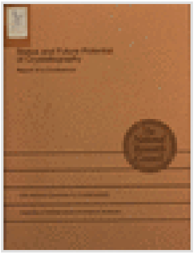

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Status and Future Potential of Crystallography

Report of a Conference

USA National Committee for Crystallography

Assembly of Mathematical and Physical Sciences

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National Academy of Sciences
Washington, D.C.
1976

NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the Committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

On February 10-11, 1975, a conference was held at the Dulles Marriott Hotel on the topic "Status and Future Potential of Crystallography." This conference, sponsored by the USA National Committee for Crystallography (USANCCr) of the Assembly of Mathematical and Physical Sciences of the National Research Council, was supported by the Chemistry Section of the National Science Foundation under Contract No. NSF-C310, T.O. 306.

The aim of the conference was to make an in-depth review of the status and future potential of crystallography. A conference organizing subcommittee of five topical chairmen was nominated by the Chairman of the USANCCr after consultation with several members of the crystallographic community. The topical chairmen were charged with nominating additional members for each of the topical subcommittees and with establishing functions and schedules for the groups.

Considerable discussion entered into the selection of the topical subcommittees in order to fulfill criteria of wide experience, a distribution of institutional representation from government, industrial, university, and private laboratories and also a range of age groups. The subcommittee on chemical crystallography was made larger than the other subcommittees to reflect the considerable activity in this research area and requirements for adequate coverage.

The topical chairmen assume responsibility for the production of the individual sections that comprise this report. Although they are mainly the results of efforts of the individual subcommittees, the drafts have been subjected to a wide review. The broad knowledgeability of the committee members provided considerable commentary and discussion at the conference as well as through mail correspondence. In addition, the topical chairmen canvassed a number of respected leaders in their respective fields. From 10 to 30 people were contacted in each group. The subcommittee on chemical crystallography also mailed 200 questionnaires to chemical crystallographers and received about 100 responses. This report, therefore, can be considered to reflect the views of a substantial segment of the community engaged in crystallographic research.

1

Introduction

Crystallography is a broad scientific discipline. In the common view, it concerns the investigation of the structure, i.e., atomic arrangements, of the various states of matter, the tools used to determine the structures, particularly diffraction techniques, and the analytic methods that are applied to the diffraction patterns. In a deeper sense, however, the techniques and results of crystallography are joined with those of various other scientific disciplines resulting in significant and, at times, dramatic developments in these fields. Crystallography encompasses in its practice topics of basic and applied interest that range in context from the physical sciences to the life sciences, contributing fundamental information and continued stimulation to these fields. It provides the precise structural information without which the application of many other spectroscopic and physical techniques would be extremely limited, if not impossible, e.g. studies of Mössbauer resonances, magnetic properties, optical phenomena, microtwinning and microtexture in relation to temperature, pressure and phase changes. An important part of the future of crystallography may be described in terms of its relationship to problems at the forefront of other scientific disciplines that comprise its concern and application. A study was recently completed for the National Science Foundation of the "Characteristics of Frequently Cited Papers in Chemistry," in which a tabulation was made of the "chemical" articles most cited in 1972.* It is of interest to note that 7 of the top 11 papers are on crystallographic subjects.

The broad range of considerations addressed by crystallography makes for some difficulty in categorizing the activities that comprise this field.** Because crystallography is largely concerned with the structure of matter and its physical, chemical, and biological implications, substances in the various states of ordering in matter come within its province. These include

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*H.G. Small, Characteristics of Frequently Cited Papers in Chemistry, Contract No. NSF-C795, September 1974 (note page 21, Table 8).

**An insight into the scope of crystallography can be obtained from a list of the categories under which papers were solicited for the Tenth Assembly of the International Union of Crystallography in Amsterdam. August 1975. This list is shown in Appendix A.

ordered and disordered crystalline substances, crystalline powders, fibers, amorphous solids, films, membranes, liquids, and gases. Crystallography is a scientific field with a long tradition around whose major analytical tool--diffraction--the present science has evolved. The study of crystals remains an important part but, nevertheless, only one part of this discipline. Even here the nature of the applications continues to expand with developments in the investigations of, for example, defects, electron distributions, solid-state reactions, and many other key studies in various scientific fields. A more generally descriptive term that encompasses the broader implications of the discipline might be the anatomy of structure or, equivalently, structural topology. Included in such terms are, of course, the tools, techniques, concepts, and ramifications that make crystallography a complete field of science.

An evaluation can be made of the potential of current techniques in the area of structure determination of crystalline materials. For good single crystals of moderate complexity, i.e., up to 100 atoms per asymmetric unit, the prospect of a successful determination of the atomic arrangements is quite good. The structures of centrosymmetric crystals are readily solvable. Among the approximately equal-atom noncentrosymmetric crystals, at least one half of them are as readily solvable as centrosymmetric ones, roughly another one quarter are solved with some difficulty, and the remaining ones are solved with considerable effort. A small number remain unsolved. It is difficult to make general statements about crystals having significantly more than about 100 atoms per asymmetric unit because not too many such crystals are readily obtainable and the ones that have been grown often give limited diffraction data. It is important to note that many crystalline substances of key importance do not form good single crystals, but their structures can nevertheless often be determined by specialists in the field of crystallography. In fact, for materials research and earth sciences, crystalline samples of limited quality seem almost to be a rule rather than the exception. Some examples are highlighted in Chapter 5.

Other examples of studies on large asymmetric units that come to mind are those of the potent frog venom batrachotoxin, a toxin that profoundly affects the ion balance at membranes and causes neuromuscular block, and of the mineral tridymite, which is of basic significance to an understanding of the structure of silicate glasses. In the case of the toxin, only one crystal was available from an extraction of about 7000 frog skins, and it had a diameter of about 0.04 mm. The x-ray scattering was very weak, and a heavy atom substituent caused a fourfold ambiguity in the interpretation of the structure. The difficulties were overcome and the structure of what has proved to be an important substance in neurophysiological research became available, thereby facilitating its synthesis and further study.

In the investigation of the structure of terrestrial low tridymite, it was necessary to unravel a fourfold twinning pattern before proceeding to locate the 240 atoms in the complex asymmetric unit of the crystal. In both cases, the developments in analytical techniques facilitated the analysis of the problems, but the solutions were achieved only by the additional application of insight, imagination, and a deeper understanding of the field of structure analysis.

The considerably more complex biological macromolecules, e.g., proteins and nucleic acids, can also be induced to form crystals. Because of positional disorders in the crystals, the data are somewhat limited relative to the complexity of the structures to be determined. Nevertherless, by application of the uniquely suited and effective isomorphous heavy-atom replacement technique for structure determination, considerable success has been achieved in unraveling macromolecular structures, giving a wealth of structural insight, and affording the basis for comprehending the functional mechanisms of these important substances in the life processes.

The purpose of this report is to examine the present status and future promise of the field of crystallography. To accomplish this, the range of concern of crystallography has been divided into five broad sections: biological macromolecules, chemical crystallography, diffraction physics, earth sciences, and materials research. In each of these sections, a number of accomplishments and significant areas for future development are briefly highlighted.

This report differs from a previous one* that dealt only with chemical crystallography and was intended to be advisory only to the Chemistry Section of the NSF. The present report considers crystallography in its broadest purview and suggests guidelines for the future development and funding of crystallography in all its aspects. In contrast to the routine aspects of crystallography, whose sole performance could result in the stagnation of the science, we are concerned here with emphasizing those problems that are both on the forefront of science and that require the specialized skills of well-trained and experienced investigators.

It is important to realize that careful crystallographic studies demand a broad knowledge of structure and a deep understanding of subjects special to the field, such as three-dimensional symmetry, diffraction theory, dislocations, and mosaic structure of real crystals. In contrast to the use of x-ray structure analysis on occasion merely as a special tool in the pursuit of a particular research goal, crystallographic investigations usually require an awareness of fundamental and subtle difficulties such as can arise from disorders, twinning, and space group identification. The investigator must be capable of understanding the rationale and objectives of modern crystallographic computational techniques and programs, and of knowing how to proceed when and if such programs do not immediately function as expected or advertised. This has important implications for the training and support of crystallographic workers whose major scientific interests and goals will be improving basic theory, techniques, procedures and instrumentation.

If this report fulfills its objectives, it will document for the reader a number of characteristics of the discipline of crystallography as a fundamental subject that affords a broad basis and the stimulation for major advances in many scientific disciplines. The accomplishments to date, while numerous, portend even greater advances in the future. These major advances are most likely to be made by workers who have broad expertise both in crystallography and other relevant fields of science.

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*"Present Status and Future Trends of Chemical Crystallography", Report of a Conference sponsored by the National Science Foundation, held at Airlie House, Va., Oct. 20-21, 1973.

2
Biological Macromolecules

Introduction

X-ray crystallography has, during the last 20 years, revolutionized the biological sciences. This fact is evidenced not only by the awards of Nobel Prizes to Crick, Watson, and Wilkins for the determination of the structure of DNA and to Perutz and Kendrew for the determination of the first protein structures but also by the evolution of the new discipline of molecular biology. Furthermore, the increase, during the last decade, in the number of macromolecular crystallographers is a further indication of the importance of crystallography to the life sciences. In 1966, there were perhaps 10 laboratories in the United States in which protein crystals were being actively studied by x-ray crystallography. At present, there are about 60 laboratories, and the number of investigators has increased from about 25 to over 300.

X-ray crystallography is the only method that permits the determination of the three-dimensional structure of biological macromolecules. Techniques, such as chemical modification, NMR, UV, IR, ESR, and mass spectroscopy may provide information that is not accessible by x-ray diffraction, but they are difficult to apply effectively to macromolecules whose structures are unknown. The most effective analyses of biological systems have come from a concerted effort using a combination of x-ray crystallography with other biochemical and biophysical techniques.

To date, the three-dimensional structures of about 70 proteins have been determined. This is only a tiny fraction of the globular proteins, let alone of all biological macromolecules, yet the impact of these discoveries has been enormous. The general nature of globular proteins has been revealed--their size and shape, the types of folding that can occur, the nature of the interactions both within protein molecules and between them, and various other properties. The geometrical arrangements of catalytically important residues have been revealed for a number of enzymes, and in some cases the mechanism of action has been defined in a manner not heretofore possible. Also, the relationships between families of proteins with related functions, such as the globins, proteases, and dehydrogenases, are becoming clearer. Comparative studies of similar proteins from different species have made it possible to begin to understand evolution at the molecular level.

Nevertheless major unanswered problems remain. For example, attempts to predict the structures of proteins from their amino acid sequences are far from satisfactory. Also, the evolutionary relationship, if any, between different structures that have certain elements in common, is not well understood. Furthermore, there are many classes of biological entities whose structures are, at present, largely unexplored although they are potentially accessible to study by diffraction techniques. Examples include membranes, glycoproteins, lipoproteins, protein-nucleic acid complexes, viruses, and assemblies of proteins such as ribosomes and multienzyme complexes.

In the following sections we briefly describe the major areas of research in macromolecular crystallography, indicating the overall impact and importance of each area and pointing out future applications and unresolved problems.

Protein Structure Determination

The first protein structure "solved" was that of myoglobin, by Kendrew and collaborators in 1960 (1). Simultaneously, Perutz and co-workers obtained a low-resolution electron density map of hemoglobin (2). It was not until 1965 that Phillips and co-workers determined the structure of lysozyme (3); however, in 1967 four new protein structures were reported (4). Since that time the annual output has steadily increased, reaching about 15 in 1974, bringing the present total of known protein structures to about 70, and including globins, proteases, lysozymes, nucleases, cytochromes, glycolytic enzymes, electron transport proteins, and immunoglobulins.

The determination of new structures remains a major activity in the field, although, as pointed out in the Introdution and below, an equally large effort is being invested in continuing analyses of "old" structures and comparisons between them.

The major problems in structure determination are often not crystallographic but rather biocrystallographic, first in obtaining suitable crystals and second in finding satisfactory isomorphous heavy-atom derivatives. Considerable experience is being accumulated in crystallization of soluble globular proteins, but a thorough understanding of the crystallization process is lacking. In particular, methods that might be applicable to the crystallization of nonsoluble molecules such as those associated with membranes have not been developed. Similarly, many successful heavy-atom derivatives have been obtained, but relatively few methods of general applicability have emerged.

The determination of the three-dimensional structure of a crystalline protein remains a major undertaking, perhaps requiring many years of effort. An even longer period may be spent developing the information that has been obtained. Nevertheless, we expect these times to decrease substantially in both areas as equipment and techniques develop.

The first protein structures indicated the general nature and complexity of protein architecture. A direct visualization of the α-helix was achieved in the electron density map of myoglobin, and subsequent structures have shown that the pleated sheet is also an important structural component.

Already four distinct families of homologous protein structures have been observed--the globins, the serine proteases, immunoglobulins, and dehydrogenases. Comparative studies within each class have provided many important insights. A comparison of hemoglobins from widely differing sources has demonstrated the conservation of three-dimensional structure during the course of evolution. Analysis of the serine proteases has revealed the structural bases for the precise specificities of these enzymes. Analysis of the crystal structures of immunoglobulins has already demonstrated the underlying basis for the diversity of antibody specificity. In the case of the dehydrogenases the surprising observation has been made of a similar nucleotide-binding region, despite the presence of quite different conformations in the substrate-specific region of the molecule. These structural comparisons have permitted an analysis of evolution at the molecular level and have made it possible to begin studying evolution of biological function. Other proteins whose structures have been determined show great diversity, suggesting the existence of many other families. At present, it appears that it will require many crystal-structure determinations to explore the possibility that proteins may belong simply to a limited number of families.

Studies of multisubunit enzymes have provided information about the mode of association in the formation of larger complexes and, in the case of hemoglobin, have already provided an example of the cooperative control of a basic biological process.

Crystal Biochemistry

X-ray crystallography has been unique in revealin the structures of biomolecules but has also been effective in allowing the visualization of complexes between proteins and their substrates. there is an abundance of evidence that the structures of enzymes in the crystalline state are similar or identical to those in solution, and it has been demonstrated in many cases that enzymes in the crystalline state are active. In contrast to crystals of small molecules, crystals of proteins have open channels through which solvent and small molecules may diffuse. Thus, by using suitable substrates, enzymatically catalyzed reactions can take place within the crystals. By using inhibitors and substrate analogs that form stable complexes with the enzyme, the structures of such complexes can be determined directly by difference techniques, which can be very powerful when applied intelligently, and have been widely applied to many different proteins. The difference technique is very versatile and can be applied to any pair of "isomorphous" crystals. In addition to studying substrate binding, crystallographic techniques have also been effective in comparing mutant hemoglobins, in determining the effect of pH changes on protein structure, in studying metal removal and replacement in proteins, and in analyzing the binding of salts and denaturants. Attempts are being made to use low-temperature crystallography to examine directly the complexes between enzymes and their natural substrates.

The detailed mechanisms of enzyme action have been worked out in a way that would have been unthinkable without x-ray crystallography. However, the x-ray techniques cannot be used to anlayze rapid dynamic processes directly. Such limitations have been overcome in a number of instances by a combination of other physical and chemical techniques. An example of this would be the application of NMR spectroscopy to the identification of active histidines, their pK's and their role in the mechanism of action of ribonuclease. Thus, it is clear that the detailed understanding of the function of biological molecules will not, in general, come from crystallography alone but rather through the skillful application of a variety of biochemical techniques.

It is important that the training of a protein crystallographer should include familiarization with at least the more important of the biophysical and biochemical methods that are currently available. Conversely, there is still a real need to educate the biochemical community in the critical evaluation of crystallographic findings.

Refinement

A protein structure, as first determined by x-ray crystallography, is usually of limited accuracy--typically the coordinates of most atoms in the structure will be determined within 0.5-1.0 Å, while local regions may be subject to larger errors. While this imperfect determination of the structure can be informative, it is desirable for a number of reasons to improve the accuracy.

This process of refinement (improvement of the first approximate molecular model) has turned out to be nontrivial for proteins. In part, the quantity of data to be manipulated is formidable, and in addition the problem is not well determined. In recent years, a considerable break-through in this area has been made, first in the laboratory of Jensen (5) and subsequently in several others. As a result, several proteins have now been determined to a coordinate accuracy of about 0.2 Å. Notwithstanding the considerable technical achievement that these results represent, the quoted accuracy is still less than that required in order to postulate detailed chemical mechanisms of enzyme action or to determine the nature of the interatomic potential functions that dictate the folding of macromolecules. Unfortunately, for many protein crystals the observable diffraction data are of limited resolution and will not allow determination of the structure to better than an accuracy of about 0.25 Å. Nevertheless, it is clearly desirable to refine as exhaustively as possible a few selected proteins that diffract well. Also, new methods of increasing the resolution of the diffraction patterns or extending crystal life in the x-ray beam would be most welcome.

Nucleic Acids

The roles played by the nucleic acids in molecular biology are, of course, central, and the recent successes of Rich's group at MIT and Klug's at the Medical Research Council in Cambridge, England in determining the three-dimensional structure of phenylalanine-tRNA have been well publicized (6). It will be desirable to solve additional such structures to illustrate the differences between the different species, and to confirm the present results. A continuing problem in this area has been the difficulty of obtaining suitable crystals.

One of the largest and most important areas in molecular biology is that of protein-nucleic acid interactions, yet the structural basis of such interactions, some of which are highly specific, is not known. Efforts to obtain large crystals of, for example, the specific complex between a tRNA and its activating enzyme, or a repressor molecule and its DNA substrate, have been made but have not yet been successful. Also, methods of determining the detailed structure of a DNA-histone complex remain to be developed.

The interaction between DNA and certain small-molecule dyes that intercalate between the bases has been effectively studied by Sobell, who has been successful in obtaining crystals of, for example, the complex between the antibiotic actinomycin D and deoxyguanosine (7). These relatively simple complexes appear to be good models for more complicated protein-nucleic interactions.

It is clear that the complete three-dimensional structure of the ribosome will be required before we understand, in detail, the process of protein synthesis. Progress is being made toward locating the nucleic acid and the different protein subunits by neutron diffraction from selectively deuterated suspensions. Yet, in spite of the fact that microcrystalline arrays of ribosomes have been seen in electron micrographs of some cells, attempts to obtain large crystals have been unsuccessful.

Neutron diffraction has also been successfully employed to locate hydrogen atoms in crystals of myoglobin and is being increasingly applied to partially ordered layer-type structures, for example, retinas and lipid bilayers.

Viruses

The study of crystalline viruses has not been a major area of macromolecular crystallography partly because of the size and complexity (molecular weight in the millions) of even the simplest viruses and also because of the limited extent of diffraction patterns from most virus crystals. Some virus crystals have been known, for a number of years, to give high-resolution diffraction patterns, but only recently has real progress been made in overcoming the enormous technical problems of data collection and heavy-atom substitution.

Low-resolution electron-density maps have already been obtained, and recent results indicate that it should be only a matter of time before the structure of a virus is determined at atomic resolution.

Partially Ordered Macromolecular Systems

Although much attention has been focused on the globular proteins, many of the important constituents of biological systems such as DNA, membrane and cell wall components, and the fibrous proteins are intrinsically unlikely to form single crystals. Nevertheless, these molecules have in some instances been induced (or observed) to form partially ordered arrays from which useful structural information can be obtained. The prime examples are, of course, the pioneering achievements of Pauling and Corey in determining the structure of α-helices and β-sheets in proteins and of Watson, Crick, Wilkins, and Franklin in elucidating the structure of DNA.

The emphasis during the last decade has been on crystalline rather than noncrystalline biomolecules; but now that the structures of a number of the soluble globular proteins are known, there is an increasing awareness of the need for information on noncrystalline proteins, in particular those associated with membranes. It is not clear at this time how best to tackle problems of this type. One approach has been to study membranes with naturally ordered components, for example, the purple membrane from halobacterium, and some promising advances have been made by using a combination of x-ray diffraction and electron microscopy.

The continuing study of the structure and the mechanism of contraction in muscle provides an elegant example of the power of electron microscopy when combined with x-ray diffraction. When new powerful sources of x-rays, such as are becoming available with the use of synchrotron radiation, are combined with position-sensitive linear detectors, it may become possible to observe the changes that accompany a single twitch of a muscle fiber.

Instrumentation

Equipment necessary to solve protein structures of moderate size (perhaps up to mol wt 200,000) is readily available. Most laboratories favor either an automatic diffractometer (computer controlled being highly desirable) or a rotating anode generator with precession cameras plus an automatic film measuring device. These two methods have been used for most structures solved to date and can be expected to be employed for some time.

There has recently been considerable interest in the use of oscillation photographs for rapid data collection, and this technique is already being routinely employed in several laboratories.

Another approach that shows great promise, and could revolutionize data collection, is to measure many reflections simultaneously by means of a computer-linked area detector. If successful, such techniques could reduce the time required for the collection of a high-resolution data set from months to hours, not only dramatically reducing the time for protein structure determination but also minimizing errors due to crystal deterioration and in addition permitting analysis of complexes too short-lived to allow conventional data collection. One type of area detector, using a fluorescent screen, together with an image-intensifer-aided detector, is being developed by Arndt in Cambridge and Reynolds and others at Princeton. Another detector, incorporating a multiwire proportional counter, is being developed by Xuong at La Jolla and seems promising. Should such data-collection schemes be successfully implemented, it might be desirable to establish several such instruments in regional centers to which protein crystallographers could bring their own crystals for the rapid collection of the bulk of their data. Such regional facilities could not, of course, supersede individual data-collection capabilities for individual laboratories.

Computing

The necessity of "good" computing facilities for the successful pursuit of macromolecular crystallography cannot be overemphasized. "Good" in this context need not imply that the available computer be a powerful one. Rather, the most important requirements are that the computing facility available to the user be responsive to his needs and provide a reasonable return in terms of the charges levied. A number of users have, over the past several years, become disenchanted with their local computing center and are seriously contemplating the acquisition of an individual laboratory computer as a preferable alternative. It appears that technology is such that a suitable in-house computer might be had for an initial investment of about $120,000, which would be offset by a continued annual saving of $20,000 - 30,000 in current computing costs for an active crystallography research group. An alternative method for satisfactory computing involves the use of a large remote computer accessed from a local terminal.

Interactive graphics systems, which have a number of advantages for the display and manipulation of complex structural models, are rapidly decreasing in price to the level that such a system could be included as part of an in-house computing facility for a relatively small increase in cost.

Conclusions

1. Among the most spectacular achievements of x-ray diffraction has been the determination of the three-dimensional structures of biological macromolecules. Such studies have revolutionized the biological sciences.
2. To understand biological processes, it is essential to know the structures of the participating entities. X-ray diffraction is by far the most powerful method available for obtaining such structural information. A large body of highly relevant structural information has already been accumulated, and new results are being obtained at an increasingly rapid rate. At the same time, many important problems potentially solvable by x-ray techniques remain to be tackled, and a number of investigators are moving in to such new and challenging areas.
3. The most fruitful analyses of the structure and function of biological macromolecules have combined x-ray diffraction with a variety of chemical and biophysical techniques. Such multifaceted approaches are to be encouraged.
4. The bulk of the structural information currently available pertains to the structures of isolated molecules. At this level, x-ray diffraction alone has sufficed. There is, however, an increasing need for structural information at higher levels of organization, e.g., for membranes, cell surfaces, ribosomes, and protein-nucleic acid complexes, and at this level there may be an increasing need for an interplay between x-ray diffraction, electron microscopy, and, in some cases, neutron diffraction.
5. Important breakthroughs in a number of areas are continually being made and are increasing the power of the x-ray technique and expanding the range of biological problems to which it can be applied. The results of macromolecular structure determination have already had a major impact in the teaching and understanding of biomedical processes. Although the influence thus far has been indirect, we are confident that in areas including enzyme modification and drug design major biomedical applications will follow.
6. The number of practicing macromolecular crystallographers and of trainees is not excessive; in terms of the potential of the field, in fact, there is ample room in the field for more personnel. On the other hand while there are at present postdoctoral-level positions available for qualified individuals, there are relatively few permanent positions. During the last few years a number of universities have, for the first time, hired a macromolecular crystallographer, and this trend can be expected to continue. Nevertheless, the number of qualified personnel is rapidly exceeding the number of permanent positions.

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3
Chemical Crystallography

Introduction

Chemical crystallography, as discussed here, covers that aspect of crystallography that has primary impact in furthering our knowledge of chemical systems. However, the borders between chemical and other fields of crystallography are often not readily definable. For example, the development of instrumentation and the improvement of structure-solving techniques properly lie within the realm of diffraction physics yet are of great concern to the chemical crystallographer; and the recent tilt of chemical research toward biologically relevant systems has shifted many crystallographic projects in that same direction. Accordingly, some of the topics discussed in this chapter are also considered elsewhere.

The contributions of crystallography to chemistry have been almost too numerous to mention. Notwithstanding the unquestioned value of IR, UV, NMR, ESR, and mass spectrometry, diffraction analysis has provided--and will continue to provide--the answer to many structural problems. A successful analysis can yield not only the gross structure and connectivity of a molecule or structural species, but in favorable cases and with appropriate care it can furnish extremely accurate values for bond lengths and angles; details of conformation, molecular packing, and intermolecular interactions; and, particularly when applied in conjunction with neutron diffraction studies, descriptions of bonding electron density distributions. Rather than dwelling on the past successes of x-ray diffraction, such as the unraveling of the structural features of peptides and of purine and pyrimidine bases, which was the cornerstone of modern molecular biology; the development of rapid structure-solving capability, which opened up the fields of organometallic and coordination chemistry; the establishment of the topochemical concept and of semiquantitative solid-state photochemistry; the measurement of accurate C-C bond lengths and angles, which provided the crucial experimental evidence for theories of aromaticity in various $4n$ and $(4n + 2)$ π-electron systems; and many others, we shall focus on those areas where diffraction techniques can be expected to provide valuable insight into future developments of chemical interest.

Of the various diffraction techniques that will be discussed, of primary importance to chemical crystallographers is single-crystal x-ray analysis, which leads most readily to a thorough and unambiguous understanding of the geometry of a chemical species. The field of neutron diffraction, which can be more useful for many systems but is presently not so readily accessible as x-ray diffraction, will also be examined. Powder diffraction has served principally as a tool for routine chemical analysis and identification but should be considered for re-evaluation as a possible tool for more complex structure analysis. Finally, noting that crystallography in its broader context encompasses such areas of structural research as gas-phase electron diffraction, we will also discuss some present and future applications of this field.

A feature that sets a crystal structure analysis apart from most other techniques of structural chemistry is that, under optimum conditions, and carried out with due care, it can provide answers that are unambiguously correct. The analysis is highly overdetermined, since the number of diffraction data available is perhaps 50-150 times larger than the number of atoms in the structural unit. Moreover, automated diffractometers have removed the human error and drudgery from the process of collecting and transcribing intensity data; modern digital computers have furnished the capability of pursuing to convergence the refinement of the structural parameters; and the development of direct methods of phasing, now available as prepackaged "structure solving routines" for automatic computer usage, has assured the correct determination of atom connectivity for the majority of moderate-sized molecules when good single crystal data are available. Accordingly, the concept has grown and is widely held that chemical crystallography is now merely a routine technique, of great use to the chemist but hardly worthy of support in its own right.

This view is misconceived. Conditions are often not optimum. In many cases the available crystals are poor: they may be extremely small or twinned or poorly shaped or highly imperfect; they may decompose with time or with exposure to x-radiation. Portions of the structure may be disordered, or there may be an intractable number of molecules per asymmetric unit. In many cases, particularly where large, chiral molecules are involved, routine application of direct methods fails. Refinement may be unsatisfactory due to hypersymmetry or to systematic errors in the data measurements. While in many instances these difficulties will not prevent the analysis from yielding an adequate picture of the gross molecular structure and atom connectivity, they will almost always demand a large amount of effort from a well-trained and experienced crystallographer if the finer details of molecular geometry are to be unraveled.

Chemical crystallography can conveniently be divided into two categories, which can be designated "analytical crystallography" and "structural crystallography." Analytical crystallography is primarily a tool for determining, rapidly and conclusively, the gross structure of a molecule and particularly its atom connectivity; structural crystallography is concerned more with the details of molecular geometry and relating them to theories of chemical bonding and electron distribution. For analytical results, it is usually sufficient to collect a limited set of intensity data and to carry refinement only to the stage where the general correctness of the structure is assured; for structural purposes, intensity data should be as extensive and of as high a quality as possible, and refinement must be pursued exhaustively. An analytical analysis may take no more than a few days; a structural analysis, several months or more.

The division of crystallography into these two categories probably lies at the root of whatever misunderstandings have arisen between chemical crystallographers and other members of the chemistry community. On the one hand, the synthetic chemist may see crystallography as a simple analytical tool and view its major objective as that of providing structure analysis on a routine basis; on the other hand, the crystallographer has to be concerned with the complex analytical techniques and instrumentation, as well as the broader chemical and structural aspects. A similar dilemma sometimes exists within the funding agencies: should support be granted for the use of crystallography as an analytical tool to be used only in conjunction with other chemical studies, or should it be supported as a basic technique for furthering our knowledge of structural chemistry? We recommend that both aspects of chemical crystallography, the structural and the analytical, should be supported.

Present Status of Chemical Crystallography

In order to allow chemical crystallographers throughout the country an opportunity to have input to this report, a questionnaire was mailed to about 200 individuals, whom we could identify as chemical crystallographers. About 100 responses to this questionnaire were received. A copy of the questionnaire and a brief and somewhat informal summary of some of the responses are given in Appendix B.

A significant result emerging from the survey returns was that most of the people who were identified as chemical crystallographers considered themselves as problem-oriented structural chemists or biologists; while in many instances they used the technique of x-ray structure analysis as their major research tool, few considered themselves as "service crystallographers" with primary interest in solving whatever crystal-structure problems they were given and with only a minor interest in the implied chemical or biological problem. The main areas of present activity in chemical crystallographic research are structure determination, studies of bonding electron density, and studies of atomic and molecular interactions. These areas are outlined below.

(a) *Structure Determination:* The stage of development in structure determination has been reached where, given a crystal large enough and of good enough quality to afford an adequate set of intensity data, the connectivity of atoms in the great majority of crystals can be determined quite rapidly--perhaps within one or two weeks, if diffractometer and computer time are readily available. In particular most inorganic and coordination compounds --which usually have a built-in heavy atom to help in the analysis--and most centrosymmetric organic compounds have crystal structures that can be solved by standard methods. However, many of the interesting high-molecular-weight organic compounds have structures that are extremely difficult to solve, particularly those without centers of symmetry. Solutions of the structures of the actinomycin-deoxyguanosine complex and of the double-helical A-U dinucleotide structures provide examples of the difficulties that can be presented and of the expertise and persistence that are necessary to overcome these difficulties.

There are other complications in present-day structural analysis that are peculiar to the nature of the crystalline state. These include twinning of the crystals, instability of the crystals due to thermal or radiation effects, disorder of the molecular arrangement in the crystal, the presence of two or more molecular units within the unit of structure, and problems associated with pseudosymmetry, which in many cases leaves the choice of space group a major problem in its own right. In many of these types of problems the most important step toward their solution may be the recognition of their existence. An inexperienced crystallographer may be unaware of the difficulties and consequently reach incorrect conclusions.

(b) *Studies of Electron Density Distributions and Chemical Bonding:* Electron density studies are most effectively carried out by a combined study involving both x-ray and neutron diffraction, the neutron diffraction results providing information concerning the locations of the atomic nuclei and the x-ray results concentrating on the distribution of valence electrons. Such studies have provided qualitative results of great interest in a large number of areas. For example, the electron density in aliphatic three-membered rings is compatible with a bent-bond description; hydrogen bonds appear to be essentially electrostatic in nature; and the electron density in an acetylene grouping is significantly perturbed when it is coordinated to a metal atom. However, progress in obtaining quantitative results is limited by experimental accuracy, and there is a need to develop improved methods of data collection and processing. This field also places greater time demands on x-ray and neutron diffractometers than does the standard structure-determination procedure, because it is necessary to collect a large amount of data of the very highest quality.

(c) *Atomic and Molecular Interactions:* The results of a careful crystal-structure analysis can provide a wealth of information concerning interatomic and intermolecular interactions. High-precision analysis is capable in many cases of providing interatomic distances to an accuracy of 0.003 Å or better; with special care and the use of low-temperature techniques, accuracies of about 0.001 Å are obtainable. These accuracies permit valuable conclusions to be drawn concerning, for example, enhanced reactivities of the "long" C-C bonds in overcrowded molecules and variations in single-bond lengths caused by lone pair interactions. There are indications of significant differences in bond lengths between the solid state and the gaseous state, particularly when strong hydrogen bonding is involved. Careful experimental work also permits the assignment of the absolute configuration of a molecule based on the anomalous scattering from atoms no heavier than oxygen or nitrogen.

Many interesting aspects of molecular interactions have been and are being studied, such as hydrogen bonding; stacking in nucleic acid components and in charge-transfer systems; clathrate and zeolite systems; interactions involving sulfur and halogen atoms; reaction pathways, as suggested by short nonbonded contacts; and the ways in which molecular arrangements in the crystal can influence the nature and direction of solid-state reactions. Of particular importance has been the improvement in the ability to locate hydrogen atoms with relatively high precision, by either neutron or x-ray diffraction studies--hydrogen atoms lie on the periphery of many molecules and hence are of dominant importance in determining intermolecular geometry. The day seems to be approaching when the crystal structure of a molecule of known conformation can be predicted from empirical interatomic potential functions, given only the unit-cell dimensions and space group. However, it is usually impossible to predict conformations for complicated molecules, and much more needs to be known as to why molecules crystallize the way they do.

In the field of electron diffraction by gases, recent improvements in data recording and processing have extended both the range of application and the reliability of the results. Studies of the limitations of the Born approximation have led to improved atomic scattering factors for elastic scattering, and improvements have also been made in evaluating inelastic scattering. The details of internal motion have been the subject of considerable theoretical investigation. As a consequence of these developments, the accuracy, detail, and facility with which molecular structure can be determined have been continuously improved. Trends in bonding as a function of chemical environment have been determined with sufficent reliability to stimulate quantum chemical studies. Particularly accurate results have been obtained from combining the results from electron diffraction with those from spectroscopy, an activity of increasing interest. Other developing areas of interest are the reaction mechanisms at high temperatures and the thermodynamic properties of molecules associated with conformational changes.

While no comprehensive studies of the status of crystallographic computing or of education in chemical crystallography were undertaken at this time, a considerable amount of information was obtained on both subjects. In particular, a brief questionnaire on education was sent to 38 graduate schools in chemistry. Some of the data obtained relating to the present status of these subjects and some tentative conclusions are included in Appendix C and D.

Future Directions

(a) *Structure Determination:* While great strides have been made in the techniques of structure solution, many formidable and challenging problems still remain. Many of the most interesting questions of molecular structure involve complex, noncentrosymmetric crystals or crystals that give a limited diffraction pattern; further progress in handling these types of systems is anticipated. There is a great need to develop improved diffractometers with better x-ray sources and better detection systems, which could lead to improved and extended data sets for marginal crystals. Research into structure solution by powder diffraction should be encouraged, in order to bring molecules that do not form large single crystals within the scope of the structural chemist. The recent availability of synchrotron facilities, with their possibilities for providing high-intensity radiation of variable wavelength, are just beginning to be exploited; it is clear that there are exciting new prospects associated with the use of anomalous dispersion for structure determination. Better understanding of thermal motion, and of the ways to treat it, will allow more meaningful results to be obtained from structural analysis, as will the development of more appropriate electron density functions to be built into the structural model. More widespread use of low-temperature equipment will extend the usefulness of crystallography in systems that are unstable at room temperature or show disorder or large thermal motions. Increased impact of neutron diffraction studies will provide further insight into problems involving highly accurate determination of the positions of hydrogen nuclei, assessment of thermal motion, and the differentiation between atoms with similar scattering powers for x-rays but differing scattering cross sections for neutrons. In summary, the techniques for structure determination and the technology of data collection offer broad and rewarding areas for future research.

(b) *Studies of Electron Density Distributions:* In order that this field may yield quantitative results that can be correlated with other physical measurements and with theoretical treatments, further developments in the technology of obtaining accurate data measurements are needed. Energy dispersive counters, synchrotron radiation, and, conceivably, x-ray lasers may have impact; improvements in low-temperature neutron diffraction techniques would also be extremely helpful. The equipment requirements in this field are much greater than in other fields of chemical crystallography. There are good prospects for developing this field into a general and detailed test for molecular and solid-state calculations and for its application to systems that now lie beyond the scope of the calculations. Interactions between crystallographers and theoretical chemists are essential to exploit these potentials. Another relatively unexplored field of chemical relevance involves the calculation of derived functions from the experimental electron densities. Examples include molecular and ionic charges, dipole and quadrupole moments, and electrostatic potentials that are of importance for an understanding of chemical reactivity.

(c) *Atomic and Molecular Interactions:* It is anticipated that the major impact of chemical crystallography will continue to focus on molecular and crystal structure. Chemical crystallography will contribute greatly to the determination of the accurate geometry of molecules and thus provide a better understanding of the basic laws that dictate their geometry; it will also provide a unique opportunity to study the ways in which molecules interact; either with themselves or with other molecules with which they can be induced to crystallize. Indeed, the prospects are for a greatly increased use of chemical crystallography in these senses, because of an increased awareness on the part of other chemists as to the power and relevance of x-ray diffraction studies. Crystallography will continue to grow as a routine analytical tool, capable of answering questions of atom connectivity quickly and unambiguously; but it will also grow as a technique for providing the finer details of intramolecular and intermolecular geometry that are necessary for understanding chemical reactivity and bonding principles.

Some specific areas of chemical research where x-ray methods may be expected to have major impact include:

1. Studies of the conformations of ring systems, where some of the more subtle aspects of chemical bonding have great influence on the molecular conformation;
2. Studies of bond lengths and angles and the extent of planarity in various aromatic systems, including those containing nitrogen and sulfur;
3. Studies of individual molecules with particularly interesting structural properties, such as helicenes, catananes, and cyclophanes;
4. Studies of the geometry of overcrowded molecules and of the influence of steric distortions on their physical and chemical properties;
5. Studies of charge-transfer complexes and of organic semiconductors;
6. Studies of unusual bonding capabilities associated with electron-deficient elements and with halogens and chalcogens;

7. Studies of coordination of various functional groups to metal atoms and correlation of structural data with other properties;
8. Studies on rare-gas compounds and metal clusters;
9. Studies on the structural details of various polymers, both natural and synthetic;
10. Studies on model compounds related to enzymes;
11. Studies on solid-state reactions;
12. Studies of intermolecular interactions in the solid state and of the role of the hydrogen atom in these interactions;
13. Studies of crystalline solvates, clathrates, channel complexes, and zeolites;
14. Studies of solid solutions and plastic crystals;
15. Studies on crystal growth and habit;
16. Studies on disorder in the solid state and on crystal decomposition;
17. Studies on the structural aspects of phase transitions;
18. Studies on intermetallic compounds, focused on the many unanswered questions of the bonding properties of metal atoms.

(d) *Electron Diffraction by Gases:* It is anticipated that there will be continued development of methods for obtaining and processing electron diffraction data, and hence there will be advances both in the complexity of molecules that can be examined and in the accuracy of the derived molecular parameters. There should also be an increased contribution from electron diffraction studies as a method for studying the details of chemical bonding as a function of chemical environment. Studies of vibrational modes should receive increased attention, and greater emphasis should be placed on the combining of electron diffraction studies with spectroscopic measurements. Work should also be encouraged on the many novel compounds that can be conveniently studied only in the gas phase.

Recommendations for Support of Chemical Crystallography

In view of the power of crystallography to provide answers to so many key questions in chemistry and of its potential for future development, we recommend that it receive strong support in the years ahead -- both in the development of further methodology and instrumentation and in its application to chemical problems.

(a) *Support for Development in Methodology and Instrumentation:* An inordinate amount of the recent development of the science and technology of crystallography has come out of nonacademic institutions such as the federally supported laboratories. Continued support of developmental research at such institutions is vital. However, there has been little support for this type of research in the academic community; here, the emphasis has shifted toward the application of crystallography as an analytical tool. We see dangers in this uneven distribution. First, the narrow base of effort in developmental aspects of chemical crystallography may well lead to stagnation, with the result that the tools and methodology that are still needed to answer many important chemical questions will not be forthcoming. Equally important, we are already seeing a tendency to train crystallographers with less than adequate knowledge of the fundamental concepts and techniques that are necessary if the field is to remain vital. We believe that support for the fundamental aspects of crystallography--techniques of data collection and structure solving, development of instrumentation, studies of scattering theories and models for thermal motion, refinement of structural parameters--should be increased; and that encouragement should be provided to those in the academic community who are concerned with passing a broad knowledge of crystallography on to the next generation of chemists. These matters are discussed further in Section 4 of this report (Diffraction Physics).

(b) *Support for Studies in Structural Chemistry:* Support for work on problems of structural chemistry seems also to have suffered from the shift of emphasis toward analytical crystallography. Indeed, there seem to be funding difficulties for those interested in the fundamental aspects of structural chemistry--the details of molecular structure and intermolecular interactions that can be brought out only by careful collection and interpretation of diffraction data. Such individuals, with a cohesive project aimed at casting a light on chemical problems of significance, will probably use x-ray or electron diffraction as their main research technique; they may work in collaboration with a synthetic or theoretical chemist. By being well trained in diffraction concepts and by keeping abreast in developments in the field, they will be able to provide help to colleagues interested in the results of analytical crystallography, and will also have an important influence in the training of future chemists. Granting agencies should take into consideration that such studies are time consuming and result in a relatively low rate of publication. We urge that support be made available to this area of structural Chemistry.

(c) *Support for Analytical Crystallography:* Continued support should also be made available to chemists who use crystallography for rapid chemical analysis in research programs of broader scope. These chemists are less involved in the basic concepts of diffraction and therefore are less likely to contribute significantly to advances in the science or to the training or the education of others. If their research program is large enough, they may need to be provided with full diffraction facilities; chemists with smaller programs may prefer to use a commercial structure-solving service. The respondents to our questionnaire showed virtually no opposition to the concept of such commercial services; indeed, many were of the opinion that such services would tend to remove internal departmental pressures and permit the structural crystallographer to devote more time to his own research interests. (The only reservations expressed concerning commercial services were that the procedures and results of an analysis, including atomic coordinates, be published in the normal way and that some level of quality control be established.) The question of the extent to which federal agencies might become involved in the establishment and funding of a structure-solving service on a national or regional basis was thought to be premature at this stage.

There are many areas of structural chemistry and crystallography that are worthy of support and it is a matter of concern that such support has not been centralized, particularly within NSF. In assigning award priorities, we believe that the quality of the work should always be the prime consideration. There may be great danger in attempting to define particular areas of chemical crystallography that are worthy of support at the expense of others.

Rather, there should be a balance in the types of programs that are supported, and this balance will be ensured if the key to support is imaginative, important, and high-quality work.

4
Diffraction Physics

Scope of Diffraction Physics

Diffraction physics in crystallography is here taken to encompass those activities that deal with the development and best use of diffraction theory for the purpose of optimizing the information obtainable from the scattering material. The information sought concerns the spatial location, migration, and thermal vibration of all the electron and nuclear scattering density in real, nonidealized, materials. All types of atomic groupings in crystalline, partially crystalline, and noncrystalline materials are included.

Scattering of x-rays, neutrons, and electrons may be elastic or inelastic while simultaneously being coherent or incoherent. The scattering may occur from materials ranging from single crystals to polycrystalline masses, through disordered crystals, to fibers, and on to noncrystalline solids and liquids. The most widely known applications of crystallography are concerned with only coherent scattering from single crystals which approximate being ideally imperfect. Hence, they fall within a single block in Table 1* (marked CC), the one in which the atomic arrangement aspect of chemical crystallography is centered. However, the rich variety of studies and the areas that lead the progress in diffraction physics are illustrated throughout Table 1. In diffraction physics one is concerned with improving knowledge of such areas as:

1. distributions of electron charge, spin, and momentum density and of nuclear charge and spin;
2. the scattering process [anomalous dispersion, dynamical diffraction, elastic coherent scattering (Bragg diffraction from crystals), elastic incoherent scattering (an important part of the scattering from noncrystalline aggregates), inelastic coherent scattering (e.g., thermal diffuse scattering), and inelastic incoherent scattering (e.g., Compton scattering of x-rays from amorphous materials, fluorescence, incoherent scattering of neutrons from liquids);]
3. instrument design (including optics); operation; and correction factors affecting precision and accuracy; e.g., instrumental profiles, slit effects, stability and resolution functions;
4. specimen factors limiting precision and accuracy; e.g., errors in corrections for absorption, extinction, simultaneous diffraction, double Bragg scattering, Compton scattering, scattering cross sections, multiple

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*See page 28

scattering, inner potentials, crystal inhomogeneity, texture and state of aggregation, plus other known and unknown factors;

5. methods for dealing with overlapped and superimposed data from several origins, e.g., separation of coherent scattering from incoherent and background scattering from liquid and amorphous materials; unresolved powder patterns; various contributions to diffuse scattering.

Some of the studies in diffraction physics concern thermal and disorder diffuse scattering, small-angle scattering, diffraction topography, (including imaging in electron microscopy), dynamical diffraction effects, scattering by defects of various kinds, and scattering from amorphous solids and liquids.

Since the theory and applications of diffraction physics undergird so many other studies, numerous aspects especially merit further development. The bulk of these aspects deal with either 1). departures of the scattering object from an ideally imperfect but stoichiometric crystal or 2). the precise determination of subtle (but important) details such as actual thermal motions, crystal field and bonding effects, and location and interactions of minor substituents. As illustrations, we take five examples for discussion.

Examples

(a) *Assessment and Reduction of Residual Discrepancies:* For the determination of subtle details, the major challenges in diffraction physics are to reduce the residual discrepancy between the calculated diffraction features of a model and the experimental measurements and, at the same time, to develop better ways of assessing the discrepancy and better indicators of accuracy in the details determined. (When R factors are low, only 2 or 3%, more sensitive indicators of improved fit are needed for reliable determination of subtle details.) The normal probability plot introduced by Abrahams and Keve (1) is a step toward better indicators; more are needed.

In the last 20 years, the "average" residual discrepancy on single-crystal x-ray work has been greatly reduced by improved instrumentation, by use of improved thermal parameters in some cases, by improvements in scattering factors including anomalous dispersion effects, by improved determination of absorption coefficients and absorption corrections, by Zachariasen's (2) contribution of effective extinction correction formulas, by procedures for handling simultaneous effects, and by better control and correction for background. Yet many workers are now finding that the residual discrepancy in their least-squares refinements is still significantly larger than can be accounted for by the known sources of error. Clearly, if these observations are correct, there exists some as yet improperly accounted for source of error that must be adequately dealt with if the information-laden subtle details observable in principle are to be observed in fact.

(b) *Small Angle Scattering:* In the last few years, small-angle scattering has become a particularly fruitful and rapidly developing field. This follows a period of many years, starting soon after Guinier's (3) effective inception of the field in 1939, during which only a handful of dedicated persons around the world kept work going in the theory and practice of small-angle scattering of x-rays. [The groups of W. Beeman (University of Wisconsin), and of A. W. Schmidt (University of Missouri) in the United States, of O. Kratky (University of Graz, Austria), and of M. Kakudo (Osaka University, Japan) come quickly to mind.]

Some of the most dramatic advances in small-angle scattering (SAS) in the past five years appear to be in the development and application of neutron small-angle scattering techniques. The complementary nature of neutron scattering and x-ray scattering can now be effectively exploited. For example, it appears that with the use of neutrons, x-rays, and solvent scattering-density variation one can determine the size, shape, and internal inhomogeneity of particles in favorable cases.

In part, these rapid advances have been made possible by the development of new equipment, notably of multiple and position-sensitive detectors and of x-ray and "high-flux" cold-neutron sources. The development of the neutron guide tube by Maier-Leibnitz's group at Garching in the early 1960's contributed an important step in the diffraction physics of the field. By 1963, W. Schmatz at Garching, Germany, was applying it to eliminate double Bragg scattering by using a wavelength longer than the Bragg cutoff. Thus, a vastly improved investigation of point-defect structures in metals could be undertaken without the vitiating problem of double Bragg scattering. The guide tube concept has now been dramatically embodied in the instrumentation developed around the high-flux reactor at the Institute Laue Langevin, Grenoble. The small-angle scattering instrument is 80 m long. It uses a specially developed area-sensitive detector that makes possible the collection of small-angle scattering (SAS) patterns in a few minutes. As always, orders of magnitude improvement in technique lead to the performance of fruitful new experiments that were previously too tedious to be considered.

Structural features of protein and other macromolecules in solution and in some cases in tissue, molecular configuration and aggregation in amorphous materials including crystalline/amorphous characterizing ratios, density fluctuations in the glass transition, and intermolecular entanglements ("kinks") are but a few of the features on which SAS studies were reported recently (See collected papers in *J. Appl. Cryst.* 7, April 1974).

As the present thrust toward taking full advantage of computerization, high-flux x-ray (and neutron) sources, and position-sensitive quantum detectors continues to build, we can probably expect to see a considerable contribution toward our understanding of inhomogeneous materials, of liquids including solutions and of biological molecules in environments (e.g., solutions) nearly like their biological environment.

Further, as both experimental and theoretical methods develop to make it possible, the use of a range of wavelengths (e.g., synchrotron sources and energy-dispersive area detectors) will add further power to the SAS technique so that, for example, size, shape, orientation, and density distribution within the scattering particle (e.g., molecule) can be determined quickly and reliably.

(c) *Lattice Distortions and Local Atomic Arrangements:* The current status of studies of lattice distortions and local atomic arrangements (defects) in real crystals was reviewed at the April 20-May 3, 1974, International Discussion meeting at Jülich on this subject (see collected papers in *J. Appl. Cryst.* 8, April 1975). The principal diffraction physics problems have been the development of combined theoretical and experimental approaches to separation and analysis of the diffuse scattering contributions from several origins, e.g., ordinary thermal vibrations, compositional and displacive fluctuations, point defects and clusters, strongly coupled thermal vibrations, and temperature-induced displacements (e.g., premonitory phenomena in phase transitions). These have led to successful and fundamentally important studies of phase transitions in alloys, magnets, and superconductors; of the dynamics of phase transitions; of the physics of fluids; of diffusion in solids and liquids including self-diffusion; and of lattice dynamics of all kinds. The importance of the separation of static and dynamic effects by use of neutron scattering was clearly demonstrated by Comes's review (4) on linear local order; much of the earlier disorder studies (e.g., those on the α-β transition in quartz or the $BaTiO_3$ ferroelectric transition) are now being continued with inelastic neutron scattering methods.

Techniques and methodology of diffuse scattering studies are in a state of vigorous development. In the study of short-range order and clustering by x-ray diffraction in highly concentrated metal alloys Gragg and Cohen, (5), and Borie and Sparks (6) for example, three-dimensional data can now be obtained and displacements caused by thermal motion and by the defect structure can be well separated so that refined lattice models based on computer simulations can be considered. In the groups of Schilling and Schmatz in Jülich, highly sensitive techniques of diffuse x-ray and neutron scattering have been developed. By the use of a 100-kW rotating anode x-ray generator and a multidetector system, Haubold (7) was able to discriminate the scattering of a 5 x 10^{-4} (atomic fraction) Frenkel defects in aluminum from the 50-times-larger Compton scattering. One result was that radiation damage effects, for example, could be followed by diffuse scattering measurements almost as they happened.

The work of Haubold and Schilling (8) in achieving a data-collection rate <u>four orders of magnitude</u> greater than "standard" shows that opportunities for scientific advancement through the development of instrumentation exist now. Synchrotron sources offer the promise of still further increases in data collection rates.

One exciting example of studies made possible by the 10^4 increase in speed is the finding that the annealing stages from radiation damage, previously thought to be various stages of recombination, are actually various stages of clustering. This new insight can be expected to play an important role in designing materials that must withstand the radiation damage in nuclear power generation and controlled thermonuclear fusion reactors. Further work is needed at lower doses, to be sure that single defects are involved initially. It would require a substantial investment to develop the instrumental capabilities for such studies in the United States.

For the elements with small incoherent-scattering cross sections (such as Al, Pb, and Nb) Bauer, Seitz, and Just (9) reported nearly comparable sensitivity for the neutron spectrometers in Jülich and Grenoble. Sufficient techniques are now available there for one to study the displacement structure of single-point defects. This situation now puts the challenge and gives needed support data to the theoreticians to develop proper many-body models for the defect structure.

Displacement fields around imperfections and solute atoms can now be measured, and experiments are needed to explore these in dilute solutions and concentrated solutions, to better understand the nature of these imperfections, interactions, and their effects on properties. Clustering of solute atoms (as in hardening alloys and steels) can then perhaps be understood in metals and ceramics. Here again a strong coupling of theory and experiment is needed.

(d) *Dynamical Diffraction Effects:* An area of diffraction physics in which there has been dramatic advances in the last 15 years is that of diffraction by nearly perfect crystals. Although the governing dynamical theory was initially expounded by Ewald (10) in 1917, the field did not start developing broadly until the 1960's following Lang's (11) pioneering work on x-ray diffraction topography. The ensuing applications have great significance. The understanding of real solids has been greatly improved. This technique is now routinely used in semiconductor production technology. Individual dislocations were visualized, confirming the theory of metallic yielding for the first time in bulk specimens. Stacking and other planar defects were visualized, and strain fields were measured to compare with and to support the development of theory. Clusters of point defects were studied via anomalous transmission methods. As theory developed, applications were made to the determination of stress produced by an oxide film on a silicon crystal (important in solid-state devices) and to quantitative studies of acoustic vibration (resonance modes) patterns in three dimensions in quartz oscillators. With the advancements being made in crystal-growth technology and with continuing progress in device physics utilizing nearly perfect crystals, for both electronic and optical applications, dynamical diffraction effects are no longer laboratory curiosities but are increasingly encountered in the course of x-ray characterization of materials. Instruments that previously had been considered to be tools for specialized research in diffraction theory at university laboratories are now found in industrial laboratories, where they are used to evaluate crystal quality. Investigators who are primarily interested in materials properties must now be prepared to deal with these more sophisticated diffraction techniques and phenomena.

Sophisticated diffraction techniques were used, for example, by Bonse and Hart, (12) while temporarily in the United States, at Cornell University, to make the x-ray interferometer. This instrument is having a strong impact in fundamental x-ray and atomic physics. For example, it has been used to make direct measurement of x-ray wavelengths in terms of the standard light wavelength. Determinations of lattice parameters with ultra-high accuracy with this instrument are leading to redetermination of the fundamental atomic constants. Other instruments of unusual capability have also resulted [e.g. Bonse-Hart SAXS (small-angle x-ray scattering] diffractometer; monochromator producing x-ray beam having much less wavelength spread than emission lines).

Lang returned to England soon after developing the topographic methods bearing his name. Bonse returned to Germany and Hart to England. Since that time the greatest portion of the development of the relevant dynamical theory and its applications has passed to workers in Japan and Europe.

(e) *Electron Microscopy (EM) and Diffraction:* An important area of diffraction physics that absolutely requires an understanding of dynamical diffraction effects is that of interpreting electron microscope images of crystalline materials. Included is the powerful new technique of lattice imaging, which is now so well developed that one can "see" structures directly in favorable cases. New techniques of high-voltage EM and scanning transmission EM offer the possibility for important new developments.

U.S. Shortfall

Unfortunately, with but few exceptions, the United States has contributed and is contributing little to the current exciting developments in diffraction physics. Even though it has at least a few good people in each of the fields, the funding agencies have not adequately supported the ongoing development of the theory and methods. Instead, the funding agencies seem to be too concerned with immediate payoffs, with applications. Generally speaking, there seems to be an unwillingness to invest in fundamentals and in development of the instrumentation for tomorrow's science (except, possibly in high-energy physics). The penalty is that U.S. science is circumscribed to a much too large extent by the type of instruments that can be bought off the shelf and has therefore had to wait for development elsewhere. Even commercial items, diffractometers and electron microscopes, for example, have generally to be obtained from foreign manufacturers. Only in the field of detectors are American suppliers keeping pace. The development of the electron microprobe (France) and the scanning electron microscope (England) are prime examples in which other countries have surpassed the United States. This is happening for many other areas, particularly in diffraction and particularly diffraction physics, for example, solid-state position-sensitive and area detectors for x-rays and area detectors for neutrons, high-intensity x-ray sources, and electron optical instruments.

In the area of electron microscopy and diffraction, in particular, the major developments of theory and technique of the last 20 years have come from Japan, Europe, and Australia. The relatively low level of fundamental work (including instrumental development, diffraction and imaging theory, advances in techniques) and lack of adequate teaching for both biological and nonbiological electron microscopy and diffraction in the United States may arise largely because most current funding for electron microscopy comes from the National Institutes of Health, which supports mostly medical research and not physics or crystallography.

One result of the lack of support for fundamental work in diffraction physics is that, where it is included at all in curricula, it is taught only at low levels in all but a few (under a dozen) U.S. schools. Even in most of those, the teaching is not done in the physics department, where one might logically expect to find vigorous courses and research in diffraction physics. This is in complete contrast to the situation in Japan in particular, and in Europe. Adequate training in diffraction physics should impart the fundamentals in most of the following areas:

1. fundamentals of kinematic and dynamical theory;
2. scattering by phonons, magnons, and plasmons;
3. scattering by defects;
4. small-angle scattering;
5. scattering from liquids and amorphous solids;
6. x-ray, neutron, and electron optics of common instruments;
7. crystal symmetry and structure determination;
8. understanding of all forms of diffuse, inelastic background scattering (needed for proper treatment of scattering from noncrystalline materials).

The dearth of graduates well trained in diffraction physics makes it difficult to estimate the potential U.S. job market for crystallographers with a broad training in diffraction physics. The few graduates of schools with strong programs in this area have encountered no particular difficulty in finding jobs consistent with their backgrounds.

Summary

Diffraction physics in crystallography is a broad field, as is indicated in Table 1, in which analytical chemical crystallography falls in only one block. Diffraction physics is the principal field of innovation in theory and techniques, and in instrumentation and methods of its use, to the end of extracting the maximum information about the locations and correlated vibrations of electrons and atoms in real materials. Five illustrative examples of problem areas have been discussed (precision in structure refinement, small-angle scattering of x-rays and neutrons, lattice distortions and local atomic arrangements, dynamical x-ray diffraction effects, and electron microscopy and diffraction.) In four of these the United States is not the leader; the leadership has passed to workers in Japan and Europe. This consequence is ascribed to past funding patterns, which have failed to give adequate support to teaching and research in the fundamentals of diffraction physics and to development of new instrumentation in the field.

TABLE 1

Some Areas of Diffraction Physics Applications

Type of scattering of X-Rays, Neutrons, and Electrons	Type of Specimens[a]								
	Single-Crystal		Polycrystalline Materials[b]				Noncrystalline		
	Perfect	Imperfect	3D	2D	1D (fibers)	pC	Gases	Solids	Liquids
Elastic Coherent (e.g., "Bragg"; correlated from liquids)	X	CC[c] X	X	X	X	X	X	X	X
Inelastic Coherent (e.g., thermal diffuse scattering)	X	X	X		X		X		X
Elastic Incoherent (e.g., disorder diffuse cattering, gases)	X	X	X				X		
Inelastic Incoherent (e.g., Compton, incoherent neutron)	X	X	X					X	X

a) X in a box means that significant applications exist.

b) 1D, 2D, 3D refer to number of dimensions in which periodic order occurs; pC, para-Crystalline.

c) CC, chemical crystallography.

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5
EARTH SCIENCES

INTRODUCTION

Historically, crystallography has played an important role in the geological sciences, especially in mineralogy and geochemistry, because geologists deal on a large scale with inorganic compounds that are almost exclusively in the solid, crystalline state. Thus, geological laboratories have long depended on the essential adjunct of x-ray methods and equipment almost as they have on the microscope. Indeed, the science of crystallography was originated and developed largely within the domain of mineralogy. After M. von Laue's discovery of x-ray diffraction in the realm of physics (1) the science of mineralogy was revolutionized by the new structure analysis techniques. The sensational revelation of the structural basis of the silicate compounds as revealed by pioneers such as W. L. Bragg, B. E. Warren, and L. Pauling (1) is well known. By the 1950's, emphasis began to shift from a preoccupation with structure determination itself to the application of structural information to the interpretation of geochemical phenomena. Since the middle 1960's, crystallography in the earth sciences has been heavily concerned with detailed studies of crystal textures on an atomic scale in relation to chemical environment, thermal history, mode of formation, and other coexisting phases. Most of the important mineral structure types are now known, but detailed and precise structure analyses using modern methods have been carried out on relatively few of the innumerable variants of these structures. They are nevertheless needed to provide essential information for the application of numerous physical studies to geologic problems.

Today the use of crystallographic techniques is widespread throughout geology, ranging from routine mineral identification with x-ray powder diffraction methods, through full-scale structure determinations involving hundreds of parameters, to investigations of chemical bonding in minerals. The full benefit of these powerful techniques is best obtained by scientists with extensive experience in the field of crystallography and crystal chemistry. In this area "black-box" procedures may easily lead to erroneous results.

Perhaps the most significant aspect of crystallography as it is being practiced today is the way it is being integrated as an essential part of other disciplines in the earth sciences. For example, field and experimental petrologists have made extensive use of sophisticated powder diffraction analysis, and many now regard the precession camera for cell and spacegroup determination as indispensable to such studies. Geophysicists have contributed greatly to our understanding of the composition and mineralogy of the upper mantle through crystallographic analysis in high-pressure experiments. Industrial applications include the design and use of diffraction facilities for the rapid analysis of large numbers of samples such as rock cuttings from holes drilled for oil. Currently, the Deep Sea Drilling Project is using automatic equipment for x-ray analysis of deep-sea samples and needs even more support to keep up with the ever-growing number of samples. There are many other examples that could be cited, but the major point to emphasize is that crystallographic activities from the most basic to the applied are being interwoven with other disciplines, thus leading to a much better understanding of the behavior of minerals and mineral systems.

A few examples of current research cited below illustrate well an important aspect of mineral crystal structures, namely, that they consist of extended bonding networks and almost never of isolated molecules. This requires an entirely different approach from that associated with organic or biological molecules and generally is much less amenable to standardized methods than structures dominated by discrete molecules.

Systematic Structure Studies

(a) *Rock-forming Silicates:* The rock-forming silicate minerals are by far the most important geologically. The basic structures of the major silicate groups worked out by W. L. Bragg, B. E. Warren, L. Pauling, W. H. Taylor, and many others in the 1930's and 1940's (2) provided the foundation upon which virtually all petrologic studies since then have been based. These discoveries were truly spectacular in their day, just as the revelation of protein structures is today. This early excitement did not climax and subside but grew in intensity as more and more mysteries were resolved through the application of the new structure theory. Up to the present, crystallographic research is demonstrating that information crucial to fundamental geochemical phenomena is revealed only by previously unsuspected structural complexities of these minerals. A prime example lies in the feldspar group of framework silicates, which form solid solutions with the deceptively simple end members $NaAlSi_3O_8$ and $CaAl_2Si_2O_8$. The detailed analysis of the last (anorthite) was accomplished only 12 years ago by Helen Megaw's group in a tetramolecular triclinic unit cell involving 156 structure parameters (thermal parameters were not refined; still far short of "modern standards"!). This analysis led to a full understanding of the subtle Si-Al ordering on the tetrahedral sites. H. D. Megaw, W. H. Taylor, J. V. Smith, F. Laves, and others (3) have shown the importance of recognizing the exact nature and degree of Si-Al order in feldspars as a clue to the temperature of rock formation. Untangling the complex diffraction phenomena resulting from the simultaneous effects of twinning, atomic substitution, site disorder, multi-phase separation, domain disorder, and diffuse scattering requires crystallographic perception of the highest order.

The pyroxene and amphibole groups of chain silicates are equally important as indicators of rock history. The former has been found in the last decade to provide the most reliable available geothermometer through a detailed knowledge of the distribution of the Mg, Fe, Mn, Ca, etc. cations over the various crystallographic sites and the latter have great potential in this application. The chemical complexity of these minerals that makes them important as geochemical indicators results again in multi-phase textural patterns, frequently on a scale of a few angstroms, requiring the utmost skill in the interpretation of their diffraction effects. The application of such studies by H. Takeda, M. Ross, J. J. Papike, S. Ghose, and many others (4) to the study of lunar rocks and their origin have been particularly noteworthy. Because lunar samples available to individual investigators have been so small, the extraordinary amount of information that could be extracted from these samples through crystallographic techniques has made these advanced crystal-structure methods indispensable.

(b) *Aluminum-magnesium Hydroxides:* Among the nonsilicates, the relationships of a series of aluminum-magnesium hydroxide-bearing compounds and minerals have been elucidated in recent years by crystallographic methods. These "basic" metal salts (carbonates, chlorides, etc.) have proved to be based on a simple concept: charged brucitelike metal hydroxide layers are interleaved with some other type of layer. The chlorite structure in which the interlayer is a micalike silicoaluminate was the first to be found of this type (1930), but crystallographic studies over the last decade or so have revealed that this structural mechanism has a far-reaching role in solid-state chemistry. Allmann and coworkers (5) found that in koenenite (Na,Mg)Cl forms an interlayer complex with $(Mg,Al)(OH)_2$ to produce crystals with strange lattice properties that would defeat anyone who did not have long experience with crystal chemistry and diffraction methods. The unusual complex represented by valleriite, $1.526\ (Mg,Al)(OH)_2\ (Fe,Cu)S_2$, which looks chemically and even crystallographically as though it were a mixture, Allmann (6) found to be a homogenous crystal structure of a most unusual type. Incidentally, this discovery provided an explanation for the puzzling behavior of certain Canadian copper ores, from which the magnesium and aluminum could not be separated by the usual flotation methods.

This example illustrates how astute crystallographic research on crystals of generally poor quality, using structure analysis methods that many crystallographers would call semiquantitative (and probably would reject the crystals as unsuitable for study at the outset), has opened up a broad area of crystal chemical insight. It also illustrates the situation typically faced by the mineral crystallographer, who is forced to deal with the crystals as they come to him from nature, in whatever twinned, deformed, or disordered state they may be. "Unsatisfactory" crystals cannot be rejected and new and better ones obtained. Much important basic information has been obtained from such crystals.

(c) *Sulfosalts:* One of the most complex mineralogical systems, and one that is basic to many ore deposits, involves the so-called "sulfosalts." Of natural phases of the type $A_xY_yZ_z$, where Y = As, Sb, or Bi, Z = S, Se, or Te, and A is commonly a combination of Cu, Fe, Ag, Pb, or Zn, Nowacki (7) has listed 177 established species among sulfides alone. The close relationship of these wholly unsaltlike phases to the PbS (or NaCl) structure (as for example, jordanite, $Pb_{14}As_6S_{23}$) or to the ZnS structure (for example, nowakiite $Cu_6Zn_3As_4S_{12}$) and varying stages in between has been revealed in recent years by W. Nowacki, M. Buerger, B. Wuensch, and others, (6) through extensive crystal structure studies of the most complex and nonroutine kind. These crystals commonly are subject to elaborate superstructure arrangements, subtle site-disorder distributions, and invidious twinning. Wherever these factors enter in, no routine approach is feasible and the experience and special insights of the crystallographer are indispensable.

(d) *Phosphates:* Another enormous group of minerals consists of the phosphate (and arsenate) species, of which there are over 300. The crystal structures of these phases are usually not as demanding of crystal structure analysis procedures as some of the above-mentioned systems. Nevertheless, a full understanding of the formation, behavior, and interrelationships of the various components of a mineral phosphate system depends heavily on the sheer geometry of the phosphate group and its association with the cations, frequently under the influence of hydrogen bonds. This understanding can only come from systematic studies by someone trained primarily in crystallography and crystal chemistry. It would generally not be feasible in such studies for a chemist or a mineralogist to collect or synthesize a number of species, submit them for structure analysis, and interpret them without the assistance of a crystallographer.

In connection with phosphates, we should take note of the implications of the apatite phases. These have been the subject of extensive structural studies not only by mineralogists and geologists in connection with phosphate rock deposits but also by biochemists interested in the hard tissues of teeth and bone and by physicists intrigued with its special solid-state properties.

(e) *Zeolites:* The properties of the zeolite group of minerals, which has ever-increasing industrial importance, depend vitally on the details of their structures. The analysis of these structures is complicated by the large unit cells of the framework aluminosilicates, the prevalence of twinning and domain disorder, and the nearly fluid nature of the cations and water molecules in the large channels and voids in the open structures. Earlier analyses generally ignored Si-Al ordering and presented degenerately symmetrical structures (frequently postulating unlikely 180° Si-O-Si linkages, for example), whereas a knowledge of the actual lower-symmetry, more ordered structures is needed for their full understanding. For example, to work out the details of such structures as that of the synthetic zeolite A, whose cubic unit cell contains $(K_2, Ca, Na_2)_{76}Al_{152}Si_{520}O_{1344}\cdot 700H_2O$ has required the thoughtful application of the most advanced crystallographic methods at every stage of the investigation (8).

(f) *Clay Minerals:* The unique physical and chemical properties of clays were long ago explained by crystallographic studies of their basic layer structures. This class of minerals is perhaps the most complex of all and is still challenging crystallographers. The broad field of clay mineralogy is based fundamentally on crystal chemical concepts. The role played by detailed x-ray analysis of clays on sedimentary deposits has been crucial to the geologic interpretation of oil bed structures. A knowledge of clay structures is vital to the understanding of weathering processes in the breakdown of rocks. Ultimately, this leads to soils, of which the major constituents are various types of clay, and it is through x-ray structure studies of the clay components that we learn the mechanisms of hydration and base exchange that are all-important in agriculture.

Future Trends In Structural Mineralogy

A major area that will require extended crystallographic and structural studies in the future is concerned with the sulfide minerals. These offer a dual opportunity for the crystallographer because they represent the primary mineralogy of the major metallic ore deposits of the earth and because their complexity and variability present a significant challenge to the ingenuity and resourcefulness of the investigator. For example, even the apparently simple compound Cu_2S (chalcocite) has an extremely complex structure that has only recently been elucidated. The equally prevalent ore mineral djurleite, $Cu_{1.965}S$, has a still more complex and as yet unknown structure. The study of ore deposits has, until recently, had little connection with studies of the silicate or carbonate rocks in which the ore bodies are found. Now, however, geologists are beginning to realize that the formation of ore deposits can be better understood when all factors such as sulfide-silicate interactions are considered. An understanding of these interactions requires a knowledge of crystal structure and of the behavior of transition metals in different chemical environments. Interest in sulfide crystal chemistry is growing, and this will undoubtedly be accelerated as more scientific effort is put into the study of the origin of ore bodies.

While in the past few years exciting progress has been made in the application of x-ray diffraction techniques to the study of mineral crystal structures at high temperatures and pressures, such studies are just in their infancy. Single-crystal diffraction experiments are now producing data of excellent quality at temperatures as high as 1200°C. In the last two years, miniature high-pressure cells for single crystals have been used to study crystal structures, compressibilities, phase transformations, and other physical properties as functions of pressure up to 50 kbar. Recently, polycrystalline samples have been examined optically or with x-rays at temperatures and pressures as high as 2000°C and 260 kbar. Because the earth's interior is composed of crystalline solids at high temperatures and pressures, the data obtained in these experiments will have a marked influence on future perceptions of the solid-state nature of the earth by geochemists and geophysicists.

The detailed examination of the kinetics and mechanisms of phase transitions by dynamic structure studies, made as they occur, will surely be important in developing our knowledge of rock-forming processes. This will include processes involved in crystallization from liquid or glassy states and studies of structures in these states. There will be ample opportunities in these studies for cooperative interdisciplinary efforts with materials scientists and physicists.

Recently, the possibility of imaging fine details of mineral crystals with the high-voltage electron microscope has deeply influenced our way of thinking about many aspects of mineral chemistry. For example, crystals of pyroxenes, which by ordinary examination appear quite homogeneous, are found to contain extraordinarily fine detail of exsolution lamellae and domains on a scale approaching unit cell dimensions. These details are closely related to the complex chemistry of these substances and help to explain subtle and complex x-ray diffraction effects of satellite spots and diffuse streaks that were previously difficult to account for. The recent techniques of electron phase imaging (9) are beginning to give us pictures of the atoms themselves and of their individual behavior in dislocations and structural irregularities that are just as significant for understanding mineral phase relationships as they are in accounting for solid-state physical phenomena. It must be emphasized again, however, that these new electron-optical imaging techniques will yield pictures with limited information, unless the detailed atomic arrangements of the various components are known from x-ray crystallographic studies.

Among other areas where advanced crystal structure studies in close cooperation with other disciplines will probably make decisive contributions in the future, we should mention the development of powder diffraction methods, which are capable of yielding far greater information than mere identification, which is currently their major application. Indexing of unknown patterns is still not generally accomplished, but when it is, structure analysis from powder data where single crystals cannot be obtained (and where the structures are not too complex) will become much more practical. In the theoretical area, the studies of coordination, linkage, and polyhedron geometry such as those initiated by A. F. Wells, University of Connecticut and P. Moore, University of Chicago are certain to broaden our insights concerning the factors that make both molecular and mineral (solid-state) structures stable. Such topological studies will need to be combined with lattice energy computations and bond theory but will be profitable only if carried out on a firm crystallographic base. Along more chemical lines, the study of relationships among cations, order-disorder defect structures, diffusion processes, and thermal history (as in the geochemistry of magmas and ores) has only just begun. Crystallography has much to contribute to such studies.

Education And Manpower

Frequently the university chemistry, biology, and physics departments send interested students to the geology department for basic courses in crystallography. Nevertheless, in the earth sciences there is no established set of standards to which colleges and universities must conform, and many offer no crystallographic instruction beyond a sophomore-level course in mineralogy; well-equipped laboratories are mainly found only in the larger universities. In the schools that do offer crystallographic training at the Ph.D. level, the general belief is that a student should graduate with a good knowledge of several aspects of geology, geochemistry, and geophysics and that specialization in crystallography, electron microprobe analysis, electron microscopy, or other disciplines should be used as support for the problems encountered rather than as ends in themselves. Many earth science departments encourage their students to take courses in physics, mathematics, chemistry, and materials science, in the interest of producing graduates who will be creative and innovative in crystallography as applied to minerals.

While there is no precise information concerning the degree of emphasis on crystallography in university programs, some notion about it may be gained from the fact that there are approximately 400 faculty members in earth science departments in the 1972 AGI Directory of Geoscience Departments who list "mineralogy-crystallography" as one of their specialties. Possibly 15%, or 60 of these, might be considered to be primarily interested in structural crystallography or crystal chemistry. Because the numbers of mineralogical crystallographers are smaller than the numbers of chemists or materials scientists, there has not been a great disparity between job openings and the number of Ph.D.'s in the field in recent years. U.S. citizens with good academic records have largely been able to find positions with duties related to their interests. Against an estimate of 20-30 Ph.D. graduates each year with some interest in mineralogical crystallography, there appear to be about 5 academic openings. The number of postdoctoral positions is difficult to determine but is probably somewhat greater. Industrial and government openings account for several more, and the remaining graduates are employed in another field or another country.

Funding

Only rough estimates of NSF support of crystallographic research in the earth sciences are available at this time; these amount to about $500,000 annually. A survey of papers published in the *American Mineralogist* in 1974 gives some indications of sources of support in this field; of 110 papers by American authors (out of a total of 154), 54 acknowledged NSF support; NASA was credited in 14, the Geological Survey in 9, and other sources in 19, while 22 did not mention any special support. Thus it appears that NSF supports about 50% of published mineralogical research, with additional support from the host institution. Our estimate of annual expenditures in this area are somewhat in excess of $1 million.

Over the years, mineralogical studies, which often inherently involve some aspect of crystallography and crystal structure, have received significant support from governmental agencies. This support has been more generous in areas that are clearly related in some way to a great national endeavor as in the search for uranium, in connection with the lunar program, and now more than ever in the press for sources of energy. Although the NSF traditionally has avoided tying grant justification to a particular mission, nowadays, the increased pressures for mission orientation and specific problem solving that seem to be generally prevalent are unmistakably felt also in the area of earth sciences.

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6
MATERIALS RESEARCH

Introduction

Rudimentary materials research and engineering has been practiced throughout the history of man, as evidenced by the names used for such major periods as the Stone Age, the Bronze Age, and the Iron Age. Until recently, the field consisted of several separate areas, primarily metallurgy, ceramics, polymers, and chemical and solid-state physics. These different areas were each concerned with the relation of structure and properties of both new and old materials. By the early 1950's, it became apparent that there was much in common within these areas, and a new interdisciplinary field arose that encompassed them all known as materials science and engineering. At a time when many processes and problems are limited by the availability of materials, opportunities for the contribution of materials research to matters of national importance have sharply increased.

Crystallography has had two major influences on materials research. It opened a new approach to the study of structure at the level of atomic arrangement and, as an interdisciplinary field itself, led to an improved appreciation of the underlying principles common to all materials research for the specialists in the previously separate areas of the field.

Crystallography will continue to have a central role in advancing the basic understanding of materials by virtue of its ability to ascertain the static and dynamic arrangement of atoms in matter and to relate that arrangement to the physical, chemical, and mechanical properties of matter.

Prior Contributions of Crystallography to Materials Research

There are few activities in materials research that have not been advanced by the science of crystallography. For example, the early discovery of more than one crystal structure of iron helped immensely in understanding the strengthening of steel. Contributions to the understanding and improvement of the properties of steels continued throughout this century, as more was learned about the various carbides and nitrides that form during heat treatment. The fundamental basis of modern metallurgy, indeed, rests upon numerous crystallographic studies of alloy systems. The atomic arrangement, strain, and defect distribution in well-characterized alloys can be directly related to their mechanical properties. Studies of preferred orientation, following recrystallization and other treatments have proved most important in improving the magnetic properties of transformer cores and the formability of sheet steels; similar studies show promise in the control of the elastic stiffness and mechanical strength of structural members. Crystallographic research on deformation, a fundamental materials process, showed that this effect is confined to specific planes, thus permitting improved control. The elucidation of metallurgical precipitation reactions, of considerable practical importance, and of metal fatigue under cyclic loading owes much to crystallographic studies. Powerful new nondestructive crystallographic tools for product control have been developed, including fluorescence analysis, measurement of residual stress, the file of standard powder diffraction patterns for reliable identification, and rapid methods for the orientation of large single crystals.

A detailed understanding of the cooperative properties of ferromagnetism and ferrimagnetism, ferroelectricity, and ferroelasticity has been achieved as the result of x-ray and neutron crystallographic investigations. Magnetic spin-array ordering and orientation have been directly determined in many materials. The atomic displacements required in reversing the spontaneous polarization in ferroelectrics and in reorienting the spontaneous strain in ferroelastics have been measured in a large number of crystals; a variety of possible device applications that make use of these properties are currently being investigated. A new technology based on magnetic "bubbles" in garnets and related materials owes much to previously acquired structural knowledge.

Crystal chemistry has often served as the most important guide in searching for new materials with certain desired properties. This is especially true in the field of high-pressure synthesis, where numerous new substances have been made in fulfillment of crystal chemical expectations, e.g., dense forms of silica, new garnets and related mineral oxides, dense boron phosphate, and dense modifications of silicon and germanium. It is noteworthy, also, that crystal chemical considerations made it possible to recognize the desirability of producing cubic boron nitride, immediately after the successful synthesis of diamond. Many other examples of synthesis based on crystallographic considerations may be cited, including the zeolites, large numbers of catalysts, and many ethical drugs.

Further examples of the applications of crystallography to materials science include recent phase equilibria studies of nitrides and oxynitrides for turbine blades; the structural studies of β-alumina and other superionic materials for batteries; studies of rare-earth borides for thermionic emitters; cation ordering and magnetic structures of $SmCo_5$ and other new magnetic materials; the observation of Guinier-Preston zones and other precipitates used in hardening metals; and the nature of the interface between ceramic prosthetic devices and human bone and body fluids.

Among the numerous needs of present-day society for materials research, several of high priority have been identified in the recent COSMAT report (1). A brief discussion follows of those research problems to which important crystallographic contributions are expected.

High-priority Applied Crystallographic Materials Research

An improved understanding of corrosion should result from a combination of reflection high-energy electron diffraction (RHEED), transmission electron diffraction (TED), and transmission electron microscopy (TEM) studies of surfaces at which corrosion has taken place. The role of protective coatings may be studied by examination of interdiffusion and intermetallic phase formation while it is occurring, using both RHEED and x-ray scattering techniques, followed by subsequent determination of the microstructure of the bulk, the interface, and the surface by TEM. Biomaterials are already extensively investigated by crystallographic methods (see Chapter 2). TEM studies of biomaterial surface architecture, and x-ray diffraction and RHEED studies of the interface between metals and polymers and between hydroxyapatite and collagen, for example, provide important information. Fracture mechanisms and defects can be fundamentally investigated by evaluation of the lattice vibrations in the distorted or defect structure in relation to the breaking strengths of crystalline materials: selected area and anomalous x-ray topography allows a direct survey of defect distributions and, in combination with x-ray line profile analysis and other crystallographic techniques, should be used under the dynamic conditions leading to fracture.

Crystallographic contributions to the field of superconductivity would be particularly valuable if the lattice constants, the atomic arrangements, and the phonon spectra could be measured over the superconducting phase change: single crystals are necessary for both elastic and diffuse x-ray and neutron scattering studies. As the search for new superconductors broadens into ternary and more complex systems, even closer cooperation will become necessary between crystallographers and alloy development specialists. Composites and concretes have been periodically studied crystallographically, but a fresh examination of the separate phases in concrete, especially their interfaces, would be valuable. Superalloys, intended for service above 500°C, are often designed on the basis of elementary concepts of the influence of electron-to-atom ratios on phase stability: protective surface-film behavior at elevated temperatures is of great importance and should be investigated both by electron diffraction and electron microscopy methods.

Ceramics and glasses with promising high-temperature properties, such as solid solutions of nitrides and oxides of silicon or aluminum, need better structural characterization. Possible correlations between ionic defects (defect-clusters) and properties should be crystallographically studied. Recent investigations of KAl and NaAl silicate glasses have shown that they are essentially isostructural to SiO_2 glass and that all these glasses possess more structural order than had been previously reported. Structural order has also been found in a number of other glassy materials. The new insights into glass structure have important implications for glass research and technology and also for geology and mineralogy.

The most pressing needs in new polymer production are solutions of technological problems, but continuing structure-property investigations are essential if real understanding is to be achieved. The complexity of polymer systems arises from their composite amorphous and crystalline nature and deserves serious attention by crystallographers interested in topological problems. Metal processing techniques may generally be improved following preferred orientation studies: new techniques such as splat cooling produce new metastable phases, often with unusual properties, which are best characterized by means of x-ray diffraction studies.

Considerable advances are now being made in understanding the nature of plastics processing through the application of crystallography. Investigation requires x-ray diffraction, scanning and transmission electron microscopy, and several noncrystallographic techniques simultaneously and has led, for example, to improved models for the mechanical properties of spun fibers under various processing conditions. The final COSMAT high-priority area, testing characterization and evaluation, is one in which x-ray diffraction has been and will continue to be among the more useful means of nondestructive characterization for all kinds of materials.

Two other major problem areas may be suggested that qualify as of high priority. In catalysis, much research is already under way to provide a more fundamental understanding. A worthwhile crystallographic approach is represented by studies of zeolites, for which it is possible to characterize in detail the active surface, the sites of molecular attachment, and the structural changes resulting from adsorption. Similar studies on other model systems would be rewarding. In the field of lubrication, knowledge of the structures of numerous materials that exhibit strong binding in two dimensions, but weak binding in the third may be of assistance in the selection of solid-state lubricants. Crystallographic study of the products of wear, and the characterization of wear surfaces, should also be undertaken.

It should be noted that the COSMAT high-priority material areas often involve polycrystals and polycrystalline aggregates, many of which are clearly composites, twins, and domains of various kinds, and which are threaded by dislocations. The periodicities, in one or more dimensions, in imperfect crystals are crystallographic features that influence crystal growth, phase transformations, processing, and many of the physical properties. It is difficult to see how the properties of such crystals can be studied without the application of crystallographic concepts and methods.

Crystallographic Materials Research Frontiers on Fundamental Properties

Several major areas, some of which have been discussed in the COSMAT report, are either now becoming active or else appear on the verge of opening up and are ready for new thought and techniques. These are now considered.

(a) *Interatomic forces, chemical bonding, lattice stability:* These topics represent the most fundamental of scientific problems-- understanding the stability of different substances from first principles. The importance of crystallography in this respect is self-evident (2), but a special feature of crystal structure that should become more developed in the future is the accurate investigation of the electron density directly associated with chemical bonding.

(b) *Phase transitions:* Complete structural studies at several temperatures, pressures, or both, on either side of the phase change are necessary for full understanding of the nature of the transition. This has been done in the case of the α-β transformation in quartz and in the ferroelectric-paraelectric transition in lithium tantalate. Diffuse-scattering x-ray and neutron studies on either side of phase changes should be made to determine if phonon condensation takes place and the nature of the interaction driving the transition.

(c) *Structure of liquids and amorphous solids:* Small-angle x-ray and neutron scattering techniques are becoming increasingly powerful, using new radiation sources and new detectors, in studying liquid structure. The extended x-ray absorption fine structure (EXAFS) technique appears of considerable potential importance in amorphous solid structure studies, because it may remove ambiguities in the determination of atomic arrangement by giving information about the average coordination of individual atomic species (3). Electron microscopy also shows considerable promise in further application to amorphous solids.

(d) *Surfaces:* In addition to low-energy electron diffraction techniques, the combination of *in situ* ultra-high-vacuum RHEED and subsequent TEM offers an extremely useful approach to the study of many surface or interfacial phenomena.

(e) *One- and Two-dimensional Systems:* The recent preparation of substances that exhibit extreme anisotropies in their properties (magnetic, electrical, or superconductive) has kindled considerable theoretical and experimental interest in one- and two-dimensional systems. The remarkable finding of high metallic conductivity in crystals containing only organic molecules has raised the possibility of high-temperature Fröhlich superconductivity in such materials. Equally important is the opportunity to explore more fully the physics of less than three dimensions. Already there are indications that the effects of lower dimensionality, particularly on collective modes, are different than believed previously. The lower dimensional physics may have important consequences to catalysis. For new areas such as this, crystallography is important in several ways. First, the understanding of anisotropic physical properties is hardly possible without a detailed knowledge of the crystal structure, including possible disorder and defect distribution. There are also special effects, such as the Peierl's distortion for one-dimensional systems, which can be ascertained from diffuse scattering studies or from neutron inelastic scattering investigations. Crystallography is expected to be of foremost importance in the elucidation of lower dimensionality effects.

(f) *Physical Properties of Polymeric Materials:* The determination of the fundamental properties of polymeric molecules from first principles requires a much better structural description than is now available. Such studies offer a major challenge to crystallographers, for example, by use of the heavy-atom substitution method in various locations in the chain.

(g) *Nonequilibrium Systems:* There already have been studies of materials under severe shock, using x-ray diffraction, with a time resolution of 10^{-9} second. This activity is in its infancy, and further studies should be fruitful in advancing our knowledge of nonequilibrium systems. Characterization of intermediate metastable structures (Guiner-Preston zones, preprecipitates, etc.) should also be made in these systems.

(h) *Dynamical Theory:* X-ray topographic studies of defects have become an important tool in research and production in the semiconductor field. The understanding and extension of this method and, more importantly, the proper understanding of transmission electron microscope images awaits new developments in dynamical theory.

Crystallographic Manpower in Materials Science

Some form of crystallography and diffraction is taught in every one of the 57 materials science departments in the United States. For the most part, the coursework is limited in scope, both in terms of the many aspects of crystallography that are available to the materials scientist or engineer and in terms of a solid conceptual foundation. It is estimated that reasonably complete coverage is given at no more than a dozen schools. There has been a considerable decline in the breadth of crystallography taught, in favor of specialization in the use of the electron microscope, and even in this field education tends to be superficial with more emphasis on skills and less on fundamentals.

However, at those schools where breadth and depth in crystallography are considered important for materials science, the science is well covered. In fact, it appears that these materials science departments are providing a solid interdisciplinary education in crystallography and may well become a natural home for a broad range of crystallographic fields. The present trend away from a thorough and fundamental approach is however proceeding much too quickly and should be reversed, for crystallography is still very much needed in every aspect of materials research work.

It is difficult to estimate the manpower in crystallography in materials science since it is so much a part of the total effort both in engineering and in research. It is fair to say that every professional materials scientist/engineer at one point or another in his career applies crystallographic tools or concepts.

References

1. *Materials and Man's Need*, Summary Report of the Committee on the Survey of Materials Science and Engineering (COSMAT), National Academy of Sciences, Washington, D. C. (1974).

2. cf. International Union of Crystallography Inter-Congress Symposium "Intra- and Inter-Molecular Forces," *Am. Crystallogr. Assoc. Program and Abstracts* 2, 150-202 (1974).

3. cf. ACA Symposium on Liquids and Amorphous Materials, *Trans. Am. Crystallogr. Assoc.*, Vol. 10, 45 (1974).

7

CONCLUSIONS AND RECOMMENDATIONS

It is apparent from the foregoing discussions that there are many important crystallographic investigations at the forefront of a considerable variety of scientific disciplines. Therefore, support for sound crystallographic programs provides broad and effective support for science in general. Knowledge of atomic arrangements, molecular packing, electron distributions, and various other structural features form a major source for mechanistic insights, theoretical calculations, and the conceptual contexts in which scientific disciplines are viewed and developed.

In the past decade, the improvements in structure analysis have been extensive and rewarding. The result of this has been the stimulation of research programs directed toward broader horizons. As is generally the case for advances in science, this circumstance should continue to prevail with the further improvement in analytical techniques.

Although the atomic arrangements for most crystals of moderate complexity can be fairly readily determined, a number of them, particularly noncentrosymmetric ones composed solely of atoms having approximately equal atomic numbers--except perhaps for hydrogen--often do not yield readily and require the perseverance and insight of an experienced analyst. If the samples are not good single crystals, they may give confusing or limited data and would be completely inaccessible to routine analysis. In many instances, the crystals associated with problems of considerable importance are of this type, and such problems can be attacked only by the well-trained scientist.

Proposals in crystallographic subjects are handled by various groups at the National Science Foundation (NSF), e.g., Chemistry, Materials Science, and Molecular Biology. It is recommended that the Foundation maintain an appropriate mechanism for consideration of proposals in an interdisciplinary subject such as crystallography. It should be noted that crystallographers working with biological macromolecules generally believe that their grant applications are handled quite satisfactorily by the NSF and do not recommend that changes be made with respect to their area.

Despite the fact that crystallography is a broad scientific discipline in its own right, it has almost always found a home in U.S. universities in established departments such as chemistry, biology, physics, and the newer materials science. Education in crystallography can benefit considerably from an interdisciplinary program encompassing these various areas. This would be a good topic for a future in-depth review and report. It is generally believed by this committee that a three-year option on postdoctoral traineeships would be beneficial. This would afford a much better opportunity for the awardee to enhance his training and make a significant contribution to his science.

In another aspect of support, the proposals of the younger people in the field must compete, with some disadvantages, with those of older established people. It is recommended that special consideration of this problem be introduced into the support philosophy; the one-year initiation grants are a helpful step in this direction.

The science of crystallography is intimately dependent on developments in the field of data processing and computing. This derives from the fact that workers in crystallography are among the major users of computers, and many of their important problems involve computational demands that currently far transcend the state of the art. Therefore, the advent of new developments in computer technology and the current planning for the establishment of a National Resource for Computation in Chemistry are subjects of vital interest to workers in this field. Because of the significance of computing in general, and the possible impact of these developments in particular, a review of the subject of crystallographic computing one or two years hence would be worthwhile and is, therefore, recommended.

A special point was made in Chapter 4 on Diffraction Physics concerning the need to look beyond immediate application toward the development of instrumentation for tomorrow's science. Areas where research in the United States was not receiving sufficient encouragement and support were listed. Some examples are high-power x-ray sources and area detectors, where many of the earlier advances originated in Europe. This subject, along with education and computing, could benefit from a detailed review.

Postdoctoral jobs appear to be available, but permanent positions within the field of crystallography are currently difficult to obtain. However, there are a number of institutions that offer a broad training in crystallography that makes persons so trained prime candidates for positions in other areas. These areas concern the many fields of science, such as computer science, which are closely related to crystallography and for which permanent positions may be more readily available. Thus, the broad training that is afforded produces scientists who are not restricted solely to working in the field of crystallography.

In terms of the many challenging opportunities for new and powerful applications of crystallographic and other diffraction methods and the need for profound and sophisticated research into the extension of existing theory and methodology, the training of manpower continues to constitute an important need. Stronger emphasis should be placed on developing innovators rather than followers of existing techniques. The current shortage of permanent jobs for crystallographers in no way negates the need for persons trained to advance the state of the science.

Since crystallography is a dynamic field whose progress is intimately related to that of many other scientific fields, an incisive evaluation of its status affords not only an insight into the viability of crystallographic programs but also that of a number of associated programs in many other disciplines.

The conference that led to this report has been stimulating and rewarding for those who took part, and similar reviews of the status of crystallography, perhaps at intervals of about five years, would be worthwhile.

Appendix A

Categories of Papers for the Tenth Assembly of the International Union of Crystallography
Amsterdam, August 1975

1. Symmetry
2. Methods of structure determination
3. Biologically important substances
4. Structures of inorganic compounds and minerals
5. Metals and alloys
6. Organic compounds
7. Organometallic and coordination compounds
8. Magnetic structures
9. Structure of amorphous and partially amorphous matter
10. Intra- and intermolecular interactions
11. Lattice dynamics of non-molecular crystals
12. Phase transitions
13. Powder diffraction
14. Physical properties of molecular crystals
15. Macroscopic description of physical properties of crystals

16. Crystal growth and morphology
17. Accurate studies of electron density distribution and atomic parameter
18. Apparatus for diffraction studies
19. Diffraction theory and related experiments
20. Crystal defects
21. Gas electron diffraction
22. Studies of crystal structures by methods other than diffraction
23. Crystallographic computer applications
24. Education and information in crystallography
25. Other topics
26. Twinning and polytypes
27. Textures
28. Chemical and physical aspects of neutron diffraction

There are several topics that come under almost all of the categories. For example, under Item 25, "Other topics," there are listed crystallographic aspects of solid state reactions, structure of surfaces (LEED and RHEED), electron microscopy of macromolecules and 3-D reconstruction of objects, and direct imaging by electron microscopy of atomic arrangements.

Appendix B

QUESTIONNAIRE ON CHEMICAL CRYSTALLOGRAPHY

For a number of years, the question "What is the Future of Crystallography" has been discussed both privately among our colleagues and more formally at various meetings. A committee, organized by the USA National Committee for Crystallography has been selected and, under the sponsorship of the National Science Foundation, will meet near Washington, D.C. on February 10 and 11, 1975 under the chairmanship of Dr. J. Karle to discuss this question.

A special task group for chemical crystallography, consisting of Helen M. Berman, F. Albert Cotton, Keith O. Hodgson, George A. Jeffrey, Richard E. Marsh, and Iain C. Paul has been formed, and this group would greatly appreciate your response to this questionnaire. Some of the questions are searching, some are blunt. The group believes that the answers to these questions can be meaningful. Reassurance should also be given that the individual responses to the questionnaires shall be kept confidential and "not used against you" in any funding decisions or the like. However, it is possible and indeed desirable that the general conclusions from the entire questionnaire responses could be distributed publicly in some fashion. An attempt has been made to select from the ACA membership list those people that can be identified as chemical crystallographers and as group (however that may be defined!) leaders. However, the questionnaire should not be thought of as confidential and you should feel free to discuss it with your colleagues. The questionnaire can be returned with the sender identified or if preferred, anonymously. Detailed answers or comments on the questions are welcome.

Finally, if people wish to address themselves to the general concern of the future of crystallography or to any particular aspect of chemical crystallography, whether touched upon in the questionnaire or not--the task group would be very happy to receive a letter from them. The questionnaire and any letters should be returned, not later than January 15, 1975, to Dr. I. C. Paul, Noyes Chemical Laboratory, University of Illinois, Urbana, Illinois 61801.

Questionnaire on Chemical Crystallography

PLEASE RETURN BY JANUARY 15, 1975 TO
Dr. I. C. Paul, Noyes Chemical Laboratory
University of Illinois, Urbana, Illinois 61801

Name (Optional)

Address (Optional)

1. Are you in a
   (i) University
   (ii) Research Institute or Foundation
   (iii) Industrial Lab
   (iv) Other

2. Are you
   (i) in charge of a group
   (ii) a member of a group, but not in charge
   (iii) work alone

   If (i) or (ii) -- how large is the group?

3. If you are in charge of a group or if you work alone, do you have any direct federal government support, or state government support?

   If so, from what agency?

   Would you give the title of your project?

In many of the following questions there may be significant differences between responses you would give as an individual and those you would give for your group. In such cases, both responses would be welcomed.

4. What percentage of your research would you classify as

   a) Crystallography
   b) Physics
   c) Chemistry

d) Biology
e) Materials Science
f) Other (please describe)

5. If you do crystal structures:

(i) Do you or does your group work mainly on molecules of molecular weight greater than, or less than 5,000?
(ii) How many structures do you (or does your group) determine per year?
(iii) How many of these are:
    a) Organic but not "biological"
    b) Inorganic, but not "biological"
    c) Small molecules, biological
    d) Mineralogical
    e) Other
(iv) How are your structures related to each other? Alternatively, what chemical, physical, biological or mineralogical problem (or problems) are you studying?
(v) Is some, and if so, how much, of your time, or that of your group, devoted to service crystallography for colleagues?
(vi) a) How many structures did your group determine in the period 1972-73?
    b) How many of these are now published, at least partially, in refereed journals? (Consider Cryst. Struct. Comm. as a refereed journal, ACA Abstracts as not.)
    c) How many of these are published in full (i.e., with coordinates in print, and no further publication planned).
    d) Do you have any suggestions for change in publication of crystallographic results? What are they?
(vii) Of the total number of structures that you have wanted to investigate during the past few years, what percentage did you abandon?

What were the reasons for abandoning them (give percentages)?
    a) Inability to obtain satisfactory crystals
    b) Loss or decay of crystals (or crystal!)
    c) Disorder or twinning
    d) Instrumental failure
    e) Inconvenient space group
    f) Too many molecules per asymmetric unit
    g) Inability to solve structure
    h) Loss of interest
    i) Lack of computing funds
    j) Insufficient time or personnel
    k) Other (please specify)

6. What percentage of your effort (if there is a clear distinction between that of yourself and your group, please specify) is devoted to methods development?

7. What percentage of your effort (if there is a clear distinction between that of yourself and of your group, please specify) is devoted to computer programming?

8. Would you describe your research effort as that of a (combinations, percentage-wise, are welcome)
   a) Chemist
   b) Chemical crystallographer
   c) Data analyst
   d) Computer programmer
   e) Crystallographic methodologist
   f) Other

9. a) How many scientific meetings do you attend per year? Of which societies (optional)?
   b) How many ACA meetings a year (on an average over the last 5 years) do you attend?
   c) Are you satisfied with the ACA meetings as a format for chemical crystallography?
   d) Could ACA meetings be improved?
   h) How?

10. How many and which journals do you
   a) Publish in
   b) Refer to most commonly in your papers
   c) Buy
   d) Consult and read regularly (twice a week)
   e) Consult and read occasionally (more than once every 2 months)

11. a) How much money does your group spend annually in computing?

   b) How much internal "funny" money (i.e., paper money which is transferred within the institution)?

   c) How much real, outside money (i.e., from outside grants)?

12. a) How do you carry out your computing tasks? (If distinction between data processing, structure solution, refinement, structure illustration, please specify)
      (i) Small, dedicated computer? Type, memory size?
      (ii) Large institutional computer - batch processing? Type?
      (iii) Remote terminal?
      (iv) Other?
   b) Are you satisfied with your present system? If not, what is your biggest gripe?

13. a) Are you aware of the proposals to organize a National Resource for Computation in Chemistry?

   b) Should crystallography be a part of this?

c) Are you in favor of one central site, or several regional sites?

14. a) What type of instrumentation is principally used to collect data in your laboratory?
    (i) Computer - controlled diffractometer
    (ii) Computer - controlled densitometer
    (iii) Automated, but not computer controlled, diffractometer
    (iv) Film methods

    b) Do you anticipate requesting substantial money, <u>i.e.</u>, greater than $40,000, from federal government agencies for new instruments in the next two years?

    Would you give details? (<u>e.g</u>. Is the new equipment to handle increased need for structure determinations, and therefore will be used in addition to your present equipment, or is it to replace "wornout" equipment, or is it to upgrade your facilities from, <u>e.g</u>. card-control to computer control?)

15. Are you satisfied with the "scientific visibility" of crystallographers and crystallography?

    Is it a) Too great?
    b) Just right?
    c) Too little?

    If (a) or (c), do you have any suggestions for change?

16. Do you believe structures can or should be done commercially?

17. The personal $64,000 question:

    Do you ask the question and then grow the crystal or vice-versa -- honestly, now?

Synopsis of Responses to the Questionnaire on Chemical Crystallography

I. People Working at Universities (74)

A. Funding Patterns

59 respondees were funded. Most crystallographers surveyed were studying inorganic structures funded by the NSF or bio-organic structures funded by the NIH.

		# of grants	
Research Program	NSF	NIH	Other
Inorganic structures	20	8	6
Organic structures	6	2	1
Bio-organic structures	9	17	2
Methods development	2	0	2

20 people had applied for funding of major equipment.

There were 15 unfunded respondees, 8 of whom work alone. They mostly work on inorganic coordination complexes and organometallic structures. Five claimed that there was no relationship among the structures they studied. Two did methods research.

B. Service Work

21 respondees do no service crystallography, 6 spend 0-10% of their time doing service, 40 spend 10-25%, and 5 spend more than 25%. There was no response from the rest.

C. Attitude toward commercial crystallography

Most said they were basically in favor. Six were absolutely opposed.

Among the reservations expressed were:

How would results get published?
How would one be assured of quality and how would the company deal with special problems?
Who pays the bills and how?

D. Publication

Respondees publish in a wide variety of journals. Fourteen of those who do mostly inorganic crystallography do not publish in Acta Crystallographica, whereas only 7 of those who study organic and bio-organic compounds did not publish there.

E. NRCC

Of all the respondees, 58 were aware of the proposals for the National Resource of Computation in Chemistry. Six felt that crystallography should not be a part of it. Most were in favor of regional sites.

II. People Working in Government Labs (8)

Average size of group was five.

A. Area of research

Most were studying bio-organic molecules.
Most spend about 20% of their time on methods research.

B. Service

4 - 10%
1 - 20%
3 - 50%

C. None were opposed to a commercial crystallography center but reservations were expressed similar to those made by the university people.

D. Publication

Again, these respondees publish in many journals. However, no one said that he or she does not publish in Acta Crystallographica.

E. NRCC

All were well aware of the proposals. One was opposed, 3 favored regional sites, and one favored a central site.

III. People Working in Research Institutes (5)

Average size of group - 8.
Only one claimed to do 0 - 10% service. The rest did none.
4 were studying bio-organic molecules and all have government grants.
All publish in <u>Acta Crystallographica</u>.
One was opposed to NRCC; two were unaware of the proposals.
One was opposed to a commercial outlet doing crystal structures.

IV. People Working in Industry (5)

Average size of group - 2.
All did more than 30% service.
3 did inorganic/organic structures.
All were aware of the proposed NRCC. Three were in favor of them but in general uncertain as to what role crystallographers should play.

Appendix C

QUESTIONNAIRE ON TEACHING OF CRYSTALLOGRAPHY

A committee, organized under the auspices of the USA National Committee for Crystallography and sponsored by the National Science Foundation has been formed under the Chairmanship of Dr. J. Karle to address the question "What is the future of Crystallography?". We would like to ask that you complete this brief questionnaire in order that we might better survey the area of Teaching Crystallography.

Please feel free to add any comments on this questionnaire or any other aspects of education in crystallography. The questionnaire should be sent to:

Dr. Keith O. Hodgson
Department of Chemistry
Stanford University
Stanford, California 94305

1. Teaching of crystallography and structural determination at an undergraduate level.
   a) Please circle all responses that apply for each of the following undergraduate courses in your department.

Course	level of crystallography taught			
	none at all	a few results	symmetry and group theory	diffraction theory
elementary chemistry				
organic				
physical				
inorganic (junior/senior level)				
analytical				
biochemistry				

   b) Do you offer any labs where students use some method of x-ray difraction?

No_____Yes_____; which lab?______________________

do they use: Powder methods _____
Single crystal camera work _______

2. Teaching on a Graduate Level.

   a) Do you offer a graduate level course on crystallography or methods for structure determination?

No_____Yes_____

If so, is it:

Techniques oriented course_____
Methodology and principles oriented course_____
Other (specify) ________________________

   b) How often is such a course given and what is the average enrollment?

About how large is your graduate student body in chemistry?

c) Is there a lab taught either in conjunction with the above course or separate where students actually participate in the structure determination?

If so, do the students actually collect data and solve structures?

d) Do you feel there is a text which adequately covers most of the areas you teach from a modern viewpoint?
Please specify title: ______________________________

e) Have you made use of computer graphics and data tables to summarize results, show packing, etc.?

f) Any other suggestions or comments?

Thank You!

Name: ______________________________
Institution: ______________________________

Analysis of the Responses to the Questionnaire on Teaching of Crystallography

In an attempt to probe the level of teaching of the discipline of crystallography in chemistry departments, a survey was prepared and sent to the 38 highest ranked graduate schools in chemistry in the Roose-Anderson report. Twenty responses were received, and these form the basis for the statistical information used in this appendix. The results are broken down into education on the undergraduate and graduate levels as taught in chemistry departments. Comments on crystallographic education in other departments may be found in other sections of this report (e.g., earth sciences, materials research).

Undergraduate

Virtually no institutions teach crystallography strictly on an undergraduate level. Most of the major chemistry departments use only final structural results in introductory courses in general chemistry and there was little evidence that such information was widely used in courses in organic chemistry. In almost no case was there evidence that any information was given to students about how to evaluate the reliability of these results. A surprisingly large number of responses indicated that no crystallography (results or otherwise) was taught in the biochemistry courses. In the upper division physical chemistry and analytical chemistry course, there appears to be more description of diffraction of crystals. Over half (14) of the schools indicated that a powder diffraction experiment was done in conjunction with the physical chemistry laboratory, while only three schools indicated that single crystal (camera) facilities were available for use in course at the undergraduate level. A number of institutions appear to deal with some aspects of symmetry (including crystallographic symmetry) in advanced inorganic chemistry courses.

It seems apparent that the major use of crystallography in most undergraduate chemistry curricula is simply the dissemination of certain crystallographic results. There seems to exist a need for more meaningful and visual methods of conveniently studying and displaying crystallographic results for large numbers of students. As an example, graphical display of enzyme-substrate complexes would be extremely useful in teaching such concepts at an undergraduate level. The best method for actually teaching crystallographic concepts to upper division undergraduates appears to be in conjunction with the type of graduate course described in the next section.

Graduate

All but one of the chemistry departments that responded indicated that a course was offered on some aspects of crystallography at the graduate level. Emphasis seems to fall either on a purely principles and results course, or on a course in which principles are actually combined with practical work. In several cases such courses were given in conjunction with earth or materials science departments. Almost all departments (2 exceptions) used the text by Stout and Jensen, although most people indicated the need for another text (Woolfson was most frequently mentioned) for more theoretical discussion.

Approximately 50% of the courses offered did not make available a laboratory for actual structural work. In general, this type of course appears to emphasize theory and methodology with some presentation of crystallographic results. Such courses should serve the useful purpose of making students aware of the potential as well as some of the pitfalls of crystallographic studies and provide some insight to their evaluation of a structure report.

The second type of course is more comprehensive and is designed to provide both theory and practice in structure determination; such a course is offered by seven of the responding institutions. Students are given the opportunity to collect data and solve new structures although the theoretical content is somewhat limited. While the students gain considerably more practical experience, there appears to be a trend towards the "black-box" concept. Students when faced with unusual cells, transformations, disordered problems, etc. are often lacking sufficient knowledge to interpret or even recognize the problem. Perhaps the best approach is to attempt to give students the knowledge to recognize when problems exist so that in these instances they may seek the advice of a more competent crystallographer.

The alternative to training students in a formal practical course is to have them interact on an individual basis with a faculty member doing research in crystallography or, if available, the department's service crystallographic operation. Such an arrangement has the advantage that the student is generally working on a problem more directly related to his own research interests.

In conclusion, it appears that most major universities, although almost none offer a degree in crystallography *per se*, teach some form of crystallographic course on a graduate level. However, the scope of these courses is not such that they can provide all the background needed in the areas of diffraction physics, computer science, linear algebra, etc. It is felt that more emphasis could probably be placed on teaching chemistry students how to evaluate crystallographic data in the light of the non-routine problems which are sometimes encountered.

More extensive use of computer graphics and structural information retrieval systems would help chemists utilize more readily and significantly the vast amount of available crystallographic information.

Appendix D
Synopsis of Computing in Crystallography

(Prepared by Helen M. Berman and Keith O. Hodgson)

The science of crystal structure determinations depends heavily on various aspects of computing. The crystallographer's need for computing may be roughly broken down into three tasks:

I Data Collection
II Structure Determination
III Structural Comparisons and Information Retrieval

Task I: Data Collection

It is now routine to use a minicomputer (usually a DEC PDP 8 or Data General Nova 1200 having 4-8 K of core) to control the four-circle diffractometer. Using machine language routines, data are usually put out onto magnetic tape but cards or paper tape are other alternatives. Such a system is clearly necessary for smooth and rapid acquisition of precise data in a laboratory where structure determination is the primary objective.

Recently two manufacturers (Enraf Nonius and Syntex) have marketed diffractometer systems in the USA that operate under FORTRAN IV language routines. Typically, these systems require about 16-24 K of core, a magnetic tape, a 1.2-million-word disk drive, and some I/O device (total cost of about $85,000). The crystallographer thus has considerable flexibilty in program modification, and program development is greatly facilitated. With the addition of floating point hardware, these systems can provide the capacity for doing actual data reduction and processing of the data as well as solving structures.

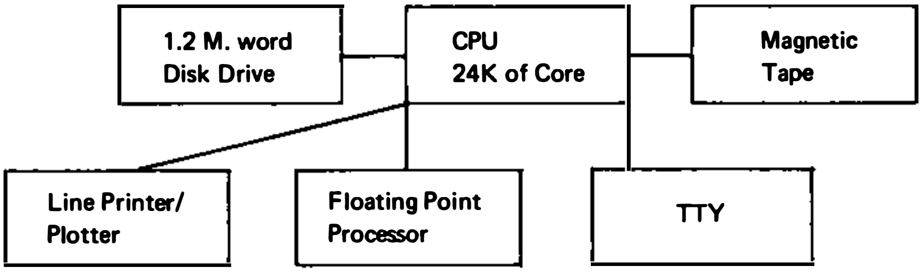
Another use of the small computer is to drive a film scanner (autodensitometer) for automated collection of data taken from film. A film can be raster-scanned and processed off line or actually scanned under dynamic computer control where the computer first generates the orientation information, indexes the reflections automatically, and then collects the data from the film. These interactive approaches have made the use of rotation films an especially attractive method of data collection for crystals with large unit cells.

TASK II: STRUCTURE DETERMINATION

A. Dedicated Small Computer Systems

Dedicated small computers clearly offer extensive possibilites for crystallographic calculations within the crystallographic laboratory. Impetus in this area has been headed by two companies (Enraf-Nonius and Syntex) who have developed and marked commercial packages for structure determination. Other users (such as the CRYSNET project[1]) have assembled programs specifically designed for small computing systems.

A typical small computer installation consists of:



Basic cost About $70,000

Additional options include: Second disk drive ($4000)
additional core ($2000 per 8K words)
card reader ($7000)

Maintenance on the basic system would run about $5000 per year.

These systems are mostly programmed on FORTRAN IV, with the exception of machine routines for Tape I/O, matrix inversion, etc.

Given unlimited time, these computing systems will handle problems in size considerably beyond most packages on large machines in common academic environments. This is simply because of the very efficient use of random access disk files. Full-matrix, least squares analysis on up to about 700 parameters, 200 atoms, and 32,000 reflections can be done. Typical execution time for one cycle of full-matrix, least squares refinement with 20 atoms handled anisotropically (191 varibles) and 3,000 observations vary between 50 and 60 minutes on the small computer assuming that floating point hardware is available. As a comparison with execution times on a typical larger machine, one cycle of full-matrix least squares refinement with 100 variables and 1000 observations takes about 15 minutes on a PDP 11-45 and 3-7 minutes on a CDC 6400.

Such a minicomputer can readily service a group of 6-10 people doing structural work. A larger group will tend to flood the I/O capability of such a small system. Considering only maintenance, expendable supplies,

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[1] H. J. Bernstein, et al., Second Annual AEC Scientific Exchange meeting, Proceedings of the Technical Program, New York, 1974, pp. 148-158.

and other miscellaneous costs it is estimated that an "average" structure (with 20 atoms, 3,000 refl.) costs less than $400 to solve and refine with anisotropic temperature factors.

Dedicated systems offer several practical advantages. Program modifications are easily done with disk file editing systems and there is no need to use continually thousands of cards. I/O and turnaround are extremely rapid in the early stages of structure solution (say 30 min. or so for a least squares-Fourier cycle in the early stages of using the heavy atom method). This contrasts sharply with the slow turn-around of many campus centers, where turnaround for such a job is generally an overnight proposition. The software that is supplied as a commercial product is generally well-supported, documented, and tested (usually using a standard IUC test structure). These packages are integrated in such a way that all the programs access common files, thus making running of the programs often a trivially easy question.

A small computing system is, however, inadequate in a large scale operation with 20 or more people. The slow turnabout time, being highly dependent on actual running time, becomes more troublesome in the final refinement stages. In addition, service problems are the responsibility of the crystallographic laboratory (rather than the University or other institution). Disc drives and magnetic tape units tend to create the most service problems. A valuable modification of this approach is to use the minicomputer at least in part as a remote terminal as described in Section C.

B. Batch Mode on Large Computers

This is the type of computing most crystallographers use, although not always by choice. The computers used for this purpose have a large range of core size and speed. Some university researchers have access to very fast and efficent computers such as the CDC 7600, others must make do with rather obsolete machines such as the IBM 7094. The large computer is generally housed in a separate computer center and operated by the personnel of that center. The programs used vary from very streamlined packages, such as XRAY '72, to individual stand-alone programs. Each university has a different accounting system for charging for this service, and, from the responses to the Questionnaire (Appendix B), it is very difficult to make judgements and assess the "real" cost of computing in this mode. The advantages of this type of computing are that maintenence of the computer is done by the personnel of the computer center, and often the charges involve internal "paper" money. The disavantages are that turnaround is often very slow because the computer is overloaded with student problems and many universities do not have computers designed for handling large scientific computations.

C. Remote Computing

This type of computing requires a very "large" computer at a central site, a terminal, a phone line or cable, and a modem. Jobs are submitted through a terminal and transmitted via the telephone to the central site.

Characteristics of the Central Site: The computer at the central site must have the hardware to accept the remote terminal input and software to decode it.

Characteristics of the Satellite Site: There must be an I/O device and a modem to modulate digital data to go over the analog telephone lines. Minimally, then, this can be achieved with a teletype or CRT - an unintelligent terminal. Intelligent terminals with varying capabilites for programming are also used. These have I/O devices such as card readers, magnetic tape read/write devices, and line printers. In this context, it should be pointed out that minicomputers can act as remote terminals. To achieve this, one must have the correct interface and a program to simulate a terminal. There are several such programs available. The costs involved in remote computing are: 1) the central site charges are highly variable as pointed out in the previous section, 2) a teletype with acoustic coupler costs anywhere from $2-5,000. A commercial intelligent remote terminal costs from $20,000 - $50,000. To adapt a minicomputer to do remote computing costs about $4,000, 3) the telephone charges are variable and depend on the location of the central site relative to the terminal. Typically it takes a user about 3 minutes to submit a job which may then be retrieved at some later time. Job retrieval time is, of course, dependent on the quantity of output; a typical structure factor listing takes about 10 minutes to retrieve.

The advantages of this type of computing are that the best computer available for a particular type of calculation can be accessed so as to achieve versatility and efficiency. In general the turnaround time is short. If the remote terminal utilized is a minicomputer, the machine is freed for smaller calculations, while the central site computer is utilized for "number crunchers." An additional expense is that of the telephone lines and calls. Another problem commonly faced by university researchers is that administrators of computer centers and universities are very reluctant to see business move away from the campus computing centers.

TASK III: STRUCTURAL COMPARISIONS AND INFORMATION RETRIEVAL

Computers have not been tapped to their fullest extent for these tasks. Data on relevant structures can be retrieved from a central file and various characteristics analyzed. For example, the Cambridge Data file has recently been adapted and categorized on the PDP-10 and sophisticated access programs have been written to retrieve important structural information. Similar efforts are being expended for the use of this file on the PDP-11. Moreover graphics displays allow ready visualization of structural features. These displays can also be interfaced to a minicomputer; programs are currently available to display and manipulate molecular structures. The cost of a graphics display varies from $10,000 to $40,000, depending on the level of sophistication. A simpler display, costing about $5,000, can be used to do graphics remotely from a large computer.

Appendix E

Drafts of the topical reports were mailed to many leading researchers. A number of the correspondents replied in detail. In all cases, the comments were seriously considered and, in general, were incorporated into the report. The present report has benefited considerably thereby. The participants at the meeting were joined by Dr. M. J. Buerger of the Massachusetts Institute of Technology and the University of Connecticut and Dr. Jenny P. Glusker of the Institute for Cancer Research, Philadelphia. Their contributions to the reports on Earth Sciences and Biological Macromolecules, respectively, are especially appreciated. We also appreciate the attendance at the meeting of Drs. O. William Adams, Abraham Clearfield and William T. Oosterhuis from the National Science Foundation. A list of correspondents for the individual topics follows:

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