

PREFACE

The Progress of Crystal Structure Analysis



1. Introduction

X-ray crystal structure analysis has become a very simple, short-time work of late. There is a marked difference today compared with the former days when I started on crystal analysis. The most important sectors of science in the 20th century are said to be quantum mechanics which has elucidated the energy state of molecule and X-ray analysis which has shed light upon the molecular structure. While the advance of quantum mechanics was conspicuous during the period from 1920s to 1930s, X-ray crystallography appears to have been flourishing in and after 1960s. It was in 1962 that Dr. Perutz and Dr. Kendrew won the Nobel prize in chemistry for protein crystal analysis and that Dr. Watson, Dr. Crick and Prof. Wilkins became Nobel prize winners in physiology and medical science for the DNA structure model. Likewise, it was in 1964 that Prof. Hodgkin was awarded a Nobel prize in chemistry for the structure analysis of physiological active molecules like vitamin B12. The 1960s was an age when X-ray analysis came into limelight following the pioneering achievements by Laue and Bragg.

2. Crystal Structure Analysis 35 Years Ago

It was in 1964 that I took the graduate course at the Institute for Solid State Physics, University of Tokyo and worked under the Supervisor, Prof. Yoshihiko Saito. I started on X-ray crystal structure analysis in his lab, and it is 35 years now since then. This institute was just set up at that time as the center of solid-state research to be utilized in common nationwide. Thus the institute was equipped with the newest facilities at the time. But the environment of X-ray crystal structure analysis was such that the Weissenberg camera played an important part to collect X-ray intensities. While this does not necessarily mean that Japan's crystal analysis was lagging behind, it appeared evident that there was no comparison with Cambridge University and Oxford University in England which produced many Nobelists as well as U.S. leading universities such as MIT and Harvard University. At the Saito lab, four Weissenberg cameras and one Precession camera were available almost at the rate of one camera for one student offering a very fortunate environment at least in Japan. Three-dimensional intensity data were collected with these cameras. About 50 hours of exposure was required in those days to get intensity data on one layer line. Night experiments were forbidden at that time and therefore about one week was needed for 50-hour exposure. Because of the presence of 6 to 7 layer lines even for a single axis, it took three months, or 100 days approximately to collect data on two axes even assuming that the experiment was conducted in a hurriest manner. Data measurement was followed by visual reading of the intensities of diffraction spots one by one that were recorded on film. This means reading of the degree of blackening (intensity) by comparing a reference spot that shows the standard blackening degree with each of the diffraction spots having the respective blackening degrees. For instance, the presence of 200 spots on one film could take a whole day to read them out. Needless to say, in view of saturation occurring quickly with a single film, exposure was made by laying plural films one upon another. Moreover, when considering the attenuation factor due to overlapping films, it was necessary to read the intensity difference in the ratio up to 1 : 5000 approximately. In short, this meant that it would take a half year to collect three-dimensional diffraction data.

There was a long way to go yet. Far more trouble was the need of calculation. Until the times slightly earlier than my days, calculations were conducted with either an abacus or a desk-top calculator with a manual-rotation handle to perform actual calculation mounted on its flank. For the value of trigonometric function this meant that we

should refer to a 7-figure logarithmic table available from MARUZEN bookstore in Tokyo. Calculations for Fourier series and those for structure factors were carried out in such a manner. As a matter of fact, several units of IBM computers were already imported to Japan for the use by big business enterprises, and they were available to us for operation if we so demanded. But the operation charge was exorbitant for university researchers to use them ordinarily. In the preceding year before I began studies at the Institute for Solid State Physics, a prototype computer, PC-2 was introduced to the institute from Fujitsu, Ltd. at long last. Huge electronic tubes like monstrous vacuum tubes called parametron were built in that computer. Nevertheless it was the newest powerful computer at the time and could not be found anywhere else except the Faculty of Science, the University of Tokyo and Toyota Motor Co., Ltd. Even so, the memory equipped to the computer was merely 8K, a capacity less than what is incorporated in current calculators. It was therefore a difficult task for such a memory to store a large quantity of values related to the system, computing programs, intensity data and so on. The language used was a machine language and individual operators' association with the computer began with the entries of most efficient programs possible by each of them. Also troublesome was the time of using the computer. The operation time available to all researchers at the institute was limited to 10.00 a.m. to 5.00 p.m. on Monday, Wednesday and Friday each week. Assuming that about 100 students and staff members at the institute would also join in the operation, then just 10 minutes would be available on the average for each individual per week. How much computation could be made in 10 minutes? What could be covered was roughly to the extent of calculating about one hundred values of the two-dimensional electronic density by use of 200 structure factors. That is, about two weeks would have passed during the course of calculating structure factors from a model structure and then calculating two-dimensional electronic densities based on that phase. At that time the direct method was not usable yet. The available method, called trial and error method, was to estimate the model structure by any means and to check the result for correctness by calculating the electronic density. Unless the unknown atomic position came out at the calculated electronic density, the same work had to be repeated over again. Under the circumstances that it took two weeks even by using simple two-dimensional data, it was no wonder and quite normal that the collection of diffraction intensity data was all that could be done for sure by spending one year. X-ray structure analysis permits many discussions once the structure is resolved; otherwise, there is no room for discussion at all. The characteristics of analysis such as this caused a problem, it appears, because they made it difficult for the students engaged in the analysis work to graduate universities or obtain a degree.

Under such circumstances, my own analysis work showed no sign of progress and the summer of my 2nd year passed bearing no fruit. Reviewing the past from the standpoint of the result, I realize that it was difficult to estimate the model structure from the two-dimensional electronic density since the molecule inclines to any axis. It was on that occasion that Prof. Saito told me "This year let's try your three-dimensional Patterson calculations with the IBM machine." If I remember rightly, the calculation took 15 minutes and it cost approximately -150,000. By way of comparison, the Saito lab's annual research budget at the time was not more than -700,000. Being keenly aware of this, I was frantically engaged in data checks for about two weeks on end. I felt nervous about the amount of money I spent. (Incidentally, the prices of commodities in those days were at such a level that one could get a bowl of 'Ramen' noodle at only -30. In other words, the above budget would come to -10,000,000 or more when converted to the current level of prices. Today, 35 years later since then, the chair and research budget for my lab falls short of 1/5 of that amount, a good proof that Japan's national universities remain not basking in its high growth of economy.) Meanwhile, I could fortunately determine the crystal structure easily through the above calculation in time for the master's course meeting for paper reading. It was from that time onward that the graduate student succeeded in analyzing an unknown structure in his master's course.

The crystal structure was analyzed at last, and I then thought hard about how to comprehend that structure. In view of the fact that the crystal in question was an electric charge moving type complex, I tried to obtain by integration the electron's quantity of moving from the electron donor molecule to the electron acceptor molecule. As a result, a very appropriate and reasonable value came out despite the precision of the data. Even today I still believe that the resultant value is not far wrong, although it seemed difficult for those people not specializing in crystallography to understand its significance well enough.

The Development of Structure Analysis Thereafter

Later, in 1967, a large computer center utilizable in common by national universities was established at University of Tokyo and the Hitachi 5020 was commissioned there. It became possible at long last to derive the

performance close to that of the IBM computer. Also, regarding computation programs, a general-purpose program UNICS featuring the ease of use came into being thanks to the great toils by Dr. T. Sakurai at the Institute of Physical and Chemical Research and Dr. Ashida at the Institute for Protein Research, Osaka University. Thus a gradual improvement was made to reduce the immense labor of crystal calculation. At that time it was a familiar sight in the large computer center that crystallographers were carrying in their hands 3000 to 4000 computer cards that weighed 5 to 6kg. Indeed, the crystal calculation was one of the three pillars at the center.

In the late 1960s, the development of computer-controlled four-circle diffractometers was started for data measurement. In Japan, Rigaku Corporation put its AFC models on the market leading to many installations at various research labs. Although the four-circle diffractometer itself already existed, the angles for the four axes had to be adjusted manually forcing an enormous labor. Now that three-dimensional diffraction data became obtainable automatically by computer control in a matter of two weeks, it made me feel miserable at one time recalling the long days and hours up until a short time before, which seemed to have been wasted insignificantly. Day in day out, I kept sitting visa-vis with the photos of diffraction patterns for a half year to get a piece of three-dimensional diffraction data. It may be said that 1970s when large computers were installed at major universities and when automatic four-circle diffractometers were brought into labs of X-ray crystallography was the age of Japan finally catching up with the West in terms of facilities and equipment.

During the period from the late 1960s to the early 1970s, a new analysis technique called the direct method was developed. While the direct method itself had been investigated for 20 years, it had lacked until that time an indispensable high-speed computer that can readily calculate numerous possible solutions. That is, this method is based on the law of probability. Thus when I entered into a research life, there was little difference environmentally from the times of Bragg in terms of progress. In fact, it is in the last ten years that the state of things have reached the today's level. This situation may be likened to a time slip taking place all of a sudden from the Nara era (A.D. 710-784) to the closing days of the Tokugawa shogunate at the end of the 19th century right before the daybreak of Japan's modernization.

The Advent of Synchrotron Radiation and Imaging Plate

The period from the late 1980s to the early 1990s saw another turnabout in X-ray crystal analysis. That is the advent of a powerful X-ray source called synchrotron radiation and an imaging plate as a two-dimensional detector as well as the trend of computers toward larger size and higher speed and the spread of personal computers. As high-speed computers reduced the time required for analysis, a reduction in the data collection time came up as a pressing problem to be resolved. In particular, for biomacromolecular crystals which involve a large number of data, rapid measurement using the synchrotron radiation and the imaging plate became the mainstream. Regarding low molecular crystals, on the other hand, there are occasions that analysis can be completed in a few hours. In the latter case, therefore, rapid diffractometers that employ an imaging plate capable of collecting data in a couple of hours have come up to supersede automatic four-circle diffractometers which needed a week to 10 days to perform the same work. Diffractometers equipped with a CCD camera have also been commercialized recently, thus giving a balance with the time required for analysis.

Time Scale for Observation

X-ray crystal analysis has made an amazing progress in terms of the method and means for the last 35 years since I started on X-ray crystal structure analysis. In retrospect, when one felt that the data collection time was too long, it was after the progress of the analysis method and computers. Conversely, when one felt that analysis took too much time, it was after the advance of diffractometer systems. The development of X-ray analysis has thus been supported by both of them like two wheels. But what should be noted here is that the above is not merely the matter of reduction in the crystal analysis time. The X-ray crystal analysis technique is namely the way of directly 'viewing' the structure of material. The reduction in the time required means a reduction in the time for structure observation. When I analyzed a crystal for the first time, it took three months to collect its data. In other words, the crystal structure I observed at the time was a structure viewed for the duration of three months. Should there occur any change in the structure during that time period, the change would slip our notice. In the same fashion, a structure analyzed with a four-circle diffractometer means a structure viewed by taking one week. In the case of the current rapid

diffractometer utilizing an imaging plate, a structure observed is in fact a structure viewed by taking a couple of hours or so. During the lapse of 35 years, the time of observation has been shortened to three orders of magnitude less. When we observe the nature, the time required for observation comes up as the biggest condition. That is, we cannot recognize things without the scale of observation time. In this regard, in a very fundamental field such as the observation of atoms and molecules, I was lucky enough to be able to engage in research work in the days which saw a change in the time scale amounting to three orders of magnitude.

Future Structure Analysis

At least I was able to discover an interesting phenomenon referred to as the crystalline state reaction in the days of time reduction from the photographic method to the four-circle diffractometer. Since, in this case, the reaction proceeds within a crystal with no damage to the crystal, one can directly view the process of a structure change under reaction. Further, with a rapid diffractometer using an imaging plate, I was able to find out more recently a crystalline state change that occurs in a shorter time. It so happened that a certain foreign researcher lately proposed the use of a term "real-time in situ chemical reaction" in place of the crystalline state reaction.

I am now thinking over the possibility of viewing a more different world, e.g. the structure of an excited molecule if a further reduction of time can be achieved. For the purpose, we are developing a new two-dimensional detector (MSGC). Under development also by us is the way of direct observation of a structure change to the extent of millisecond or less by using synchrotron radiation. We have only one year to go before the arrival of the 21st century, so it is my earnest wish to attain some work close to making visible the structure of an excited molecule within this century.



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