QUARTERLY REVIEWS

# MOLECULAR STRUCTURE DETERMINATION BY *X*-RAY CRYSTAL ANALYSIS: MODERN METHODS AND THEIR ACCURACY

By G. A. JEFFREY, Professor of Chemistry, University of Pittsburg, and
D. W. J. CRUICKSHANK, Lecturer in Mathematical Chemistry,
University of Leeds

(With a preface by E. G. Cox, Professor of Inorganic and Structural
Chemistry, University of Leeds *)

IN concluding his Hugo Müller lecture [82] J. D. Bernal deplored the fact that (in 1945) structure analysis " is looked on somewhat as a mystery and [that] it is difficult for any chemist brought up on existing lines even to understand the meaning of its results ". This may have been unduly pessimistic, but it is certainly true that most statements about diffraction methods and their results contained in books on molecular structure and valency written in the last ten years do little to dispel the mystery and certainly give no help to the chemist who wishes to assess the worth of diffraction results in particular cases. There is undoubtedly a perennial need for such help, but a review aiming to give it and to survey the current state of accurate *X*-ray analysis is particularly appropriate at the present time because the problems of locating atomic centres in molecules are now well understood and largely solved, and crystallographers are beginning to turn their attention to new problems such as that of determining the distribution of valency electrons.

In the 'thirties the major weapons with which modern structure analysis is carried out were forged and tested. The heavy atom and isomorphous replacement techniques, first used by Cork on the alums,[83] were applied to organic molecules with such success that in 1936 it was found possible to make a complete structure analysis of a centro-symmetrical molecule without the assistance of chemical information; [19] three-dimensional methods were used, first in the extension of the Patterson synthesis,[84] then with the Fourier synthesis to a limited extent, *e.g.*, on pentaerythritol,[5] and in 1939, combined with the isomorphous replacement technique, in the first determination of the structure of an asymmetric substance,[85] again without the help of chemical information. In spite of these successes, however, progress in general was rather slow, and the results obtained, while satisfactory enough when only problems of stereochemistry or of general

---

* This review develops, much more fully than was then possible, the theme which I took for my Tilden Lecture to the Chemical Society in 1947.—E. G. C.

molecular dimensions were in question, could not be used with confidence in discussions of valency problems involving variations of a few hundredths of an Ångstrom unit, since there were no certain criteria for assessing their accuracy.

Since the war, apart from the increase in tempo which structure analysis has experienced in common with most other sciences, the situation has been changed completely by a number of factors of which the chief probably are (*a*) the development of many derivative Fourier methods such as difference and differential syntheses ; (*b*) the application of punched-card and, more recently, electronic digital machines to the calculation of three-dimensional syntheses and of structure factors ; and (*c*) the recognition of the different classes of errors to which structure analysis is susceptible, the development of methods for correcting systematic errors, and the application of statistical methods to determine as precisely as possible the effect of random errors on the probable accuracy of the results.

It will be observed that these three kinds of development are all concerned with the *interpretation* of the experimental data, and indeed the emphasis in recent years has been on the better utilisation of the experimental results rather than on raising the accuracy of the latter ; in fact, until the methods of dealing with errors referred to under (*c*) had been developed, there was no very clear means of deciding how extensive or how accurate the experimental results ought to be. This is not to say that experimental techniques have been neglected ; many improvements have been made, but experimental error has not at any stage in recent years been the factor limiting further advance, although it might become so in the near future. As shown in Section 10 (p. 373), in some recent analyses rather less than half the residual errors appear to be due to errors in the experimental observations. It should be noted, however, that these remarks apply primarily to organic substances which are reasonably stable solids under ordinary laboratory conditions ; a notable feature of experimental advances in recent years has been the development of techniques for the *X*-ray examination of substances which require low temperatures, inert atmospheres, or other special conditions for the experiments, and the results obtained in such circumstances may not be as extensive or as accurate as is necessary for a fully detailed structure analysis. In the case of benzene, for example, it is unlikely that accurate measurement of the bond lengths will be possible without a considerable improvement in experimental technique (involving very low temperatures) because, down to − 20° at least, the thermal motion of the molecules is so great that perhaps only a quarter of the total number of reflections theoretically possible with copper radiation can be observed. Experimental difficulties may also set a limit to the accuracy with which compounds containing very heavy atoms can be analysed ; thus an accurate determination of the positions of the nitrogen atoms in lead azide is difficult because the *X*-ray scattering from the lead atoms " swamps " that from the nitrogen atoms, whose contribution thus becomes comparable with the experimental errors.

Nevertheless, there are very many cases where no such difficulties arise, and the successful prosecution of the analysis then depends only on overcoming the interpretational difficulties. In the following Review an attempt has been made to give a connected account of modern methods of doing this which we hope may enable structure analysts to take stock and may give others fairly precise indications of the power and limitations of present-day $X$-ray analysis ; such an account cannot unfortunately be divested entirely of technicalities, but we hope that some chemists will find the details interesting and that still more (*pace* Professor Bernal) will understand the conclusions and their implications.

Of the major technical advances referred to above, the significance of those relating to errors and accuracy will be immediately recognised by anyone interested in correlating observed bond lengths and bond angles with other molecular properties and particularly with the results of wave-mechanical calculations ; they will be even more important in the future when, as we hope, the refinement of structure analyses will be carried far enough to show the distribution of valency electrons in bonds. Errors and questions of accuracy are dealt with fully in later sections of this Review, as are also the various newer methods of Fourier synthesis, but it is perhaps not out of place to comment briefly on mechanical and electrical aids to computing. Punched-card methods, operated by professional computers in collaboration with crystallographers, were used during the war in the successful structure analysis of penicillin ;[86] it was subsequently found [48, 49] that it was possible for crystallographers themselves to operate punched-card methods of varying degrees of complexity, and during the past few years the analyses of many structures have been greatly speeded up and increased in accuracy with their help. In the last year or two, electronic digital computers have been applied to crystallographic calculations,[38, 50, 51, 72] and it already seems likely that they will revolutionise structure analysis. Enormous though the help of punched-card machines has been, everything which they have done could have been done in principle by means of desk machines, and it is not greatly exaggerating to say that it could in actual fact have been done that way, although naturally with much greater expenditure of time. At the present time, the same calculations can be done on electronic digital machines in a tenth to a twentieth of the time required on punched-card machines ; this ratio, however, is largely determined by the relatively long time taken to prepare the material, to feed it into the machines and to print out the results, for the actual calculating speed of electronic machines is enormously greater than that of any other type. The refinement of a crystal structure, as will be clear from the account given below, is an iterative process, and whereas until very recently it has been necessary to take results from the machine at each stage and use them to prepare new data to put back into the machine for the next stage, it will shortly be possible to arrange an electronic digital machine to make the necessary adjustments to the data between stages internally without wasting time in printing out. When such a programme has been perfected, a structure analysis will then be taken from the approximate correct structure (see Fig. 1) to the end of the refinement in a few hours instead of as at present (usually) many weeks, and because of the very high speed it will probably also be cheaper. This is already much more than could possibly be envisaged with punched-card machines, but it is not too much to hope that the solution of the phase problem (see p. 342) is attainable by means of electronic machines. If this should prove to be so, interpretative techniques would seem to have very little further to go for some time, and the pendulum of development would swing to the experimental side, where among other things strong efforts would no doubt be made to raise the speed of intensity measurements, although physical laws would limit what could be done without loss of accuracy in this direction.

## 1. Introduction

An $X$-ray single-crystal structure analysis can be separated into a series of operations of which the difficulties vary considerably from one crystal structure to another. There is, however, sufficient uniformity in the method to make it possible to outline a general plan. This is shown in Fig. 1 as a block diagram which forms the framework of our subsequent discussion. As we are mainly concerned with the bearing of recent advances in the technique of refinement and in the estimation of accuracy on the study of molecular structures, the initial stages of the method are reviewed briefly and are discussed in detail only when relevant to the question of reliability of the final results.

It is convenient for the purpose of this article to have in mind a particular problem of average difficulty ; for example, the structure analysis of a non-planar organic molecule with about ten atoms (carbon, nitrogen, or oxygen) apart from the hydrogens. Much of this account will apply similarly to far simpler and to much more complex structures, though the emphasis at the various stages would then be different in each case. In dimethyltriacetylene,[1] for example, the structure is so simple that there is essentially no *phase problem*, whereas in ribonuclease [2] the *phase problem* is so complicated that it is difficult at present to visualise a detailed refinement.

Before discussing the scheme in Fig. 1 in detail, a brief account will be given of the method as a whole, in order to show the relationships of the various sections to each other and of the results at each stage to the final electron distribution in the crystal.

The preliminary $X$-ray examination of the crystal aims to find the unit-cell dimensions, the number of molecules in the repeating unit, and the symmetry relations between molecules, ions, or atomic groups which are conveniently expressed as the *space group*. Other relevant physical observations which may help the structure determination are the cleavage and measurements of refractive indices, and pyro- and piezo-electricity. This part of the research may occupy anything from a day to a month, depending upon the nature and structure of the crystals. It is preliminary to the structure analysis proper, because it is upon its results that the crystal-

[1] Jeffrey and Rollett, *Proc. Roy. Soc.*, 1952, *A*, **213**, 86.

[2] Carlisle and Scouloudi, *ibid.*, 1951, *A*, **207**, 496.

lographer bases his judgment as to whether it is worth while proceeding to a complete analysis, which will be a much more extensive research. A good estimate of the time for the more straightforward part of the work can then be made, but as only indirect methods are available for solving the *phase problem*, it is not generally possible to predict the whole course of the analysis. If the objective is information about a particular group of atoms which occurs (with, so far as is known, no significant variation) in a number of different crystalline substances, the wisest procedure is evidently to determine the space groups of as many as possible of them in order to select the most promising for the detailed analysis.

If an analysis is to be carried to the limit of present-day technique, as discussed in this Review, a complete experimental record must be made. This consists of the measurements of the intensities of *all* the observable diffraction spectra under the optimum conditions for accuracy. From these measurements the *amplitudes* of the structure factors can be calculated but not their *phases*, and it is the indirect deduction of these structure phases which constitutes the *phase problem.* The detailed methods at present available for solving this fundamental problem are of great technical interest to the crystallographer and have recently been discussed elsewhere ; [3] a description of them is outside the scope of this Review, although it is relevant later to give a brief enumeration of those which are particularly effective.

The attempts at solution of the phase problem lead to *trial structures*, and when a correct one has been found the refinement is theoretically a straightforward if somewhat formidable iterative process. In practice, as shown in Fig. 1, the refinement is usually broken down into two stages : the so-called two-dimensional and three-dimensional analysis. There is a good practical reason for this distinction with a structure of average complexity ; the calculations of the first part can be dealt with by means of a desk calculator, while the second part usually requires large-scale computing equipment of the Hollerith or electronic type. The two-dimensional refinement of the projections of the molecules in the unit cell is therefore pursued as far as possible before the structure is examined in all three dimensions simultaneously. Before 1945, this was, with a few exceptions, the end of the analysis. With corrections for certain systematic errors which would now be applied, it is still a point at which the analysis can be concluded if the objective is solely to determine configuration or some broad feature of stereochemistry.

The three-dimensional refinement of atomic co-ordinates may proceed either by Fourier or by least-squares methods. There is a formal equivalence of the two methods, although they differ in application and the results are not usually exactly coincident owing to different relative weightings of the experimental observations. This Review is mainly written in the terms of the Fourier methods, but the least-squares treatment is discussed more briefly in a separate section.

Until very recently the determination of the atomic co-ordinates from

---

[3] " Computing Methods and the Phase Problem in X-ray Analysis ", Edit., Pepinsky, The Pennsylvania State College, U.S.A., 1952.

the three-dimensional refinement corrected for systematic errors was the end of the analysis. It is still the point of conclusion if the object of the research is to elucidate a problem connected with the bond lengths or to represent the molecule in terms of bond character and valence-bond diagrams. Although the maxima of the atomic peaks are accurately known at this stage, other features of the electron density are much less certain. More information can be obtained by further refinement if, as is often the case, the experimental errors are less than the discrepancies between the observed structure amplitudes and those calculated from the final atomic co-ordinates. This additional information may be about the location of the hydrogen electrons or about the asymmetry of the electron distribution around the atomic centres which can arise from thermal motion and from the participation of atomic electrons in the bonds between atoms. For most structure analyses, the computations associated with these last stages of refinement are extremely laborious, and it is only in a few selected examples that results of this nature have so far been obtained.

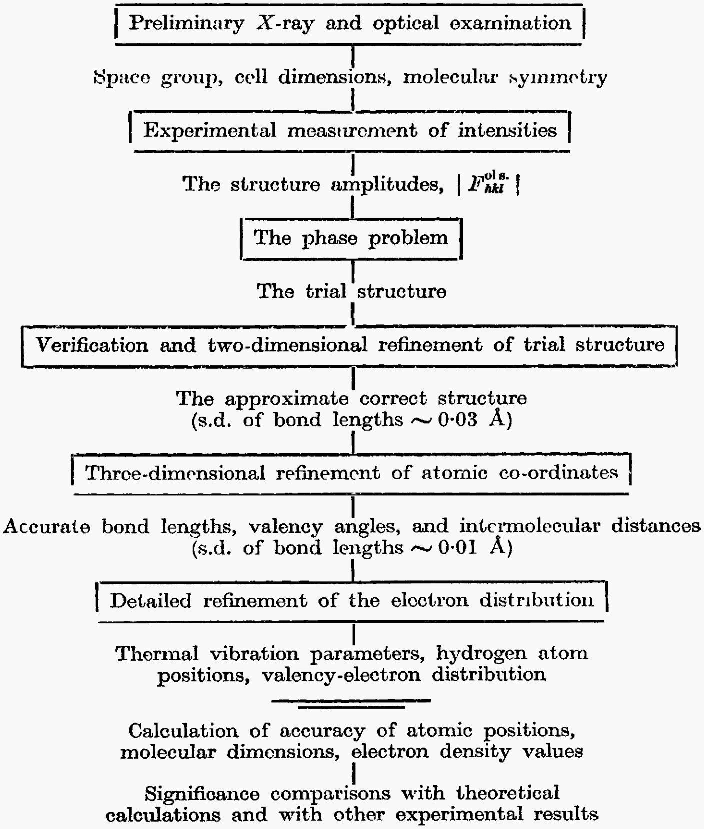


FIG. 1

*Schematic* X-*ray structure analysis.*

## 2. Information from Optical and Preliminary Crystal Data

If crystals of 0·02—0·10 cm. can be grown, the optical and preliminary $X$-ray examination presents no difficulty, and even if all solvents yield only minute, mal-formed, or twinned specimens, insurmountable experimental difficulties are seldom encountered. These measurements give much important information relevant to the crystal-structure analysis, *viz.*, the unit-cell dimensions, the number of molecules in the unit cell, the space group or a choice of alternative space groups, the refractive indices, and the cleavage.

The determination of the unit-cell dimensions from the measurement of the directions of the diffracted spectra can be accurate to 0·001 Å under good experimental conditions. Together with the observed density, these data provide the well-known $X$-ray method of determining molecular weights, the dominating factor in the accuracy of which is the difficulty of measuring the densities of small crystals.

Of the 230 possible space groups, only 60 are uniquely characterised by the $X$-ray diffraction spectra. Fortunately, these include $P2_1/c$ which, if optically active substances are excluded, is by far the commonest for organic crystal structures. The ambiguities among the other 170 arise from the inability of the $X$-ray diffraction to reveal the asymmetry of a structure. All crystal structures diffract as if they were centro-symmetrical,* and it is only when two elements of translational symmetry in combination require a centre that the space group assignment is unique. Examination by optical or pyro- and piezo-electric methods does not entirely resolve the problem, for the external form of the crystals is never absolutely reliable and the electrical measurements cannot detect weakly polar structures. This is illustrated by the historic case of pentaerythritol where, in spite of intensive study of the symmetry (Vol. 1 of the " Strukturbericht", 1929, gives 15 references), investigators could not distinguish between two space groups. One of these required the valencies of the central carbon atom to be pyramidal, while the other allowed the tetrahedral arrangement, later established by a detailed analysis.[5] An $X$-ray method based on the statistical distribution of the intensities of the diffracted spectra has been developed since 1945.[6] It is most effective, but suffers from the inconvenience that it gives reliable decisions only with a large number of $X$-ray intensities, whereas it is often desirable that the space group be known before undertaking the bulk of the experimental intensity measurements, owing to the considerable difference in the work involved in an analysis of a centrosymmetrical and a non-centrosymmetrical structure.

The information about the molecular arrangement in the crystal which can be deduced from the preliminary data depends very much upon the type

---

[4] Peerdeman, van Bommel, and Bijvoet, *Proc. K. Akad. Amsterdam*, 1949, **52**, 313.

[5] Llewellyn, Cox, and Goodwin, *J.*, 1937, 883.

[6] Wilson, *Acta Cryst.*, 1949, **2**, 318 ; Rogers, *ibid.*, 1950, **3**, 455 ; Howells, Phillips, and Rogers, *ibid.*, p. 210.

* Under very special conditions, not applicable in ordinary structure analysis, this is not true, and absolute configurations of asymmetric substances have been determined.[4]

of molecule and the crystal class. In layer structures and those with large planar molecules, the dimensions of the unit cell together with the refractive indices often reveal the broad features of the molecular packing and put a limit to the range of the possible molecular orientations. In the crystal structure of a roughly spherical molecule such as a methyl-substituted *cyclo*hexane or a hexose, on the other hand, it is unlikely that the shape and symmetry of the crystal lattice will give any clues to the solution of the structure analysis; for in these, the molecular packing will conform to some three-dimensional system of intermolecular forces and there will be no chain or layer aggregation which can be revealed by the physical properties of the crystals.

In diamond,[7] which is a particular example of a giant molecule, where each carbon atom occupies a special position in a highly symmetrical cubic lattice, the interatomic separation is determined directly by measurement of the cell dimension. This parameter has been measured by the very accurate divergent-beam technique [8] to 0·00005 Å. The cell sides of individual diamonds vary over a range of $a = 3{\cdot}55970 \pm 20kX$ at 18°, which corresponds to a C–C separation of $1{\cdot}54447 \pm 0{\cdot}00009$ Å. There are inorganic covalent or ionic structures which resemble diamond in the simplicity of their structures and many in which a proportion of the atoms can be exactly located from the cell dimensions and space group (as a group the minerals provide the most examples). The most favourable cases in organic molecular structures are those in which the symmetry of the crystal structure corresponds with the symmetry of the molecule and thereby reduces the number of unknown parameters in the analysis. There are many examples of this for molecules with centres of symmetry, and fewer for those with mirror planes or two-fold axes. It is not the general rule, however, and is exceptional with molecules of higher symmetry. For example, although several methane derivatives such as tetranitromethane [9] crystallise with cubic symmetry, the six-fold axes of hexamethylbenzene [10] and coronene [11] are not reproduced in the crystal symmetry.

## 3. The Solution of the Phase Problem

From a known or postulated electron distribution in a crystal it is possible to calculate the directions and intensities of all the diffracted spectra produced under any given experimental conditions. If the reverse were true, *X*-ray structure analysis would be a straightforward procedure leading directly from the experimental measurements to the calculation of the final result. In fact there is an intermediate step which requires deductive methods and is generally called the *phase problem.*

The structure factor of the diffracted spectrum is denoted by $F_{hkl}^{\text{obs.}}$, where *hkl* is the order of the spectrum; $F_{hkl}^{\text{obs.}}$ is a complex number giving

---

[7] Structure Reports for 1947—8, Vol. 11, Vosthoek, Utrecht.

[8] Lonsdale, *Phil. Trans.*, 1947, *A*, **340,** 219.

[9] Oda, Iida, and Nitta, *J. Chem. Soc. Japan,* 1943, **64,** 616.

[10] Brockway and Robertson, *J.*, 1939, 1324.

[11] Robertson and White, *J.*, 1945, 607.

the amplitude and phase of the diffracted wave relative to that from an isolated electron at the origin of co-ordinates under the same experimental conditions. The intensity $I_{hkl}$, which is measured by photographic blackening or some equivalent method, is related to $F^{\text{obs.}}_{hkl}$ by

$$I_{hkl} . L_{hkl} = | F^{\text{obs.}}_{hkl} |^2 \quad . \quad . \quad . \quad . \quad (1)$$

where $L_{hkl}$ contains Lorentz, polarisation, and other known factors and $| F^{\text{obs.}}_{hkl} |$ is the amplitude. The phases, $\alpha_{hkl}$, cannot be measured experimentally, and must be deduced during the course of the analysis if use is to be made of the refinement methods discussed later.

An obvious method of solving a structure is to postulate a succession of atomic arrangements until one is found from which the calculated amplitudes $| F^{\text{calc.}}_{hkl} |$ agree with the experimental values. This trial structure, even if only approximately correct, may then serve to give sufficient knowledge of the phase angles to permit the completion of the analysis by means of Fourier methods. This trial and error method of deduction is very laborious for problems with more than a few independent parameters, and important advances have been made in the last few years in the use of Fourier transforms in conjunction with optical analogue methods [12] to replace the numerical calculations.

There are also two direct approaches to the problem of structure solution, one discovered in 1935 by Patterson [13] and the other in 1945 by Harker and Kasper.[14] Patterson's method depends upon the fact that while the $F^{\text{obs.}}_{hkl}$ relate to the distribution of atoms in the crystal, the $| F^{\text{obs.}}_{hkl} |^2$ relate to the distribution of interatomic distances. Since $| F^{\text{obs.}}_{hkl} |^2$ is known from (1), this distribution is known and is conveniently evaluated by means of the Fourier synthesis expressed in equation (2) and generally called the *Patterson synthesis* :

$$P(xyz) = \frac{1}{V} \sum \sum \sum | F^{\text{obs.}}_{hkl} |^2 \cos 2\pi(hx + ky + lz) \quad . \quad . \quad (2)$$

This method has had many successful applications and is especially useful if the molecules contain a relatively few atoms of atomic number much greater than the majority. It becomes ineffective for organic structures containing many carbon, nitrogen, or oxygen atoms because of the multiplicity of interatomic vectors of equal weight which cannot be resolved.

The more recent method is only useful for centrosymmetrical structures where the phase angles are 0 or $\pi$. It uses the conditions that the electron density is nowhere negative and is represented approximately by a set of spherical atoms, in conjunction with the mathematical relationships known as the Schwarz and Cauchy inequalities. A number of structures has been solved with the partial help of this method and a smaller number by this method alone. It has the limitation that it requires several of the $X$-ray intensities to be exceptionally strong, and the chance of this decreases as

---

[12] Lipson and Taylor, *Acta Cryst.*, 1951, **4**, 458.
[13] Patterson, *Z. Krist.*, 1935, **90**, 517, 543.
[14] Harker and Kasper. *Acta Cryst.*, 1948, **1**, 70.

the number of atoms in the asymmetric unit increases.[15] A recent statistical application appears to extend its scope.[16] Other related methods of direct sign determination have been proposed which have had a more limited success.[17, 18]

There are also methods which depend upon special characteristics of the structure under investigation ; the most familiar of these are the heavy-atom method [19] and the isomorphous-replacement method.[19] By whatever method the phase problem is solved, with the possible exception of the last two, it is seldom immediately apparent that a correct solution has been found, and the real test generally lies in the progress of the subsequent structure refinement.

## 4. Verification of the Trial Solution

The proof that a set of co-ordinates or of phases constitutes a correct solution to the deductive part of the analysis is provided only when it is shown to lead to a structure which refines satisfactorily. The procedure of solution and refinement can be regarded as an attempt to minimise the discrepancies between the observed and calculated amplitudes by adjusting the atomic positions in the unit cell and the atomic scattering factors, *i.e.*, to minimise some weighted function of the observed and calculated amplitudes ; *e.g.*,

$$\begin{aligned} R_1 &= \sum_{hkl} w_{hkl} \left( | F^{\mathrm{obs.}}_{hkl} | - | F^{\mathrm{calc.}}_{hkl} | \right)^2 \\ &= \sum_{hkl} w_{hkl} \left[ | F^{\mathrm{obs.}}_{hkl} | - \left| \sum_{N} f_i \exp \left( -2\pi i \, hx_i + ky_i + lz_i \right) \right| \right]^2 \quad . \qquad (3) \end{aligned}$$

where $w_{hkl}$ is the weight attached to the observation with indices $hkl$, $f_i$ is the scattering factor of the $i$th atom whose atomic co-ordinates are $x_i$, $y_i$, $z_i$ in fractions of the unit cell edges ; $\sum_{hkl}$ is summed over all observations ; and $\sum_{N}$ is summed over the $N$ atoms in the unit cell. The precise form of $R$ depends upon the method of refinement, but whatever it is, $R$ is a function of $3N$ variables which are the co-ordinates in the unit cell of the $N$ atoms ($3N-1$ in a non-centrosymmetrical structure). The aim of the refinement process is to find the lowest minimum in this $3N$-dimensional function. In a technically perfect analysis the residual discrepancies would then be due to experimental errors alone.

The possibilities of what may happen in refinement can be discussed by considering three forms for the variation of $R$ with change of parameters.

*Case* 1 : $R$ has a single minimum only. A form of $R$ in a one-parameter problem might be as shown in Fig. 2. For this case the trial structure can be any spatial combination of the atoms in the unit cell (with approximately correct scattering factors), and the correct structure within the limits of

---

[15] Hughes, *Acta Cryst.*, 1949, **2**, 34. [16] Zachariasen, *ibid.*, 1952, **5**, 68.
[17] Sayre, *ibid.*, p. 60. [18] Cochran, *ibid.*, p. 65. [19] Robertson, *J.*, 1936, 1195.

the experimental errors will be the automatic result of an iterative refinement calculation. There is really no phase problem to solve.

It is only in this case that the general method of steepest descents [20] will lead to a solution for any trial set of co-ordinates. For multi-parameter structures this is a very special case.

*Case* 2 : $R$ has two (or more) identical minima. A one-parameter problem might be as in Fig. 3. This is the *Patterson ambiguity*,[21] and is so called because both (or all) the structures which correspond to the minima in $R$ have exactly the same distribution of interatomic vector distances. They are therefore equivalent interpretations of the Patterson synthesis (equation 2), and of the experimental observations, and can in no way be distinguished by $X$-ray data alone. This is not altogether a hypothetical case, and a well-known example is the one-parameter problem of locating the metal ions in bixbyite, $(Mn,Fe)_2O_3$.[22] In this structure there are two physically distinct arrangements which give the same $X$-ray intensities. This, however, is only because the diffraction by the oxygen atoms is so small as to be negligible compared with that of the metal ions. In principle, and probably in practice, the two structures could be distinguished with very accurate intensity measurements. This was not necessary because one structure could be rejected as it required the oxygen atoms to occupy chemically implausible positions.

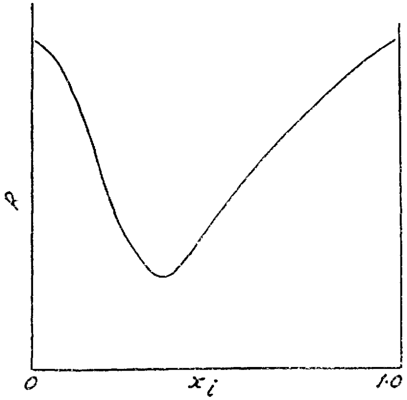


FIG. 2

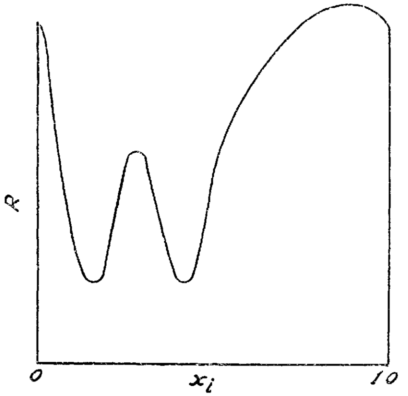


FIG. 3

If a Patterson ambiguity should occur in the analysis of an organic molecular structure, it is even less likely to be unresolved than in the compact arrangements of inorganic crystals, as the criteria of chemical sense are then more exacting. A mathematical study of the ambiguities in a general one-dimensional array of atoms has been made by Patterson.[21]

*Case* 3 : $R$ has one minimum which is the best fit between the observed and calculated amplitudes and many others for which the agreement is

---

[20] Booth, *Nature*, 1947, **160**, 196 , *J. Chem. Phys.*, 1947, **15**, 415.

[21] Patterson, *Phys. Review*, 1944, **65**, 195.

[22] Pauling and Shappell, *Z. Krist.*, 1930, **75**, 128.

more or less inferior. This is the general case which includes all multi-parameter analyses with few exceptions. In a one-parameter problem, the form of $R$ might be as in Fig. 4. For an iterative refinement to the true solution to be possible, it is essential that the trial structure lies on the slope of the trough that leads to that solution. A trial structure at $A$ will refine to $B$, whereas one at $C$ can only proceed to $D$. The only way of deciding whether a trial structure is at a position like $A$ or $C$ is to proceed some way along the refinement process. This is why the approximate true structure is represented in the block diagram in Fig. 1 as known for certain only after the first stage of refinement of the analysis. The distinction between a good trial structure, *e.g.*, $A$, and a bad one, *e.g.*, $C$, although not immediately apparent, is usually clearly defined in practice at an early stage of this first refinement. With a good trial structure the agreement between observed and calculated amplitudes improves progressively at each reiteration of refinement until the minimum is reached, at which two conditions are fulfilled : (i) the agreement is ‘ satisfactory ’, and (ii) the atomic parameters correspond to a molecule which is chemically sensible. In contrast, with a bad trial structure, successive refinement does not improve the agreement beyond an unsatisfactory stage, and the parameters do not conform to a sensible arrangement of atoms.

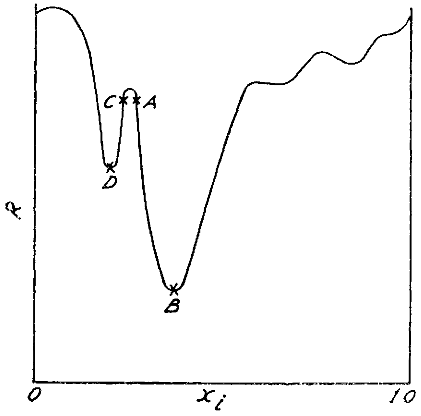


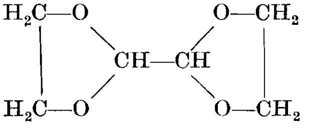
FIG. 4

A qualitative agreement between the observed and calculated amplitudes is not always sufficient to confirm a correct choice of trial structure and it is useful to have a numerical test of agreement. One that has been very generally adopted is the sum of the differences between the observed and calculated amplitudes divided by the sum of the observed amplitudes for all measured reflexions :

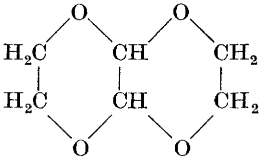
$$R = \frac{\sum_{hkl} \left| \, |F^{\text{obs.}}_{hkl}| - |F^{\text{calc.}}_{hkl}| \, \right|}{\sum_{hkl} |F^{\text{obs.}}_{hkl}|} \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Expressed as above, where it is necessarily less than 1, it is called the agreement index, (or disagreement index !) $R$ ; as a percentage $100R$ is the percentage discrepancy.

An interesting example of a false trial structure is provided by the analysis [23] of 2 : 2′-di-(1 : 3-dioxa*cyclo*pentyl) (I). Chemical evidence supported the *cis*-1 : 4 : 5 : 8-tetraoxadecalin configuration (II), and a trial structure based on this refined from $R = 0{\cdot}55$ to $0{\cdot}38$ but no further. When this was rejected, a trial structure based on (I) refined from $R = 0{\cdot}55$ to $0{\cdot}13$, and provided the correct solution. The Fourier projection corresponding to the incorrect trial (Fig. 5) was good enough to be misleading, although it implied a C–O bond length of 1·80 Å. It has much in common with the correct electron-density map (Fig. 6).



(I)



(II)

The agreement index, $R$ in equation (4), does not correspond exactly to the function minimised by either the Fourier or the least-squares method of refinement,[24] but it is easily computed and is often used as an indication of the merit of an analysis. In no way does it replace the proper quantitative calculations of accuracy described later, being necessarily a rough assessment for quick inspection. As a guide to this diagnostic use it is helpful to consider the values of $R$ for (i) a random array of the atoms with no relationship to the true structure, (ii) a promising trial structure, and (iii) a confirmed true solution. For (i) Wilson [25] has shown that the average value is 0·828 for a centrosymmetrical structure and 0·586 for a non-centrosymmetrical structure. Clearly, any trial structure which gives values greater than this is not worth pursuing.

A theoretical discussion which has bearing on (ii) has recently been given by Luzzati,[26] who has derived a relationship between $R$ and $|\Delta \mathbf{r}| . |s_{hkl}|$, where $|\Delta \mathbf{r}|$ is the root-mean-square of the errors in the atomic positions, and $|s_{hkl}| = 2 \sin \theta_{hkl}/\lambda$ is the reciprocal of the spacing of the crystallographic planes. This relation is shown graphically in Fig. 7, where the full and the broken lines refer to centrosymmetrical and non-centrosymmetrical structures, respectively. As would be expected, a particular root-mean-square error in the atomic co-ordinates results in a more serious discrepancy between observed and calculated amplitudes for a plane of small spacing than for one of large spacing. The $R$ values shown in Fig. 7 exclude the experimental errors ; they may therefore be 0·05—0·20 less than actual values, and the relation is not relevant to the accuracy of a fully refined analysis.

---

[23] Furburg and Hassel, *Acta Chem. Scand.*, 1950, **4**, 1584.

[24] Vand, *Acta Cryst.*, 1951, **4**, 285.

[25] Wilson, *ibid.*, 1950, **3**, 398.

[26] Luzzati, *ibid.*, 1952, **5**, 802.

From general experience it is found that, with a centre of symmetry, an agreement index better than 0·50 corresponds to a reasonable trial structure. With a correct solution, $R$ should improve on successive refinement to 0·20

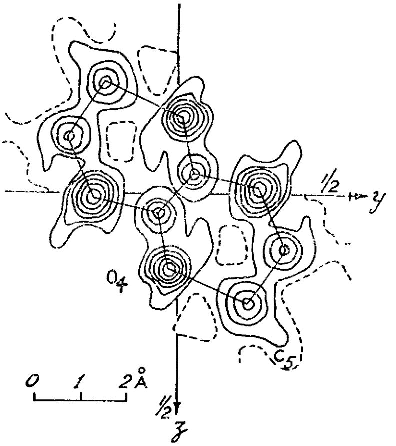


FIG. 5

*The electron-density map corresponding to the limit of refinement with the incorrect trial structure based on* (II).

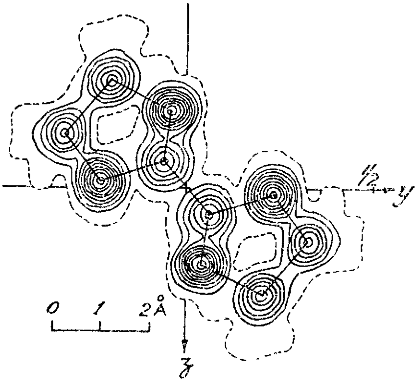


FIG. 6

*The electron-density map corresponding to the limit of refinement with the correct trial structure based on* (I).

(Figs. 5 and 6 reproduced, by permission, from Furberg and Hassel, *Acta Chem. Scand.*, 1950, **4**, 1584.)

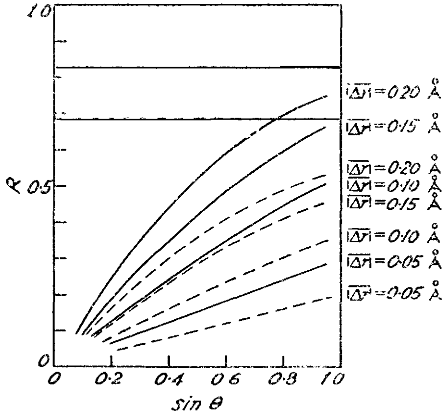


FIG. 7

*Variation of* R *with* $\sin\theta$ *for various values of* $|\Delta r|$.

(Reproduced, by permission, from Luzzati, *Acta Cryst.*, 1952, **5**, 802.)

or better; further improvement by the inclusion of hydrogen scattering and anisotropic scattering factors is discussed later. For a non-centrosymmetrical structure the values of $R$ should be about $\frac{2}{3}$ of those for centrosymmetrical structures, other things being equal.

## 5. Fourier Refinement of Atomic Co-ordinates

Apart from providing an elegant representation of the experimental data in terms of an electron-density map,[27] the Fourier synthesis is a means of progressing from a crude towards an exact analysis of the structure. A very approximate electron-density map based on a few known phases can be extended in favourable circumstances to include all the experimental amplitudes by the well-known *method of successive Fourier refinement.*[28] This was the first systematic method of structure refinement and is still the most efficient means of carrying out this stage of the analysis. As the refinement of a single structure may require six or more successive Fourier computations, this method has stimulated the design of a number of special machines, the most outstanding of which is the X-RAC,[3] where the electron-density contour map is presented on the screen of a cathode-ray tube.

The successive Fourier refinement in the centrosymmetrical structure has converged completely when all the observed amplitudes have been assigned phases and there are no changes of phase from the previous step (the non-centrosymmetrical case, which has not been properly understood until recently, is more complicated and will be discussed later). As is apparent from the discussion in the previous section, the method will only lead to the true answer if the first set of co-ordinates correspond to a correct trial structure. The *cis*-1 : 4 : 5 : 8-tetraoxadecalin example (p. 347) shows how successive refinement on an incorrect trial structure failed to converge to the true structure.

The actual appearance of the electron-density map is often used to judge the progress of the refinement and to make the decision whether to pursue or reject a trial structure. The two features which should improve with each successive refinement are (1) the shape of the contours near the atom centres, which should be almost circular, and (2) the electron density away from the atoms, which should nowhere have an appreciable negative value (in the use of X-RAC this condition [3] is the basis of a technique of phase determination for rapid refinement without calculation).

The Fourier synthesis may be used to represent the distribution of the electron density in the unit cell of a crystal in the three different ways expressed in the equations (5), (6), and (7) where $a$, $A$, and $V$ are the length of an axis, the area of a projection, and the volume of the cell respectively :

$$\rho(x) = \frac{1}{a}\sum_{-\infty}^{\infty} |F_{h00}| \cos(2\pi hx - \alpha_{h00}) \quad . \quad . \quad . \quad . \qquad (5)$$

$$\rho(xy) = \frac{1}{A}\sum_{-\infty}^{\infty}\sum_{\infty}^{\infty} |F_{hk0}| \cos(2\pi\, hx + ky - \alpha_{hk0}) \quad . \quad . \qquad (6)$$

$$\rho(xyz) = \frac{1}{V}\sum_{-\infty}^{\infty}\sum_{-\infty}^{\infty}\sum_{-\infty}^{\infty} |F_{hkl}| \cos(2\pi\, hx + ky + lz - \alpha_{hkl}) \quad . \qquad (7)$$

---

[27] Bragg, *Phil. Trans.*, 1915, **215,** 283.

[28] Robertson, *Rep. Progr. Phys.*, 1938, **4,** 332.

These correspond to the one-, two-, and three-dimensional Fourier syntheses respectively. In the one-dimensional synthesis, the data for the orders of a principal reflection ($\sim$ 10 observations) are used to calculate the projection of the electron density in the whole cell on to a principal crystallographic axis. Except in the simplest of structures the electron density of many of the atoms in the cell becomes superimposed and it is generally impossible to obtain any useful information. The two-dimensional synthesis, which employs the data from a principal zone of reflections ($\sim 10^2$ observations), is much more commonly used. This gives the projection of the electron density on to a face of the unit cell; if each atomic peak is resolved in at least two of the three projections the three co-ordinates of each atom can be deduced.

The three-dimensional synthesis uses all the available experimental data ($\sim 10^3$ observations) and gives the atomic co-ordinates directly. Since atoms in crystals are always more than 1 Å apart, there is no ambiguity due to the overlapping and non-resolution of atomic peaks, which is often a source of difficulty in the interpretation of the projections in complicated structures. In every respect but one the three-dimensional synthesis is superior to the two-dimensional. This important disadvantage is that the computation of the electron density even at comparatively large intervals ($\sim$ 0·2 Å) throughout the unit cell is a major task; it is the chief reason why most structure analyses before 1945 were two-dimensional. Now that the requisite large-scale computing methods have been developed, three-dimensional syntheses can be tackled as a matter of routine, and they are generally applied to complicated organic structures and to those where the desired standard of accuracy can only be achieved by making use of all available $X$-ray intensity data.

To some extent the recent developments in refinement technique, and in particular *the method of difference syntheses*, have overcome the difficulties which restricted the usefulness of the two-dimensional synthesis, and these still play an important role in the modern analysis. The three-dimensional refinement is more cumbersome even with large-scale computing equipment, and it is commonsense practice to extract as much information as possible from the principal zone reflections before undertaking the full ($hkl$) computations.

The improvements in Fourier refinement technique introduced since 1945, although closely inter-related, are conveniently discussed under three separate headings: (*a*) correction for termination of series errors, (*b*) the use of *difference syntheses*, and (*c*) the refinement of unresolved projections. (*a*) applies equally to two- and three-dimensional syntheses; (*b*) is also important for both but has so far been used mainly in projections.

(*a*) *Termination of Series Errors.*—Since the first use of Fourier methods, it has been realised [29] that systematic errors will occur in the electron-density distribution as a consequence of the use of a finite number of $|F_{hkl}^{\text{obs.}}|$ in a summation which theoretically requires an infinite series [equations (5), (6), and (7)]. These are variously called *diffraction errors*, *finite series errors*,

---

[29] Bragg and West, *Phil. Mag.*, 1930, **10,** 823.

*termination of series errors*, or simply *series errors*. The effect for a single peak is illustrated in Fig. 8.

The diffraction ripples from one atomic peak shift the maxima of others, and in combination they introduce spurious features on the electron-density map which can obscure and distort fine detail concerning lighter atoms or valency electrons. Another consequence of the finite series is a reduction in the height and curvature of the maxima.

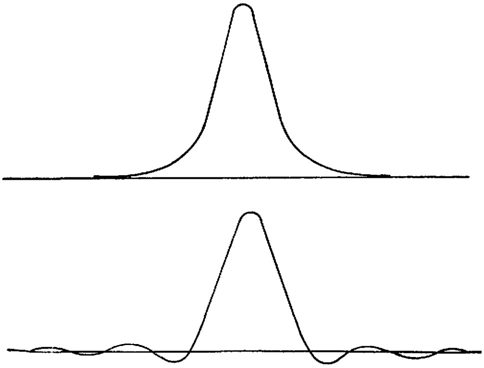


FIG. 8

(Top) *A single peak from an infinite Fourier series.*
(Bottom) *A single peak from a finite Fourier series.*

A similar effect, quite separate from the diffraction errors, arises from the spread of the electron cloud by the thermal motion which results in *overlapping* of the peaks. A consequence of this temperature effect is that the positions of the maxima of the electron density at the experimental temperature are not necessarily the same as those at absolute zero. As an example, Cruickshank [30] has shown that, with the thermal motion appropriate to dibenzyl at room temperature, two carbon atoms placed 1·386 Å

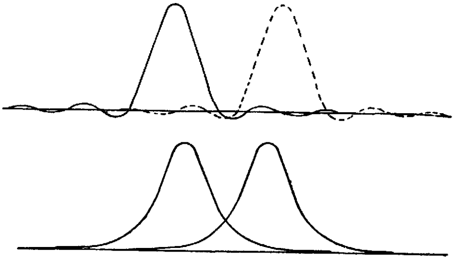


FIG. 9

(Top) *Two peaks from finite Fourier series, with small thermal motion.*
(Bottom) *Two peaks from finite Fourier series, with large thermal motion.*

---

[30] Cruickshank, *Acta Cryst.*, 1949, **2**, 65.

apart will appear 0·009 Å closer in the infinite series electron density; at 1·540 Å, the contraction is 0·005 Å.

As explained below, the corrections for both the diffraction and the overlapping errors are usually made simultaneously, the whole correction being called the *finite series correction*, although strictly this is a misnomer.

Before 1945, attempts were made to eliminate the diffraction errors by applying an *artificial temperature factor*[29] to the observed structure amplitudes; this had the effect of flattening and spreading the peaks as illustrated in Fig. 9, thereby increasing the *overlapping errors.* A simple and effective way of correcting for both diffraction and overlapping errors was proposed by Booth.[31] In the final stages of refinement of a structure analysis there will be close agreement between the observed and calculated $F$'s, and the two Fourier syntheses computed with $F^{\text{obs.}}$ and $F^{\text{calc.}}$ as coefficients will be subject to approximately the same systematic errors provided that both summations are over exactly corresponding sets of terms. The effects of series errors on the maxima in the $F^{\text{calc.}}$ synthesis can be known, for they are the differences between the co-ordinates for which the $F$'s were calculated and those of the corresponding maxima in the synthesis. These differences can then be applied with reversed signs as the corrections to the co-ordinates of the maxima in the $F^{\text{obs.}}$ synthesis. Because the sequence in a structure analysis is to calculate the $F$'s from the co-ordinates, $\boldsymbol{x}^{\text{obs.}}$, of the maxima in the observed synthesis and then to compute an $F^{\text{calc.}}$ synthesis to obtain the $\boldsymbol{x}^{\text{calc.}}$, the true co-ordinates, $\boldsymbol{x}^{\text{t}}$, are given by

$$\boldsymbol{x}^{\text{t}} = \boldsymbol{x}^{\text{obs.}} - (\boldsymbol{x}^{\text{calc.}} - \boldsymbol{x}^{\text{obs.}}) \quad . \quad . \quad . \quad . \quad (8)$$

and hence this is sometimes called the *back-shift*[32] method of correction.

In non-centrosymmetrical structures, any change in co-ordinates brings about a change in the phases, which can have any value between 0 and $2\pi$; this in turn results in new co-ordinates and the successive Fourier refinement theoretically never ends. Cruickshank[33] has shown that in the limit this infinite process together with the termination of series corrections is equivalent to a resultant co-ordinate shift of twice that appropriate for a centrosymmetrical structure. This *double-shift rule* applies to all co-ordinates in the space group $P1$, and in other non-centrosymmetrical space groups to those whose directions have no components normal to symmetry axes, *i.e.*, those parameters determined only by $F$'s with general phases. For corrections in directions normal to symmetry axes, *e.g.*, $x$, $z$ in $P2_1$, an n-*shift-rule*[32] is applicable, where $n$ has a value between 1 and 2 depending upon the proportions of real and complex $F$'s. The factor $n$ can conveniently be introduced into the calculation of the series errors by giving the general asymmetric $F$'s twice the weight of those whose phase-angles are integral multiples of $\pi$.[34] The $n$-shift rule can only be applied where no one atom predominantly determines the phases; if this is not the case a more elaborate treatment is necessary, as, *e.g.*, in the analysis of $NaNO_2$.[35]

---

[31] Booth, *Proc. Roy. Soc.*, 1946, *A*, **188**, 77.

[32] Shoemaker, Donohue, Schomaker, and Corey, *J. Amer. Chem. Soc.*, 1950, **72**, 2328.

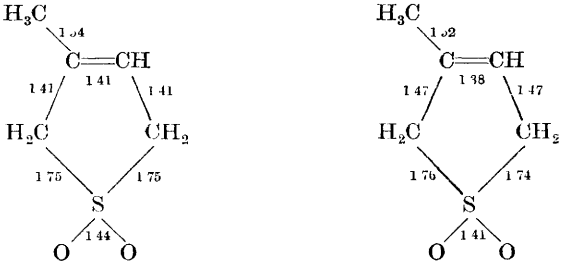
[33] Cruickshank, *Acta Cryst.*, 1950, **3**, 10.

[34] *Idem, ibid.*, 1952, **5**, 511.

[35] Truter, *ibid.*, in the press.

The magnitudes of series corrections to atomic positions are not inconsiderable, particularly if the structure contains light and heavy atoms; this is illustrated by the analysis of β-isoprene sulphone.[36]

*Bond lengths in β-isoprene sulphone:*



*without series correction* *with series correction*

These corrections, although never larger than 0·06 Å, were in such directions as to alter profoundly the interpretation of the results. In the analysis of thiophthen,[37] which also contains sulphur and carbon atoms, the greatest series correction resulted in a C–C bond length change of 0·035 Å. In the dibenzyl [30] analysis the biggest change was 0·037 Å; in naphthalene and anthracene the effects were smaller [38] (Tables 1 and 2).

TABLE 1. *Bond lengths* (Å) *in naphthalene*

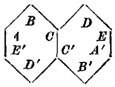
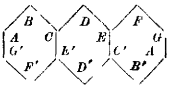
| | Bond | With series correction | E.s.d.* | Without series correction |
|---|---|---|---|---|
|  | *AB* | 1·369 | 0·010 | 1·363 |
| | *BC* | 1·426 | 0·007 | 1·421 |
| | *CD* | 1·424 | 0·009 | 1·420 |
| | *DE* | 1·362 | 0·008 | 1·354 |
| | *AE′* | 1·404 | 0·009 | 1·395 |
| | *CC′* | 1·393 | 0·010 | 1·395 |

TABLE 2. *Bond lengths* (Å) *in anthracene*

| | Bond | With series correction | E.s.d. | Without series correction |
|---|---|---|---|---|
|  | *AB* | 1·365 | 0·009 | 1·361 |
| | *BC* | 1·428 | 0·007 | 1·426 |
| | *CD* | 1·393 | 0·007 | 1·387 |
| | *DE* | 1·398 | 0·006 | 1·395 |
| | *EF* | 1·418 | 0·008 | 1·412 |
| | *FG* | 1·375 | 0·007 | 1·366 |
| | *AG′* | 1·408 | 0·010 | 1·390 |
| | *CE′* | 1·436 | 0·007 | 1·440 |

* E.s.d = estimated standard deviation (see p. 366).

---

[36] Jeffrey, *Acta Cryst.*, 1951, **4,** 58. [37] Cox, Gillot, and Jeffrey, *ibid.*, 1950, **3,** 243.

[38] Ahmed and Cruickshank, *ibid.*, 1952, **5,** 852.

In all these examples the experimental data were obtained with Cu-$K$ radiation. If the use of a shorter-wave-length radiation increases the number of terms in the Fourier synthesis the finite series corrections are reduced. For example, in the resolved projection of oxalic acid dihydrate the mean shifts [39] were 0·017 Å with the data [40] from Cu-$K$ radiation and 0·002 Å with those from Mo-$K$ radiation.[41]

The finite series errors also affect the relative peak heights. In anthracene, the contours in the observed synthesis vary from 7·56 eÅ$^{-3}$ to 9·76 eÅ$^{-3}$, but 1·16 eÅ$^{-3}$ of this variation has been shown [38] to be due to finite series. In dimethyltriacetylene [1] a variation of 0·35 eÅ$^{-3}$ from the mean in the uncorrected synthesis was reduced to 0·06 eÅ$^{-3}$ by correction.

(*b*) *Use of Difference Syntheses.*[42, 43]—The difference synthesis is a Fourier synthesis, with coefficients $(F^{\text{obs.}}_{hkl} - F^{\text{calc.}}_{hkl})$, summed only for those planes for which there is a corresponding term in the $F^{\text{obs.}}$ synthesis [*i.e.*, if $F^{\text{obs.}} = 0$, $(F^{\text{obs.}} - F^{\text{calc.}}) = 0$]. The series corrections calculated from an $F^{\text{obs.}}$ and an $(F^{\text{obs.}} - F^{\text{calc.}})$ synthesis will be identical with those from two separate $F^{\text{obs.}}$ and $F^{\text{calc.}}$ syntheses; but, apart from the computational advantage that the coefficients of difference syntheses are small numbers, other uses are made of the fact that they express in graphical form the discrepancies between the observed and calculated electron densities.

The criterion for refinement by difference syntheses is to adjust the co-ordinates of the atoms (from which the $F^{\text{calc.}}$ are calculated) until the gradients in the difference synthesis at the atomic positions are zero; this implies that the gradients in the $F^{\text{obs.}}$ and $F^{\text{calc.}}$ syntheses are equal:

$$\frac{\partial(\rho^{\text{obs.}} - \rho^{\text{calc.}})}{\partial x} = \frac{\partial(\rho^{\text{obs.}} - \rho^{\text{calc.}})}{\partial y} = \frac{\partial(\rho^{\text{obs.}} - \rho^{\text{calc.}})}{\partial z} = 0 \quad . \quad . \quad (9)$$

where $(\rho^{\text{obs.}} - \rho^{\text{calc.}})$ is the electron density on the difference synthesis.

The aim is to flatten out the difference map, and the appropriate adjustments to the atomic co-ordinates or to the scattering factors ($f_i$ in equation 3) can be deduced either by direct calculation or by qualitatively interpreting the appearance of the difference map and trying out the effect of successive parameter changes. As all sources of discrepancy between $F^{\text{obs.}}$ and $F^{\text{calc.}}$ superimpose their effects, it is always necessary to confirm that a parameter change has resulted in an overall improvement of the synthesis, and the trial method has much to recommend it in complicated cases.

The characteristic feature of a *difference map* associated with a co-ordinate shift is illustrated in Fig. 10 in profile and contour. This arises when the observed and the calculated maxima do not become superimposed. Fig. 11 shows an actual example from the analysis of adenine hydrochloride.[44] The formulæ for the calculation of the co-ordinate shift from the values of the *difference* gradient and $F^{\text{obs.}}$ curvature at the 'observed' co-ordinates are given by Cochran [44] and Cruickshank.[33]

---

[39] Ahmed and Cruickshank, *Acta Cryst.*, 1953, **6,** 385.

[40] Robertson and Woodward, *J.*, 1936, 1817.

[41] Brill, Hermann, and Peters, *Ann. Physik*, 1942, **42,** 357.

[42] Booth, *Nature,* 1948, **161,** 765.

[43] Cochran, *Acta Cryst.*, 1951, **4,** 408.

[44] *Idem, ibid.*, p. 81.

The difference synthesis is also used to extend the information which can be obtained from projection data, to locate hydrogen atoms, and to study the asymmetry of electron density about atom centres , these applications are discussed in the next and later sections

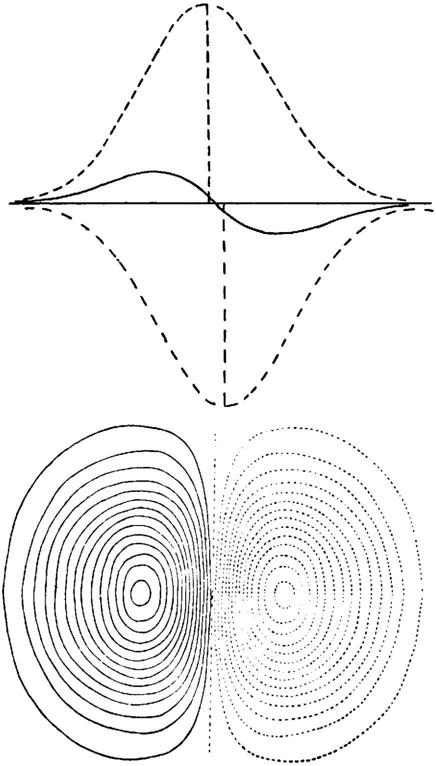
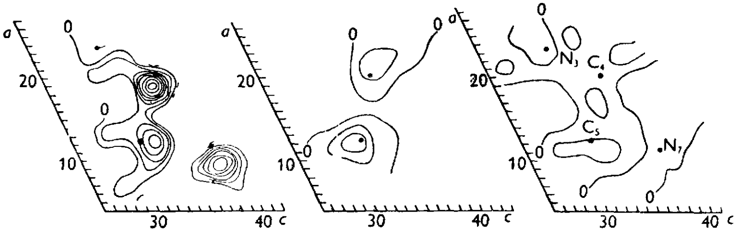


FIG. 10

*Theoretical* difference *map feature corresponding to a co ordinate shift On lower diagram, full lines positive, broken lines negative*



(a) (b) (c)

FIG 11

*Example of three successive stages in a* difference *map refinement by co ordinate shifts of four atoms Contours at intervals of* 0 25 eÅ$^{-2}$, *zero contour indicated by* 0, *negative contours broken*

(Reproduced, by permission, from Cochran *Acta Cryst*, 1951, **4**, 81 ) (*c*) *The Refinement of Unresolved Projections.*—A common restriction to the usefulness of Fourier projections is the non-resolution of electron-density peaks, which arises when atoms in the same or adjacent molecules overlap in the projections of the unit cell. This is one reason why many of the successful earlier analyses of organic structures were achieved on planar molecules, where, by assuming planarity, ambiguities could be resolved. The difficulty is well illustrated by the comparison of the two-dimensional projection [45] and three-dimensional sectional representation [46] of the electron-density maps of single molecules of dibenzyl (Fig. 12).

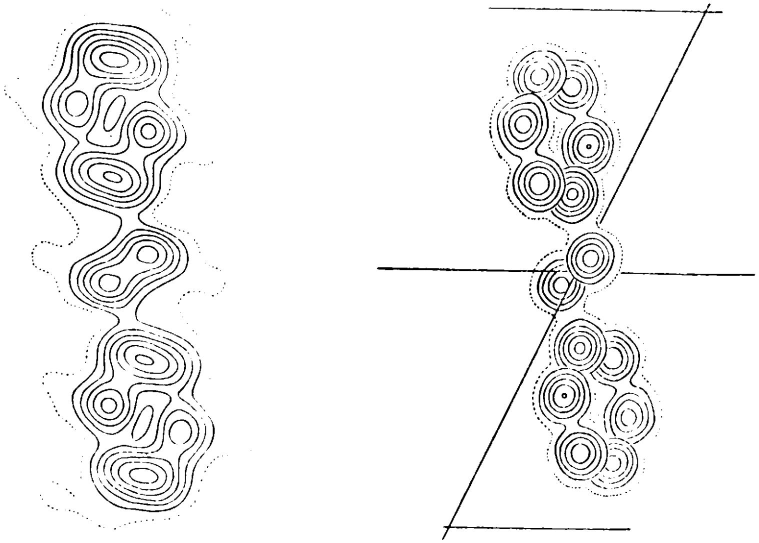


**Fig. 12**

(Left-hand side) *A two-dimensional projection of the electron density in dibenzyl. Contour intervals,* 1·0 Å$^{-2}$.

(Reproduced, by permission, from Robertson, *Proc Roy Soc*, 1935, *A*, **150**, 348 )

(Right-hand side) *The three-dimensional sections of the electron density in dibenzyl. Contour intervals are* 1·0 eÅ$^{-3}$, *zero omitted and one-electron line dotted.*

(Reproduced, by permission, from Jeffrey, *Proc Roy Soc*, 1947, *A*, **188**, 222 )

In some analyses the *method of bounded projections* [47] can be very useful, especially for resolving overlapping molecules. It has the disadvantage that it frequently requires computations of the same magnitude as for three-dimensional syntheses without a comparable increase in accuracy.

The criterion for applying *difference syntheses* to find the positions of unresolved atoms in projections is the same [34] as for the correction of single-atom co-ordinates, *i.e.*, equation (9). The equations given by Cruickshank [34] for the calculation of the shifts from the assumed to the true atomic positions

---

[45] Robertson, *Proc. Roy. Soc.*, 1935, *A*, **150**, 348.

[46] Jeffrey, *ibid.*, 1947, *A*, **188**, 222.

[47] Booth, *Trans. Faraday Soc.*, 1945, **41**, 434.

involve the gradients in the difference synthesis and some second differential quantities, which have to be computed separately. An example of the use of this technique is the two-dimensional refinement of the structure of oxalic acid dihydrate.[39] In practice the ($\rho^{\text{obs}} - \rho^{\text{calc.}}$) maps are more complicated than for resolved atoms, and the technique of flattening them by trial shifts of the co-ordinates is usually the more efficient. The qualitative features of difference syntheses which correspond to assumed positions too close together and too far apart are shown in Figs. 13 and 14.

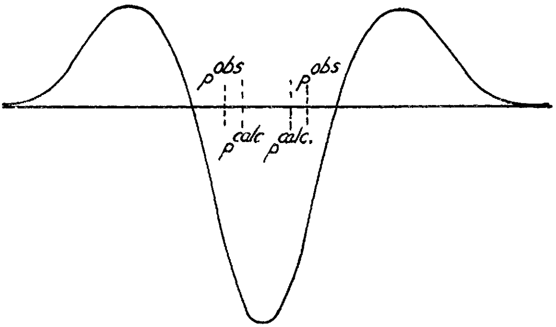


FIG. 13

*Theoretical difference map feature corresponding to unresolved atoms placed too close together, in profile.*

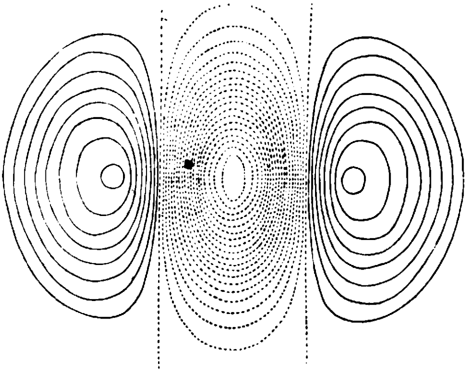


**FIG. 14**

*Theoretical difference map feature corresponding to unresolved atoms ; atoms placed too close together, full lines positive, broken lines negative ; atoms placed too far apart,* vice versa.

## 6. The Computational Problem and the Use of Differential Syntheses

The refinement of a crystal structure analysis is necessarily an iterative process with the alternate calculation of Fourier syntheses and structure factors. Even in the two-dimensional analysis these calculations are sufficiently laborious to inspire the numerous " aids " to crystal analysis which range from simple slide rules or graphical methods to costly electronic special-purpose machines. For three-dimensional analysis, large-scale computation equipment is a necessity. The B.T.M.[48] and I.B.M.[49] punched-card machines have been successfully applied to these calculations, and more recently use has been made of the electronic digital computers at Cambridge,[50] Manchester,[51] and elsewhere. The speed and capacity of the electronic machines is such that, with the Manchester machine, programmes have now been devised which make it possible to proceed from the correct trial structure to the refined atomic co-ordinates by computations carried out cyclically within the machine.

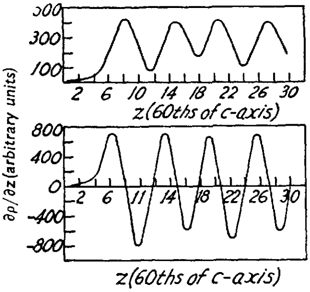


FIG. 15

*Comparison of Fourier and* differential *Fourier syntheses along the molecular axis in dimethyltriacetylene.*

(Reproduced, by permission, from Jeffrey and Rollett, *Proc. Roy. Soc.*, 1952, *A*, **213**, 86.)

For the refinement from the confirmed correct trial structure to the accurate atomic co-ordinates, the usual form of the three-dimensional Fourier synthesis computation given by equation (7) is very inefficient, for the electron density is computed at many unnecessary points in the unit cell. This inefficiency is enhanced by the fact that the printing-out of the results from an electronic computer is at present some hundreds of times slower than the internal arithmetical operations; to a lesser degree, the same is true of punched-card equipment.

The *differential Fourier synthesis* [52] is more suitable for large-scale computing, since the values of the gradients and curvatures at a point close to a maximum provide a sensitive method of calculating its exact co-ordinates (cf. Fig. 15). In place of the summation given in equation (7), the method in general requires summations for $\partial\rho/\partial x$, $\partial\rho/\partial y$, $\partial\rho/\partial z$ of the type shown in equation (10), and for $\partial^2\rho/\partial x^2$, $\partial^2\rho/\partial y^2$, $\partial^2\rho/\partial z^2$, $\partial^2\rho/\partial x\,\partial y$, $\partial^2\rho/\partial x\,\partial z$, $\partial^2\rho/\partial y\,\partial z$ of the type shown in equation (11).

$$\frac{\partial\rho}{\partial x} = -\frac{2\pi}{aV}\sum\sum\sum h\,|\,F^{\text{obs.}}_{hkl}\,|\,\sin\,(2\pi\,hx + ky + lz - \alpha_{hkl}) \quad . \quad . \quad (10)$$

$$\frac{\partial^2\rho}{\partial x^2} = -\frac{4\pi^2}{a^2V}\sum\sum\sum h^2\,|\,F^{\text{obs.}}_{hkl}\,|\,\cos\,(2\pi\,hx + ky + lz - \alpha_{hkl}) \quad . \quad (11)$$

where $x$, $y$, $z$, is a point close to the maximum of the $i$th atom. The

---

[48] Cox and Jeffrey, *Acta Cryst.*, 1949, **2**, 341; Cox, Gross, and Jeffrey, *ibid.*, p. 351; Greenhalgh and Jeffrey, *ibid.*, 1950, 311; Cox, Gross, and Jeffrey, *Proc. Leeds Phil. Soc.*, 1947, **5**, 1; Greenhalgh, *ibid.*, 1950, **5**, 301; Truter, *ibid.*, in the press.

[49] Shaffer, Schomaker, and Pauling, *J. Chem. Phys.*, 1946, **14**, 648, 659; Donohue and Schomaker, *Acta Cryst.*, 1949, **2**, 344; Grems and Kasper, *ibid.*, p. 347.

[50] Bennett and Kendrew, *ibid.*, 1952, **5**, 109.

[51] Ahmed and Cruickshank, *ibid.*, 1953, **6**, 765.

[52] Booth, *Trans. Faraday Soc.*, 1946, **42**, 444.

shifts $\varepsilon_x$, $\varepsilon_y$, $\varepsilon_z$ are given by the three equations of the type

$$\frac{\partial^2\rho}{\partial x^2}\varepsilon_x + \frac{\partial^2\rho}{\partial x\,\partial y}\varepsilon_y + \frac{\partial^2\rho}{\partial x\,\partial z}\varepsilon_z = -\frac{\partial\rho}{\partial x} \quad . \quad . \quad . \quad (12)$$

## 7. The Location of Hydrogen Atoms

Since the contribution to the diffracted intensity for each atom depends upon the square of the numbers of electrons, the effects of hydrogen atoms are small and their positions can only be detected, if at all, in the final stages of an accurate analysis. In a number of investigations, *e.g.*, of DL-alanine [53] and *N*-acetylglycine,[54] the agreement index was significantly improved when contributions were included for the diffraction by the hydrogen atoms. In the analysis of methylammonium chloride,[55] in which the parameters were refined by the least-squares method, an improved agreement resulted from the inclusion of the hydrogen contribution of a rotating methyl group. In these and similar examples the hydrogen positions were assumed from the stereochemistry of the adjacent carbon atoms. More recently, hydrogen atoms have been seen directly on the $F^{\text{obs.}}$ Fourier maps as ill-defined inflexions or small peaks close to the peaks of the heavier atoms ; *e.g.*, anthracene [56] (Fig. 16), hexamethylenediamine,[57] $\text{L}_s$-threonine,[32] decaborane,[58] pentaborane.[59]

A much clearer definition of the hydrogen atom electron density is obtained from *difference syntheses* with Fourier coefficients ($F^{\text{obs.}} - F^{\text{calc.}}$), in which hydrogen atoms are excluded from $F^{\text{calc.}}$. This both removes the peaks of the heavier atoms and eliminates the spurious background effects due to series errors. In the two-dimensional analysis of adenine hydrochloride,[44] which was based on very accurate Geiger counter intensity measurements, a *difference synthesis* refinement was carried through in considerable detail to reveal the hydrogen electrons, without any previous assumptions about their positions (Fig. 17).

In dimethyltriacetylene [1] the hydrogen electron density of a rotating methyl group is comparatively well defined in the *difference syntheses,* although barely apparent in the syntheses with $F^{\text{obs.}}$ ; Fig. 18 shows the distribution of electron density above 0·3 eÅ$^{-3}$ about a circle coaxial with the linear molecule ; Fig. 18 is a section which includes the axis of the molecule and is perpendicular to that shown in Fig. 19.

The effect on the agreement index of including hydrogen contributions to the scattering is generally to produce a small but definite improvement, and in favourable cases values of $R$ lower than 0·10 have been reported.

---

[53] Levy and Corey, *J. Amer. Chem. Soc.*, 1941, **63,** 2095.

[54] Carpenter and Donohue, *ibid.*, 1950, **72,** 2315.

[55] Hughes and Lipscomb, *ibid.*, 1946, **68,** 1970.

[56] Sinclair, Robertson, and Mathieson, *Acta Cryst.*, 1950, **3,** 251.

[57] Binnie and Robertson, *ibid.*, p. 424.

[58] Kasper, Lucht, and Harker, *ibid.*, p. 436.

[59] Dulmage and Lipscomb, *ibid.*, 1952, **5,** 260.

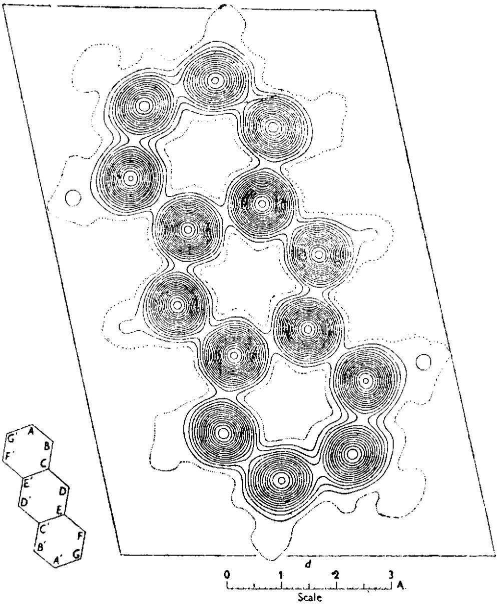


FIG. 16

*Three-dimensional Fourier section in the plane of the molecule of anthracene. Contour intervals are* 0·5 eÅ$^{-3}$, *the half-electron line being dotted.*

(Reproduced, by permission, from Sinclair, Robertson, and Mathieson, *Acta Cryst.*, 1950, **3**, 245.)

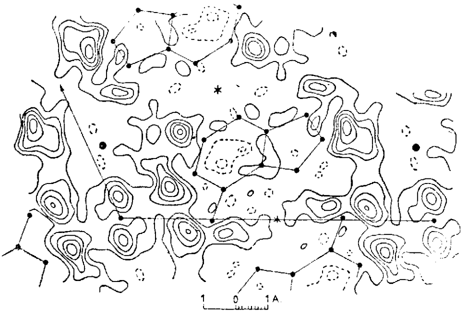


FIG. 17

*The hydrogen electron density in adenine hydrochloride. The difference between the electron density projected on* (010) *and that calculated for isolated* Cl, O, N, *and* C *atoms whose centres are indicated by dots ; contour intervals* 0·2 eÅ$^{-3}$, *negative contours broken.*

(Reproduced, by permission, from Cochran, *Acta Cryst.*, 1951, **4**, 81.)

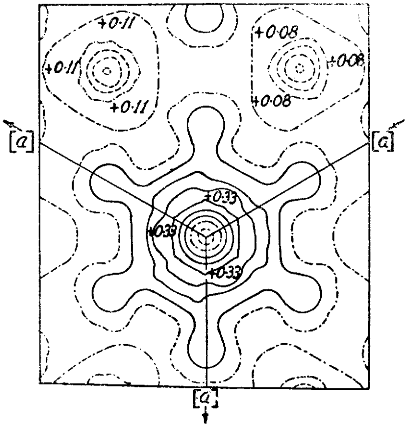


FIG. 18

*The hydrogen electron density in dimethyltriacetylene. Section of three-dimensional difference synthesis, normal to the molecular axis. Contour intervals are* 0·1 eÅ$^{-3}$ *; full lines positive, broken lines negative, and* — · — · — *zero level.*

(Figs. 18 and 19 reproduced, by permission, from Jeffrey and Rollett, *Proc. Roy. Soc.*, 1952, *A*, **213**, 86.)

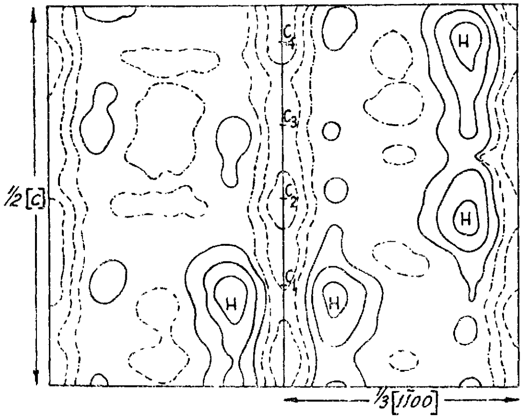


FIG. 19

*The hydrogen electron density in dimethyltriacetylene. Section of three-dimensional difference synthesis containing the molecular axis. Contours as in Fig.* 18.

## 8. The Thermal Motion

From the first stages of a crystal analysis allowance must be made for the effect of the thermal motion of the atoms on their *X*-ray scattering power.[60] For isotropic thermal motion the scattering factors for a particular atom, $f_i$, are calculated from the expression

$$f_i = f_i^0 \exp\,(-B\sin^2\theta/\lambda^2) \quad . \quad . \quad . \quad . \quad (13)$$

where $f_i^0$ is the theoretical scattering factor calculated and tabulated for the electron distribution of the atom *at rest*, and the exponential term allows for the increased spread of the electron cloud. In this expression $B = 8\pi^2\overline{u^2}$, where $\overline{u^2}$ is the mean-square displacement of the atom in the crystal lattice. The average value of $B$ for all the atoms in the crystal under the experimental conditions can be determined by a statistical method from the slope of a plot of $\log\,(|F^{\text{obs.}}|\,/\,|F^{\text{calc.}}|)$ against $\log S + B\sin^2\theta/\lambda^2$, where $S$ is the scale factor for converting the observed structure amplitudes, $|F^{\text{obs.}}|$, into absolute values, and the $|F^{\text{calc.}}|$ are the calculated amplitudes for a true structure with the atoms *at rest.* It is usually necessary to adjust the constants $S$ and $B$ several times during a structure refinement.

The value of $B$ for diamond at room temperature calculated from specific-heat data is 0·147, of which 0·127 is the effect of zero-point vibration.[60] In organic structures, values for $B$ calculated by the method given above vary from close to zero to the order of 10 for molecular structures of low melting point, *e.g.* 0·6 Å$^{-2}$ in α-anhydrous oxalic acid,[61] 10·0 Å$^{-2}$ in pentaborane [59] at − 115°, which correspond to mean displacements of 0·087 Å and 0·36 Å, respectively. These are not, however, absolute values, for $B$ is a measure of the *apparent* spread of the electron cloud and will include the

---

[60] James, " The Optical Principles of the Diffraction of X-Rays ", 1948, Bell, London.

[61] Cox, Dougill, and Jeffrey, *J.*, 1952, 4854.

effect of all small and random displacements of the atoms from their mean positions. Any detailed study of these atomic thermal motions should also include corrections for certain systematic factors in intensity measurement and in crystal absorption, which are often justifiably ignored in an analysis where the object is molecular-structure determination. The absorption corrections for the equatorial reflections from a cylindrical specimen,[62] for example, lie on a smooth curve which rises with increase of sin $\theta/\lambda$; the omission of these from the $L_{hkl}$ in equation (1) acts in the opposite sense to the effect of increased thermal motion in that it will sharpen the atomic peaks in an $F^{\text{obs.}}$ Fourier synthesis, and so operate in the structure refinement as a weighting factor in favour of the high-order reflections.

In layer structures it may be necessary to introduce at a comparatively early stage in the refinement an anisotropic thermal factor in the form

$$f_i = f_i^0 \exp\{-(A + B\cos^2\phi)\sin^2\theta/\lambda^2\} \qquad . \quad . \ (14)$$

where $A$ and $(A + B)$ are constants for reflecting planes parallel and perpendicular to the direction of maximum vibration of the molecule as a whole, and $\phi$ is the angle between the normal to the reflecting plane and the direction of maximum vibration.[63]

In the general case, the thermal motion is best studied by means of *difference syntheses*, and a refinement of the thermal parameters (if necessary different for each atom) can be carried out simultaneously with the co-ordinate refinement.[43, 44] A discrepancy between $F^{\text{obs.}}$ and $F^{\text{calc.}}$ due to anisotropic motion results in characteristic difference map features, and the semi-qualitative trial method discussed previously for the adjustment of co-ordinates can also be used for determining the thermal constants. Fig. 20 shows the idealised effect of anisotropic motion on a difference map; in practice there is often an associated scale error, so that the $\rho^{\text{obs.-calc.}}$ is not zero at the atom centre and the map appears as in Fig. 21.[44]

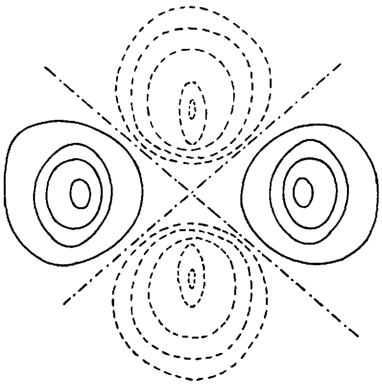


FIG. 20

*Theoretical difference map feature corresponding to anisotropic thermal motion.*

The inclusion of the thermal parameters in $F^{\text{calc.}}$ generally brings about small changes in the *back-shift* corrections to the atomic co-ordinates, which can be assessed directly from the difference synthesis. Ideally, the refinement of both thermal and co-ordinate parameters should be pursued until the difference map appears to relate only to the random errors of the experimental measurements, and shows no systematic features that can be associated with the structure. The detailed procedure will vary from one

---

[62] " Internationale Tabellen zur Bestimmung von Kristallstructuren ", Vol. II, 1935, Borntraeger, Berlin.

[63] Hughes, *J. Amer. Chem. Soc.*, 1941, **63**, 1737.

structure analysis to another ; an example is the refinement of adenine hydrochloride by Cochran.[44]

In a complete analysis, each atom will be defined by three co-ordinates and six thermal parameters, all of which have been conjointly adjusted to give the best agreement between $F^{\text{obs.}}$ and $F^{\text{calc.}}$. There is, however, a danger in this procedure of attempting to ascribe to thermal motion all the anisotropy of the electron densities about the atoms, as this may partly or wholly obscure that due to the distribution of the valency electrons. From a single electron-density distribution it is difficult to distinguish the effects of thermal motion and bonding-electron distribution (cf. the structure analysis of dimethyltriacetylene[1]). The ambiguity can be resolved in two ways : (1) by two complete analyses at very different temperatures ; and (2) by determining the thermal motion parameters from consideration of the high-order reflections only, for which the major part of the $X$-ray scattering is from the inner electrons.

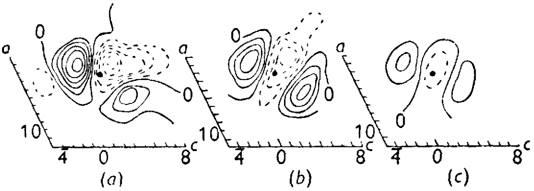


FIG. 21

*Examples of three successive stages in a difference refinement for co-ordinates and anisotropic thermal motion of a chlorine atom in adenine hydrochloride. Contours at an interval of* 0·5 eÅ$^{-2}$*; zero contour indicated by* 0, *negative contours broken.*

(Reproduced, by permission, from Cochran, *Acta Cryst.*, 1951, **4**, 81.)

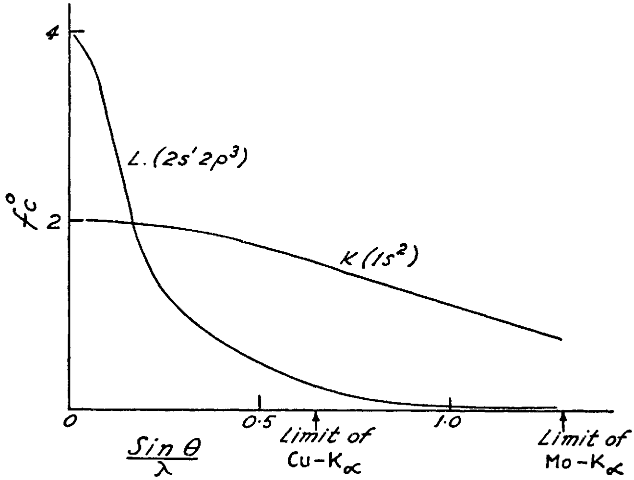


FIG. 22

*The contributions to the atomic scattering factor for carbon from* K *and* L *electrons.*

Fig. 22 shows the dependence upon sin $\theta/\lambda$ of the contributions to the atomic scattering power of the electrons in the $K$ and $L$ shells of a carbon atom from the calculations of McWeeny.[64] Beyond the limiting value of $\sin\theta/\lambda$ for Cu-$K$ radiation the inner $K$ electrons are responsible for more than 85% of the scattering; the outer $L$ electron distribution becomes important only for reflections with $\sin\theta/\lambda < 0{\cdot}5$. Thus if the high-order reflections are adequate to define the thermal motions, the difference synthesis method applied to the low-order reflections will reveal the anisotropy of the electron distribution due to chemical bonds. At room temperature, in hydrogen-bonded and high-melting structures the experimental measurements can be adequately obtained with Mo-$K$ radiation, but with crystals melting below 100° it will be necessary to obtain the experimental results at low temperatures so as to reduce the thermal motion and extend the range of observations to sufficiently high $\sin\theta/\lambda$ values.

In this discussion, the thermal motion has been regarded merely as an added complication to the problem of obtaining accurate molecular dimensions and electron-density distributions. In some structures the thermal behaviour of the molecules is of considerable interest in the study of intermolecular forces, particularly in those cases in which rigid-body angular vibrations take place; examples of this are geranylamine hydrochloride [65] and anthracene.[56, 38] More detailed studies of these and other examples can be expected in the future.

## 9. The Least-squares Method of Structure Analysis

In the structure analysis of melamine [63] the difficulty that the atoms overlapped in the projections was overcome by refining the parameters by the method of least squares. This was the first application to $X$-ray analysis of this well-known method,[66] in which parameters are determined by making a function of the observed and calculated intensities a minimum. The two functions commonly used in $X$-ray analysis are

$$R_1 = \sum_{hkl} w_{hkl}\,(\,|\,F^{\text{obs.}}_{hkl}\,| - |\,F^{\text{calc.}}_{hkl}\,|\,)^2 \quad . \quad . \quad . \quad (15)$$

or

$$R_2 = \sum_{hkl} w''_{hkl}\,(\,|\,F^{\text{obs.}}_{hkl}\,|^2 - |\,F^{\text{calc.}}_{hkl}\,|^2)^2 \quad . \quad . \quad . \quad (16)$$

where $w$ and $w''$ are weights. The parameters are refined by the standard least-squares procedure of successive solution of $n$ simultaneous linear equations in the $n$ unknown parameters (the normal equations). The least-squares method gives a solution even if there are only as many observations as parameters, but to achieve the best accuracy it is usual to employ all the available data. The computational problem is then of the same order of magnitude as in a Fourier refinement.

The relation between the Fourier and least-squares methods was found by Cochran [67] in 1948, who showed for resolved peaks that the co-ordinates

---

[64] McWeeny, *Acta Cryst.*, 1951, **4,** 512.

[65] Jeffrey, *Proc. Roy. Soc.*, 1945, *A*, **183,** 388.

[66] Whittaker and Robinson, "The Calculus of Observations", 1944, Blackie, London and Glasgow.

[67] Cochran, *Acta Cryst.*, 1948, **1,** 138.

found by least squares from the function $R_1$ with $w = 1/f$ are the same as those found in the Fourier method when the back-corrections for finite series are used. This connection has been examined in detail by Cruickshank,[33, 34] who has shown the similarities of the full set of normal equations with the equations used in refining *difference* syntheses when all the peaks are assumed to overlap. When the peaks do not overlap the non-diagonal terms between different atoms in the normal equations can be neglected, and the use of the least-squares method is then similar to refinement by *differential* syntheses with back-corrections. Except for the different weighting there is essentially no difference between the use of the least-squares method and the analytical refinement of difference syntheses. The use of $R_2$ is related to the use of the difference Patterson syntheses. Analyses done with the aid of least squares thus do not call for any further discussion, and their results are automatically corrected for the finite-series effect.

The accuracy of co-ordinates found by the least-squares method is given by standard formulæ,[66] and the relation of these error estimates to the Fourier estimates, to be discussed shortly, is similar to that for the refinement equations.[68, 69] With correct weighting the least-squares method gives slightly more accurate co-ordinates than does the ordinary Fourier method, though in several analyses, in which co-ordinates have been found by both methods, the least-squares errors were estimated to be the larger ; *e.g.*, in threonine [32] the mean co-ordinate estimated standard deviations were 0·0061 Å by the Fourier method and 0·0063 Å by the least-squares method. This reversal is probably due to the least-squares weights being inappropriate to the overall errors. In the threonine analysis the root-mean-square difference of the co-ordinates determined by the two methods was 0·0069 Å which is an indication of the effect of the different weighting of the data in the two methods.

The use of the least-squares method is not restricted to the finding of atomic co-ordinates, and it may be applied to the adjustment of atomic scale and temperature factors.[55] Cochran has related this to the corresponding difference synthesis procedures.[43]

The least-squares method requires that the electron density be represented by a finite number of parameters of known type. In this respect it is inferior to the Fourier synthesis method for it does not give the overall representation of the electron density, which is not only an aim of the analysis but is also an invaluable guide in steering the course of the refinement.

## 10. The Accuracy of the Crystal Structure Analysis

Up to about 1945 the accuracies of *X*-ray analyses were judged by the consistency of the results or by the effect of variation of the parameters on the agreement index. In favourable cases bond-length errors were estimated at ± 0·02 to ± 0·08 Å. No theoretical justification for this had then been given, and it was sometimes even suggested that the accuracy of atomic

---

[68] Cruickshank, *Acta Cryst.*, 1949, **2**, 154.

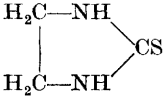
[69] Cruickshank and A. P. Robertson, *ibid.*, 1953, **6**, 698.

positions was determined by the resolving power $0{\cdot}6\lambda/2 \sin \theta_{\text{max.}}$. This situation was largely cleared up in 1945—1947 by the efforts of a number of workers,[70, 55] but particularly by Booth's theoretical work [31, 71] on diffraction ripples and the effects of experimental errors, which confirmed the possibility of obtaining atomic positions with the order of accuracy claimed from consistency. His treatment of diffraction ripples led to the back-shift method of finite-series correction already discussed, and his methods of estimating the other errors have been developed by Cruickshank [30] into the general quantitative method of estimating the standard deviations of atomic positions discussed below.

For conciseness, the estimated standard deviations will be referred to as e.s.d.

(*a*) *Consistency Tests.*—A preliminary remark is necessary on the meaning of such phrases as " This bond length is accurate to ± 0·05 Å " which sometimes occur in descriptions of structures for which no direct error estimate has been made. The usual meaning seems to be that the errors are unlikely to exceed 0·05 Å, and not, as is usual in statistics, that the standard deviation (root-mean-square error) is 0·05 Å. This confusion is avoided in the quantitative error method by finding the e.s.d., and then discussing the likely limits of error by statistical significance tests.

The use and limitations of consistency estimates of the errors can be illustrated by considering what may happen when a detailed analysis of benzene is carried out. The only symmetry element provided by the crystal space group for each molecule is a centre of symmetry, so that there will be crystallographically independent determinations of three of the six carbon atoms. If the molecule is assumed planar, one estimate of the errors will be given by the deviation of one carbon atom from the plane through the other two and the centre of symmetry. If the ring is assumed to be a regular hexagon, another estimate will be given from the variation of the three C–C bond lengths. The first limitation of the consistency method is thus that it assumes what may require to be proved. In the structure analysis of ethylenethiourea [72] (tetrahydro-2-thioglyoxaline) (III), the S atom is displaced 0·03 Å from the plane of the five-membered ring. An accuracy estimate based on consistency might have taken this as the order of magnitude of the errors, but the application of the quantitative method showed that the displacement was highly significant.



(III)

The second limitation of the consistency method is that its estimates of error are based on very few determinations of a parameter, so that its

---

[70] Van Reijen, *Physica*, 1942, **5**, 461.
[71] Booth, *Proc. Roy. Soc.*, 1947, *A*, **190**, 482.
[72] Wheatley, *Acta Cryst.*, 1953, **6**, 369.

reliability is low even when the assumptions are justified. The third limitation is that systematic errors are not revealed. In benzene the effect of finite series and peak overlapping will tend to alter all the bond lengths equally without distorting the planarity, so that an analysis uncorrected for finite series will tend to show the same deviations as a corrected analysis. Nevertheless, if the limitations are borne in mind, consistency estimates of the errors can be a useful guide to the progress of an analysis, particularly in the early stages when any real departures from, say, planarity are likely to be small in comparison with the errors. Other rough consistency checks on the progress of an analysis are given by comparisons of similar chemical groupings in different structures, or by the comparison of bond lengths with the sums of covalent radii.

(*b*) *The Sources of Errors.*—The errors in the final results of a structure analysis arise from two entirely different sources, the errors in the experimental measurements and those in the interpretation of the measurements. The experimental errors are due to (i) errors in the determination of the cell dimensions and (ii) errors in the $| F^{\text{obs.}}_{hkl} |$. The interpretative errors are due to (iii) approximation errors in the computations and (iv) imperfections in the model used for the $F^{\text{calc.}}$'s, causing phase-angle errors and inaccurate finite-series corrections.

The overall accuracy of an analysis is found by estimating the resultant of these effects ; ordinarily (ii) and (iv) are the most important.

(i) By an appropriate experimental technique the cell side errors can be reduced to the order of 0·001 Å, and they can then be ignored in comparison with the other errors. However, cell dimensions found from the layer line spacings have e.s.d.'s of the order of 0·01 Å, and then their errors must not be entirely neglected. The *fractional* atomic co-ordinates given by the refinement process are, of course, independent of the cell side errors.

(ii) In the majority of the crystal-structure analyses mentioned in this Review, the *X*-ray reflections were recorded photographically and the intensities estimated visually. Photometry is a slower and more tedious method and in general when several hundred values have to be measured, greater accuracy is obtained in a given time by visual estimation.

In dibenzyl,[46] for 94 reflections the s.d. of the difference between independent measurements by photometer and by visual estimation was 5·0% of the mean $| F^{\text{obs.}} |$. Such a comparison is not generally possible, but the usual practice is to record and visually to estimate each intensity more than once. In threonine,[32] for example, where a careful study of the accuracy was made, of the 620 possible reflections, 65 were too weak to be observed, 74 were estimated once only, 303 twice, and 178 three times ; the final s.d. of the amplitudes were estimated at 3·5% for the majority of reflections, and somewhat more for the weak and the very strong.

Recently, Geiger counters have been used for measuring intensities, giving a considerable improvement in accuracy and in the detection of weak reflections. In a comparison of the relative merits of Geiger-counter and photographic methods, Cochran reports [73] e.s.d. of 1—2% of $I_{hkl}$ for the former against 12—18% of $I_{hkl}$ for the latter.

Apart from the random errors of experimental measurement, there are systematic errors due to absorption and extinction.[60, 74] Absorption is well understood, and corrections can be made according to the shape of the crystal, although this may involve tedious numerical integrations for the (*hkl*) intensities. Frequently the problem is avoided by using specimens of such dimensions that the absorption errors are of the same magnitude as the random experimental errors. For example, in dimethyltriacetylene the errors of both absorption and visual estimation had e.s.d. $0{\cdot}05\ |F_{hkl}^{\text{obs.}}|$, giving a combined value $0{\cdot}07\ |F_{hkl}^{\text{obs.}}|$. It is much more difficult to avoid the errors due to extinction. This effect is a departure from the ideal relation of equation (1), which results in low values for the structure amplitudes of strong reflections with small $\sin\theta_{hkl}$. Sometimes extinction can be reduced by immersing the crystals in liquid air.[5, 74] Usually, extinction affects only a few reflections, but if it is suspected that a large number are concerned a lengthy empirical study is necessary. There is no satisfactory theoretical method which can be applied. Extinction is a much more serious obstacle to the study of the positions of hydrogen electrons and valency electrons than to the determination of atomic co-ordinates, as the accuracy of the latter depends on quantities such as $\left\{\sum h^2(\Delta F)^2\right\}^{\frac{1}{2}}$, the high $\Delta F$ values of the extinguished low-order planes being compensated by their low indices.

(iii) Computational rounding off errors are usually small, although inadequate methods have sometimes been used. The accuracy of the popular Beevers–Lipson strips for Fourier synthesis has been examined by Cochran [88] and Cruickshank,[30] and they have been shown to be adequate for most work on projections. In the three-dimensional Fourier analysis of dibenzyl the co-ordinate e.s.d. arising from their use were shown to be only 0·004 Å.[30] If co-ordinates are determined from difference syntheses with scaled-up coefficients, the strips are adequate for almost any purpose.

Of perhaps greater importance is the manner in which the positions of the maxima are inferred from the arrays of numbers given by the Fourier syntheses. Graphical methods or a combination of graphical and analytical methods are very convenient, but may not be sufficiently precise for the later stages of an accurate analysis. Strange to say, hardly any analyses have been reported using proper two- or three-dimensional interpolation formulæ, such as the finite-difference form of the equations (12). A sound but laborious analytical method, employing more than the minimum of data, is the least squares fitting by a Gaussian function of the 27 densities in a $3 \times 3 \times 3$ block enclosing the maximum.[32]

The use of differential syntheses [52] for finding the maxima is more economical, and in its full form gives correct positions if the refinements are small. However, there may be slight errors if assumptions are made about the peak shapes to save computing the cross derivatives of the type

---

[73] Cochran, *Acta Cryst.*, 1950, **3**, 268. [74] Lonsdale, *Min. Mag.*, 1947, **28**, 14.

$\partial^2\rho/\partial x\,\partial y$.[52] For one of the atoms in ethylenethiourea [72] a difference of 0·005 Å was obtained for one co-ordinate between the determination using the exact values of the six second derivatives and that using only one independent second derivative, a spherical peak being assumed.

The most important computational problem is to ensure that no mistakes have been made. The difficulties arise not from the big mistakes, which are almost sure to be noticed, but from the smaller ones. A good check is given if the shifts in the last stages of refinement become successively smaller ; ideally, the computations should be repeated by a different though equivalent method.

(iv) True phase angles and finite-series corrections can only be obtained from the unknown true electron density, so that those obtained from the idealised model from which the $F^{\text{calc.}}$'s are derived are necessarily imperfect, and some allowance for this must be made. Fortunately it is not usually necessary to estimate this error separately, as a simple method is available for estimating the combined effects of this and the experimental errors.

(c) *Quantitative Accuracy Theory.*—The electron density (7) may be written

$$\rho(xyz) = \frac{1}{V}\sum_{\text{indep.}} |\,F_{hkl}\,| \left[\sum_{\text{form}} \cos\,(2\pi\,\overline{hx + ky + lz} - \alpha)\right] \quad . \quad . \quad (17)$$

where the inner summations are over those planes having the same $|\,F_{hkl}\,|$ by symmetry, *e.g.*, in $P2_1/a$, $|\,F_{hkl}\,| = |\,F_{h\bar{k}l}\,| = |\,F_{hk\bar{l}}\,| = |\,F_{h\bar{k}\bar{l}}\,|$ . Accordingly, if $\sigma(F_{hkl})$ is the standard deviation of $F_{hkl}$, the standard deviation of the electron density is [75]

$$\sigma[\rho(xyz)] = \frac{1}{V}\sum_{\text{indep.}} \sigma^2(F_{hkl}) \left[\sum_{\text{form}} \cos(2\pi\,\overline{hx + ky + lz} - \alpha)\right]^2 \quad . \quad . \quad (18)$$

For any general ($x$, $y$, $z$) position this has the approximate value [30]

$$\sigma(\rho) = \frac{1}{V}\left\{\sum_h \sum_k \sum_l \sigma^2(F)\right\}^{\frac{1}{2}} \quad . \quad . \quad . \quad (19)$$

At special positions in the unit cell, such as (0,0,0) or (0,0,$z$) a more general formula has to be used.[75] For example, in dimethyltriacetylene, space group $R\bar{3}m$, the estimated error at (0,0,0) was three times that at the general ($x$,$y$,$z$) positions.[75]

The values of co-ordinate standard deviations depend on the peak curvatures and on the errors in the slopes of the electron density. The simplest formula occurs for a well-resolved spherical peak in a centrosymmetrical structure with orthogonal axes, when

$$\sigma(x) = \sigma\left(\frac{\partial\rho}{\partial x}\right) \Big/ \left|\frac{\partial^2\rho}{\partial x^2}\right| \quad . \quad . \quad . \quad . \quad (20)$$

where for a general position

$$\sigma\left(\frac{\partial\rho}{\partial x}\right) = \frac{1}{V}\left\{\sum_h \sum_k \sum_l h^2\sigma^2(F)\right\}^{\frac{1}{2}} \quad . \quad . \quad . \quad (21)$$

As for the density, a more general formula than (21) is required if an atom

---

[75] Cruickshank and Rollett, *Acta Cryst.*, 1953, **6**, 705.

is at a special position in the unit cell.[75] If the peaks are not spherical or the axes not orthogonal, the formulæ given by Cruickshank must be used.[30] To estimate the co-ordinate errors of peaks in unresolved projections the altogether more general formulæ given by Cruickshank and A. P. Robertson are needed.[69] In non-centrosymmetric structures the errors in the phase angles have to be allowed for. In the simpler cases the errors are $n$ times those estimated by the centrosymmetrical formulæ, $n$ being the same constant as in the $n$-shift refinement rule discussed in Section 5($a$).

These formulæ can be used to estimate the density or co-ordinate errors if estimates of the $\sigma(F)$ can be made. A simple way of estimating the combined effects of the experimental errors, (ii), and the model imperfections, (iv), is to use $\Delta F = \left| \, |F^{\text{obs.}}| - |F^{\text{calc.}}| \, \right|$ as an estimate of $\sigma(F)$.[30] The merit of this method is that the degrees of accuracy of the measurements and of the precision of the calculated model are reflected in the $\Delta F$ values. It is open to the criticism that it treats the errors (iv) as random, whereas they are systematic in the sense that the errors in different $F^{\text{calc.}}$'s are correlated, but, provided the difference map shows no strong features attributable to the calculated model, the method gives a satisfactory overall estimate of the errors. An equivalent method of estimating $\sigma(\partial\rho/\partial x)$, suggested by Cochran,[44] is to average $\partial(\rho^{\text{obs.}} - \rho^{\text{calc.}})/\partial x$ at a number of points where $\rho^{\text{obs.}}$ is expected to be small.

If it is of interest to find the errors produced by the errors in the $|F^{\text{obs.}}|$ only, estimates of $\sigma(F)$ of the kind discussed in Section 10($b$) (ii) may be substituted in (18) or (21).

($d$) *Examples of Co-ordinate Errors.*—The most accurate method at present practicable of determining co-ordinates would be to use Geiger-counter-measured intensities in a three-dimensional analysis. No such analysis has so far been reported for an organic structure. The best results to date have been obtained from three-dimensional analyses using photographic intensities from Cu-$K$ radiation. The lowest e.s.d. yet reported for carbon co-ordinates, estimated by using $\Delta F$ for $\sigma(F)$, is 0·0050 Å in dimethyltriacetylene,[1] a structure with agreement index $R = 0{\cdot}080$. Other low estimates are 0·0052 Å in $\alpha$-anhydrous oxalic acid [61] ($R = 0{\cdot}145$), a mean of 0·0053 Å in anthracene [38] ($R = 0{\cdot}182$), a mean of 0·0058 Å in naphthalene [38] ($R = 0{\cdot}168$), and 0·0067 Å in threonine [32] ($R = 0{\cdot}112$, non-centrosymmetric). All these analyses were corrected for termination of series, and in dimethyltriacetylene [1] and threonine [32] the effects of hydrogen atoms were allowed for.

In hetero-atom structures the co-ordinates of the heavier atoms are more accurate because of their greater peak curvature ; thus the e.s.d. of the oxygens were 0·0044 Å in $\alpha$-oxalic acid and 0·0050 Å in threonine. On the other hand, the presence of the heavier atom is detrimental to the accuracy for the lighter atoms because of the lower absolute accuracy of the $|F^{\text{obs}}|$ ; thus in $\beta$-isoprene sulphone [36] the carbon e.s.d. are 0·0167 Å, although the sulphur e.s.d. is only 0·0037 Å. In ethylenethiourea [72] the carbon e.s.d. are 0·008 Å and those of sulphur 0·002 Å ($R = 0{\cdot}13$).

The accuracy of the results obtained from two-dimensional analyses depends primarily on whether or not the peaks are resolved. Direct comparisons between the accuracy of a three-dimensional analysis and two-dimensional resolved projections are available for dibenzyl,[30] where the carbon e.s.d. are 0·0074 and 0·0170 Å respectively ($R = 0{\cdot}15$), and dimethyltriacetylene,[1] 0·005 and 0·010 Å. Good carbon e.s.d. obtained in resolved projections with photographic intensities from Cu-$K$ radiation are 0·008 Å in ammonium oxalate hydrate [76] ($R = 0{\cdot}115$), and 0·013 Å in oxalic acid dihydrate [39] ($R = 0{\cdot}146$). In spite of the effects of the heavier chlorine atom, still better results have been obtained in adenine hydrochloride [44] by using Geiger-counter measurements of intensities from copper and (in part) molybdenum radiation, together with finite series corrections from a model with carefully chosen anisotropic thermal parameters, giving carbon e.s.d. of 0·007 Å ($R = 0{\cdot}061$).

The use of the shorter-wave-length Mo-$K$ radiation increases the number of intensities which can be measured, though it is more difficult to measure them accurately. In the resolved projection of oxalic acid dihydrate [39] the e.s.d. of the carbon co-ordinates are 0·0065 Å ($R = 0{\cdot}144$), as compared with 0·013 Å from Cu-$K$ intensities.

An example of the accuracy of co-ordinates in unresolved projections is given by the $yz$ projection of the same structure in which the carbon and the carbonyl-oxygen atom overlap seriously, their centres being 0·60 Å apart. After co-ordinates had been found by the analytical treatment of the difference synthesis mentioned above, the carbon $y$ co-ordinate e.s.d. was estimated at 0·031 Å for the Mo data, and 0·049 Å for the Cu data only. The errors would have been considerably larger if the co-ordinates in the unresolved peak had not been found by difference syntheses or some equivalent method.

(*e*) *Errors in Molecular Dimensions.*—From the chemical point of view the interest lies in the errors of the molecular dimensions, the bond lengths and the bond angles. The s.d. $\sigma(l)$ of a bond between two atoms whose positions are determined independently is

$$\sigma(l) = [\sigma^2(\mathrm{A}) + \sigma^2(\mathrm{B})]^{\frac{1}{2}}$$

where $\sigma(\mathrm{A})$ and $\sigma(\mathrm{B})$ are the atomic co-ordinate s.d. For two independent atoms of the same kind $\sigma(l) = \sqrt{2}\sigma(\mathrm{A})$. For a bond across a centre of symmetry, $\sigma(l) = 2\sigma(\mathrm{A})$. Thus, apart from the special cases of diamond and graphite, the most accurate determinations of C–C bonds yet made have e.s.d. of 0·007 Å, or 0·010 Å if across a centre of symmetry (co-ordinate e.s.d. 0·005 Å).

The s.d. $\sigma(\theta)$ of an angle $\theta$ between three independent atoms A, B, C with co-ordinate s.d. $\sigma(\mathrm{A})$, $\sigma(\mathrm{B})$, $\sigma(\mathrm{C})$ is given by [69]

$$\sigma^2(\theta) = \frac{\sigma^2(\mathrm{A})}{\mathrm{AB}^2} + \sigma^2(\mathrm{B})\left(\frac{1}{\mathrm{AB}^2} - \frac{2\cos\theta}{\mathrm{AB.BC}} + \frac{1}{\mathrm{BC}^2}\right) + \frac{\sigma^2(\mathrm{C})}{\mathrm{BC}^2} \quad . \quad . \quad (22)$$

For $\sigma(\mathrm{A}) = \sigma(\mathrm{B}) = \sigma(\mathrm{C}) = 0{\cdot}005$ Å, and AB = BC = 1·40 Å, $\sigma(\theta) = 0{\cdot}46°$ for $\theta = 120°$.

---

[76] Jeffrey and Parry, *J.*, 1952, 4864.

If the molecular symmetry can be assumed to be higher than the crystallographic symmetry, the averaged bond lengths will be more accurate than the individual bond lengths. This can be illustrated by reference to the finite-series-corrected bond lengths of naphthalene and anthracene [38] given, together with their e.s.d., in Tables 1 and 2. None of the pairs of chemically equivalent bonds in either molecule differs by more than the e.s.d. of their differences, so that there is no evidence for differences in the bond lengths caused by intermolecular forces. The averaged bond lengths are given in Tables 3 and 4, allowance having been made for the negative correlation of BC and CD in naphthalene through their common atom C, and similarly for CD and DE in anthracene. The e.s.d. of the averaged bonds are also given in these tables, the most accurate bond being CD in anthracene with e.s.d. 0·004 Å. Tables 1 and 2 also illustrate two other features. First, the lower accuracy of bonds further from the centres of the molecules, owing to the rigid-body angular oscillation in the thermal motion causing the outer peaks to be less sharp; and, secondly, that though atom C is itself the most accurately defined in naphthalene, the bond CC′ is the least accurate as it is across the centre of symmetry.

TABLE 3. *Chemically independent bond lengths* (Å) *in naphthalene*

| Bond | Exptl. | E.s.d. | Theor. | Bond | Exptl. | E.s.d. | Theor. |
|---|---|---|---|---|---|---|---|
| *AB* | 1·365 | 0·006 | 1·384 | *AE′* | 1·404 | 0·009 | 1·406 |
| *BC* | 1·425 | 0·005 | 1·416 | *CC′* | 1·393 | 0·010 | 1·424 |

TABLE 4. *Chemically independent bond lengths* (Å) *in anthracene*

| Bond | Exptl. | E.s.d. | Theor. | Bond | Exptl. | E.s.d. | Theor. |
|---|---|---|---|---|---|---|---|
| *AB* | 1·371 | 0·006 | 1·382 | *AG′* | 1·408 | 0·010 | 1·410 |
| *BC* | 1·424 | 0·005 | 1·420 | *CE′* | 1·436 | 0·007 | 1·430 |
| *CD* | 1·396 | 0·004 | 1·406 | | | | |

(*f*) *Examples of Electron-density Errors.*—Equation (18) shows that the error in the electron density increases with the number of planes observed. Electron-density errors thus do not have the same absolute significance as co-ordinate errors, and are necessarily relative to the number of terms included in the synthesis. However, by way of examples, in dibenzyl [30] the e.s.d. is 0·125 $eÅ^{-3}$, using $\Delta F$ as an estimate of $\sigma(F)$; in the two-dimensional projection of adenine hydrochloride [44] the e.s.d. is 0·1 $eÅ^{-2}$; and in dimethyltriacetylene [1] the e.s.d., due to the random errors of intensity estimation only, is 0·02 $eÅ^{-3}$ at the general positions in the unit cell.

Especially in metallic structures, there is considerable interest in the number of electrons associated with each atom; the errors in counting electrons in peaks have been discussed by Douglas [77] and by Cochran.[44]

---

[77] Douglas, *Acta Cryst.*, 1950, **3**, 19.

(*g*) *Possible Improvements in Accuracy.*—From the general connections between the least-squares and the Fourier method mentioned earlier, it can be shown [68] that the most accurate co-ordinates from a given set of data are obtained either from the correctly weighted least-squares equations or by using a weighted Fourier series

$$\frac{1}{V}\sum_h \sum_k \sum_l w'_{hkl} f_{hkl} \mid F_{hkl} \mid \cos\,(2\pi\, hx + ky + lz - \alpha) \quad . \quad (23)$$

where $w'$ is a weight and $f$ is the scattering factor. It is estimated for dibenzyl [68] that this would improve the co-ordinates e.s.d. by about 25% from 0·0074 Å to 0·0056 Å. Accordingly, large improvements in accuracy are not to be found by any new method for handling the data. Such improvements will depend on more and better experimental data and on the use of more elaborate models for the $F^{\text{calc.}}$'s in the refinement process. More data can be obtained by the use of low temperatures with sufficiently short wave-length radiation. The problems of obtaining more accurate data have already been discussed in Section 10(*b*) (ii), but it is important to realise that reduction of the random errors of intensity estimation is only part of the obstacle to increased accuracy. In the two-dimensional projections of dibenzyl [30] the effect of the random errors of the photographic estimation is estimated as a component of 0·006 Å out of the total of 0·017 Å. In dimethyltriacetylene,[1] where a more refined calculated model was used, the photographic random intensity errors were estimated at 0·003 Å out of the total of 0·005 Å, leaving 0·004 Å due to other causes. These instances show that the photographic method with visual intensity estimates gives good results when used with care, and that there is no point in making accurate intensity measurements, unless corresponding trouble is taken both with the absorption and extinction errors and with the refinement of the calculated model. A study of Cochran's account of the refinement of adenine hydrochloride,[44] where Geiger-counter intensities were used, will show the importance of the latter effects. The use of more elaborate models for the $F^{\text{calc.}}$'s is primarily a difficulty of the labour of computation, as the principles involved in allowing for bonding electrons and anisotropic thermal motion now seem to be well understood.

## 11. Comparison of Experimental and Theoretical Molecular Dimensions

The probability distribution for the errors in the bond lengths and bond angles approximately follows the Gaussian error law, so that one can never be certain that the actual error is less than any given amount. Accordingly, it has been suggested [30, 69] that statistical significance tests should be used in comparing experimental and theoretical results, and in comparing two sets of experimental results.

The problem of comparing experimental and theoretical results is usually a matter of testing the hypothesis that the theoretical values are the true ones. For example, if a bond length determined experimentally, with e.s.d. $\sigma$, differs by $\partial l$ from a theoretical value, the question to be decided is whether the difference might easily occur by chance due to the experimental errors or whether the difference is real and the hypothesis, that the theoretical value is the true value, is false. A standard statistical procedure for making such decisions is as follows. On the hypothesis that the theoretical value is correct, let $P$ be the probability that a difference $| \partial l |$ or greater can be observed. If $P$ is very small the hypothesis is regarded as doubtful. On the other hand, if $P$ is not small, the experimental values are regarded as not being inconsistent with the theoretical values' being correct, though of course they cannot prove this. When $P$ is so small as to cast doubt on the hypothesis, the difference is said to be significant ; just how small $P$ has to be for this is arbitrary, but most purposes are served by taking $P < 0{\cdot}01$ as significant. Values between 0·05 and 0·01 are sometimes taken to be possibly significant, and those $\leqslant 0{\cdot}001$ to be highly significant. For these values of $P$, the corresponding values of $t = \partial l/\sigma$ for the Gaussian distribution are :

$$P = 0{\cdot}05, \quad t = 1{\cdot}960 \; ; \quad P = 0{\cdot}01, \quad t = 2{\cdot}576 \; ; \quad P = 0{\cdot}001, \quad t = 3{\cdot}291 \; ;$$

thus for practical purposes a difference of more than three times the e.s.d. may be taken as real.

In testing the hypothesis that two experimental bond lengths refer to the same true value, $\sigma$ is taken as the e.s.d. of their difference.

The use of significance tests can be illustrated [38] for the naphthalene and anthracene results already discussed. These are particularly important examples, as both molecules have been the subject of detailed theoretical study by Coulson, Daudel, and Robertson.[78] Tables 3 and 4 show the theoretical bond lengths found by the molecular-orbital method. For naphthalene the differences on the bonds BC and AE′ are not significant. For the bonds AB and CC′, $0{\cdot}01 > P > 0{\cdot}001$, so that the differences between theory and experiment are significant. For anthracene the only notable difference is for CD, with $t = 2{\cdot}5$ giving $0{\cdot}05 > P > 0{\cdot}01$ which is possibly significant.

Comparisons of this sort taking the bond lengths one at a time give very useful valuations of a theory, but they do not give any overall figure of merit for a molecule as a whole. To overcome this difficulty Cruickshank and Robertson [69] have proposed the use of multivariate significance tests, in which, by taking account of the mutual correlations of error, a simultaneous comparison of a number of parameters can be made. The simultaneous comparison [69] for the four chemically non-equivalent bond lengths of naphthalene gave $P = 0{\cdot}0001$. For the five bonds of anthracene $P = 0{\cdot}05$. Thus treating the molecules as wholes the difference between theory and experiment is highly significant for naphthalene, but only possibly significant for anthracene. These comparisons neglected the admitted imperfections of the theory,[78] which are estimated to produce corrections up to about 0·015 Å per bond, but their importance is that they show that it is hardly necessary to postulate any errors in the theory for anthracene, but that the errors for naphthalene though small are very significant. They support

---

[78] Coulson, Daudel, and Robertson, *Proc. Roy. Soc.*, 1951, *A*, **207**, 306.

the view [79] that the molecular-orbital theory becomes progressively better as the size of the molecule increases.

## 12. The Relation between Experimental and Theoretical Electron-density Distributions

Hitherto the discussion of the results of molecular-structure analyses has been based on the comparison of bond lengths and valency angles, either from different experimental sources, or from corresponding experimental measurements and theoretical predictions. The remarkable degree of correlation which can be obtained for the latter under favourable conditions is illustrated by the naphthalene and anthracene examples discussed in the last section.

Not nearly so much attention has been given to those aspects of the electron-density maps which are not directly concerned with the measurement of molecular dimensions. Although in isolated examples [80, 44, 1] some partial success has been attained in trying to interpret electron densities in terms of bonding electrons,* it is also very important to try to extend the comparison between experiment and theory to include the overall electron density distribution. Such a comparison would in fact be more direct than that relating to bond lengths, for there would be no necessity for the intermediate use of empirical bond order–length relations.[81] There is, however, an important gap between the experimental and theoretical descriptions of the electron densities, which must be bridged before any useful comparisons can be made. First, the experimental electron-density map calculated by Fourier synthesis is not the true distribution in the crystal, for it is distorted by the finite series errors ; secondly, the theoretical calculations refer to the *isolated* molecule *at rest.* It would be unsound to deduce a sharpened infinite-series electron-density map from the more diffuse observed map, for trivial irregularities due to experimental errors might be magnified into apparently significant detail. The procedure must therefore be reversed, and the theoretical electron distribution must be given the experimentally determined thermal parameters and then converted into the corresponding series-terminated map. A direct comparison could then be made by means

---

[79] Coulson, *J. Phys. Chem.*, 1952, **56**, 311.

[80] Brill, *Acta Cryst.*, 1950, **3**, 333.

[81] Cox and Jeffrey, *Proc. Roy. Soc.*, 1951, *A*, **207**, 110.

[82] Bernal, *J.*, 1946, 643.

[83] Cork, *Phil. Mag.*, 1927, **4**, 688.

[84] Harker, *J. Chem. Phys.*, 1936, **4**, 381.

[85] Cox and Jeffrey, *Nature*, 1939, **143**, 894.

[86] Crowfoot, Bunn, Rogers-Low, and Turner-Jones, " The Chemistry of Penicillin ", Oxford Univ. Press, 1949, p. 310.

[87] Cochran, *Acta Cryst.*, 1953, **6**, 260.

[88] Cochran, *ibid.*, 1948, **1**, 54.

* A recent analysis [87] of salicylic acid carries the interpretation of the electron density further than in any previous work, and interesting deductions are made concerning the bonding-electrons distribution and the anisotropic thermal motion of the atoms.

of an $(F_{hkl}^{\text{obs.}} - F_{hkl}^{\text{theor.}})$ difference synthesis, which would show in convenient graphical form the overall differences between the electron distribution in the theoretical molecule and in the true molecule in the crystal environment.

The Reviewers express their thanks to Dr. Maryon W. Dougill for assistance with the Figures.