Gerhard Schmidt (1919–1971) and the Road to Chemical Crystallography

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Although personal reminiscences are usually regarded as out of place in a scientific article, I feel that they may be acceptable and possibly even desirable here, if only to establish my credentials for writing this article. I knew Gerhard Schmidt over a period of about 25 years. Our first meeting was in October 1946, when he was a graduate student in Dorothy Hodgkin's laboratory at Oxford; our last was in July 1971, in Zurich, the day before he finally succumbed to the illness he had borne so bravely. I think I can claim that I got to know him fairly well during the intervening years. First of all, there were the two years in Oxford, where we shared the large room in the University Museum that served as communal office and workroom for Dorothy's entire research group. Gerhard and I were both rather nocturnal so we preferred to work during the evening and on into the night when there were not so many people around anyway. Mostly we worked, but for distraction Gerhard sometimes played his flute and more often we talked – about everything under the sun. Above the mantelpiece of the room stood an engraved inscription from Hippocrates to remind us of the transience of our life and the hazards of our craft
ΒΙΟΣ ΒΡΑΧΥΣ · ΤΕΧΝΗ ΜΑΚΡΗ · ΚΑΙΡΟΣ ΟΞΥΣ · ΠΕΙΡΑ ΣΦΑΛΕΡΗ · ΚΡΙΣΙΣ ΧΑΛΕΠΗ.
Outside the door, in the dimly lit hall of the Museum stood a reconstructed life-size skeleton of Tyrannosaurus Rex with its fearsome jaws.
In the summer of 1948 we both left Oxford in opposite directions. I went to a postdoctoral Fellowship at Caltech, Gerhard went to build up a new laboratory for X-ray crystallographic structure analysis at the Weizmann Institute. But our paths crossed occasionally and from 1958 or so onwards we must have met about once a year on the average. Gerhard was never an easy-going person and many people found him difficult to get along with; he set high standards for himself and he expected the same from others. I am sure he was fully aware of his stature as a scientist and of the significance of his work – yet he was usually self-deprecatory about these matters to an almost unnatural degree, as anyone who heard him lecture can confirm. Most people did not realize that when he seemed to be overcritical in his appreciation of the work of others, he was simply applying the same quality standards as he applied to himself.
Crystal structure analysis has advanced a long way since the time when Gerhard and I started. Nowadays several thousand crystal structures of all degrees of complexity are solved every year, mostly by methods that require only a minimum of human intervention at the

various stages of the analysis. We have become so accustomed to the availability of automated four-circle diffractometers for collecting the intensity data, of computers for processing these data and of programmes for solving the phase problem and carrying out least-squares refinement, that we tend to forget that things were not always like that. To give some idea of the technical problems chemical crystallographers were up against in the mid-40's it seems worthwhile to describe the state of development at that time.

Crystal Structure Analysis in 1945

In 1934 A. L. Patterson had shown that the information contained in a diffraction pattern was equivalent to the self-convolution of the electron density distribution in the crystal with itself and thus gave information about the distribution of interatomic vectors within the crystal, all drawn from a common origin. Simple crystal structures, very simple ones, could, in principle, be deduced from the Patterson function, but for organic molecules containing, say, a dozen atoms of roughly similar scattering power (C, N, O) the problem of unscrambling the vector distribution into information about the atomic positions was not one that could be easily solved. Introduction of an atom of markedly stronger scattering power makes it much easier to identify some of the vectors, those involving the heavy atoms, and hence to calculate a set of approximate phase angles from which, in turn, a rather confused and distorted electron-density map could be reconstructed. With any luck, a pattern of peaks corresponding to some molecular fragment might be recognized, and if so, the new information could be used to calculate an improved set of approximate phase angles. In favourable cases, iteration of the process could lead ultimately to the complete structure. The heavy-atom method, introduced by J. M. Robertson in his determination of the structure of phthalocyanine, provided the only possible approach in those days to the structure analysis of complex organic molecules, but there were some serious difficulties. The first difficulty was that of recording and measuring the raw experimental data, the intensities of several hundred or, for molecules of any complexity, several thousand diffracted spectra. Most laboratories used photographic methods. To record the complete diffraction pattern of a crystal in such a way that the reflexions could be easily indexed was quite a tedious process, involving up to a hundred or so separate films. The reflexions had to be indexed and their relative intensities estimated visually, by comparing the relative blackenings of the spots on the film with those of a calibrated set of spots. A few hours of this sort of work was sure to produce a headache, if nothing else.

The second difficulty was that of carrying out the numerical calculations. In the absence of computers, these had to be done by hand, with the help of an adding machine if one could be found. After applying various corrections to the raw intensity data to convert them to relative $F_{obs}(hkl)$ values, the calculations were mainly of two kinds.

(1) Given a set of proposed atomic positions, to calculate the corresponding structure factors, $F_c(hkl)$, which are, in general, complex quantities having both magnitude and phase angle, but which reduce to real quantities for centrosymmetric structures.

(2) Given a set of $|F(hkl)|$ values as coefficients, to evaluate Fourier syntheses of the general form $\varphi(xyz) = \Sigma\Sigma\Sigma |F(hkl)| \cos 2\pi [hx + ky + lz - \alpha(hkl)]$ for a sufficiently large number of x, y, z coordinates to get a resonable picture of the function $\varphi(xyz)$, which might be the

Patterson function (coefficients $F^2(hkl)$, phase angles all zero) or an approximate electron-density distribution, depending on the nature of the coefficients.

I shall pass over the problems involved in the first kind of calculation – after all, this is not intended to be a primer of X-ray analysis, but we might consider for a moment the effort required to carry out the second kind. Suppose we have a unit cell about 10 Å along each edge and that we wish to sample the electron-density distribution at intervals of 0.25 Å – the density peak corresponding to an atom extends typically over somewhat more than 1 Å so this would give about four points per atom along any line passing through its centre. Suppose we have 1000 Fourier coefficients. We then have to carry out $40 \times 40 \times 40 = 64\,000$ sums, each consisting of about 1000 products of $F(hkl)$ with trigonometric factors that have to be evaluated separately for each $F(hkl)$ value and for each value of x, y, z. Such a calculation takes only a few minutes on a modern electronic computer, but just think of carrying it out by hand!

Our main computational help consisted of Beevers-Lipson strips. These were thin paper strips imprinted with values of $A \cos 2\pi hx/60$ or $A \sin 2\pi hx/60$ for $x = 0, 1, 2 \cdots 15$, one strip for each integral A value from -100 to $+100$ and for integral h values from 0 to 20. They came in stout wooden boxes, one box for the cosines, one for the sines, 4200 strips in each. It was essential not to damage or lose them, and it was also important to preserve their sequential arrangement in their boxes – otherwise it was almost impossible to find the particular strips one needed. It was a minor disaster when an open box was dropped so that its contents were spread in hopeless disorder over the floor! Even with the help of Beevers-Lipson strips (and they were really invaluable!) and allowing for various tricks to simplify the calculation, I estimate that the summation described above could hardly be done by hand in less than a year. Moreover, the result would almost certainly have been vitiated by numerical errors.

According to a reliable bibliographical source [1] the number of organic crystal structure analyses published by 1945 amounted to about 50. Some of these analyses were possible because the crystals showed a high symmetry that happened to coincide with a high molecular symmetry, a happy circumstance that greatly simplified the analysis, e.g. hexa-methylene tetramine. However, symmetry considerations of this kind could be dangerous and they led, in a few cases, to grossly incorrect conclusions, for example, to the proposal of a non-tetrahedral C atom in pentaerythritol $C(CH_2OH)_4$, which was happily remedied several years later. Most structures were solved by trial-and-error methods; a molecular model was postulated and its position and orientation in the cell varied until the calculated intensities of a few selected reflections could be brought into qualitative agreement with observed values. The approximate structure found in this way could then be refined by Fourier series calculations in two dimensions, to provide a picture not of the complete three-dimensional electron density distribution but of its projection on some crystal plane. A two-dimensional Fourier synthesis involves only about a hundred, rather than about a thousand, coefficients and it could be calculated by hand in a fraction of the time required for a three-dimensional one. This sort of analysis was developed to a fine art, particularly by J. M. Robertson and his school, who applied these methods to the analysis of naphthalene, anthracene and many other planar, aromatic molecules during the 1930's. But the method was only practicable provided that the molecule was fairly flat, that its structural formula was known, and that the molecular arrangement in the crystal was such that individual molecules did not overlap too severely in projection.

Trial-and-error methods were not so suitable for the analysis of more complex organic molecules, particularly those of unknown or dubious structural formulae, because of the excessive number of parameters required to define the atomic positions in such molecules. Moreover, it is only in exceptional cases that two-dimensional projections of the electron density distribution can be expected to reveal much structural detail. In general, for molecules having a complicated three-dimensional form, the three-dimensional density distribution is required, or at least, the distribution along certain selected lines or in certain planes through the crystal. For non-centrosymmetric crystals, which include those of all optically active compounds, there is another difficulty; the phase angles can adopt any value between 0 and 2π (for centrosymmetric crystals they are restricted to 0 or π) and the calculated values are critically sensitive to the exact details of the postulated trial structure. A misplaced atom tends to persist in the electron-density distribution calculated on the basis of the trial phase angles, and an atom omitted from the phasing calculation appears with only a small fraction of its actual density. This could make progress painfully slow.

By 1945 Oxford had established itself as the stronghold of this kind of research. The structure analysis of cholesteryl iodide [2] by C. H. Carlisle and D. Crowfoot (three-dimensional intensity data, heavy atom method, calculation of electron density along lines in three-dimensional space) was one important step forward, and it was followed soon afterwards by an even more impressive feat, the determination of the structure of benzylpenicillin [3], starting more or less from scratch as far as chemical information was concerned. This work involved preliminary measurements on a dozen derivatives, extensive measurements on three salts (rubidium, potassium and sodium), long series of calculations (aided by primitive machine computational assistance) and inspired combination of slender threads of evidence. It was during this work that Gerhard made his first appearance on the crystallographic scene. He played a minor role in the penicillin analysis and promptly took on two other research projects that, if crowned with success, would have put even the penicillin analysis in the shade.

One project was the structure analysis of gramicidin-S, a cyclic decapeptide antibiotic now known to have the chemical structure (L-val-L-orn-L-leu-D-phe-L-pro)$_2$. More than twenty crystalline derivatives were examined, but none of them were deemed promising enough to undertake a more complete analysis at the time – perhaps just as well, for even if the intensity measurements of the 3000–4000 reflections required for a detailed analysis had been carried out, it is hard to imagine how the crystal structure could have been solved and refined with the primitive computing resources available then. Several years later, a complete structure analysis of an N-acetyl derivative was attempted – unsuccessfully [4]. In the meantime, gramicidins have been shown to act as ionophores, that is, to have the property of being able to transport alkali cations across cell membranes. Presumably their antibiotic action arises from this ability to make the bacterial membranes leaky towards such ions, thus upsetting the normal balance. Structural studies have now revealed the details of how alkali cations can be complexed by other classes of ionophoric antibiotics. One would like to know the molecular conformation of uncomplexed gramicidin S and of one of its alkali cation complexes, but, as far as I am aware, this part of Gerhard's doctoral research project is still, after the passage of 30 years, awaiting completion.

The other project is also incomplete. Gerhard managed to obtain some quite large crystals of tobacco necrosis virus (they were grown under carefully controlled conditions over a

period of more than a year). He showed that single crystals of such a virus give good X-ray diffraction patterns, extending to about 2.8 Å resolution, and thus established, for the first time, that the atomic arrangement in these giant molecules repeats itself quite precisely in the regular periodic array of the crystal. The X-ray photographs could be indexed to yield an enormous unit cell with a content of several million daltons, and from certain features of the intensity pattern, it could be inferred that the virus particles were roughly spherical objects with a radius in the range 80 to 100 Å [5]. During the intervening years, much effort has been invested in the attempt to describe the structure of such spherical, or rather polyhedral, plant viruses in better detail by X-ray diffraction and electron microscope techniques. A recent investigation of a closely similar, possibly identical, species is currently aimed at achieving an electron density map at 10 Å resolution [6]. The results obtained so far show that the surface of the virus particle contains 60 identical protein subunits with icosohedral symmetry.

Why did Gerhard take on these hopelessly complex and difficult problems at the outset of his scientific career? He was certainly not the person to be satisfied with an easy, ready to solve, problem; in any case, there were no easy problems in organic crystal structure analysis those days – only difficult ones, very difficult ones, and unsoluble ones. But, after all, Gerhard was, even then, primarily a chemist and he was quick to see the chemical implications of crystal structure analysis; there were countless problems where a couple of years of resolute work would have had a good chance of producing results of direct interest and importance for chemistry. When there were such attractive fruits in prospect, why did he devote those years to scratching a refractory soil that was unlikely to yield a harvest within the foreseeable future?

I do not know the answer, but it seems likely that he was strongly influenced by Dorothy Hodgkin, his research supervisor at the time. Dorothy was convinced that structures of apparently hopeless complexity could be solved by X-ray analysis, and she could show relentless determination in trying every possible avenue that might bring her nearer to her goal. Gerhard's efforts with gramicidin and the spherical virus crystals could not be expected to lead to any immediate victories, only to reverses, but they were necessary, in a sense, in order to encounter the obstacles that lay in these unexplored territories and come to actual grips with them. Only in this way could the lessons be learned for advancing, once the technical possibilities for such an advance were to become available. Gerhard was aware of the unpromising nature of his research, and it says something for his character that he did not pack it up and look for a more tractable project – he could have found one without too much trouble, and Dorothy could almost certainly have been persuaded to agree to the change.

Crystal Structure Analysis since 1945

In 1948, in the first volume of the newly founded journal *Acta Crystallographica*, appeared a paper by David Harker and John Kasper with the revolutionary title "Phases of Fourier Coefficients directly from Crystal Diffraction Data"[7]. It was revolutionary because it went against the generally held belief that the phases (or signs) of the Fourier coefficients could not be obtained directly from a knowledge of the amplitudes, except in the special circumstance of isomorphous replacement. The argument behind this belief seemed irrefutable: every possible assignment of phase angles to a set of Fourier coefficients

corresponds to *some* kind of density of scattering matter, so clearly any method of phase determination must be based on structural assumptions that provide criteria by which correct or nearly correct distributions can be distinguished from incorrect ones. Harker and Kasper showed, however, that certain limitations on the phase angles (expressed in the form of inequality relationships) could be derived from very general assumptions about the nature of the density distribution. For example, any physically reasonable electron-density distribution would have to correspond to a superposition of positive, approximately spherical density peaks. For relatively simple crystals with only a few atoms in the unit cell, e.g. oxalic acid dihydrate, the limitations set in this way suffice to produce an approximate density distribution in which the atomic positions can clearly be recognized.

It was not long before other, more powerful "direct methods" were developed, notably by Sayre, Zachariasen, Cochran, and Karle and Hauptmann. During the 50's, the main application was to centrosymmetric structures, where the phase problem reduces to one of ambiguity in the sign to be associated with each Fourier coefficient. The more general problem presented by non-centrosymmetric structures, where the phase angles are not restricted to the values 0 or π, was hotly debated during these years. Some claimed that the problem was insoluble, others that it had already been solved – in principle, at least, the only difficulty being that the calculations required were of an iterative nature and so long drawn-out that they could not be carried out with the computers available at the time. Once the computing facilities became available – in the mid-60's – the pessimists were proved wrong. Nowadays, thanks to further improvements in the methods and computing facilities, non-centrosymmetric structures containing more than 200 atoms of roughly equal scattering power in the unit cell are routinely solved by "direct methods", and the controversy of the mid-50's makes interesting reading.

In 1945 there was still no way of telling which of a pair of enantiomorphic structures in space corresponded to a given chiral compound. At an early stage of their studies, X-ray crystallographers were confronted with Friedel's Law, which stated essentially that X-ray diffraction effects are centrosymmetric, whether the diffracting crystal itself has a centre of symmetry or not. In other words, the diffraction patterns from a pair of enantiomorphic crystals were supposed to be indistinguishable from one another. Friedel's Law rests on the assumption that the intrinsic phase changes during the scattering process are the same for all atoms in a crystal. If this is true, then phase differences between different reflections depend only on differences in path length, so there is nothing to distinguish propagation of X-rays in one direction from that in the opposite direction. In fact, Friedel's Law is not strictly true because the assumption on which it rests is only approximately valid. If the X-ray wavelength is close to an absorption edge of some of the atoms in the crystal, these atoms do not scatter exactly in phase with the others. There is a slight "phase lag". For propagation along two opposite directions, the phase differences due to the arrangement of atoms in space are simply reversed, but the same phase lag applies to both. For non-centrosymmetric crystals, this leads to a difference between the intensities of pairs of reflections propagated in opposite directions.

The breakdown of Friedel's Law had been demonstrated as early as 1930, when Coster, Knol and Prins [8] were able to determine the sense of polarity of a single crystal of zincblende by observing intensity differences between reflections from the (111) and ($\overline{1}\overline{1}\overline{1}$) faces. It was J. M. Bijvoet who saw that the same principle could be used for determining

absolute configuration. Once the relative positions of the atoms in a chiral crystal are known, the absolute frame of reference can be derived from observed deviations from Friedel's Law. For crystals of one enantiomer, the (hkl) reflection will be stronger than $(\overline{hkl})$; for the other enantiomer, the opposite will hold. In principle, the absolute configuration can be derived from a single pair of reflections showing an appreciable intensity difference, but in practice, of course, several such pairs are examined to check the self-consistency of the measurements.

In 1951 crystals of $RbNaC_4H_4O_6 \cdot 4H_2O$ prepared from dextrorotatory tartaric acid were examined with $ZrK\alpha$ radiation, which was known to produce an appreciable phase lag in the scattering by the rubidium atoms. The analysis of the Bijvoet differences showed that the configuration of the $(+)$-tartaric acid molecule depicted by the conventional Fischer projection happened to be correct [9]. Stereochemistry had been put on an absolute basis.

During the last twenty years the absolute configurations of several hundred chiral molecules have been determined by X-ray analysis and have provided the basis for correlation of chirality with other chiroptical properties, both for carbon compounds and those whose optical activity stems from asymmetric atoms other than carbon. In general, Bijvoet differences are more readily detectable from crystals containing heavy atoms, for these produce a larger phase lag than light ones. Most of the earlier analyses were of heavy-atom derivatives or salts, but, with improvements in the experimental accuracy, Bijvoet differences can be measured for atoms as light as oxygen. In another later development of the method, the observed Bijvoet differences are utilized to derive the phase angles directly so that as the atomic arrangement begins to emerge from the electron density maps it is already in an absolute reference frame. In this way the correct chirality sense of a complex molecule can be established before one knows its complete chemical structure, far less its relative configuration!

In my opinion, which I think Gerhard would have shared, Bijvoet's transformation of stereochemistry from a relative to an absolute basis represents one of the major achievements of science in this century, although it does not seem to be generally recognized as such. It gets only a couple of sentences in most text-books of organic chemistry and is not even mentioned in Martin Gardner's otherwise excellent book "The Ambidextrous Universe"[10] which deals in a semi-popular fashion with problems of asymmetry in chemistry, biology and physics. As far as practical chemistry is concerned, it does not make the slightest difference whether the Fischer convention is right or wrong. Nevertheless, Bijvoet found the way to answer a question that must have obsessed many scientists and philosophers since 1874: is it possible to make a direct correspondence between molecular chirality and our everyday concepts of left and right? It is true that several attempts have been made to calculate the sign of the optical rotation corresponding to a given arrangement of atoms defined in an absolute coordinate system, using both classical and quantum mechanical methods, but the results of such calculations appear to be very sensitive to the nature of the unavoidable approximations that have to be introduced. Other proposals involve observation of the relative growth rates of hemihedral faces of chiral crystals and the attempt to relate these differences to the chirality of the molecules that make up the crystals. However, none of these alternative methods can be regarded as completely reliable, and any assignment of absolute configuration based on them still has to be treated

with a certain measure of reserve. The Bijvoet method seems to be, so far, the only one that tells us in a clear and unequivocal fashion on which side of the mirror plane do our pictures of the chiral molecules of life on this planet stand.

Even with the advent of direct phase determination and of methods for establishing absolute configuration, the main factors in the development of X-ray crystallographic techniques since 1945 have come as a by-product of the phenomenal advances in electronics and computer technology. The most obvious result has been a tremendous increase in the number of structure analyses carried out each year. The number of complete structure analyses (organic and organometallic only) mentioned in the bibliographic work "Molecular Structures and Dimensions"[1] is 8 for 1945, 18 for 1950, 34 for 1955, 118 for 1960, 416 for 1965 and approximately 1000 for 1969; it is now running at the rate of several thousand a year. This increase in sheer number of publications has been accompanied by an equally impressive increase in the complexity of the structures analysed and by a vast improvement in the accuracy and reliability of the results.

The electronic computer made it possible to carry out structure factor calculations and Fourier summations in a fraction of the time required previously. Calculations using three-dimensional data, formerly a rarity, gradually became routine. Instead of terminating an analysis once reasonable agreement between observed and calculated $F(hkl)$ values had been attained, least-squares methods could be applied to obtain an optimal fit of the structural parameters to the experimental data. In this way, information could be obtained not only about the spatial arrangement of the atoms, but also about their vibrational amplitudes and directions. Such calculations involve a multiple regression of several hundred parameters (9 per atom in the asymmetric unit) on several thousand observational data. Although least-squares analysis had been proposed by E. W. Hughes in the early 40's [11] the computations required to form the $N \times N$ normal equations matrix and to solve the system of N simultaneous equations in N unknowns were quite out of the question in those days, except for very simple structures.

The parallel progress in electronic gadgetry made it possible to develop vastly improved diffractometers for measuring the intensities of the X-ray reflections. In the earlier models, the orientation of the crystal and counting device for each reflection was changed and adjusted by hand; modern instruments are usually under the control of a computer, which calculates the required orientation of crystal and counter, drives the circles to the correct settings, and measures background and integrated intensity for each reflection in sequence. Apart from increased convenience and efficiency (several hundred reflections per day can be measured, and the automated diffractometer can work overnight and during weekends and holidays), these instruments, properly used, provide far more accurate intensity measurements than were obtainable by visual estimates of the blackening of the spots on photographic films. It is only by virtue of this improvement in the accuracy of the experimental data that extensive refinement of the structural model become worthwhile in terms of the significance of the results obtained.

These developments did not all happen at once but only gradually, over a couple of decades. In the early 50's the structure analysis of a complex natural product molecule was still a formidable problem for X-ray analysis, one that could be solved only under rather favourable circumstances and even then with considerable trouble. Several such analyses, abandoned at the time because of insuperable difficulties, were taken up again a few years later and solved without too much trouble. By the early 60's it was becoming apparent

that problems of molecular structure could in many cases be solved far more quickly by X-ray methods than by chemistry, a state of affairs referred to by some chemists at the time as "the crisis in organic chemistry". What they meant was that traditional degradative methods of structure analysis that had contributed so much to the development of chemistry were in danger of becoming obsolete. As Sir Derek Barton has pointed out [12], organic chemistry not only survived this crisis but became stronger as a result of it, because the energy and talent formerly invested in degradative studies could be turned towards synthesis.

Chemically oriented crystallographers have had to pass through a similar crisis. In the early days, a crystal strucure analysis was a problem in itself, one that could be solved only by a happy conjunction of professional skill, intuition and inspiration, helped along by a few strokes of good luck. The road was long, full of blind alleys and beset with traps that could catch the unwary student and hold him till his hair turned grey. For those fortunate enough to complete such a journey, the reward was a sense of deep achievement, fully comparable, I imagine, to that felt by those who were successful in deciphering the structure of a natural product molecule from the scraps of clues accumulated in the course of long drawn-out degradative studies. Nowadays, thanks to prodigious technical advances, crystal structure analysis has become so automatized that some of us cannot help feeling sometimes that, with all our skill and experience in structure solving, we too are becoming redundant. Yet, I cannot imagine that any of us wants to return to the days when it took six months of eyestrain to estimate a set of three-dimensional intensities and an eternity to compute a three-dimensional Patterson function!

But even if X-ray crystallography should develop into a completely routine tool for scientists studying the structure of matter, this should be no grounds for pessimism, for such a development is the normal way of the world in science. Something that was yesterday full of adventure is transformed today or tomorrow into something taken for granted, a set of standard techniques to be used in exploring new, more complex phenomena. Many of the people who will use the automated diffractometers and computer programmes will not think of themselves as crystallographers and will not need to know too much about the subject – just enough to be able to check that their equipment is performing well enough so that the experiments or calculations are being carried out properly. We should not discourage people who want to use X-ray crystallography as a standard tool by overemphasizing the difficulties of the subject.

Towards Chemical Crystallography

I think that Gerhard was aware of some of these problems long before they became acute. He obviously realized quite early that, however fascinating the details of individual crystal structures might be, conclusions and inferences of more general chemical interest were only going to emerge from systematic studies of whole series of related structures.

The role of the chemical crystallographer, as he saw it, was not only to determine crystal and molecular structures as well as possible, but also to seek ordering principles in terms of which the structural facts could be systematized and perhaps correlated with aspects of chemical behaviour. With his background of chemistry, Gerhard knew that progress in his subject has come about more as the result of systematization than of theory. Of course, it is very difficult to find an ordering principle when hardly any facts are available or when

the ostensible facts are unreliable. So first establish the facts as reliably as possible, then find the ordering principle, and the theory will take care of itself – this, approximately, was Gerhard's programme.

Gerhard's first major work, a systematic study of the structures of "overcrowded" aromatic molecules, was aimed at assessing the importance of non-bonded interactions in deforming molecules from the idealized structures that might be expected for them in the absence of such interactions. Here is a statement of what was hoped to be achieved [13]:

"In many aromatic overcrowded molecules the compression of non-bonded atoms may be partly relieved through the adoption by the aromatic system of a non-planar configuration. Such molecules are of interest in that they permit a direct observation of the equilibrium between interatomic repulsion and the chemical forces tending to maintain planarity. Thus we may hope, on the one hand, for information about the nature of short-range repulsion forces between non-bonded atoms, which should be useful for an understanding of steric influences in general. On the other hand, the organic chemist may expect information about the manner in which a conjugated molecule reacts to static mechanical stresses. Thus, where measurable distortions are produced by repulsion forces in an overcrowded compound, the distorted molecule, regarded as an elastic mechanical system, permits a direct intercomparison of the bending force constants of the distorted bonds. These force constants which, except in fairly simple molecules, cannot be derived from infrared spectra, are of particular interest because of the possibility that they may eventually be correlated with such molecular properties as bond orders and resonance energies.

Furthermore, one would expect the distortion of bond angles in an aromatic molecule to affect the state of hybridisation of the atoms involved; e.g., it will be instructive to determine the degree of bending to which an exocyclic bond of a benzene ring may be subjected before the planarity of the six-membered ring itself is affected. Of particular interest also is the manner in which the effects of overcrowding in one part of a highly conjugated molecule may be transmitted to distant parts of the conjugated system.

Such distortions of aromatic ring systems must lead to wider variations in bond lengths and electron-density distribution than have so far been found in "normal" molecules like naphthalene, anthracene, etc.; correlation of these variations with the chemical properties of the overcrowded compounds may possibly lead to a better understanding of the relation between structure and reactivity.

Finally, the static deformations of the aromatic system within an overcrowded molecule owing to intramolecular compression may be expected to serve as models for the dynamic distortions produced by the approach of a reagent molecule towards the normal aromatic system in the course of a chemical reaction. These distortions are not, of course, susceptible to direct observation; nevertheless, the mode of deformation of an aromatic system produced by the penetration of its van der Waals envelope, by an uncharged (free-radical) reagent in particular, and the structure of the activated complex formed by the coalescence of the two components may well become deducible by analogy with overcrowded structures."
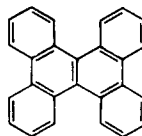
From two-dimensional studies of dianthronylidene (I), 3:4-benzophenanthrene (II) and tetrabenzonaphthalene (III) it was concluded that overcrowded aromatic molecules suffer just enough distortion from planarity so as to bring distances between non-bonded carbon atoms into the range 2.9–3.0 Å. At shorter distances the potential energy curve
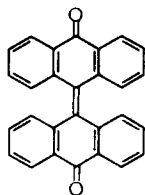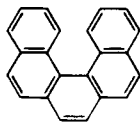
(I)   (II)   (III)

describing the interaction must begin to rise so steeply that the atoms cannot be compressed more tightly together.

From today's perspective, the actual results achieved may seem rather modest. But the ideas behind the work still have quite an up-to-date flavour after the passage of more than twenty years. I am particularly struck by the suggestion that relative values of bending force constants should be estimable from measured static distortions of strained molecules, because this is a line we tried to follow in Zürich many years later. I do not recall being impressed by the idea when I first read those papers in 1954; if it stuck at all, it was completely forgotten by the time we began our own work – but this is a good opportunity to acknowledge Gerhard's prescience. I am sure that Gerhard would have been pleased to know that relative bending force-constants in aromatic and conjugated molecules have recently been estimated [14] by just the method he proposed, and that they do correlate very nicely "with such molecular properties as bond orders".

There was another occasion several years later when our own attempts at systematizing structural facts overlapped directly with Gerhard's. In 1965 we determined the crystal structure of cyclohexane-1,4-*trans*-dicarboxylic acid and found that the carboxyl groups adopted an unsymmetrical conformation with the $C=O$ bond *syn*-planar to one of the C_α-C_β bonds of the ring [15]. This provided the stimulus to look up the conformations adopted by carboxyl and amide groups in other known crystal structures; in almost every case the torsion angle C_β-C_α-$C = O$ was close to zero. It is always gratifying to discern an element of order in the world of molecular structure, so I was rather pleased about this. Shortly afterwards, in early 1966, I was visiting the Weizmann Institute and naturally, I seized the opportunity to tell Gerhard about our recent findings. He listened politely until I had finished, then turned to his desk, extracted a reprint of a paper [16] published a few months earlier and drew my attention to a couple of relevant paragraphs, where he and Leslie Leiserowitz had pointed out just the same regularity as we had found.

Gerhard's major contribution to science is undoubtedly his synthesis of crystallography and chemistry, heralded by the now classical paper entitled "Topochemistry, Part I. A Survey", by M. D. Cohen and G. M. J. Schmidt, and set forth in the series of papers that have been gathered together in this volume. The possible role of topochemical factors in influencing or even controlling the photochemical behaviour of molecules in crystals must have been going round in Gerhard's mind for many years. David Ginsburg, in his preface [17] to the Memorial Issue of the Israel Journal of Chemistry, has suggested that the seeds were planted shortly after Gerhard's arrival at the Weizmann Institute, in the course of a conversation with Herbert Bernstein about the intricacies of cinnamic acid photodimerizations. However, Gerhard's acquaintance with the early literature in this field goes back farther, to his Oxford years, for in late 1946 the name of Ciamician came up

very frequently in our discussions. At that time, Dr. J. D. Fulton of the Medical Research council was investigating the nature of the toxic material produced when solutions of the drug stilbamidine (4,4'-diamidinostilbene-di-β-hydroxyethanesulphonate) are exposed to sunlight. He had converted the irradiation product into a hydrocarbon that proved to be identical with one of the tetraphenylcyclobutanes obtained by irradiation of stilbene, and he came to the Oxford laboratory several times to try to persuade someone to determine the configuration of this isomer by X-ray analysis [18]. Gerhard's acquaintance with the photochemical dimerization reaction thus goes back at least to 1946, but it is clear that he read extensively in this and related fields during the years that followed.

As far as organic chemistry is concerned, the main role of X-ray crystallography during its first half-century of existence was to provide information about molecular structure. The crystals as such were of little interest, they served merely to hold the molecules down in an three-dimensionally periodic array so that X-ray diffraction patterns could be obtained and interpreted. In this way, interatomic distances and angles were measured for many molecules and systematized to yield values characteristic of the various types of bond and characteristic separations between non-bonded atoms. X-ray crystallography also, of course, gradually began to be applied to determine the spatial arrangement of the atoms in molecules of dubious or unknown structure, and occasionally, the constitutions, configurations and conformations so determined were useful for interpreting details of chemical reactivity. However, for most chemists who worked with solutions, a molecule in a crystal was a dead molecule, although it was well known to them that chemical reactions were going on in crystalline solids. Such reactions were usually regarded more as a nuisance than as a respectable subject for scientific investigation.

The main advantage of studying chemical reactions in crystals is that, in contrast to solutions, the beginning and end of the reaction coordinate can be mapped quite precisely, at least in principle. The molecules in a given crystal occur in a quite definite conformation (rarely in more than one) and the ways in which the reacting molecules can approach one another are also quite well defined. Thus, when different polymorphic forms of the same compound show different chemical behaviour, the differences are usually ascribable to differences between these purely geometric factors. The first systematic application of these ideas was to the photo-dimerization of cinnamic acid derivatives and it led immediately to a relatively simple interpretation of a most complicated set of phenomena.

"The crystal structures of substituted cinnamic acids can be divided into three groups (α, β, γ) according to their cell dimensions. These structure groups coincide with the three types of photochemical behaviour reported in Part II: dimerisation to (1) α-truxillic or (2) β-truxinic acid, and (3) light-stability.

X-ray analyses of members of the α- and β-classes indicate that in these photo-active structures the conformation of the dimers can be correlated with the packing arrangement of nearest-neighbours in the monomer lattice: dimerisation takes place at $>C=C<$ separations of 3.6–4.1 Å and preserves in the (molecular) symmetry of the cyclobutane derivative the (crystallographic) symmetry element relating nearest-neighbour monomers. The separation between $>C=C<$ of 4.7–5.1 Å in the light-stable γ-structures is interpreted as too long for dimerisation to be possible."[19]

Everything fell into place; order had been created out of chaos.

This correlation of crystal structure with photo-reactivity was based on the principle that reaction in the solid state occurs with a minimum of atomic or molecular movement – the

topochemical principle – and the collection of papers in this volume describe the subsequent explorations, applications, ramifications and limitations of this principle during the last seven years of Gerhard's life. About 50 or 60 crystal structures – I have not actually counted – nearly all determined at the Weizmann Institute, are referred to in these papers. Unlike most crystal structure analyses, these were not carried out to determine the molecular geometry but rather to find out the nature of the molecular packing and to relate it to the chemical reactivity of the crystals. A decade earlier it would have been virtually impossible to solve so many crystal structures in such a short time and the work would have ground to a halt for lack of the necessary structural information. With the improved technical resources, Gerhard and his colleagues could not only open the field but advance into it in several directions.

Evidence gradually accumulated to show that topochemical control may be exercised at structural imperfections, as well as in the bulk of the crystal. For photo-dimerization reactions this will be the case, for example, if the bulk phase is non-reactive and if excitation-energy transfer is efficient enough so that the photoreaction need not occur at or close to the photon absorption sites.

Gerhard always considered that there were two aspects to his work on solid-state photo-reactivity. One was to understand the conditions that have to be fulfilled for specific photochemical reactions to proceed in crystals. The other was to utilize this understanding to control photochemical reactions to give desired products. For this it would be necessary to produce crystal structures with just the right kinds of intermolecular contact to lead to the photoproduct in question.

The factors that control crystal packing are still not well understood, although certain trends are beginning to become apparent from empirical and semi-empirical studies. A given crystal structure corresponds to a free energy minimum. In most cases this can be identified with a potential energy minimum, i.e. to a balance between attractive and repulsive forces. There is no lack of concepts for factorising the potential energy into component parts – hydrogen bonds, donor-acceptor interactions, electrostatic interactions, polarizabilities, steric repulsions, van der Waals attractions, and so on – but we have to admit that, except for a few simple cases, any predictions about how molecules are going to pack must still be regarded as highly speculative. We also know that quite different modes of molecular packing may correspond to local free-energy minima that do not differ by more than a few hundred cal mole^{-1} or even less. In other words, polymorphism seems to be a rather widespread phenomenon. Indeed, one might conjecture that almost all compounds are polymorphic, if the right conditions for crystallizing the various polymorphic forms could be found. Important progress in the development of useful models for predicting crystal structures of approximately rigid, not too complex molecules can be expected during the next few years. Until this is achieved, "crystal engineering" is likely to remain a rather hit-or-miss affair, but once it becomes possible, the phase of systematic solid-state chemistry can begin.

Another area where progress is essential for a more complete understanding of solid-state reactivity is the study of the nature and distribution of crystal imperfections. X-ray diffraction methods provide very detailed information about the space-averaged time-averaged atomic arrangement but very scanty information about the nature of the fluctuations from this idealized arrangement. As long as the averaged distribution of scattering matter corresponds to that expected for a single molecule carrying out only small-amplitude

vibrations or librations about an equilibrium position, it can safely be assumed that the fraction of molecules in wrong sites or in wrong orientations is negligibly small – although the presence of even a negligibly small fraction of such wrong molecules may be crucial for certain kinds of solid-state reactions and for the physical properties of the crystal. In some crystals, however, the molecules are statistically distributed over two or more sites or orientations, in which case the averaged distribution of scattering matter corresponds to the appropriate superposition of the distributions of the individual molecules. Such crystals are described as having disordered structures. The degree and nature of the disorder present in a crystal can be expected to vary with the temperature. At high temperatures molecules will flip from one arrangement to another (dynamic disorder), whereas at low temperatures the different possible arrangements may be frozen in (static disorder). As the result of improvements in the accuracy of X-ray intensity measurements and in the efficiency of refinement procedures, it is beginning to become apparent that many crystals which would previously have been regarded as ordered are actually disordered. Nevertheless, such crystals sometimes do not seem to behave as typical mosaic crystals. On the contrary, they may show strong extinction effects that suggest that large parts of the bulk crystal are composed of regions that show few, if any, imperfections. These apparent anomalies point to the existence of large lacunae in our understanding of the nature of crystal imperfections, in spite of important progress recorded in an excellent review article that has appeared recently [20].

Gerhard Schmidt's work is being continued, both at the Weizmann Institute and at several other laboratories in different parts of the world. Even more important, perhaps, his way of looking at a crystal, not merely as a static geometric array but as the product of a rudimentary chemical reaction and as a template for further possible chemical transformations, is gradually permeating into the general consciousness. The implications for crystallography and for chemistry have hardly begun to be realized.

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