CHIMIA

Volumen 17 Fasc. 6 1963 Pag. 169-216

Laboratoriums- und Meßtechnik in der Chemie

Methoden der Konstitutions- und Strukturaufklärung (II)

The Determination of Molecular Structure by X-Ray Methods[*]

By J. D. Dunitz
Laboratorium für organische Chemie der ETH, Zürich

The discovery that X-rays are diffracted by crystals was made fifty years ago by M. von Laue, W. Friedrich and P. Knipping. Within a few months of their discovery it had already been used by W. H. and W. L. Bragg to analyse the structures of simple crystals and exploration of the sub-microscopic world of molecules and ions had begun. Although the basic principles of X-ray analysis were all established within two or three years of von Laue's discovery, the range and complexity of the structural problems that can be handled have increased steadily over the last half-century with improvements in the experimental, conceptual and mathematical techniques. The last decade has seen especially spectacular progress, which can be attributed mainly to the increasing power and availability of high speed computors and of devices for the rapid, automatic, measurement of diffracted X-ray spectra. At present, X-ray analysis seems to be one of the most powerful methods for studying the spatial arrangement of atoms and is being used to investigate problems of crystal and molecular structure that arise in a number of different scientific disciplines—crystallography and solid state physics, metallurgy, inorganic and organic chemistry and, youngest of all, molecular biology.

In spite of the central position that X-ray analysis now occupies in the physical and biological sciences, the techniques is not well understood outside a small circle of specialists. This is a pity for, as long as X-ray analysis is regarded as something rather mysterious, the meaning of its results cannot be properly comprehended. Moreover, neither the experimental nor the theoretical aspects of the subject are difficult to understand in principle, however complicated they may be in practice. In this paper, I shall address myself to the non-specialist and shall try to sketch some of the steps that are involved in the course of a typical analysis of an organic substance of unknown chemical constitution. Many of the arguments, however, will be of a fairly general nature and are therefore also relevant to analyses of other classes of compounds; in particular, they are intended to serve as an introduction to the more complex problems involved in the analysis of proteins and other macromolecules.

X-ray analysis begins naturally with X-rays but there is little that need be said here about them. They are electromagnetic waves that can be produced by causing a stream of high energy electrons to strike a suitable target material. For the analysis of organic compounds it is convenient to use either copper or molybdenum targets, which yield characteristic radiations of 1.54 and 0.71 Å respectively. For inorganic compounds the choice of radiation will depend on the elements that are present. Modern, commercially available, high tension generators with sealed, interchangeable X-ray tubes are reliable instruments; they are stable and simple to operate, they can be run for long periods without trouble, and they meet the required standards of safety. We do not need to discuss them further.

The experimental technique is basically very simple and may also be summarized in a few words. A small crystal is placed in the path of a narrow beam of monochromatic X-rays. As the orientation of the crystal to the X-ray beam is varied, conditions for diffraction are successively satisfied and diffracted beams are emitted

---

[*] Lecture presented at the Technical Congress of the 2nd International Exhibition of Laboratory Measurement and Automation Techniques in Chemistry (ILMAC), October 15th to 20th 1962, in Basel (Switzerland).

in various directions. The resulting diffraction pattern can be observed either on photographic film or with the aid of proportional or scintillation counters.

The most striking feature of the diffraction pattern produced by a crystal is that it is composed of a set of sharp, discrete spots which can be arranged on the points of a lattice. One layer of such a lattice is shown in Figure 1. This striking effect arises because the crystal is built by regular repetition in three dimensions of a structural unit known as the unit cell. As the X-rays pass through the crystal the electrons are set into vibration about their nuclei by the rapidly oscillating electric field. Each electron vibrates with exactly the same frequency as the incident radiation and, according to electromagnetic theory, it acts as a point source of a scattered wave of just this frequency. Because of phase differences, scattered waves emitted at different points in the crystal interfere with one another and unless the waves scattered by corresponding points in different unit cells are exactly in phase with one another the net intensity of scattering is vanishingly small. At certain scattering angles, however, every unit cell throughout the crystal scatters in phase to produce a sharp, intense. diffraction maximum. The array of spots thus corresponds to the set of diffracted beams produced by a three dimensional diffraction grating. Just as each diffracted beam from a one dimensional grating may be designated by a single integer *h* describing its order of diffraction, so each diffracted beam from a three dimensional grating is designated by a number triple *hkl*. Alternatively, each diffracted *hkl* beam may be regarded as arising by reflection of the X-rays from the crystal plane with Miller indices (*hkl*). The two descriptions are completely equivalent and it is a matter of convenience which one we choose to use. The relative intensities of the diffracted beams depend on the distribution of scattering matter within the unit cell. Given this distribution, $\varrho(xyz)$, the intensities may be directly calculated. In structure analysis, however, we are faced with the converse problem. Given the intensities, can we calculate the distribution of scattering matter? We shall see that there is no simple answer to this problem but, before discussing it in more detail, I should like to remind you of some properties of periodic functions.

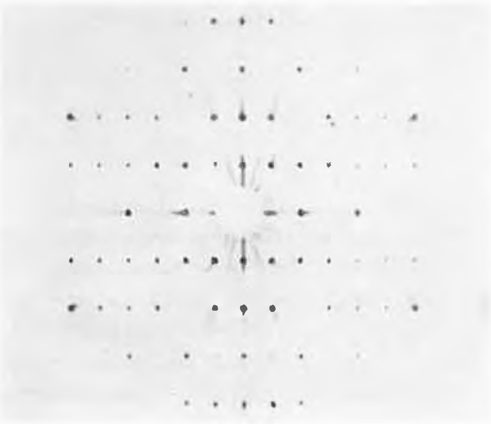


Figure 1. A layer of the diffraction pattern produced by a crystal of acenaphthene

It is well known that any periodic function can be expressed as a sum of cosine waves with appropriate amplitudes and phase relationships (Fourier series). Thus, if a function $\varrho(x)$ repeats itself in distance a it can be written in the following equivalent forms

$$\begin{aligned}\varrho(x) &= \sum |F(h)| \cos 2\pi\,[hx/a - \alpha(h)]\\ &= \sum A(h) \cos 2\pi\, hx/a + B(h) \sin 2\pi\, hx/a\end{aligned}$$

where $A(h) = |F(h)| \cos 2\pi\,\alpha(h) \quad B(h) = |F(h)| \sin 2\pi\alpha(h).$

The important things to note are:

1. The wavelengths of the component Fourier waves are restricted to integral sub-multiples of the fundamental wavelength a; this is necessary since every component wave must fit exactly into the given periodicity.
2. The amplitude and phase of each Fourier wave can be represented as a vector of length $|F(h)|$ and inclined to an arbitrary at an angle $\alpha(h)$, as shown in Figure 2. The components of the vector parallel to and normal to the axis are $A(h)$ and $B(h)$ respectively.

If the function $\varrho(x)$ is given, the components $A(h)$ and $B(h)$ and hence the amplitude $F(h)$ and phase $a(h)$ of every Fourier wave can be calculated by integration

$$A(h) = \frac{1}{a}\int_0^a \varrho(x) \cos 2\pi\, hx/a \; dx\,,$$

$$B(h) = \frac{1}{a}\int_0^a \varrho(x) \sin 2\pi\, hx/a \; dx\,.$$

We can thus reconstruct the original function $\varrho(x)$ by adding together the individual Fourier waves with the correct amplitudes and phases (Figure 2).

Since a crystal is built by regular repetition in three dimensions of a basic structural unit, the electron den-

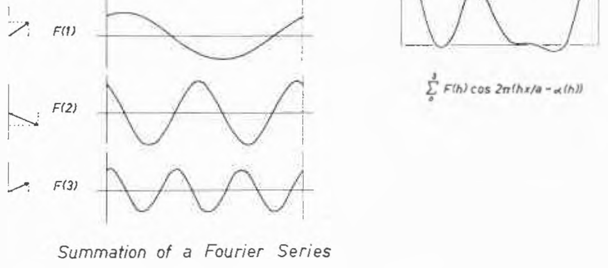


Figure 2. The periodic function on the right can be broken down into the four Fourier waves illustrated. The amplitude and phase of each Fourier wave can be represented by a vector

sity within the crystal is a three dimensionally periodic function and it can be represented as the sum of a Fourier series of electron density waves.

$$\varrho\,(xyz) = \sum\sum\sum \left|F\,(hkl)\right| \cos 2\pi\,[hx/a + ky/b + lz/c - \alpha(hkl)]$$

where a, b and c are the three periodicities that define the dimensions of the unit cell. Each density wave has the property that it can reflect the X-ray beam at a definite angle of incidence, the intensity of the reflected radiation being proportional to the square of the amplitude $|F(hkl)|$ of the wave. Indeed, each diffracted or reflected beam that is observed can be associated with a density wave of order *hkl* and its intensity gives a measure of the corresponding amplitude $|F(hkl)|$. The relative phase relationships cannot, however, be measured experimentally and this means that it is not possible to proceed in a straightforward manner from the experimental data directly to the structure. Without knowing the phase angles we cannot add together the density waves in the correct way to obtain the electron density; we do not know whether each wave starts off at the origin with a maximum or a minimum or with some intermediate displacement. If the crystal can be shown to have a centrosymmetric structure, intermediate displacements can be ruled out for in this case each density wave must have either a maximum or a minimum at the origin, otherwise the centre of symmetry would be destroyed. For centrosymmetric crystals, therefore, the phase problem is reduced to an ambiguity of sign of each amplitude. This is an enormous simplification but even so, for N observations, there are 2^N different ways of allocating these signs, each way corresponding to a different electron density distribution. The essential problem of structure analysis is just that of deriving, somehow or other, the missing phase angle or sign relationships for only when these are known can the individual electron density waves be combined in the correct way to produce the electron density distribution in the crystal. Given this distribution or even, in favourable circumstances, a projection thereof, the arrangement of the atoms within the unit cell can be recognized in the arrangement of electron density maxima (Figure 3). Molecules are thus made visible and the details of molecular architecture can be seen even by the inexperienced eye.

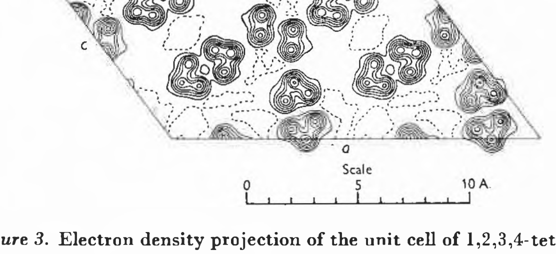


Figure 3. Electron density projection of the unit cell of 1,2,3,4-tetraphenylcyclobutane (centrosymmetrical isomer)

Although no general way of solving the phase problem for every crystal has been found, a number of different methods have been developed, each offering some hope of success under certain circumstances. These methods may be divided into two classes; those that lead from the observed intensities or amplitudes to partial or approximate structural information; and those that lead directly to limitations on the phase angles. The division is somewhat arbitrary for, naturally, the two kinds of methods must be interrelated. Partial or approximate structural information can be utilized to limit the phases and, conversely, limitations on the phase angles can be utilized to give approximate structural information.

One method of obtaining an approximate structure is by guessing. For relatively simple crystals containing molecules of known constitution and form, this can actually be done although it demands a certain degree of skill and experience. Once a plausible model is found it is tested by comparing the set of observed amplitudes $|F(hkl)|$ with the calculated ones based on the model in question. In calculations of this kind, it is convenient to describe the model in terms of discrete atoms, occupying definite positions in the unit cell, rather than as an electron density distribution. In other words, integration over an electron density distribution is replaced by a sum over a fixed number of atoms of known or assumed electron densities. For each reflection *hkl*, the contribution of each atom to the structure factor can be represented by a vector of length proportional to its scattering power (roughly to its atomic number). The direction of the vector depends on the position assigned to the atom. The resultant of all the atom vectors is the calculated structure factor $F_c(hkl)$ (Figure 4) which can be compared with the observed structure amplitude $|F(hkl)|$. If the magnitudes of these quantities agree for

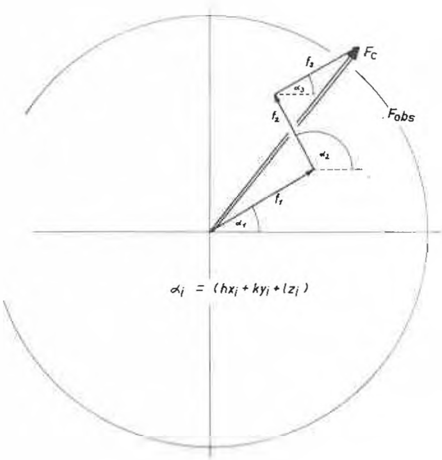


Figure 4. The structure factor, F_c, for the *hkl* reflection, is the sum of a number of vectors, f_i, each corresponding to an atom. The lengths of the vectors depend on the scattering powers of the atoms, the phase angles depend on their positions.

$$F_c(hkl) = \sum f_i \exp\,[2\pi i\,(hx_i + ky_i + lz_i)]$$

a reasonable number of reflections we may assume that the model is at least roughly correct and can then proceed to carry out a Fourier summation in which each density wave is assigned its observed amplitude together with the phase angle derived from the model. The resulting distribution will represent an improvement on the assumed model, which can be adjusted accordingly. The cycle can be repeated if necessary until no further improvement is obtained by continuing. If the observed and calculated amplitudes do not agree then the model is wrong and another guess must be made. This method, if one may call it a method, can be described as analysis by trial and error, and almost all the early work on the structures of organic compounds was based on it. Trial and error analysis has provided us with much information on the sizes and shapes of molecules of already known constitution but it is hardly practicable in the case of complex molecules of unknown constitution with many configurational and conformational possibilities. For these, a more direct method is obviously needed.

We have seen that in order to reconstruct the electron density distribution by Fourier synthesis, a knowledge of the phase angles $\alpha(hkl)$ is required. There is another distribution function

$$P(xyz) = \sum \sum \sum F^2(hkl) \cos 2\pi (hx/a + ky/b + lz/c)$$

which can be calculated directly from experimentally available quantities and which must be related in some way to the electron density distribution. The properties of the function $P(xyz)$ were first described by A. L. PATTERSON, who showed that it contained maxima at the positions of interatomic vectors, all drawn from a common origin. Every pair of atoms in the unit cell gives rise to a peak whose position corresponds to the vectorial distance between the atom pair and whose height is roughly proportional to the product of the two atomic numbers. If the unit cell contains N atoms, then $P(xyz)$ will contain $N(N-1)$ peaks arranged in pairs across the origin.

The set of vector peaks corresponding to a simple arrangement of points is shown in Figure 5. The problem of deriving the point set form the vector set is an interesting one but it can be solved, provided that the individual elements of the vector set are resolved from one another — as they are in the example shown. But as the number of atoms in the unit cell increases, the number of vector peaks goes up as N^2 while the volume of the unit cell depends only on N. Thus the density of vector peaks, the number per unit volume, increases with N and a stage must be reached, for any given degree of resolution, where the vector peaks merge into one another and cease to be recognizable as individuals. In practice, this limit is reached with about 25 to 50 atoms in the unit cell, which may contain two, four, or even more molecules. In view of this limitation, the method does not appear to offer very wide possibilities.

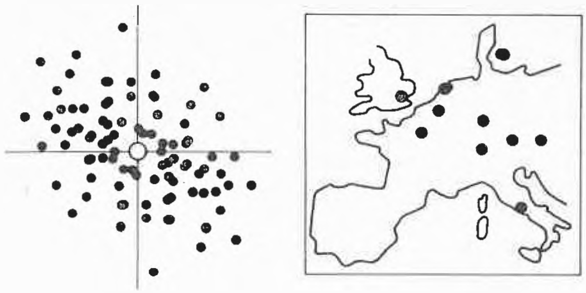


Figure 5. The distribution on the left shows the terminations of all possible intercity flights, but starting at a common origin. It is the "vector set" corresponding to the "point set" of airports

The situation is quite different if one or two atoms of much higher atomic weight than the others are present. Suppose that a heavy atom, say iodine, is introduced into a complex organic molecule of unknown constitution and that we have available the vector distribution function of a crystal of this iodinated material. Suppose, too, that the unit cell contains more than one molecule. We can divide the vector peaks into three groups. Those due to iodine-iodine vectors have heigths proportional to $53^2 \sim 2800$. On the same scale, those due to iodine-carbon and carbon-carbon vectors have heights of $53 \times 6 \sim 320$ and $6^2 \sim 36$ units respectively. Under these conditions, the carbon-carbon peaks may be virtually ignored since they provide only a background on which the iodine-iodine and iodine-carbon peaks are superimposed. The iodine-iodine peaks, on the other hand, will dominate the function and be clearly recognizable. The spatial relationships that exist between relatively heavy atoms in a crystal can thus be found directly from the observed data without too much trouble, even in the presence of hundreds of lighter atoms.

From this point, it is possible to proceed in either of two ways. We could try to identify and unravel the system of iodine-carbon vectors and thereby deduce the arrangement of carbon atoms relative to the known framework of the iodines; or alterantively, we could sum the density waves with the phase angles due to the iodine contributions alone. These phase angles are certainly not the correct ones and some will be seriously in error but they are better, on the average, than a purely random selection. The resulting distribution function should represent an improvement on the model consisting only of iodine atoms, an improvement that will manifest itself in a tendency for small accumulations of density to occur at the positions of the carbon atoms. If some of these can be recognized, the phase angles can be recalculated using this extra structural information and the process repeated, just as in the trial and error method. Although the process is to some extent self-correcting in the sense that an incorrectly chosen atom can usually be detected in subsequent stages, skill, experience and imagination are required for recognizing correct groupings of atoms and for disregarding the spurious peaks that inevitably arise in the early and intermediate stages. Chemical information, if available, can be a help but only in limited degree because until all, or nearly all, the atoms have been correctly located it is difficult to know where one molecule ends and another begins. Besides, the temptation to make the data agree with preconceived ideas about the molecule must be avoided.

This method is usually known as the heavy atom method and a number of variations have been developed. One method of attack is to use not one heavy-atom derivative but two or three different ones. If these form a series of isomorphous crystals that differ only in the positions or scattering powers of the heavy atoms then it may be possible to place extra limitations on the phase angles, in some cases even to define them completely. This variation has proved especially valuable in the analysis of protein crystals. Another variation is to irradiate the crystals with X-rays whose energy lies close to the excitation energy of the K- or L-electrons of the heavy atom. Under these special conditions, the wave scattered by the heavy atom has a small component whose phase is advanced by 90° with respect to the main component, which is reduced somewhat from its normal size (Figure 6). This effect makes it possible not only to define the magnitudes of the phase angles but also their absolute signs. Under normal circumstances, a pair of enantiomorphous crystals give exactly the same X-ray diffraction pattern. For both crystals, $|F(hkl)| = |F(\bar{h}\bar{k}\bar{l})|$ and $\alpha(hkl) = -\alpha(\bar{h}\bar{k}\bar{l})$. Under conditions of anomalous dispersion, the out-of-phase component can lead to a detectable difference (Figure 7) in the magnitudes of $|F(hkl)|$ and $|F(\bar{h}\bar{k}\bar{l})|$ which makes it possible to establish the chirality of the structure. Anomalous dispersion was used by J. M. **Bijvoet** in his classical determination of the chirality of sodium rubidium D-tartrate, which put stereochemistry on an absolute basis.

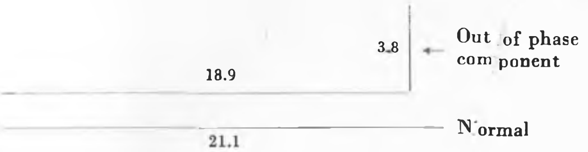
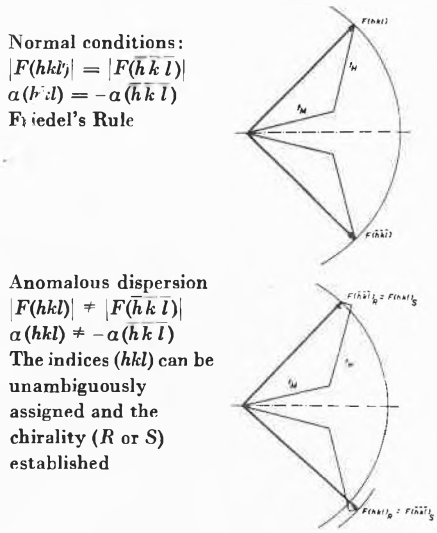


Figure 6. Anomalous phase-change. Scattering power of cobalt (K absorption edge, 1.60 Å) with CuKα incident radiation ($\lambda = 1.54$ Å)

Methods that use relationships among the observed amplitudes or intensities to assign or place limitations on the phase angles have also been developed. Every possible assignment of phase angles to a set of Fourier waves of given amplitudes corresponds to some kind of distribution of scattering matter. Any method of phase determination must accordingly be based on structural assumptions that provide criteria by which a correct or approximately correct assignment can be selected. Direct methods rest on structural assumptions that are of an extremely general nature, for example, that the electron density in the crystal is nowhere negative, or that it is restricted to a maximum possible value. They have been applied with considerable success to a number of centrosymmetric structures, where the phase problem reduces to one of ambiguity in the sign to be associated with each observed structure amplitude. The more general problem that is presented by non-centrosymmetric structures is much more difficult to solve and no successful applications to non-centrosymmetric structures have been reported so far. Here the heavy atom method and its variations appear to offer the only possibility for successful analysis.



Normal conditions:
$|F(hkl)| = |F(\bar{h}\bar{k}\bar{l})|$
$\alpha(hkl) = -\alpha(\bar{h}\bar{k}\bar{l})$
Friedel's Rule

Anomalous dispersion
$|F(hkl)| \neq |F(\bar{h}\bar{k}\bar{l})|$
$\alpha(hkl) \neq -\alpha(\bar{h}\bar{k}\bar{l})$
The indices (hkl) can be unambiguously assigned and the chirality (R or S) established

Figure 7. Use of anomalous dispersion to establish chirality (absolute configuration)

It is now time to mention some of the practical difficulties that have to be overcome in the course of a structure analysis by X-ray methods. First, there is the problem of collecting the necessary experimental data, the intensities of the diffracted beams. Depending on the complexity of the structure, several hundred to several thousand intensity observations are required. In many crystals, the atoms undergo vibrations of fairly large amplitude at room temperature. These movements are associated with a decline in the diffracted intensity at high scattering angles. If the resultant diminution in intensity is very severe, the high order reflections may become so weak as to be virtually unobservable. In such cases, an increase in the intensity of these reflections can be brought about by cooling the crystal during the exposure time.

The reflections are usually recorded on series of photographic films and the intensities estimated either visually or with a microdensitometer. In general, several exposures of each photograph are required to cover an adequate intensity range; moreover, multiple observations of certain groups of reflections must be made for correlation purposes. Thus, in the course of collecting the data, an individual reflection may be measured not once but several times. Photographic methods have the advantage that whole groups of reflections can be observed simultaneously on a single film but they have other, less attractive aspects. The process of estimating the intensities is a long, tiresome business that demands more or less full-time concentration of a competent person over a period of several months and the accuracy attainable, although adequate for many purposes, does not really meet the standards that are desirable.

The increasing use of X-ray methods in the study of complex substances has emphasized the need for accurate, fast, automatic methods of measuring large numbers of intensities. Various kinds of automatic or semiautomatic diffractometers, which measure the diffracted intensities directly by means of proportional or scintillation counters, have been developed to meet this need and are rapidly coming into general use. With these instruments, several hundred intensity measurements per day can be made with much higher accuracy than that attainable by photographic methods. The use of automatic diffractometers will probably become even more widespread although it is unlikely that photographic methods, with their special advantages, will be entirely displaced.

Once the experimental data have been collected, there arises the problem of carrying out the numerical calculations that are involved at nearly every stage of the analysis. Except for very simple cases, these calculations are of such formidable dimensions that they can hardly be performed without computing aids of one kind or another. The evaluation of a typical three dimensional Fourier synthesis containing a few thousand terms at sufficient points over the unit cell to give an adequate picture of the electron density is a task which would keep someone busy for several years and strain the patience and perseverence of the unfortunate victim to unbearable limits. Remembering that a structure analysis may involve not one but several such syntheses, in addition to other no less extensive computations, it is not surprising that X-ray analysts tended to avoid such problems until suitable computing aids became available. Until the early 1950s, three dimensional calculations were the exception rather than the rule and most structure analyses were based on two dimensional data, leading to projections of the electron density down suitably short crystal axes. The computational labour involved here is much less, but so is the information that can be gained from such limited studies.

The general introduction of three dimensional methods only became possible with the development of electronic computors. As these have become more powerful and more widely available, X-ray structure analysis has been extended to the study of more and more complex substances. It has been extended in depth as well as in range for it now became possible, for the first time, to extract all the information that was hidden in the experimental data. The intensities of the diffracted beams depend not only on the positions but also on the vibrations of the atoms in the crystal. Previously, because of the extra computational labour involved in further refinement, analyses had usually been terminated with the determination of the approximate atomic positions. With improved computing facilities, the thermal motions can be taken into account and the atomic positions determined with greater accuracy.

For these refinement stages, the parameters describing a particular molecular model must be adjusted by comparison with the experimental data; this can be done either by Fourier methods or by procedures that depend on the least squares principle. In Fourier methods, the electron density corresponding to the particular model is usually subtracted from the one derived from the experimental data. Careful scrutiny of the details of the resulting difference function then suggests ways in which the model may be improved to bring it into better accord with experiment. It has often been said that hydrogen atoms cannot be detected by X-ray analysis, because of their low scattering power, but this is not the case. They can be seen fairly well in difference functions, even in the presence of relatively heavy atoms such as chlorine or bromine, although naturally their positions cannot be measured as accurately as those of heavier atoms (Figure 8). In least squares methods, the details of the model are adjusted by the condition that the calculated intensities should agree with the observed ones as closely as possible. The two methods are more or less equivalent but the least squares one has the advantage that it is particularly well suited for automatic, iterative, machine operation.

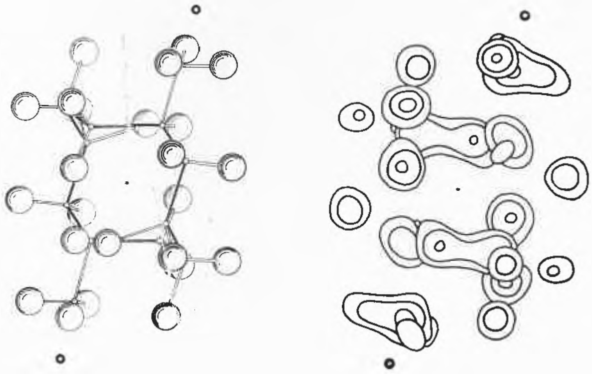


Figure 8. Electron-density distribution of 1,6-*trans*-diaminocyclodecane dihydrochloride after subtraction of the carbon, nitrogen and chlorine atoms. The residual distribution reveals the positions of the hydrogen atoms

Largely because of these improvements in computing techniques, the last few years have seen a series of X-ray structure determinations of complex natural products of unknown or only partially known chemical constitution. I shall not repeat the list of compounds whose structures have been determined in this way but shall only remind you that the structures were obtained complete with all details of configuration and conformation—in some cases with absolute configuration. The most complex compound whose structure has been fully determined in this way is probably vitamin B_{12}, $C_{63}H_{88}O_{14}N_{14}PCo$. It is probable that most of these structure determinations were carried out faster and more economically—I am thinking of the cost in man-years—by X-ray analysis than they could have been done by chemical methods. The disparity is likely to increase with time because so many of the steps in an X-ray analysis can be automatized.

It should be obvious, however, that the usefulness of X-ray analysis in organic chemistry is not restricted to the investigation of complex natural products of unknown constitution. It may also be applied to quite simple substances of known constitution to derive interesting and important structural information. Such analyses have provided most of our information on interatomic distances and valency angles in molecules, and all of it about how molecules pack in the solid state. Information of this kind is essential if we are ever to have a clear understanding of how molecules interact with one another in the course of chemical reactions. In my own laboratory in Zurich, we have been studying the conformations of the medium sized cycloalkanes and their derivatives; the results, though by no means complete, have provided a good basis for the understanding of the rather peculiar chemical properties of this class of compounds. There are many other problems where it is almost impossible to come to reliable structural conclusions by ordinary chemical methods, and I may refer here particularly to various classes of organometallic compounds with structures that defy description in terms of normal chemical bonds.

I have tried to provide a short introduction to the theory and practice of X-ray crystal structure analysis, as it is being applied to structural problems of organic chemistry. I hope that I have shown that the subject involves no intrinsically difficult ideas. To be sure, complications arise in practice and one can hardly demand that every chemist should be capable of carrying out his own X-ray analysis. I believe, however, that a certain level of acquaintance, sufficient at least to comprehend the significance of the results, should be of advantage to every chemist. Each year, X-ray investigations of several hundred crystal structures are carried out, often by people who have not been trained as chemists and who are not quick to see the chemical implications of their work. A vast amount of quantitative information on many aspects of molecular structure is thus being accumulated. While much of this information may merely confirm what we, as chemists, already know, some of it is new, some of it can easily be incorporated into existing theories, some of it is puzzling—and to be honest, some of it is wrong. If this brief review helps anyone to see the potentialities and limitations of X-ray analysis, then it will have served its purpose.

Suggestions for further reading

An excellent introduction to the study of crystals by X-ray and optical methods is:

C. W. Bunn, *Chemical Crystallography*, 2nd edition, Oxford University Press, 1961.

Technical aspects of X-ray analysis are covered at a more advanced level in:

M. J. Buerger, *Crystal Structure Analysis*, John Wiley, New York/London 1960.

H. Lipson and W. Cochran, *The Determination of Crystal Structures*, Bell, London 1953.

A. Guinier, *Théorie et Technique de la Radiocristallographie*, 2e édition, Dunod, Paris 1956.

The following book and articles provide fairly recent reviews of the results of structure determinations by X-ray methods:

S. C. Nyburg, *X-Ray Analysis of Organic Structures*, Academic Press, New York/London 1961.

A. McL. Mathieson, The Direct Determination of the Molecular Structures of Natural Products, *Pure Appl. Chem. 2* (1961) 505–32.

A. Rich and D. W. Green, X-Ray Studies of Compounds of Biological Interest, *Ann. Rev. Biochem. 30* (1961) 93–132.