fiber optics model. A polarizing attachment and a rotating sample stage are also necessary to assist in assessment of quality. The microscope should have variable magnification, at least to 50X. We found that 50X is not enough for the small crystals we routinely handle for our rotating-anode diffractometer. Samples 0.01–0.02-mm across are not unusual. We installed an objective to allow 100X magnification and found it to be very useful.

And last, but not least, the work chair at the microscope should be of high quality, and very easily adjustable, to allow for different body sizes and shapes, and for quick get-up once a crystal has been picked up. It is impossible to do our best at a difficult task if our seating is uncomfortable.

C. Crystal Selection

A transparent crystal that is also birefringent can rotate the plane of polarized light, so that it appears brightly lit in the dark field of two crossed polarizers. Rotating the crystal may extinguish this light. The sharpness of the light–dark transition provides information about the crystal quality. A sharp transition is a sign of a good crystal. A gradual change, or the absence of full extinction, signal problems, such as twinning. A larger crystal that extinguishes well, but has poorly developed faces, may well be a better choice than a much smaller crystal with beautifully developed faces. If effective methods of testing are used, it will in general pay to gamble on the larger sample initially. This technique will not always work, but the probability of success is remarkably high. In the absence of unusually high absorption, crystal sizes in the range 0.5–1.0-mm across are usually appropriate.

For many years I instructed undergraduate laboratory classes in physical chemistry, with one experiment being an X-ray structure determination. The instructor has learned many valuable lessons from these activities. Because of lack of experience many students will pick crystals that are "obviously" too large. These crystals generally result in excellent structures, as judged from estimated standard deviations (esds) of geometric parameters, reproducibility of known structural features, such as C—C bond lengths, or H atom positions, and R indices. The main lesson learned is that counting statistics is by far the most important factor in a structure determination.

This result does not mean that samples containing only small crystals should be rejected. It means instead that in this case the measurements will take longer, or if data collection with a sealed-tube generator is cumbersome, a rotating-anode generator should be used instead. Unfortunately, this is not yet an option in most small-molecule laboratories, but if current trends continue, it will soon become more common.

D. X-Ray Measurements

The determination of the primitive unit cell is usually not complicated, unless the crystal is twinned or cracked. The most common response to an indexing problem would be to find a new crystal. If this does not help, it may become necessary to work with a flawed sample. However, if indexing is at all possible, there is usually little danger in working with a twinned or cracked crystal.

Final responsibility for the determination of the correct unit cell dimensions and Laue symmetry may still be left to the user, although quite reliable automated procedures have become available. Unless cell dimensions and Laue symmetry have been correctly determined, one can end up with seriously incomplete data sets, a situation that normally precludes success in structure determination. Examination of axial oscillation photos prepared on the diffractom-

eter is an effective way of ensuring proper cell and symmetry information. The process can also be performed automatically, with virtually no chance of failure. Presently, the automatic procedures tend to be slower than the photographic ones.

Assuming that indexing has gone well, there are three key data-collection parameters to be determined: scan range, background definition, and scan speed. Probably the most widely used method of determining the scan range makes use of visual inspection of peak profiles. Scans are extended to capture the part of the peak that can be distinguished from the background. Different laboratories may use slightly different criteria, but as long as all peaks are measured in the same way, and there is no gross anisotropic truncation of scans, the impact of the scan range may not be all that great. The choice of background measurement is probably more critical. "Backgrounds" should certainly not be measured inside a peak, neither the one being measured nor a neighboring one. Errors here can have devastating consequences. Although it is common practice, measurements at the ends of scan ranges are likely to exaggerate the background intensity. Nearly all background measurements in this laboratory are taken at some distance away (in ω) from the scan limits. An exception is required if filtered, rather than crystal monochromated radiation is used. White radiation streaks, especially at low angle, generally necessitate backgrounds to be measured very close to the scan ends.

A special situation arises when the peaks are so wide that they are not fully separated in a peak scan. In this case the solution is to construct a background curve as a function of 2θ, or if it is indicated, a background surface as a function of 2θ, ϕ, and χ. The crystal structure of $Pt_2[\mu\text{-}(Ph_2P)_2py]_2Cl_4 \cdot 6CH_2Cl_2$, where py is pyridine, (6) provides a good example. Typical ω scans of the crystals were 4° or wider. It was impossible to scan the entire peak without picking up parts of neighboring reflections, and individual backgrounds could not be measured. Intensities were measured by 1.3° ω scans, and a background curve was obtained from regions with no discernible peaks. The structure refined to $R = 0.066$, and the majority of H atoms could be found in a difference map.

The most interesting of the scan parameters is the scan speed. Early diffractometers typically allowed maximum scan rates of 2–4° min^{-1}. Although much higher speeds started to become available about 20 years ago, very little practical use has been made of this. A paper by Hope and Nichols (7) described the results of a comparison of structures based on 2° min^{-1} and 60° min^{-1} ω scans. The only difference in final results was that bond length and angle esds for the fast data increased by 50% over the slow data results. From about the time these results were obtained, the idea of higher speed data collection has been generally adopted in this laboratory. Several consequences of this are worth mentioning. Most important is the fact that it is possible to measure the data and determine a structure in just a few hours. A chemist works most effectively if he/she has virtually immediate access to the correct structure of a newly

obtained product. There will be no interruption of the overall thought process, as would be the case if there were a delay of several days or weeks. Long waits also have a tendency to cause a waning of interest, and of awareness of additional, potential chemical consequences of a project. Immediacy and continuity of thought have important psychological advantages in a chain of inventiveness.

In the early days of fast data collection we were often faced with strong criticism from referees; at present this is less common, but not absent. A commonly repeated theme was that the chemical community could afford to wait another couple of weeks for these results. If we are addressing one single structure, this may be an understandable observation. However, the cumulative effects of 2-week delays are devastating. A fivefold decrease in productivity would mean that results available today could be delayed for 50 years, hardly a sensible outcome, just for the sake of tradition. Fortunately, most journal editors have now agreed that the 50-year wait is too long.

The key to success is of course the insistence on safe cell-determination procedures and on appropriate counting statistics. It is not the time it takes to make an intensity measurement that determines its statistical reliability, but rather how many counts were accumulated. If the count rate is high enough, it need not take long to accumulate the required number of counts. High count rates are related to relatively large crystals, low temperature, and intense radiation sources. How does one then determine the appropriate scan speed? We found empirically that if 50%, or more, of reflections in the upper 5° (2θ) of the data set are above 3 esds, there is enough intensity for a good structure. About 50 reflections well distributed in reciprocal space at high 2θ will give sufficient sampling to determine that the data set about to be measured will attain this. The main adjustable variable is the scan speed, but it is well to remember that very often there is a choice in crystal size as well.

How many reflections are needed? For a reliable structure determination it is generally found that about 5 reflections per structural parameter is sufficient. A higher number (10–20) will lead to better resolution and lower esds, but may be of little chemical significance. Traditional upper limits in 2θ for Mo $K\alpha$ are between 45 and 55 °, and for Cu $K\alpha$ between 100 and 130°. The choice depends on the required precision, and to a large extent also on crystal quality. If intensities are weak, the return for a high 2θ cutoff may be excessive measurement time, or a large number of intensities indistinguishable from background, or both. Each case should be decided from a combination of project need and return on investment in measurement time.

E. X-Ray Generators

The standard X-ray source for small-molecule crystallography has been the conventional sealed-tube generator. These machines are stable, low-mainte-

nance workhorses. The tubes tend to have a long life, 10,000–20,000 h. Only very recently has the rotating anode generator seen extensive use in small-molecule laboratories. Early rotating anode generators were high-maintenance devices that often required an on-site technician for successful operation. Improvements in design and manufacturing have now resulted in equipment with sufficiently low-maintenance requirements that it is a viable alternative to the sealed-tube generators. It is, therefore, necessary to consider the potential advantages and disadvantages of a higher intensity source. A typical load for a normal focus sealed tube is around 2 kW. A rotating anode with similar focus will typically run at 12–15 kW. The actual increase in intensity is about 7–10-fold. It is immediately obvious that this intensity enhancement can be utilized in two ways. First, data collection speed can be correspondingly increased. Crystals that otherwise would require several days of measurement can often be measured in hours, thus eliminating long waits for the chemist. Second, much smaller crystals can be successfully handled. We have used a Siemens rotating anode in this laboratory for about 3 years. In this time a number of situations have come up where the available samples could only be handled with great difficulty, or could not be handled at all with conventional equipment because the crystals were too small.

The current practical size limit in our laboratory appears to be about 100 ng. The ability to make use of very small crystals turns out to be of great benefit to the synthetic chemist. With traditional requirements the production of suitable crystals often is a time and labor consuming task. Resources are expended solely for the purpose of satisfying the requirements of a diffraction experiment. However, crystals in the 100–200-ng range often can be produced with much less effort. The net result of having access to a rotating anode source is the transfer of effort from a labor-intensive chemical laboratory to an instrument-intensive X-ray laboratory. In this way the chemists can spend more of their time on directly productive chemistry, and the crystallographer is satisfied that his/her work benefits chemistry.

When good-quality crystals are available, experiments that otherwise would be very time consuming can be handled with relative ease. For example, the measurement of high-angle Mo data required for a high-quality electron density study with a sealed tube can take several weeks. With a near 10-fold intensity increase the time is reduced to just days, making such studies more feasible.

F. The Diffractometer

For mass data collection of small-molecule data the computer-controlled automatic diffractometer has been the only practical choice for many years. Two geometric approaches are in use: the four-circle geometry (sometimes called "Eulerian cradle," from the days when the χ circle was not a complete circle,

but more cradlelike) and the κ geometry. The author is not aware of any decisive advantages of one over the other; both form the basis for fully functional diffractometers. The κ geometry is attractive for its lack of machine parts that would obstruct the X-ray beam path, and for relatively unhindered access to the crystal. Full-circle diffractometers are very stable mechanically, and the unavoidable blind regions do not give rise to any serious, everyday problems.

Until recently there was in reality no choice in detectors. A scintillation detector with a Tl-doped NaI scintillator and photomultiplier tube was the choice. Two advantages are low cost and excellent stability. The limitations are maximum count rate around 50,000–100,000 counts s^{-1} and no position sensing ability. Recent developments now present us with more choices. A fast detector with an organic scintillator is being marketed by Siemens. The detector response remains virtually linear up to several million counts per second. It is useful in connection with a rotating anode X-ray generator. One disadvantage is that a given scintillator is only usable for a very limited wavelength range, so that a separate detector is needed for each wavelength one might use. Siemens also markets a multiwire area detector. It is most suitable for Cu radiation, but for software reasons it has seen no practical use in small-molecule crystallography. It is not suitable for high count rates.

The FAST area detector by Enraf-Nonius can be used over a much wider wavelength range, and responds well to both Cu and Mo radiation at high count rates. The detector was developed for use in biocrystallography, but the manufacturer is actively pursuing small-molecule applications. A brief description of this use has been given by Hursthouse and co-workers (8). A number of structures based on data from this detector have been published from their laboratory [see, e.g., (9)]. In terms of structural results the area detector data are not conspicuously different from standard data. For data sets over 10,000 reflections there probably is a speed advantage.

Imaging-plate technology (10) is another area of increasing importance. The active component of an imaging plate is Eu-doped BaFBr. This composition can store a latent X-ray image; the image can be "developed" to emit light in proportion to the X-ray exposure with light from a He–Ne laser. Several makes of imaging-plate detectors have been constructed for macromolecule diffraction with synchrotron or rotating anode radiation sources. Extremely high count rates can be recorded. Molecular Structure Corporation/Rigaku have shown interest in the use of imaging plate technology for small-molecule crystallography. A paper mentioning its use for small-molecule data collection has recently appeared (11). The results appear to be comparable to standard diffractometer data in quality, and there is a promise of greatly reduced measuring time.

At this early stage it is impossible to predict which, if any, of the approaches mentioned here will eventually play an important role in small-molecule structure determination. However, it seems likely that the next few years will see a

trend away from the traditional diffractometer–scintillation detector equipment. Area detectors have transformed biocrystallography. It seems highly likely that small-molecule crystallographers will want to take advantage of emerging technology that can simplify and speed up their work.

G. Choice of Radiation

There are three main design goals for a data set: there must be appropriate counting statistics, resolution must be adequate, and systematic errors (mainly from absorption) must be kept at a minimum. For this discussion we will assume that the diffractometer is suitably aligned, that all electronic components function well, and that the crystal is not too large for the uniform portion of the incident beam. In practice there are two types of radiation readily available in an X-ray laboratory: Mo $K\alpha$ and Cu $K\alpha$. Other generally available targets are Ag, Fe, Co, and Cr. Most structures reported today have been determined with Mo $K\alpha$ radiation. An important factor in selecting radiation is the degree of absorption by the crystal. Many inorganic compounds contain heavy elements with high absorption coefficients. Historically, this may be a major reason for the prevalence of Mo $K\alpha$ in most laboratories. With conventional sealed-tube radiation sources this is probably the best overall choice. However, if crystals are on the small side, or contain light atoms only, Cu $K\alpha$ may well be a better choice. Ag radiation will generally show smaller absorption effects than Mo. Where absorption is not of great concern Fe or Co radiation may be useful for special projects, such as absolute configuration determinations with small anomalous effects.

If the crystals at hand are of good quality, diffract well, and any desired size is available, the choice of radiation is not of great consequence. One would use whatever is installed at the moment, and select a crystal that does not lead to excessive absorption effects. Any introductory text in X-ray structure determination will discuss this.

The question becomes less straightforward for very small crystals. The essential problem will then be to optimize the number of recorded counts. Several factors are of importance. One is the X-ray flux with the desired wavelength. In general the higher the atomic number of the anode material, the lower the yield of $K\alpha$ radiation per kilowatt of tube power (12). The shorter the characteristic wavelength, the higher the tube voltage will be for optimum yield. Copper requires about 45–50 kV for best yield, Mo or Ag require a substantially higher voltage. Current equipment does not exceed 60 kV, and even at that voltage shielding problems become serious. With normal operation, the yield of $K\alpha$ radiation is higher for Cu than for Mo, by about a factor of 2 (13).

The scattering efficiency is a function of wavelength: The intensity is proportional to λ^3 (14), so that from this alone Cu $K\alpha$ has a 10-fold intensity

advantage over Mo $K\alpha$. The combined enhancement with Cu $K\alpha$ can be as much as 20-fold. For very small crystals, in the near 100-ng range, Cu $K\alpha$ will then almost always be the best choice, because of the great intensity advantage, and because absorption is much less of a problem with small crystals. It must be remembered, however, that absorption of Cu $K\alpha$ radiation in a crystal only 0.02 mm thick need not be negligible. If μr is 0.1 (i.e., $\mu = 5$ mm^{-1}), the transmission factor is already as low as 0.9.

H. Absorption

Absorption is probably the most important cause for systematic errors in intensity measurement. These errors normally will have only a minor effect on gross structural aspects, but finer detail is often obscured. Correction for absorption is generally desirable. There are several options. These options can be analytical, based on crystal dimensions and orientation, or empirical, essentially based on differences between intensities of equivalent reflections, or on differences between observed and calculated intensities. Presumably, the most accurate results can be obtained from an analytical approach. This approach would require the careful measurement of crystal geometry, and is not well suited for crystals mounted in oil or in glass capillaries. A popular method is based on the measurement of a few reflections as a function of ψ rotation. Walker and Stuart (15) devised a method based on ΔF differences. This method is convenient in that it does not require any measurements in addition to normal data collection. Another method, also based on ΔF differences (16), has been used in our department for many years, with very satisfactory results. The simplicity of the ΔF methods and their general effectiveness argue for their use with most data sets. The quality of a structure can be improved quite significantly, especially if absorption is not negligible.

III. LOW-TEMPERATURE CRYSTALLOGRAPHY

A. General Notes

There are major advantages to keeping the sample at cryogenic temperature rather than at room temperature during data collection. The major advantages are: decay is prevented, whether it would be caused by chemical instability, or by radiation damage; diffraction intensities increase; mechanical stability of crystal mount is improved; and sample mounting time is shortened. Discussion of these points follows.

For many years the standard method of protecting reactive crystals from the ill effects of contact with the atmosphere was to place the crystal inside a glass

capillary that was then sealed. The widespread use of this technique attests to its effectiveness. However, there are many associated problems. To begin with, a glovebox is usually required, and many people find the manipulation of crystals and capillaries inside a glovebox to be very difficult. Securing the crystal so it does not move in the capillary may not be easy. The capillary can give rise to anisotropic absorption effects that are intractable by analytic means. And in general, the process is time consuming.

With low-temperature data collection, we have used a much simpler and faster mounting method for many years (17). The essence of the method is to place the sample in a viscous hydrocarbon oil, and to utilize the oil as a protective barrier during crystal handling. (We have used Paratone-N® from Exxon with excellent results.) The crystal, with the protective coating, is cooled directly on the diffractometer. The oil hardens on cooling, and becomes rock hard, providing an absolutely rigid mount. Major advantages are that it is fast, easily learned, and all operations can be carried out in the open.

B. Procedures

The procedure we use in nearly all cases is as follows: Use a small (5 cm) glass Petri dish. Add oil to a depth of 3–5 mm. Open the container holding the crystals in their mother liquor. It is best to keep a stream of inert gas flowing in the container. Scoop up crystals with a spatula and immediately stir them into the oil. Most reactive crystals will keep long enough in the oil to allow selection and mounting. Use standard crystal handling tools. Typically, these are a needle in a pin vise and a razor blade. While in the oil the crystals can be cut and cleaned as usual. After a crystal of appropriate size has been selected, it is picked up with a glass fiber attached to a mounting pin, and immediately transferred to a running cold stream on the diffractometer. The crystal will always sit in a drop of oil. It is best to keep the drop as small as practicable, taking crystal stability into account. Excessive oil can be removed with a pointed piece of absorbent paper. From then on, procedures are generally the same as for a room temperature experiment, but with restrictions on diffractometer movements imposed by the low-temperature attachment.

On rare occasions solvent of crystallization will diffuse into the oil so quickly that the crystal is damaged. In such cases we have found it helpful to add some of the solvent to the oil before crystals are added.

Very thin crystals do not tolerate cooling in oil very well. The crystals tend to crack or bend, giving rise to widened ω scans. Teng (18) described a solution to this problem. The crystals are mounted in a small loop, supported in a thin film of oil, or other supporting liquid. This technique keeps the crystal planar, so that no measurable distortion occurs. The first loops were made from metal wire, but many other materials can be used, such as glass, textile fibers, or human hair.

C. Experimental Consequences

Thermal motion in the crystal causes a decrease in diffraction intensity with increasing diffraction angle. In its simplest form the temperature factor is $t = \exp(-8\pi^2 U \sin^2\theta/\lambda^2)$. The effect on the diffraction intensity can be dramatic. The factor t is applied to the structure factor F, and the intensity is proportional to $|F|^2$. The coefficient U is approximately proportional to the kelvin temperature. The ratio of an intensity at 100 K to one at 293 K is then approximately $\exp(100\ U \sin^2\theta/\lambda^2)$. For a room temperature U of 0.05 $Å^2$ (a value often seen with well-behaved structures) at $\sin\theta/\lambda = 0.6$ $Å^{-1}$ the ratio is about 6. Because the number of reflections in a given $\sin\theta/\lambda$ shell is proportional to $(\sin\theta/\lambda)^3$, the majority of reflections will be enhanced by a factor of 5 or more. With higher U values the ratio becomes even higher. This result obviously has important implications for the total measurement time. We estimate that the acquisition and use of a liquid N_2 cooling attachment is the functional equivalent of using two or three *additional* diffractometers. From this perspective a low-temperature attachment is a spectacular bargain. There are also important consequences for the quality of the resulting structure, and for the amount of labor that goes into solution and refinement. Enhanced intensities at higher diffraction angles generally lead to easier solution and more concise refinement. For example, the F atoms in hexafluorophosphates often have U values about 15 $Å^2$ at room temperature, making a structure description quite cumbersome. At cryotemperature the corresponding U values could be about 5 $Å^2$, resulting in a well-described structure.

At this point a note to discourage undue optimism is in order: Although lower temperature generally leads to lower U values, one cannot expect low temperature to rectify most disorder problems. Static disorder usually persists after cooling. Dynamic disorder may become less severe, but a transition to frozen-out static disorder is common.

The crystal mount attained with the oil mounting technique is extremely stable, provided an appropriate mounting pin is used in a stable goniometer head. Diffractometer control programs typically have a provision for automatic redetermination of the orientation matrix. This is done because at room temperature a crystal either attached with an adhesive, or mounted in a capillary, has a tendency to change orientation during data collection. At low temperature this problem is completely avoided. There is no need to check for slippage of the mount.

Because of the ease and simplicity of the mounting technique, initial quality checking of a new sample is relatively fast. An ω scan of the first reflection found will usually reveal crystal quality problems, and if need be, a new crystal can be selected within minutes. Because the procedure is so fast, there is little resistance to changing samples when needed. Reactive crystals also have a bet-

ter chance of not decomposing if one can act quickly, so that on average crystal quality is improved. These factors can make a clearly visible difference in the overall quality of data.

D. Low-Melting Compounds

Boese and co-workers (19) described an apparatus that allows growth of high-quality crystals in a capillary, directly on the diffractometer, and refer to it as "programmed crystal growth on a diffractometer with focused heat radiation." In essence it is a process that can transform a quick-frozen, polycrystalline sample into a single crystal by a zone refinement technique. A focused beam of IR radiation traverses the length of the sample, in a capillary, which is being cooled with a conventional cold gas stream. A number of structures of low-melting compounds have been determined in the laboratory of Mootz.

An interesting method for growth of spherical crystals on the diffractometer has been reported (20), but it has not seen much use.

E. Phase Transitions

A small fraction of crystals cooled to near liquid N_2 temperature will undergo a destructive phase transition. From our experience this will happen with about 1% of the samples. The usual remedy has been to raise the temperature to a few degrees above the transition point. The transition point can be found by slowly cooling a crystal from room temperature until the transition occurs, as evidenced by a sudden change in a diffraction intensity.

F. Why Is Low-Temperature Data Collection Not More Common?

With the clear advantages to low-temperature data collection one would think that it would be widely used. This is not the case. Perhaps 2–3% of all published structures are based on low-temperature data. What are the reasons for this discrepancy? Probably a major reason is a lack of understanding of the advantages of cryocrystallography. After all, many data sets can be obtained at room temperature, and they obviously lead to solved structures. The loss is mainly in productivity. Another major reason is the general difficulty in setting up and running low-temperature equipment. Commercially available apparatus is not nearly as well designed as is desirable. In most instances it is not possible to just buy an apparatus, install, and run it. Modifications are required, and if the device does run, the consumption of liquid N_2 is excessive—often several liters per hour. A well-designed apparatus should not require more than about 0.7 L h^{-1} at 85 K. Successful installation usually requires substantial inventiveness on the part of the user. Most are unwilling, or unable to invest the time it takes

to make a setup functional, and as a result a large proportion of equipment that has been acquired remains unused, or is used infrequently.

It is well to bear in mind that low-temperature techniques can be learned. The few laboratories where serious efforts have been made tend to use low temperature data collection as their standard mode of operation. Over the past 20 years we have not had a single graduate student who did not become a proficient user after a couple of hours of instruction and practice. It is also well to note that in a laboratory starting completely from the beginning, without outside help, the learning period may well be several months, so some perseverance is required.

IV. THE CHEMIST AND THE CRYSTALLOGRAPHER

X-ray crystallography is a branch of science in its own right, with its own motivations and research projects, many of which have little to do with chemistry. But it remains a fact of life that X-ray crystallography is an indispensable tool in chemistry, and many research advances have had a dramatic impact. Most will agree that in small-molecule crystallography the outstanding accomplishments have been in structure solution methods, starting with the introduction of the Patterson function, and culminating with present day, nearly automated direct methods. Countless other projects have contributed to make the science what it is today. A well-informed crystallographer must and will have a large body of specialized knowledge from which to draw. From observation one knows that the situation where the chemist and the crystallographer is the same person is not rare, but in general it is not reasonable to expect a synthetic chemist, or a natural products chemist to have detailed, profound knowledge in a field as esoteric as advanced X-ray crystallography. However, it is to the chemist's advantage to be well-informed about the potential of crystallography as it develops. The limitations should be of much less concern. It is in the crystallographer's domain to work to move the limits away from where progress is hampered. It is of course also the crystallographer's responsibility to keep the chemist informed, by way of example in producing results, by informed advice, and by instruction in the basics of sample preparation.

The crystallographer's attitude is important. Some are tempted to accept only projects involving attractive-looking samples that lead to wonderful diffraction patterns, low R indices, beautiful thermal-ellipsoid plots, and amazingly low esds for structural parameters. It is not that such experiments are of no intrinsic value. Quite to the contrary. These experiments can be very valuable for calibration of methods and for producing standards quality data. However, chemical reality makes this ideal situation a rare one. A large proportion of crystals produced in a typical chemistry department cannot be described as attractive.

The crystallographer must then accept this, and realize that it is the chemistry that is of prime interest, and that the utility of a structure determination is measured by the chemical information it provides, not by how low the R index is.

Part of the problem is possibly a fear of making a mistake. Quite obviously one should not provide erroneous structural information. The danger is very small, however. So long as the crystal has been correctly indexed, and intensities have been measured with sufficient counting statistics and appropriate background estimates, the probability of ending up with substantial misinformation is remote. A structure usually provides a number of internal cross-checks, such as known geometric parameters, reasonable electron densities, and explainable thermal parameters.

Never make fun of the chemist for guessing the wrong structure—not even good-natured ribbing. The sample is analyzed to discover what it is, not to confirm essentially certain knowledge. We have had our share of novel gold complexes that turned out to be pure sulfur, or exciting new uranium complexes where the heaviest metal was lithium. That is the way it should be. X-ray analysis is fast, inexpensive, and reliable. It should be the *first* resort.

The chemist will understand that in spite of tremendous progress in the field, X-ray crystallography is not magic—it is physics, with good help from mathematics, and all laws of nature are obeyed. But there *are* samples that are intractable, on occasion a data set takes time to yield a structure, and there are times when the equipment breaks down. Sometimes the crystallographer's work is heard described as "routine." If it is, the responsibility usually rests with the crystallographer who keeps it that way. But it is rare to find a chemist who does not realize that the inventive handling of his/her low-quality, highly reactive crystals to provide a reliable structure is not a routine job.

How can the chemist be of help to the crystallographer? First of all by not destroying the crystals by drying; leave them with some mother liquid. Do not worry much about purity; if it crystallizes, it is generally (but not always) pure enough. Providing the hoped-for formula may not be particularly helpful, because the probability of getting it right may not be high. On the other hand, describing all ingredients added to the reaction vessel is useful. It can allow easier recognition of strange-looking fragments.

V. RESULTS

Measurement speeds of 500–700 reflections h^{-1} are common. This speed, coupled with use of modern computing methods results in same day, or overnight delivery of the major results for structures of moderate size. Consistent use of rapid X-ray structure determination as the primary structure tool has decreased the dependence on spectroscopic methods, and has enabled chemists

to concentrate on problems of synthesis or biogenesis rather than on uncertain structural assignments.

Two explicit examples will indicate the level of attainment. (1) A crystal containing decanuclear vanadium(IV) clusters gave insufficient intensity for reasonable measurement on a sealed-tube diffractometer. The crystal measured 0.06 $\times$ 0.16 $\times$ 0.65 mm^3. With Cu radiation from a rotating anode over 20,000 reflections were measured in 52 h. The structure, consisting of 211 non-H atoms (and 179 H atoms found), was solved with no difficulty, and refined to R = 0.085 for 12,000 intensities with $I > 3\sigma(I)$ (21). (2) A crystal of $C_{60}[IrCOCl(PPhMe)_2]_2$, measuring 0.01 $\times$ 0.02 $\times$ 0.08 mm^3 (mass 30 ng), was used in the measurement of 4423 Cu $K\alpha$ reflections in 30 h. The structure was solved by automatic Patterson interpretation (2) and refined to R = 0.036 for 3379 reflections with $I > 3\sigma(I)$ (22).

Productive students in the department may synthesize over 50 new compounds and determine their X-ray structures as part of their thesis work. Numerous publications from the groups of A. L. Balch, P. P. Power, and K. M. Smith describe successful structure determinations. Current production in the laboratory is about 400–500 structures per year. Many samples require the measurement of 10,000–15,000 unique reflections, and most are highly reactive.

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