Molecular Structure and Biological Activity

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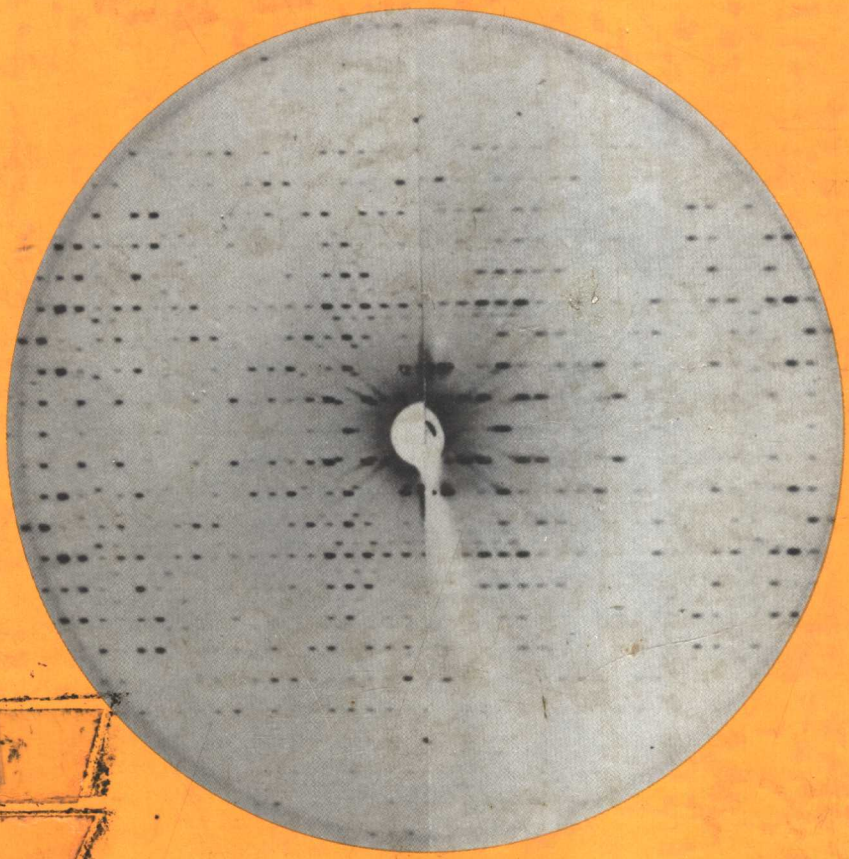

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Molecular Structure and Biological Activity

Proceedings of a meeting in honor of David Harker, Buffalo, New York, U.S.A., August 26–28, 1981

Editors:

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Foreword

This book is the proceedings of a meeting held in Buffalo, August 26-28, 1981 as an associated meeting of the International Union of Crystallography XIIth Congress. The aim of the meeting was to bring together scientists working on the structure and function of macromolecules of biological importance, proteins and polynucleotides, and those who attempt to correlate structure and activity of small biologically important molecules - hormones, cofactors, ionophores, drugs and inhibitors - which interact with either proteins or DNA. We felt that at this meeting it was appropriate to honor David Harker on the occasion of his seventy-fifth birthday. Dr. Harker, as pointed out by Herbert Hauptman in his introduction, made fundamental contributions to both of these areas, contributions so important that it is difficult to imagine this meeting with its avowed aim if Dr. Harker had not focused his intellectual curiosity and discipline on certain crystallographic problems. Happily for us he did and the scope of the subjects covered in this meeting is evidence of the importance crystallographic results have had in explaining biological mechanisms at the molecular level.

After seventy years of development, dating from von Laue's paper in 1912 on the diffraction of X-rays by crystals, the technique of X-ray crystallography has become the *sine qua non* for elucidating the three-dimensional structures of biologically interesting large and small molecules, providing the proverbial "picture that is worth a thousand words".

This volume does not propose to cover any one area of structural biochemistry in depth. Rather its aim is to provide examples of how crystallographic analyses can contribute to understanding the fine details of the interactions between protein or nucleic acid with effector molecules. For instance, Matthews shows that the structures of avian and bacterial dihydrofolate reductase have similar overall shapes, even though sequence identity is less than 30%. While the overall shape remains relatively constant, the real differences account for specificity of agonists and antagonists and different reaction rates.

No area of structural biochemistry has had the explosion of information-rich, exciting, and unexpected results as the nucleic acid field in the last two years. The elucidation of the structure of Z-DNA or lefthanded DNA by Alex Rich's group provided the first solid evidence for a different and unpredicted helical conformation for DNA. The biological significance of this form is being worked out at present. The polynucleotide papers in this volume focus on the interactions of DNA with other species - drugs, ions, water, polyamines and proteins. Although the sequence structure of DNA contains the genetic informa-

tion for what proteins are to be made, it follows that these other interactions are responsible for the conformational changes which must take place in DNA to account for all of its functions, such as turning on and off protein manufacture, regulating amounts produced, and even splicing together bits of proteins into a functional whole.

Richard Ebright suggests that a specific base-pair sequence is the binding site for the *E. coli* catabolite gene activator protein (CAP) which regulates transcription of mRNA. A non-crystallographer, he has looked at the structure of CAP published by McKay and Steitz and proposed a radically different mode of binding of CAP-CAMP to DNA than that proposed by the original authors. Science thrives on such controversies.

We have stretched the meaning of conformational analysis to include a number of systematic approaches which structural scientists have developed to make sense out of a large body of data, to make comparisons intelligible to a broad scientific community, or to examine structure-function in a new and graphic way.

The editor acknowledges the assistance of Deanna Hefner, Brenda Giacchi, Jean Gallmeyer, Kathleen McCormick, Melda Tugac, and Gloria Del Bel in the preparation of this volume.

We would like to acknowledge the financial assistance of the International Union of Crystallography, the U.S.A. National Committee for Crystallography, Organon International, Schering-Plough Corporation and the Xerox Corporation.

Jane F. Griffin
William L. Duax
February, 1982

INTRODUCTION OF DAVID HARKER

If I were to follow the usual custom in introducing Dave Harker I would mention his most important discoveries. I would note for example the celebrated Harker Section discovered by him in 1936, often used to this day despite the enormous amount of work done since then in methods of structure determination; the formulation in 1948 of inequalities among the structure factors, done in collaboration with John Kasper, which marked the beginning of direct methods, and the first application to the solution of the decaborane structure; his elegant geometric interpretation in 1956 of the method of multiple iosmorphous replacement, the indispensable tool for the solution of macromolecular crystal structures; the solution of the ribonuclease structure in 1967 in collaboration with Kartha and Bello; and finally his important recent work on colored symmetry. However, since every one here is already familiar with Dave's major contributions, it seems pointless to dwell on them in greater detail once again. It seems to me instead that a more appropriate introduction would say something more fundamental about the man to whom this meeting is dedicated.

I have known David Harker for more than 30 years. During this time, a major segment of any man's life, it seems to me that Dave has not changed at all. Now I thought at first, and many of you will no doubt also feel, that the reason for this is that we have both grown older together. But on further reflection I am convinced that this is not the explanation. It seems to me instead, that, in all the ways that really matter, Dave has in fact not changed at all. These ways consist, first and foremost, in his love of the science of crystallography which, because of his varied and fundamental contributions, he has, in a very real sense, made his own. From this love of his science flows a boundless enthusiasm which one feels in any discussion with him. This love and enthusiasm, combine with his ability to look below the surface of things, his intellectual acuity, and his single-minded dedication to his science to make almost inevitable the fundamental contributions to X-ray crystallography which he has in fact made during the period of the last 35 years. I am honored indeed to present this exceptional man who, at 75, is as young as he ever was.

Herbert Hauptman
Buffalo, New York
August 26, 1981

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MOLECULAR STRUCTURE AND BIOLOGICAL ACTIVITY
Jane F. Griffin and William L. Duax, editors

EARLY X-RAY CRYSTALLOGRAPHY OF PROTEINS: RECOLLECTIONS

DAVID HARKER
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My first contact with the notion that the structures of proteins could be worked out by X-ray crystallographic methods was, I think, in early 1938. I was an Instructor in Chemistry at Johns Hopkins University from 1936 to 1941. Dr. Irving Langmuir came each spring to visit our Chemistry Department, give a lecture, and, I think, report to the Trustees on the goings-on in the Chemistry Department. Dr. Dorothy Crowfoot of Oxford University had just published some X-ray crystallographic results she obtained from rhombohedral zinc insulin crystals; and her paper contained reproductions of Patterson projections down the three-fold axis. Dr. Langmuir visited my laboratory with a copy of this paper in his hand, together with another paper by Dr. Dorothy Wrinch, also of Oxford, showing diagrams of a cage-like structure which she was proposing for a protein of about the right molecular weight for a trimer of insulin. Langmuir asked me whether the Crowfoot Patterson function could be produced by the Wrinch "Cyclol" - the above mentioned cage-like structure. After some study of the figures, and some measurements of them, I could only say that it was possible. I also said that other structures could probably be found that would also be compatible with the Crowfoot Patterson projection, and that many more X-ray diffraction data were needed before a firm statement about the insulin structure could be made.

Dr. Langmuir and I got along very well. He introduced me to a Mr. Bell, then President of the Cyanamide Company, who, in turn, introduced me to Dr. R. W. G. Wyckoff, who was in charge of X-ray diffraction work at the Cyanamide Research Laboratories in Stamford, Connecticut. I outlined a program for working out the detailed structure of a protein molecule by X-ray diffraction methods, but Wyckoff discouraged financial support for work of this kind, until X-ray crystallography had developed more power.

In 1939 Dr. Langmuir invited me to work during the summer at the Research Laboratory of the General Electric Company in Schenectady, New York, and two years later I left Johns Hopkins to join the staff of the General Electric Research Laboratory. Although I kept up an interest in the problem of finding the three-dimensional atomic arrangement in a protein molecule, I didn't do much about it for ten years.

During the decade we were all involved one way or another in World War Two, so that work on problems of non-military interest was mostly postponed. When the war ended in 1945, about the only laboratories where X-ray crystallographic research on proteins was going on were in England. Dr. Crowfoot - who had married and become Dr. Hodgkin - continued her work at Oxford on insulin; this has only recently resulted in a knowledge of its molecular structure. At Cambridge and at the Royal Institution in London structural studies of myoglobin and hemoglobin had begun, and these efforts resulted in a detailed knowledge of their structures about fifteen years later. Drs. Kendrew and Perutz received the Nobel Prize for this work in 1962.

To return to the early days: - In 1948 I was head of the Crystallography Division of the Research Laboratory of the General Electric Company. In that capacity I had been involved with problems concerning the atomic arrangements in metals, and in a few other substances with rather small molecules. One of these was decaborane, $B_{10}H_{14}$. This structure turned out to be of a completely new type, and its solution did not take place until Dr. Kasper and I had discovered some relations between certain of the intensities of the X-rays diffracted from a crystal and the phases of other such diffracted beams; these relations have been called the "Harker-Kasper Inequalities". This discovery produced in me a certain amount of euphoria, and led me to accept the responsibility for heading a group devoted to solving the structure of a protein molecule, when the opportunity to do so appeared.

This happened because Irving Langmuir and his brother Dean Langmuir made contact with a wealthy couple whom they convinced to set up a foundation for that very purpose, and to ask me to take charge of the research work. This offer was so attractive to me that I left the General Electric Research Laboratory and set up the Protein Structure Project at the Polytechnic Institute of Brooklyn on June 1st, 1950.

The enzyme ribonuclease had been crystallized - by Dr. Moses Kunitz of the Rockefeller Institute - and we were given 20 grams of it by Armour and Co. of Chicago. This protein has a small molecular weight, about 13,700, and its amino acid sequence had been worked out by Drs. Stein, Moore, and Hirs who were colleagues of Dr. Kunitz. All we had to do was determine its structure.

Dr. Carlisle at the University of London had also decided to work out the structure of ribonuclease using X-ray diffraction methods, so there was some talk about duplication of effort and so on. I thought about this question, and concluded that the problem was so important that it would be beneficial if more than one research team worked on the same protein structure. If the two teams

produced the same structural result, each would have verified the other's work. If the results differed, neither result could be accepted, and further efforts would need to be made. When I publicly announced this attitude toward parallel work by different research groups, Professor Bragg, who was in the audience clapped and shouted, "Hear, hear!" I was very glad of his approval.

Very early in the history of the X-ray crystallography of proteins - about 1938 or so - it was discovered that protein crystals contained a considerable amount of the solvent from which they were crystallized, and that they could lose much of this solvent without changing to a different crystalline modification; however, they became much less perfect as they dried. The X-ray diffraction patterns of wet crystals often showed useable reflections out to a resolution of better than 2 Ångströms, while air dried crystals usually gave no appreciable reflections for spacings smaller than about 10 Ångströms. Thus it was necessary to mount protein crystals in an atmosphere saturated with solvent vapor in order to obtain X-ray diffraction data from which atomic positions could be found. Protein crystallographers overcame this difficulty by mounting their wet crystals, together with some of the solution from which they had crystallized, inside sealed capillaries of thin, X-ray-transparent glass. Problems too numerous to mention had to be solved before it was routinely possible to obtain stably mounted wet protein crystals sealed in such thin-walled capillaries.

X-Ray diffraction patterns obtained from a single protein crystal soon revealed that the crystals deteriorated during exposure to X-rays. It was therefore necessary to use many crystals in order to collect complete X-ray diffraction data from a single crystalline species of a protein. Placing on the same scale the intensities of the various diffracted beams from the many different mounted specimens of a crystalline protein also turned out to present another tricky set of experimental problems. The end result of the process of data collection was a table stating the relative intensities of up to about twenty thousand different diffracted beams, each identified by a triple of Miller indices hkℓ. In the 1950's and 1960's, protein crystallographers were quite proud to publish such tables in which the accuracy of each reflection intensity was estimated at no better than about 10%!

The only practical way to find by X-ray diffraction methods the positions of the atoms in a non-centrosymmetric crystal consisting of molecules weighing thousands of daltons is still to use the method of "Multiple Isomorphous Replacement" (M.I.R.). For this purpose, at least three (preferably more) isomorphous crystals containing the protein structure of interest and different

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