

The Past and Future of X-Ray Crystallography.

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THE relationship between chemistry and mineralogy, for the exposition of which these lectures were founded, cannot better be exemplified than in the subject of crystal chemistry. There, particularly since the discovery of the X-ray analysis of crystals, we find the explanation in physical and chemical terms for nearly all the phenomena of form and properties by which the older mineralogists classified their specimens. Through modern crystal chemistry, mineralogy has become a special branch of the general study of chemical combination in the solid state. But the origin of crystal chemistry goes back very much further than that of X-ray analysis. It is indeed practically contemporaneous with that of the recognition of crystals as objects for scientific study. In these early times we can distinguish three major periods: the period of Huyghens and Steno, the period of Lavoisier and Haüy, and the great nineteenth century period from Mitscherlich to Groth. The geometrical regularity of crystal form established by Steno in 1669 found an explanation by Newton and Huyghens in the later seventeenth century as representing the outward expression of regular arrangement of atoms. Newton, in his "Optics," talks of the atoms and the crystals being arranged in "rank and file." Huyghens goes much further in his attempt to explain the peculiar optical properties of the cleavage rhombs of Iceland spar. He notes with remarkable foresight how similar they are to the cleavage cubes of rock-salt but, as it were, squeezed along the cube diagonal, and explains this by postulating ellipsoidal atoms themselves optically anisotropic. If we take the CO₃ groups for these atoms this is almost the same model as used by Bragg in calculating the double refraction of calcite.

These early speculations, however accurate, required a much more extensive examination of crystals of different kinds before they could lead to a comprehensive understanding. This examination was carried out in the eighteenth century by collectors as a result of an increasing interest in mining. Through the influence of Linnæus the mineral kingdom began to acquire the same binomial classification as had been so successful with the animal and vegetable kingdoms. People still thought of minerals as growing in the earth in an almost organic way. Nevertheless it became apparent before the end of the century that the geometrical description based on angles was more certain than that based on general appearance and this led Haüy and Romé de Lisle to make the next logical step and discover the law of rational indices, itself a direct consequence of the "rank and file" definition of Newton. From now on crystal species could be defined precisely by a minimum number of parameters, the axial ratios, and descriptive crystallography became an exact science.

The connections of this science with chemistry were very close from the outset. The new nomenclature of Lavoisier and its extension through Dalton's atomic hypothesis helped to establish the idea that every definite chemical compound had an equally definite crystallographic form. But this law was soon found to be doubly defective. The same chemical substance was often found to have different crystal forms (polymorphism, discovered by Mitscherlich in 1821), and different chemical substances to have the same crystal form (isomorphism, discovered by Mitscherlich in 1819). Isomorphism provided the first positive and useful connection between crystallography and chemistry. It served to indicate likenesses between elements and thus, in the hands of Berzelius and Mendeléeff, to determine the valencies of beryllium, tellurium, and indium, besides predicting those of germanium and scandium.

All through the nineteenth century crystallography went hand in hand with chemistry; the chemists analysed new minerals described by the crystallographers, the crystallographers measured crystals of new substances prepared by the chemists. This produced a vast mass of material, represented on the one hand by the classical text book of Dana's "Mineralogy" and on the other by Groth's "Crystal Chemistry." This crystallographic work was of immediate and permanent value both for identification of mineral and chemical substances and for classification. In the middle of the century crystallography contributed to chemistry in an entirely different way when Pasteur resolved tartaric acid by picking out right- and left-handed crystal forms and thus laid the foundations of stereochemistry.

While all this was going on the theorists were not idle. Successively, the fourteen space lattices were established in 1850 by Bravais, the thirty-two crystal classes in 1866 by Gadolin and Von Lang, the sixty-five rotational space groups in 1879 by Sohncke, and, finally, by a magnificent triple effort, the 230 space groups by Schoenflies, Feodorov, and Barlow in 1890. All these workers held as their basic assumption that crystals were built up from regular arrangements of atoms; they had determined with more and more completeness what the geometrical possibilities of such arrangements might be. But they still lacked any clue as to what the actual arrangements of any atoms were in any crystal. Crystallography, however exact and mathematical, remained a descriptive science.

There have been few examples in the history of science more dramatic than the discovery of the diffraction of X-rays by crystals by Laue in 1912 and its almost immediate application to the analysis of crystal structure by the Braggs in 1913. What had been previously a totally unknown world was almost at the outset reduced to order and measure. Yet there was a link between the older crystallography and the new structure analysis. Barlow may be reckoned as a prophet of structural crystal chemistry; he anticipated the explanation of close packing of metals and actually put forward the correct structure of rock salt as early as 1906. Unfortunately his association with Pope in the delusive valency-volume theory has led to his contribution being almost completely overlooked.

The effect of Sir Lawrence Bragg's determination of the rock-salt structure was completely revolutionary in more than one direction. The fact that it showed the crystal to be composed of ions with no trace of molecules upset the older chemists for whom the chemical molecule was a legitimate end of all structural research—including such mighty molecules as are even to this day postulated for the micas and feldspars. But it did more. It introduced the true metrical atom scale to chemistry. It showed that the atomic theory with its structural formulæ that Ostwald had considered near the end of the nineteenth century merely as a convenient hypothesis was in fact a precise spatial description. The "billiard ball" atom was back again and this time with its size directly measured. The early structures worked out by the Braggs covered, as we now know, practically the whole range of the major structure types of crystal chemistry. Rock-salt, blende, pyrites, diamond, naphthalene, were the archetypes of all the more complicated structures that we study to-day. To complete the picture, all that was needed was the determination of close packed metal structures by Debye and Hull.

At first the world revealed by these crystal structures—a world as startling as and far more important to us than that shown by Galileo's telescope—was difficult to understand on the basis of older chemical preconceptions; particularly difficult was the relation between the metals and their salts. Following Lothar Meyer's table of atomic volumes, it seemed rational at first to take the metal atoms as large and the non-metal atoms as small, and it was not until the time of Goldschmidt in 1928 that the modern clear distinction between the small metal ion and the large metal atom were realised. Goldschmidt, with his extensive work on simple compounds, laid the basis for metrical crystal chemistry and closed the first—what may be called the heroic—period of crystal chemistry.

It was by then apparent that the solid state could not be explained by one set of laws: that there were, as Fajans and Joos had pointed out, four major types of solid—metallic, ionic, adamantine, and molecular—with any number of intermediate types and sub-types. These types of structure depended on the predominance, in the final building up of the structure, of the metallic, ionic, co-valent, and van der Waals forces, the explanations of which were appearing in contemporary theoretical chemistry with the advent of the new quantum theory. From then on it is reasonable to state that the history of crystal chemistry developed along three main lines—metallic, ionic, and molecular. (The adamantine class represented by diamond itself and a few other very hard substances has not been extensively studied and its physics are still in the stage of acute but probably fruitful controversy.)

It was clear long before the advent of crystal chemistry that the laws of combination of elements in alloy structures had little in common with those prevailing in the rest of chemistry. Intermetallic compounds, it is true, did exist but these were very far from being chemically identifiable substances of invariable composition, and when their composition was determined it often corresponded to no simple stoichiometric ratio. It was clear that the rules of ordinary chemistry simply did not apply to metals. Crystal chemistry almost from the first shed light on this situation. It showed that the great majority of metals and alloys were characterised by the one common property of close atomic packing, embracing relatively trivial distinctions involving small energy changes between the three canonical types of cubic face centred, hexagonal, and cubic body centred packing. Where more complicated structures occurred they could be derived from the simple ones by slight distortion or internal arrangement as in the classic case of α -brass. In simple solid solution alloys, atoms of different kinds seemed to be arranged entirely at random, though careful cooling in certain cases brought about disorder-order transformation theoretically explained by Bragg and Williams.

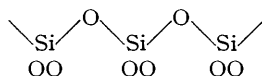
The great work of Westgren, who pioneered the X-ray studies of particular alloy systems, showed that phases of corresponding structures did not have corresponding chemical formulæ. This was explained through the brilliant intuition of Hume-Rothery's rule which stated the fundamental law of metal crystal chemistry—that the structure of a metallic compound is a function of the ratio of the number of free electrons to the number of atoms and is, apart from geometrical effects, due to markedly different sizes of positive ions, independent of the chemical nature of the elements which form the compound. The emphasis thus placed on the electron fitted in with the newer conception of a degenerate electron gas as the cohesive medium in metals and led to the explanation of the Hume-Rothery rules by Jones in terms of the Brillouin zones of electron energy discontinuities whose form determines the stability of the metal crystal lattice. Since that time the intricacies of metal crystal chemistry have been more and more studied, particularly by the school of Bradley and Lipson. Most of this work tended to bring out for the first time the relations between the constituents of metals and alloys and those mechanical and electrical properties of strength, ductility, conductivity, permeability, and coercivity which are all-important in the industrial uses of metals and alloys and which could not conceivably be derived from a mere knowledge of their chemical composition. The elucidation of order-disorder phenomena, together with that of the mechanism of separation of phases of very similar energies, led to an explanation of the phenomena of age-hardening and hysteresis which can now be analysed and predicted with increasing accuracy. There is clearly here an enormous field for future work, one in which comprehensive theory of the fundamental processes involved will come to take the place more and more of the extremely empirical methods that have hitherto ruled in metallurgy.

The effect of X-ray studies on inorganic chemistry have been almost as revolutionary as those on metallurgy. This is the field that mineralogy and chemistry have in common and it can be said that structural analysis has reduced what was previously a confused domain to an exact science. The initial discovery that sodium chloride contained ions and not atoms was the starting point for a logical building up of the laws of combination of charged particles held together by Coulomb forces. The extremely simple structures of the alkali halides and alkali earth oxides made it possible for Born and his co-workers to provide an almost complete theory of the

interaction of ions and to predict interatomic distances and forces from a knowledge of the quantum physics of the atoms of which they were composed. In no other part of chemistry has anything like this degree of accuracy been achieved. Born showed, however, that the crystallographic differences that exist between the different forms correspond to very small changes of energy and that consequently the prediction of precise structures will always be fraught with great difficulty.

The general principles, however, of ionic crystal chemistry were clear. The dominating conception that the packing of ions of one sign round ions of the other and the major factors that influenced this packing appeared to be the simple electrical geometric factors of ion charge and ion radius. These principles were applied by Pauling in his celebrated rules for the structure of ionic crystals which are based on the conception of ionic valency, defined as the ratio of the charge on an ion divided by the number of ions of the opposite sign in its co-ordination polyhedron. They are equivalent to the hypothesis that the lines of forces originating on any ion of a stable structure terminate on ions of the opposite sign in its immediate co-ordination polyhedron.

While these rules were being elaborated, the great work of the Manchester school under Sir Lawrence Bragg had established the structures of the most complex, though the most common, of inorganic substances—the silicates. The general classification of the silicates arrived at by the mineralogists by chemical and morphological means was found to correspond extraordinarily well with the logic of their structures. The basic silicates contained separate SiO_4^{4-} groups, the metasilicates having instead of the ion SiO_3^{2-} the polypyrosilicate ion



which gave them their fibrous qualities. The fissile micas and clays in turn depended on an aluminosilicate sheet ion, $(\text{SiAl})_2\text{O}_6$, and, finally, the acid silicates such as the feldspars had complete aluminosilicate framework ions, $(\text{AlSi})\text{O}_2$, in which were inserted positive ions to balance the charge. Thus, in the place of the complicated and unreal formulæ for the molecules of silicates, the Bragg school developed structural interpretations into which the complex replacement rules of the nineteenth century mineralogists fitted most naturally, showing here again the dominance of ionic size in ionic chemistry.

The same success followed the later work on the structure of complex ions and co-ordinated compounds. It now appeared that the whole of inorganic chemistry, as far as the structure of low energy phases was concerned, could almost be deduced from a knowledge of a few properties of the ions. How far this work has progressed is well illustrated in A. F. Wells's new text book on "Structural Inorganic Chemistry." The ionic approach to chemistry, however, is very simple except when either small, highly charged, or large easily deformed ions are involved; here it passes over, by something like the correspondence principle of Bohr, into homopolar chemistry. There is a large field where a particular atomic combination is undoubtedly held together mainly by electron exchange forces but at the same time carries localised charges which are all-important in their relation to other elements of the crystal. A particularly important example of this, because of its all-pervasiveness in chemistry, is that of hydrogen. Hydrogen, attached to nitrogen or oxygen, forms a highly localised dipole the strength of which depends very much on the other attachments of the nitrogen or oxygen atom. The more polarising this is, as for example in the series of Na^+ , Mg^{2+} , Al^{3+} , Si^{4+} , P^{5+} , S^{6+} hydroxides, the easier it is to detach the hydrogen ion. The alkaline-acid series finds its expression in the strength of the hydroxyl and hydrogen bonds.

Another range of deviation from simple ionic considerations is found to be due to the polarisability of atoms, particularly those of the lower rows of the periodic table. With sulphur and chlorine, and even more with tellurium and iodine, the distortion of the anion by polarisation comes to play a leading rôle. Where the cations are also polarisable or have electron defects in their inner shells, the structures of the crystals containing them deviate more and more from the ionic expectations and approach more closely those of metals. This is a sphere which as yet has not received anything like the attention it deserves from X-ray crystallographers. The whole range of minerals of the sulphide-arsenide-antimonide groups are still, except for their simplest members, unstudied. Considering their importance in mining and smelting practice this study would seem well worth undertaking.

In organic chemistry the crystal chemical position is very different from that in the other fields. Here the molecule is a real physical entity and its structure can be—and is—elucidated by means of extraordinarily subtle and complex logic based on chemical transformations. It was perhaps not surprising, therefore, that for many years crystal analysis could do little more than confirm the structures already well known to the organic chemist. However, in the later twenties, the work of Sir William Bragg's school, particularly Lonsdale, Robertson, and Cox, showed that even with well-known organic compounds there was much to be learned from crystal analysis. The chemical formula, hitherto purely topological, could in the hands of the crystal analyst become geometrical. Bond lengths and angles came to be measured with greater and greater accuracy, and these measurements themselves tended to show what was already becoming apparent for quantum chemical reasons, that the old distinctions between single, double, and treble bonds could not be maintained, but that every bond was to a certain extent *sui generis* and its finer points could only be explained in relation to the molecule as a whole.

X-Ray analysis, however, did not rest there. Robertson and Woodward in 1940 succeeded in achieving for the first time in organic chemistry what the Braggs had previously done in inorganic chemistry, the determination of a complete structure without any chemical assumptions. Their classic analysis of phthalocyanine

demonstrated physically for the first time that organic structural formulæ corresponded to physical realities. In other words had there been no development of organic chemistry, *X-ray analysis*, based on nothing more than the mathematical theory of diffraction, could have determined the structure of organic molecules.

Meanwhile another application of *X-ray analysis* was being made in a far cruder way. From cell sizes and general indications as to molecular orientation it had been possible, without being able to deduce precise formulæ, to discriminate with certainty between rival formulæ for naturally occurring substances. In this way the modern, accepted carbon skeleton of the sterols was determined and its relationship with that of the sex hormones and cardiac poisons established. *X-Ray analysis* was to prove a most powerful weapon in speeding up the work of the chemist in determining the structure of unknown substances.

These two approaches were combined in the work of Mrs. Hodgkin who, after completing with Carlisle a detailed absolute analysis of cholesteryl iodide, applied the full battery of *X-ray analytical technique* to the structure of penicillin, a molecule of most unusual type, and succeeded in determining its structural formula well in advance of its chemical analysis. Full proof of this formula can only come when penicillin has been synthesised, but in the meantime it has been demonstrated that any compound capable of being crystallised in association with a heavy atom or ion can be completely analysed by *X-ray methods*. Sooner or later this will lead to a major revolution in chemical analytical technique.

While *X-ray methods* were showing their value in the field of classical organic chemistry, they were also being used at the other end of the scale to elucidate the most complex examples of biological structures: those of natural polymers such as polysaccharides, the nucleic acids, and, above all, the proteins. The pioneer work of Astbury on organic fibres established the basic pattern of polypeptide chains underlying the structure of hair, muscle, and tendon and showed that in the whole range of animal life there appeared to be only two major arrangements—the keratin–myosin type which could exist in a stretched or curled form, thus giving the first hint as to the molecular nature of biological contractility and the action of muscle, and the more inert collagen chains of connective tissue.

In contrast to these fibrous proteins, the soluble crystalline proteins were found to consist of large but perfectly definite globular molecules whose structures are being attacked at the present day by the schools of Mrs. Hodgkin and Drs. Perutz and Fankuchen. It is in the analysis of protein structure that the *X-ray method* is being pushed to its utmost. In conjunction with all other physical methods, with chemical analysis, centrifugation, and electrical measurements, we may yet hope in the near future, if not to determine the complete structure of these vastly complicated molecules, at least to understand the principles on which they are constructed and to make use of that knowledge in the fields of biology and medicine.

This necessarily brief survey of the field of structural crystallography almost inevitably, of itself, points towards the future. Many of the lines of advance are inherent in the work already being done and are in fact actively being pursued; but it may be worth while examining the field as a whole in order to see whether this progress is as widespread or as intense as it should be in relation to its possible importance both as an intrinsic study and for other sciences. By now the actual methods of *X-ray crystallography* have been brought to a remarkable pitch of perfection. The old trial and error methods of the "heroic" period have been superseded by a logical and precise sequence of manageable mathematical operations. The gain in accuracy and scope has been attained, however, only at the expense of a far greater laboriousness involving an enormous increase in man-hours per structure. Even with mechanical aids the labour involved in crystal analysis is bearing heavily on the meagre resources of *X-ray crystallographers*. For a structure like penicillin several hundred intensities had to be accurately measured and in all several thousand computations made. When it is realised that for hæmoglobin 8,700 intensities have already been measured, the magnitude of the task can be seen. Nevertheless this development is in line with the general tendency of modern science where results far more valuable than any that our ancestors dreamed of can now be obtained with certainty but only by carrying out the operations of scientific discovery itself on a semi-industrial scale. This implies, further, that the choice of substances to be analysed has to be planned and cannot be left to chance or caprice. For this the closest collaboration is absolutely necessary between chemists, engineers, and biologists; but the full battery of analytical method does not need to be turned on to every chemical problem; there are thousands where some comparatively simple measurement of cell size or space group is adequate to save the chemist many weeks of laborious work.

It is clear from this that the organisation of *X-ray crystallography* should be two-fold. We must have highly specialised analytical centres working as part of big chemical enterprises and, at the same time, a wide distribution of *X-ray apparatus* and the knowledge of how to use it in every chemical laboratory, routine as well as research. Naturally in certain fields, notably metallurgy, the value of routine *X-ray examinations* has been recognised by equipment manufacturers, and the substitution of the Geiger counters and electrostatic recording for the photographic plate makes it possible to devise automatic checks for the structural quality of any product. All this implies the introduction of the knowledge of structure analysis much earlier and much more widely in chemical curricula. It is a disgrace, for which the war is, however, in part responsible, that we have only one school in the whole of England where structure analysis is systematically taught; it is consequently looked on somewhat as a mystery and it is difficult for any chemist brought up on existing lines even to understand the meaning of its results. This will certainly come about in time but it is to be hoped that with the new turn towards making chemistry an exact science and less of a formulary, and with the increased recognition of the interdependence of the sciences, the change will be welcomed and even assisted by the main body of chemists.