The Symbolic Addition Procedure for Phase Determination for Centrosymmetric and Noncentrosymmetric Crystals

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The theoretical background and practical procedures for phase determination by the symbolic addition method are discussed. Phase determining formulas are presented for centrosymmetric and noncentrosymmetric crystals. A probability formula is employed to evaluate the reliability of phase determination for centrosymmetric crystals and a formula for the variance is utilized for the same purpose in noncentrosymmetric ones. These probability measures play a key role in overcoming the main problems involved in carrying out the procedure, namely the nonuniqueness of the internal consistency criterion as applied to the phase determining formulas, and questions concerning the proper circumstances for assigning symbols. The method is generally applicable to centrosymmetric crystals and has been successful in several applications to noncentrosymmetric ones. Some auxiliary phase information is probably required to make the symbolic addition procedure a general one for noncentrosymmetric crystals.

1. Introduction

During the decade from 1950–60, many structure investigations of centrosymmetric crystals were carried out employing direct methods of phase determination based on algebraic and probability concepts. As a consequence of this experience, certain rather striking general features emerged whose interpretation has led to the formulation of a simple and efficient phase determination procedure for centrosymmetric crystals. For example, it has been observed that a set of relatively few properly chosen signs is required to be known initially, in order to proceed with the phase determination, when probability concepts are made an integral part of the procedure. With three-dimensional data, formulas employing the very largest normalized structure factor magnitudes, in a set of data from the copper sphere of scattering, are highly reliable, in good agreement with the expectations from probability theory. After the phases of the larger normalized structure factors have been determined, the atomic positions can be readily obtained from Fourier maps calculated from these structure factors as coefficients, the so-called E maps (Karle, Hauptman, Karle & Wing, 1958).

These observations were made in the course of carrying out the phase determining procedure of ACA Monograph 3 (Hauptman & Karle, 1953). According to the monograph, a basic set of signs is first determined from probability formulas utilizing the measured X-ray intensities, and then this basic set is used in conjunction with additional probability formulas to proceed with the phase determination. It became apparent that a simple and reliable method for phase determination would obtain from a revision of the logic of the phase determination procedure of the monograph still utilizing the probability formulas and concepts. Instead of first determining a basic set of signs and then proceeding from this basic set, the phase determining procedure can be initiated and carried out in terms of a small, properly chosen set of specified signs and unknown symbols, the symbolic addition procedure. The advantage in employing symbols at the start is that it permits the use of Σ_2 (formula 4.1) with the very largest structure factor magnitudes immediately, without the requirement for establishing their signs initially. For some of the structure factors of largest magnitude, this could be difficult or involve extensive, time-consuming calculations which are now obviated. Ordinarily, only after the phase determination in terms of the symbols has been completed would it be desirable to compute some phases from the formulas previously used for starting purposes. Other devices are also available for distinguishing among the alternative possible sets of phases and will be discussed. The first application of symbols for facilitating a procedure for sign determination was made by Gillis (1948) who used inequalities.

Although the presently described symbolic addition procedure arose as a direct development of the implications of ACA Monograph 3, there are several similarities between the procedure of Zachariasen (1952) and the present one as applied to centrosymmetric crystals. These include the use of symbols to facilitate the application of the phase determining relations and the restriction of attention to the structure factors of larger magnitude so that the indications would be more probably correct. The present method differs in its manner of handling two significant problems which occur in the use of symbols with the phase determining formula. The first problem is that there is a very great number of sets of signs in general which are essentially internally consistent with respect to the phase determining Σ_2 relation. The physically correct set is buried somewhere among them. The second problem concerns the questions of how many symbols to assign and under what circumstances. In the symbolic addition procedure these problems are overcome by the introduction of probability measures developed in ACA Monograph 3.

In the application which Zachariasen (1952) made to the structure determination of metaboric acid, both problems were overcome by using initially auxiliary phase information from an inequality relation. The inequality afforded a firm basis for proceeding with the sign determination and served as a vehicle for introducing the unknown symbols employed for facilitating the procedure.

It has long been recognized that the main phase determining formula, Σ_2, does not usually lead to the physically correct solution in a unique fashion without the introduction of auxiliary phase information. In the course of the years various algebraic and probability methods have been developed to provide this information. The present method is based on the recognition that with the proper use of probability information, the number of ambiguous sets of signs can, in general, be kept to a very small number, with the assurance that the desired physical answer be contained among the small number of possibilities generated by the procedure. Another special feature of the present method is the manner in which the specification of symbols is made in a step-by-step fashion contingent upon the requirements for proceeding with the determination and the reliabilities indicated by the probability measures.

Other investigators have suggested procedures to facilitate finding the physically correct set of signs. For example, Rumanova (1954) developed a systematic method for applying the relation for sign determination by making use of symmetry relations in the centrosymmetric space groups. She has used it in connection with Zachariasen's (1952) procedure and has carried out several successful structure determinations. Cochran & Douglas (1955) introduced a so-called χ function based on probability considerations in order to choose the correct set of signs from among a very large number of sets generated by a computer. Although successful in several instances the limitation of this manner of using probability information arises from the fact that the probability measure in the form of the χ function was applied to an entire set of signs, rather than to individual terms in a step-by-step fashion. This led to an insensitivity to the correct set and the need to consider a great many possibilities. A procedure for decreasing the number of possibilities which required consideration was suggested by Woolfson (1957), but this number still remained quite large.*

The new procedure has been applied to numerous structure investigations of centrosymmetric crystals and has been found to be quite effective and simple to apply, e.g. cyclohexaglycyl (Karle & Karle, 1963), jamine (Karle & Karle, 1964a), hydrolyzed cocarboxylase (Karle & Britts, 1966), and other examples published after 1963 in *Acta Crystallographica, Zeitschrift für Kristallographie* and the *Journal of the American*

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* For further details concerning the development and application of procedures for phase determination, the reader is referred to the review article by Karle (1964).

Chemical Society. In each case the phase determination was carried out by hand in a relatively short time. The question naturally arises whether there exists a straightforward generalization of the procedure which would have practical significance for noncentrosymmetric crystals. A generalization has been found and has been applied to the study of several noncentrosymmetric crystals, for example L-arginine dihydrate (Karle & Karle, 1964a), and panamine (Karle & Karle, 1966). It involves the use of a new formula which again has probable validity for the phases associated with the larger normalized structure factor magnitudes. However, the number of ambiguous sets of phases generated for noncentrosymmetric crystals is often rather large, so that the procedure, for general applicability, appears to require some auxiliary phase information.

The main phase determining formulas for both centrosymmetric and noncentrosymmetric crystals to be discussed here involve the addition of particular combinations of phases. They may therefore be termed addition formulas. Since the procedure is generally facilitated by the use of a few unknown symbols, we have termed this procedure the symbolic addition procedure.

The purpose of this paper is to describe the conceptual basis of the method in terms of the main phase determining formulas, to present a detailed description of the phase determining procedures and to discuss the features of these procedures on the basis of our experience to date. The main phase determining formulas are listed in § 4.

2. Background

As is well known, a set of inequalities which proved useful for sign determination was derived by Harker & Kasper (1948). It was shown (Karle & Hauptman, 1950) that these inequalities arose from the positivity criterion, namely that the electron density distribution had to be a non-negative function*. On the basis of this positivity criterion, Karle & Hauptman (1950) derived a complete set of inequalities which are valid for all the space groups. The inequalities could be written as a sequence of relations of successively increasing complexity. The first three are,

$$F_{000} \geq 0 , \tag{2.1}$$

$$|F_{hkl}| \leq F_{000} \tag{2.2}$$

and

$$\left| F_{h_1+h_2,\ k_1+k_2,\ l_1+l_2} - \frac{F_{h_1k_1l_1}F_{h_2k_2l_2}}{F_{000}} \right|$$

$$\leq \frac{\left| \begin{matrix} F_{000} & F_{\bar{h}_1\bar{k}_1\bar{l}_1} \\ F_{h_1k_1l_1} & F_{000} \end{matrix} \right|^{\frac{1}{2}} \left| \begin{matrix} F_{000} & F_{\bar{h}_2\bar{k}_2\bar{l}_2} \\ F_{h_2k_2l_2} & F_{000} \end{matrix} \right|^{\frac{1}{2}}}{F_{000}} . \tag{2.3}$$

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* C. H. MacGillavry independently observed that Harker & Kasper implicitly assumed the non-negativity of the density distribution in their derivation.

The first two inequalities state that F_{000} is non-negative and that the magnitude of any structure factor is less than or equal to F_{000}. For the case of crystals having a small number of atoms, the third relation (2.3) can provide a basis for phase determination in both centrosymmetric and noncentrosymmetric crystals. To understand this we rewrite (2.3) in the form

$$|F_{\mathbf{h}} - \delta| \le r ,\qquad (2.4)$$

where

$$\delta = \delta(\mathbf{h, k}) = F_{\mathbf{h-k}} F_{\mathbf{k}}/F_{000} ,\qquad (2.5)$$

$$r = \frac{\begin{vmatrix} F_{000} & F_{\mathbf{h-k}}^* \\ F_{\mathbf{h-k}} & F_{000} \end{vmatrix}^{\frac{1}{2}} \begin{vmatrix} F_{000} & F_{\mathbf{k}}^* \\ F_{\mathbf{k}} & F_{000} \end{vmatrix}^{\frac{1}{2}}}{F_{000}} ,\qquad (2.6)$$

and $\mathbf{h} = \mathbf{h}_1 + \mathbf{h}_2$ and $\mathbf{k} = \mathbf{h}_2$. Equation (2.4) implies that the complex structure factor $F_{\mathbf{h}}$ is bounded by a circle in the complex plane whose center is δ and whose radius is r (Fig. 1). If the magnitude of $F_{\mathbf{h}}$ is known, it will be bounded by the dotted line between the points A and B. The larger the values of $|F_{\mathbf{k}}|$ and $|F_{\mathbf{h-k}}|$, the smaller will be r, and the closer will $F_{\mathbf{h}}$ be to the complex number δ. Since the vector $\mathbf{k}$ can be varied arbitrarily, many different relations of the type (2.3) and (2.4) would exist. From the foregoing discussion, one would expect that $F_{\mathbf{h}}$ would be proportional to an average over the various $\delta(\mathbf{h, k})$ involving the larger $|F|$ as $\mathbf{k}$ is varied,

$$F_{\mathbf{h}} \propto \langle F_{\mathbf{k}} F_{\mathbf{h-k}} \rangle_{\mathbf{k}} .\qquad (2.7)$$

This follows since for the larger $|F|$, the quantities $\delta(\mathbf{h, k})$ would cluster in a particular region of the complex plane and $F_{\mathbf{h}}$ would be located within this cluster. It could be described geometrically by several interlocking circles drawn as in Fig. 1, each with a new δ and a new r. It also follows from the previous discussion and Fig. 1 that if we consider the larger structure factor magnitudes and write
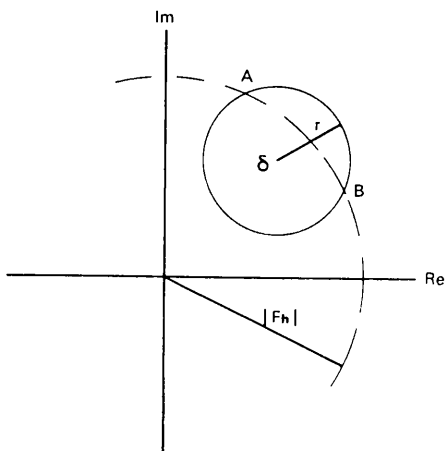

Fig. 1. Construction showing how $F_{\mathbf{h}}$ is limited by the inequality (2·4). $F_{\mathbf{h}}$ is contained within a circle of radius r whose center is δ. When the value of $|F_{\mathbf{h}}|$ is given as indicated, $F_{\mathbf{h}}$ lies anywhere along the broken line within the circle, *i.e.* between the points A and B.

$$F_{\mathbf{h}} = |F_{\mathbf{h}}| \exp{(i\varphi_{\mathbf{h}})} ,\qquad (2.8)$$

we may conclude that approximately

$$\varphi_{\mathbf{h}} \approx \langle \varphi_{\mathbf{k}} + \varphi_{\mathbf{h-k}} \rangle_{\mathbf{k}} ,\qquad (2.9)$$

where $\varphi_{\mathbf{k}} + \varphi_{\mathbf{h-k}}$ is associated with the complex number $\delta(\mathbf{h, k})$ through the relation

$$\delta(\mathbf{h, k}) = |\delta(\mathbf{h, k})| \exp{[i(\varphi_{\mathbf{k}} + \varphi_{\mathbf{h-k}})]} .\qquad (2.10)$$

For the special case of centrosymmetric crystals, it is seen how the Sayre (1952) relation follows from (2.7), namely the sign of $F_{\mathbf{h}}$ would almost certainly be the same as that of $\langle F_{\mathbf{k}} F_{\mathbf{h-k}} \rangle_{\mathbf{k}}$ if large structure factor magnitudes were involved. It should be noted, as pointed out by Gillis (1948, p. 179), that the predominant phase indication given by an inequality is probably the correct one, even though the structure factor magnitudes involved are not quite large enough to give a definitive result.

The sign relationship for centrosymmetric crystals and some further implications for noncentrosymmetric ones are contained in relation (20) of Harker & Kasper (1948), although the general phase expression (2.3) and its implication (2.7) is not. The interpretation of the inequality expressions such as (2.3) in terms of (2.4) for the largest structure factors was presented in the paper by Karle & Hauptman (1950), and thus the phase relation (2.7) was recognized and understood from this work. Sayre (1952) and Zachariasen (1952) made a valuable contribution in emphasizing the significance and potential of (2.7) for sign determination in centrosymmetric crystals. In his paper, Sayre (1952, p. 64) pointed out the parallel between his results and the earlier work mentioned above.

Examination of formulas such as (2.7) and (2.9) indicates that it is necessary to have a basic set of phases in order to use them for obtaining additional phases. A basic set may be composed of those phases which can be specified in order to fix the origin in the crystal, and some additional phases denoted by symbols, corresponding to the largest structure factor magnitudes. If it is not necessary to assign many symbols, (2.9) would be immediately useful as a general phase determining relation. It will be seen that if certain rules are followed for choosing a basic set and unknown symbols are introduced in a stepwise fashion, paying close attention to associated probability measures, very few symbols are, in fact, required for centrosymmetric crystals. This appears also to be true for many noncentrosymmetric crystals, but it is not possible to generalize at this time.

As the complexity of crystals increases, the quantity r in (2.4) becomes disproportionately large, until in general the inequality (2.4) by itself imposes no restriction on the phase of $F_{\mathbf{h}}$. The arguments in this section must then be augmented by a more detailed analysis involving algebraic considerations and probability theory. When this is done it is found that the phase determining formulas such as (2.9) remain valid

and it is also possible to obtain additional useful phase determining relations.

The phase relations and the implications drawn therefrom are strengthened by dividing the Fourier coefficients by a function of the atomic scattering factors which effectively concentrates the scattering material about the atomic coordinates to form the unitary structure factor, U_h (Harker & Kasper, 1948), or the normalized structure factor, E_h (5.1).

Probability formulas for evaluating the reliability of a sign determination for centrosymmetric crystals were derived by Hauptman & Karle (1953), using the joint probability distribution. The results were obtained in the form of a series. For the present applications we prefer the hyperbolic tangent form obtained by Woolfson (1954). The relation between the two forms has been shown by Karle (1964, p.73). Additional algebraic and probability considerations applicable to noncentrosymmetric crystals will be discussed in the next section.

3. Analysis

3.1 Algebraic considerations

We define the quasi-normalized structure factor (Karle & Hauptman, 1959):

$$\mathscr{E}_k = \sigma_2^{-1/2} \sum_{j=1}^{N} Z_j \exp(2\pi i\, k \cdot r_j) , \qquad (3.1)$$

and the quasi-normalized structure factor for the squared structure

$$\mathscr{E}'_h = \sigma_4^{-1/2} \sum_{j=1}^{N} Z_j^2 \exp(2\pi i\, h \cdot r_j) , \qquad (3.2)$$

where Z_j is the atomic number of the jth atom, having coordinates represented by the vector r_j in a unit cell containing N atoms, and

$$\sigma_n = \sum_{j=1}^{N} Z_j^n . \qquad (3.3)$$

Then,

$$\mathscr{E}_k\, \mathscr{E}_{h-k} = \sigma_2^{-1} \sum_{j=1}^{N} Z_j^2 \exp(2\pi i\, h \cdot r_j)$$

$$+ \sigma_2^{-1} \sum_{\substack{j \neq j' \\ 1}} \sum Z_j Z_{j'} \exp\{2\pi i\, [k \cdot r_j + (h-k) \cdot r_{j'}]\} , \qquad (3.4)$$

and if we average over all values of k, the average of the double sum becomes zero and we obtain, using (3.2),

$$\langle \mathscr{E}_k \mathscr{E}_{h-k} \rangle_k = \sigma_2^{-1} \sum_{j=1}^{N} Z_j^2 \exp(2\pi i\, h \cdot r_j) = \sigma_4^{1/2} \sigma_2^{-1} \mathscr{E}'_h . \qquad (3.5)$$

Rearranging, we have the general result from (3.5),

$$\mathscr{E}'_h = \sigma_2 \sigma_4^{-1/2} \langle \mathscr{E}_k \mathscr{E}_{h-k} \rangle_k . \qquad (3.6)$$

This expression can also be derived by means of the joint probability distribution. For equal atoms $\mathscr{E}'_h$ coincides with $\mathscr{E}_h$, $\sigma_2 \sigma_4^{-1/2}$ equals $N^{1/2}$ and (3.6) becomes in this special case,

$$\mathscr{E}_h = N^{1/2} \langle \mathscr{E}_k \mathscr{E}_{h-k} \rangle_k . \qquad (3.7)$$

Formula (3.7), which is exact for equal atoms was derived originally for centrosymmetric crystals by Hughes (1953) in terms of unitary structure factors, $U_h = F_h / \sum_{j=1}^{N} f_j$. When the atoms are equal, Hughes (1953) also noted that in this case formula (3.7) is valid for noncentrosymmetric crystals. An expression similar to (3.6), in terms of unitary structure factors, has been obtained by Cochran (1955) from probability considerations. Karle & Hauptman (1956) have found a relation for $\mathscr{E}_h$ instead of $\mathscr{E}'_h$ by probability methods,

$$\mathscr{E}_h \approx \sigma_2^{3/2} \sigma_3^{-1} \langle \mathscr{E}_k \mathscr{E}_{h-k} \rangle_k , \qquad (3.8)$$

which also may be compared to (3.6). They wrote (3.8) in a form which has proven to be quite useful in application. If we write $\mathscr{E}_h = |\mathscr{E}_h| \cos \varphi_h + i\, |\mathscr{E}_h| \sin \varphi_h$, (3.8) becomes,

$$|\mathscr{E}_h| \cos \varphi_h \approx \sigma_2^{3/2} \sigma_3^{-1} \langle |\mathscr{E}_k \mathscr{E}_{h-k}| \cos(\varphi_k + \varphi_{h-k}) \rangle_k , \qquad (3.9)$$

$$|\mathscr{E}_h| \sin \varphi_h \approx \sigma_2^{3/2} \sigma_3^{-1} \langle |\mathscr{E}_k \mathscr{E}_{h-k}| \sin(\varphi_k + \varphi_{h-k}) \rangle_k , \qquad (3.10)$$

and dividing (3.10) by (3.9) gives

$$\tan \varphi_h \approx \frac{\langle |\mathscr{E}_k \mathscr{E}_{h-k}| \sin(\varphi_k + \varphi_{h-k}) \rangle_k}{\langle |\mathscr{E}_k \mathscr{E}_{h-k}| \cos(\varphi_k + \varphi_{h-k}) \rangle_k} . \qquad (3.11)$$

For the larger structure factor magnitudes $|\mathscr{E}|$, (3.8) leads to a new approximate formula which plays a significant role in the initial stages of phase determination. Equation (3.8)* can be rewritten,

$$1 \approx \sigma_2^{3/2} \sigma_3^{-1} \langle |\mathscr{E}_h^{-1} \mathscr{E}_k \mathscr{E}_{h-k}| \exp[i(-\varphi_h + \varphi_k + \varphi_{h-k})] \rangle_k . \qquad (3.12)$$

It has been shown by means of probability arguments, to be discussed below, that for the largest $|\mathscr{E}|$ values, $\varphi_h - \varphi_k - \varphi_{h-k}$ is distributed about zero and generally, assumes small values. We then write

$$1 \approx C \sigma_2^{3/2} \sigma_3^{-1} \langle |\mathscr{E}_h^{-1} \mathscr{E}_k \mathscr{E}_{h-k}| [\cos(-\varphi_h + \varphi_k + \varphi_{h-k})$$
$$+ i \sin(-\varphi_h + \varphi_k + \varphi_{h-k})] \rangle_{k_r} , \qquad (3.13)$$

where k_r represents the restricted values of k for which the corresponding $|\mathscr{E}_k|$ and $|\mathscr{E}_{h-k}|$ values are large and

$$C \approx \sigma_2^{-3/2} \sigma_3 \langle |\mathscr{E}_h^{-1} \mathscr{E}_k \mathscr{E}_{h-k}| \cos(-\varphi_h + \varphi_k + \varphi_{h-k}) \rangle_{k_r}^{-1}$$

$$\approx \sigma_2^{-3/2} \sigma_3 \langle |\mathscr{E}_h^{-1} \mathscr{E}_k \mathscr{E}_{h-k}| \rangle_{k_r}^{-1} \left\langle \frac{I_0(\kappa)}{I_1(\kappa)} \right\rangle_{k_r} \qquad (3.14)$$

from use of (3.37) and (3.38) and the assumption that the $|\mathscr{E}|$ values vary over a restricted range. Restricting attention to the imaginary part of (3.13) gives

$$\langle |\mathscr{E}_k \mathscr{E}_{h-k}| \sin(-\varphi_h + \varphi_k + \varphi_{h-k}) \rangle_{k_r} \approx 0 . \qquad (3.15)$$

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* We work with the approximate equation (3·8) rather than the exact (3·6) since it defines the phase for $\mathscr{E}_h$, rather than for $\mathscr{E}'_h$ which is associated with the squared structure. Actually the $\mathscr{E}_h$ and $\mathscr{E}'_h$ of large magnitude do not differ greatly from each other, even when atoms of considerably different atomic number are present in a crystal.

We take the first term in the Taylor expansion of the sine function since its argument is generally small and obtain,

$$\langle |\mathscr{E}_k \mathscr{E}_{h-k}| \, (-\varphi_h + \varphi_k + \varphi_{h-k}) \rangle_{k_r}$$
$$\equiv p^{-1} \sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}| \, (-\varphi_h + \varphi_k + \varphi_{h-k}) \approx 0 , \quad (3.16)$$

where there are p terms designated by k_r. Equation (3.16) may be rewritten to give a new phase determining formula,

$$\varphi_h \approx \frac{\sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}| \, (\varphi_k + \varphi_{h-k})}{\sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}|} \quad (3.17)$$

in which the φ_h are defined as linear functions of other phases, specifically the weighted averages of $\varphi_k + \varphi_{h-k}$ associated with the largest $|\mathscr{E}|$ values. If all the $|\mathscr{E}|$ are roughly of the same order of magnitude, we obtain

$$\varphi_h \approx \langle \varphi_k + \varphi_{h-k} \rangle_{k_r}, \quad (3.18)$$

in agreement with (2.9) which was suggested by an interpretation of the inequality (2.4).

3.2 Probability considerations

It is now of interest to consider the probability distribution for $\varphi_h - \varphi_k - \varphi_{h-k}$ and to relate it to the previous assumption that this linear combination is distributed about zero with values generally close to zero. Cochran (1955) (employing somewhat different notation) found that the probability distribution for φ_h, given a fixed $\varphi_k + \varphi_{h-k}$ and the accompanying $|\mathscr{E}|$ values, is given by

$$P_k(\varphi_h) \approx [2\pi I_0(\kappa)]^{-1} \exp[\kappa \cos(\varphi_h - \varphi_k - \varphi_{h-k})], \quad (3.19)$$

where I_0 is a Bessel function (Watson, 1945, p. 77) and

$$\kappa = \kappa(\mathbf{h}, \mathbf{k}) = 2\sigma_3 \sigma_2^{-3/2} |\mathscr{E}_h \mathscr{E}_k \mathscr{E}_{h-k}| . \quad (3.20)$$

The joint probability distribution for φ_h, φ_k and φ_{h-k} found by Karle & Hauptman [1956, equation (5.39)] is in agreement with this result. The first two terms of the distribution, which were explicitly calculated, are to be compared with the first two terms of the exponential expansion of (3.19). Clearly, (3.19) has a maximum when $\varphi_h = \varphi_k + \varphi_{h-k}$ or $\varphi_h - \varphi_k - \varphi_{h-k} = 0$, and the larger the value of κ, i.e. the larger the $|\mathscr{E}|$ values, the steeper will this maximum be. Cochran (1955) has studied the probability distribution (3.19) in considerable detail and has computed a table which facilitates the estimation of its sharpness.

It is possible to use (3.19) as a basis for an alternative derivation of the phase determining formulas (3.11), (3.17) and (3.18) from probability rather than algebraic considerations. Given several fixed 'addition pairs' $\varphi_k + \varphi_{h-k}$, we may multiply the individual probability distributions to obtain the approximate form,

$$P(\varphi_h) = \prod_{k_r} P_k(\varphi_h) \approx A \exp\left[\sum_{k_r} \kappa(\mathbf{h}, \mathbf{k}) \cos(\varphi_h - \varphi_k - \varphi_{h-k})\right], \quad (3.21)$$

where A is a normalizing constant and, again, the summation over k_r involves the larger $|\mathscr{E}|$ values. The maximum of the probability distribution, $P(\varphi_h)$, is obtained as usual by the condition,

$$\frac{dP(\varphi_h)}{d\varphi_h} \approx -A \exp\left[\sum_{k_r} \kappa(\mathbf{h}, \mathbf{k}) \cos(\varphi_h - \varphi_k - \varphi_{h-k})\right]$$
$$\times \sum_{k_r} \kappa(\mathbf{h}, \mathbf{k}) \sin(\varphi_h - \varphi_k - \varphi_{h-k}) = 0 . \quad (3.22)$$

This gives with the aid of (3.20),

$$\sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}| \sin(\varphi_h - \varphi_k - \varphi_{h-k}) = 0 . \quad (3.23)$$

Since (3.23) divided by the number of contributors to the sum is the same as (3.15), it follows that from the point of view of probability theory the new phase determining formulas (3.17) and (3.18) appear as approximate conditions for locating the main maximum of the probability distribution given by (3.21). Equation (3.23) may also be rewritten in the form,

$$\sin \varphi_h \sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}| \cos(\varphi_k + \varphi_{h-k})$$
$$- \cos \varphi_h \sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}| \sin(\varphi_k + \varphi_{h-k}) = 0 , \quad (3.24)$$

which becomes, by rearrangement, the more accurate equation (3.11), except that here, of course, the range of k has been restricted.

3.3 Variance

The probability distribution (3.21) can be used to determine the variance of φ_h for a given set of $(\varphi_k + \varphi_{h-k})$ and κ. Equation (3.21) may be rewritten in the form

$$P(\varphi_h) = [2\pi I_0(\alpha)]^{-1} \exp[\alpha \cos(\varphi_h - \beta)] , \quad (3.25)$$

where

$$\alpha = \left\{ \left[\sum_{k_r} \kappa(\mathbf{h}, \mathbf{k}) \cos(\varphi_k + \varphi_{h-k})\right]^2 \right.$$
$$\left. + \left[\sum_{k_r} \kappa(\mathbf{h}, \mathbf{k}) \sin(\varphi_k + \varphi_{h-k})\right]^2 \right\}^{\frac{1}{2}} \quad (3.26)$$

and

$$\beta = \tan^{-1} \frac{\sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}| \sin(\varphi_k + \varphi_{h-k})}{\sum_{k_r} |\mathscr{E}_k \mathscr{E}_{h-k}| \cos(\varphi_k + \varphi_{h-k})} . \quad (3.27)$$

The form of (3.25) and the definition (3.27) clarify the result obtained in (3.23) and (3.24). We wish to find from (3.25), the variance,

$$V = \langle (\varphi_h - \langle \varphi_h \rangle)^2 \rangle = \langle \varphi_h^2 \rangle - \langle \varphi_h \rangle^2 . \quad (3.28)$$

We consider first

$$\langle \varphi_h^2 \rangle = [2\pi I_0(\alpha)]^{-1} \int_{\beta - \pi}^{\beta + \pi} \varphi_h^2 \exp[\alpha \cos(\varphi_h - \beta)] d\varphi_h, \quad (3.29)$$

which becomes on substituting $x = \varphi_h - \beta$,

$$\langle \varphi_h^2 \rangle = [2\pi I_0(\alpha)]^{-1} \int_{-\pi}^{\pi} (x + \beta)^2 \exp(\alpha \cos x) \, dx . \quad (3.30)$$

The squared term in the integrand of (3.30) may be written $x^2 + 2x\beta + \langle \varphi_h \rangle^2$ since $\beta = \langle \varphi_h \rangle$. If we note that x makes the integrand of (3.30) odd and then refer to definition (3.28), we find that

$$V = [2\pi I_0(\alpha)]^{-1} \int_{-\pi}^{\pi} x^2 \exp(\alpha \cos x)\, dx . \qquad (3.31)$$

From the theory of Bessel functions (Watson, 1945 pp. 22 and 77) we have,

$$\exp(\alpha \cos x) = I_0(\alpha) + 2 \sum_{n=1}^{\infty} I_{2n}(\alpha) \cos 2nx$$

$$+ 2 \sum_{n=0}^{\infty} I_{2n+1}(\alpha) \cos(2n+1)x . \qquad (3.32)$$

The substitution of (3.32) into (3.31) gives, on integrating,

$$V = \frac{\pi^2}{3} + [I_0(\alpha)]^{-1} \sum_{n=1}^{\infty} \frac{I_{2n}(\alpha)}{n^2}$$

$$+ 4[I_0(\alpha)]^{-1} \sum_{n=0}^{\infty} \frac{I_{2n+1}(\alpha)}{(2n+1)^2} . \qquad (3.33)$$

The infinite series converge quite rapidly for the values of α ordinarily encountered in practice. Expression (3.33) gives the variance of φ_h for a fixed set of $(\varphi_k + \varphi_{h-k})$ and κ.

3.4 Expected values

We can obtain the expected values of $\cos(\varphi_k + \varphi_{h-k})$ and $\sin(\varphi_k + \varphi_{h-k})$ for a fixed value of κ from the probability distribution (3.19). We have,

$$\langle \cos(\varphi_k + \varphi_{h-k}) \rangle = [2\pi I_0(\kappa)]^{-1} \int_{-\pi}^{\pi} \cos(\varphi_k + \varphi_{h-k})$$

$$\times \exp[\kappa \cos(\varphi_h - \varphi_k - \varphi_{h-k})]\, d(\varphi_k + \varphi_{h-k}) . \quad (3.34)$$

By means of the expansion (3.32) (where for a single contributor α is replaced by κ) and orthogonality properties which permit a contribution to (3.34) only from the $n = 0$ term of the last summation in (3.32), we obtain for a fixed κ,

$$\langle \cos(\varphi_k + \varphi_{h-k}) \rangle = \frac{I_1(\kappa)}{I_0(\kappa)} \cos \varphi_h . \qquad (3.35)$$

where I_1 is a Bessel function (Watson, 1945, p. 77). In a similar fashion we obtain also,

$$\langle \sin(\varphi_k + \varphi_{h-k}) \rangle = \frac{I_1(\kappa)}{I_0(\kappa)} \sin \varphi_h . \qquad (3.36)$$

In practice there would not be many addition pairs, $\varphi_k + \varphi_{h-k}$ for fixed κ and fixed h; and we would therefore have to allow for some variation in κ as k varies over a restricted set of values. We are therefore led to the approximate formulas

$$\cos \varphi_h \approx \left\langle \frac{I_0(\kappa)}{I_1(\kappa)} \right\rangle_{k_r} \langle \cos(\varphi_k + \varphi_{h-k}) \rangle_{k_r} , \qquad (3.37)$$

$$\sin \varphi_h \approx \left\langle \frac{I_0(\kappa)}{I_1(\kappa)} \right\rangle_{k_r} \langle \sin(\varphi_k + \varphi_{h-k}) \rangle_{k_r} . \qquad (3.38)$$

The ratio of (3.38) to (3.37) gives a formula for $\tan \varphi_h$ which may be compared to the more accurate (3.11). The sine and cosine terms from (3.37) and (3.38) are unweighted. If, however, the range of $|\mathscr{E}|$ values covered by k_r is not large, the weighting does not play an important role.

4. Phase determining formulas

The main formulas to be used in the phase determination are listed here.

Centrosymmetric crystals

$$sE_h \approx s \sum_{k_r} E_k E_{h-k} , \qquad (4.1)$$

where s means 'sign of'. This formula was termed Σ_2 in the monograph of Hauptman & Karle (1953), and is the probability equivalent of the inequality (2.3). The associated probability function, $P_+(h)$, which determines the probability that the sign of E_h be positive was given in the monograph, but it is most conveniently applied in the form given by Woolfson (1954) and Cochran & Woolfson (1955),

$$P_+(h) \approx \tfrac{1}{2} + \tfrac{1}{2} \tanh \sigma_3 \sigma_2^{-3/2} |E_h| \sum_k E_k E_{h-k} . \quad (4.2)$$

Noncentrosymmetric crystals

$$\varphi_h \approx \langle \varphi_k + \varphi_{h-k} \rangle_{k_r} , \qquad (4.3)$$

$$\varphi_h \approx \frac{\sum_{k_r} |E_k E_{h-k}| (\varphi_k + \varphi_{h-k})}{\sum_{k_r} |E_k E_{h-k}|} , \qquad (4.4)$$

$$\tan \varphi \approx \frac{\sum_k |E_k E_{h-k}| \sin(\varphi_k + \varphi_{h-k})}{\sum_k |E_k E_{h-k}| \cos(\varphi_k + \varphi_{h-k})} . \qquad (4.5)$$

Either (4.3) or (4.4) may be used in the beginning stages of the phase determination. The symbol k_r implies that k ranges only over those vectors associated with large $|E|$ values. Formula (4.3) is the same as (3.18). The average in (4.3) is to be taken in a sense of maximum clustering, *i.e.* a minimum deviation of the contributions of individual addition pairs, $\varphi_k +$
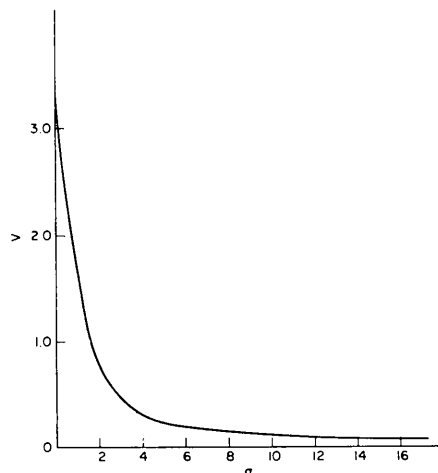

Fig. 2. Curve showing the variance, V (in square radians), of a phase angle determined from known values of other phase angles. The variance is expressed as a function of α defined in (3·26).

$\varphi_{\mathbf{h}-\mathbf{k}}$, from the average value. Since all φ are kept in a range $-\pi < \varphi \leq \pi$, the attainment of maximum clustering requires the addition of 0, $+2\pi$ or -2π to each addition pair. This matter complicates the application of (4.3) to noncentrosymmetric crystals and will be discussed further below. In analogy to the probability formula (4.2) for centrosymmetric crystals, we employ the variance given by (3.33) and plotted as a function of α in Fig. 2 in order to evaluate the reliability of contributors in (4.3).

Formulas (4.4) and (4.5) are analogous to (3.17) and (3.11), respectively, except that the quasi-normalized structure factor, $\mathscr{E}_{\mathbf{h}}$, has been replaced by the normalized structure factor, $E_{\mathbf{h}}$. It is preferable to use the latter, since the $E_{\mathbf{h}}$ are corrected when $\mathbf{h}$ belongs to a subgroup affected by space group extinctions [see § 5, I(a)]. Under those circumstances the $\mathscr{E}_{\mathbf{h}}$ might be rather large in magnitude and could make an unwarrantably large contribution to formulas (3.17) and (3.11).

5. Procedures for phase determination

I. *Centrosymmetric crystals*
(a). *Preparation of normalized structure factor magnitudes*

Normalized structure factor magnitudes, $|E_{\mathbf{h}}|$, are defined by

$$|E_{\mathbf{h}}|^2 = \frac{|F_{\mathbf{h}}|^2}{\epsilon \sum\limits_{j=1}^{N} f_j^2(\mathbf{h})}, \qquad (5.1)$$

where $|F_{\mathbf{h}}|$ is the structure factor magnitude, f_j is the atomic scattering factor for the jth atom in a unit cell containing N atoms, and ϵ is a number which corrects for space group extinctions*.

A data reduction program, written in the FORTRAN language, which processes the measured intensity data, makes all the necessary corrections automatically and produces the normalized structure factor magnitudes, $|E_{\mathbf{h}}|$, has been written by H. Norment and revised by S. Brenner, both of this laboratory. For the proper application of the phase determining formulas, all reflections contained within the experimental sphere of reflection are considered available for use, not merely the independent reflections.

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* For the case that none of the indices is zero, the quasi-normalized structure factors, $\mathscr{E}$, are the same as the normalized structure factors, E. When there are systematic absences due to space group extinctions among reflections for which at least one of the indices is zero, the quasi-normalized structure factors have to be rescaled to equal the normalized structure factors. If, for example, half of the reflections in a particular set, such as the $h0l$ reflections in space group $P2_1/c$, then the appropriate quasi-normalized structure factors must be divided by $2^{\frac{1}{2}}$, *i.e.* $\mathscr{E}_{h0l}/2^{\frac{1}{2}} = E_{h0l}$. The rule is $|\mathscr{E}|^2(1-q) = |E|^2$, where q is the fraction of reflections in the set which are space group extinctions. We are considering here only primitive unit cells. Our choice of primitive cell for conventionally centered cells is given in previous papers (Hauptman & Karle, 1959; Karle & Hauptman, 1961).

(b) *Listings of the data*

After the $|E_{\mathbf{h}}|$ have been obtained, it is convenient to divide them among the eight subgroups defined by the parity of the h, k and l indices. In each of these subgroups the $|E_{\mathbf{h}}|$ are listed in the order of decreasing magnitude. For the space groups of higher symmetry, a further subdivision of the subgroups may be desirable.

Another useful listing consists of all the combinations of $\mathbf{k}$ and $\mathbf{h} - \mathbf{k}$ for a given $\mathbf{h}$ to be used with formula (4.1). It is called a Σ_2 listing and a FORTRAN program for carrying this out has been prepared by H. Norment and revised by P. Gum and S. Brenner. The list is restricted since we only consider those indices associated with the $|E|$ of sufficiently large value. This value is, of course, arbitrary and is dictated by experience and the size of the unit cell of the crystal being studied. However, it is often set at $|E| \geq 1.5$. Along with each pair, $\mathbf{k}$ and $\mathbf{h} - \mathbf{k}$, the value of the function $\sigma_3^7 \sigma_2^{-3/2} |E_{\mathbf{h}} E_{\mathbf{k}} E_{\mathbf{h}-\mathbf{k}}|$ is listed. This facilitates the evaluation of the probability formula (4.2).

(c) *Specification of origin, assignment of unknown symbols and phase determination*

Origin specification is made by assigning phases arbitrarily to a properly chosen set of $|E_{\mathbf{h}}|$ (Hauptman & Karle 1953, 1959). In making the phase assignments the largest suitable $|E_{\mathbf{h}}|$ should be used. The choice will be partly determined by the extent to which a particular $\mathbf{h}$ enters into the combinations required by formula (4.1) as noted from the Σ_2 listing. Occasionally a structure factor of large magnitude does not form many combinations.

After the phase specifications which determine the origin have been made, some additional symbols are assigned in a step-by-step fashion as needed to other large $|E_{\mathbf{h}}|$ which appear to enter into many combinations as required by formula (4.1). In this way it is possible to proceed with the phase determination by hand and obtain the phases of many of the remaining large $|E_{\mathbf{h}}|$ in terms of the phase specifications and the unknown symbols.

(d) *Phase determination*

In proceeding by hand with (4.1) the following steps have generally been followed:

1. A listing is made of five to ten of the largest $|E|$ in each of the parity subgroups mentioned in (b). This short list not only facilitates the specifications but it also restricts the initial stages of the phase determination to the very largest $|E|$ values.

2. The signs which specify the origin and one unknown symbol are assigned, bearing in mind that the particular reflections chosen should enter into many combinations such as are required by (4.1).

3. Equation (4.1) is employed to define as many signs of the largest $|E_{\mathbf{h}}|$ as possible in terms of the specified ones and others that have been newly determined. It is important to take advantage of the fact that when the sign of a reflection is known, the signs

of all the symmetry related reflections are known. In the higher space groups this greatly facilitates the phase determining procedure. Often, the probability formula (4.2) will indicate a high probability for the initial combinations. As the determination proceeds and the smaller $|E|$ values enter, the probability estimates from (4.2) should be carefully considered. A working rule is that a phase should not be accepted if $P_+(\mathbf{h}) < 0.97$ as given by (4.2), whether there is only one term in the sum over $\mathbf{k}$ or several. On rare occasions in the triclinic system it has been found necessary to relax this rule slightly in order to proceed. In the initial stages it is also recommended that in all but the triclinic system combinations of $\mathbf{h}$, $\mathbf{k}$ and $\mathbf{h} - \mathbf{k}$, in which all three vectors are one- or two-dimensional, should be avoided. An automatic computer program for phase determination should take this type of decision process into account.

4. The next five to ten largest $|E|$ in each subgroup are added and eventually full use is made of the listing of all the combinations of $\mathbf{k}$ and $\mathbf{h} - \mathbf{k}$ for a given $\mathbf{h}$ found in (b).

5. Additional unknown symbols are added as required in order to determine the signs of the majority of the larger $|E|$ in terms of the specified signs and unknown symbols. A new symbol should be assigned if the phase indications by (4.1) for some subset of reflections are either too weak ($P_+(\mathbf{h}) < 0.97$) or absent altogether. Sometimes no symbols need be specified. This is more likely to happen in space groups of higher symmetry and when heavy atoms are present. In space group $P\bar{1}$, if there is no heavy atom at the origin, at least one symbol must be assigned and, in the case of only one assignment, it must be negative. We have not found it necessary to assign more than six symbols, and they would reduce to four or less at the completion of the phase determination.

If there have been p unknown symbols assigned, at most 2^p Fourier maps need be computed. In actual practice, there are many ways in which this number may be reduced, although, with the fast computers now available, this reduction is generally more a convenience than a necessity. The following is a list of ways in which reduction may be effected:

(i) Often, as the phase determination employing (4.1) proceeds, certain of the unknown symbols are found to be definable in terms of others. Relationships among the symbols should be accepted only with great care and generally at the end of the procedure. Numerous indications of the relationship should occur. If they occur only rarely or only among E values of moderate magnitude, the relationship is to be considered as only probable.

(ii) Phase determining formulas which define phases in terms of the structure factor magnitudes may be employed, e.g. the Σ_1 formula (Hauptman & Karle, 1953) or $B_{3,0}$ and $I_{3,0}$ (Karle & Hauptman, 1959). Examples may be found in the studies of 1-cyclohexenyl-1-cyclobutenedione (Karle, Britts & Brenner, 1964) and allylthiourea (Dragonette & Karle, 1965).

(iii) The absence of a peak at the origin would eliminate a combination of values for the symbols for which the signs were predominantly plus. Likewise a predominantly negative set would also be unacceptable. This criterion should be employed with some caution, since such an imbalance may occasionally occur among the phases associated with the largest $|E|$. An example of this was found in the study of a dimer of hexafluorobutadiene (Karle, Karle, Owen & Hoard, 1965).

(iv) Some assignments of signs for the symbols may lead to a relatively large number of inconsistencies among the contributors to (4.1). Those sets of signs associated with fewer inconsistencies would be considered the more probably correct ones and E maps for them would be computed first. It should be noted, however, that often the most internally consistent set is not the correct one, e.g. the study of jamine (Karle & Karle, 1964b).

(v) Known special features of particular structures can be used to indicate the values of certain phases. Heavy atoms or isomorphous substitutions can provide the basis of elegant phase determination procedures which are complete in themselves. However, in the present context an example would be the case of jamine, wherein the large $|E_{020}|$ and the large $|E_{002}|$ would need to be associated with negative signs in order to keep the large molecule from getting too close to centers of symmetry.

6. Using the $E_\mathbf{h}$ whose signs have been determined, Fourier maps are calculated with these $E_\mathbf{h}$ as coefficients. Generally, the three-dimensional E maps will be computed with approximately ten to fifteen of the largest independent $|E_\mathbf{h}|$ per atom in the asymmetric unit. In maps which are incorrect, only parts of structures may appear, and, in general, the peaks do not satisfy distance criteria properly or make good chemical sense.

The procedure described here can reveal the existence of homometric structures if the calculation of E maps is not discontinued as soon as a crystallographically suitable structure has been found, but rather all possible E maps are computed.

II. Noncentrosymmetric crystals

(a) Preparation of normalized structure factor magnitudes

The discussion in I(a) applies equally well for non-centrosymmetric crystals.

(b) Listings of the data

Listings are made as in I(b) for application initially with formula (4.3). κ is also listed along with each pair, $\mathbf{k}$ and $\mathbf{h} - \mathbf{k}$, for use with the probability formula (3.19) or the variance (3.33). Again, $\mathscr{E}_\mathbf{h}$ has been replaced by $E_\mathbf{h}$.

(c) Specification of origin and enantiomorph and the assignment of unknown symbols

The method for specifying origin and enantiomorph for a given noncentrosymmetric space group has been

determined (Hauptman & Karle, 1956, Karle & Hauptman, 1961). In making the phase assignments, the largest suitable $|E_\mathbf{h}|$ should be used. The choice will be partly determined by the extent to which a particular $\mathbf{h}$ enters into the combinations required by formula (4.3), as shown by a Σ_2 listing.

The enantiomorph is determined by the assignment of a sign to a particular linear combination of phases which satisfies the definition of an invariant (or seminvariant, when appropriate). The magnitude of this linear combination of phases must not be 0 or π. For practical purposes it should not be near 0 or π. In space group $P1$, for example, all invariants are of the form $\varphi_{\mathbf{h}_1} + \varphi_{\mathbf{h}_2} + \varphi_{\mathbf{h}_3}$ where $\mathbf{h}_1 + \mathbf{h}_2 + \mathbf{h}_3 = 0$; and in space group $P222$, a phase of type φ_{ggg} (g even) is an invariant. Only the signs of such phases or combinations of phases may be specified in order to determine the enantiomorph. In some other space groups, *e.g.* $P2_12_12_1$, it is possible to choose an enantiomorph by specifying the value of a phase whose magnitude is known to be $\pi/2$. A discussion of this point may be found elsewhere (Karle & Hauptman, 1956, p. 645 ff.). If an unknown symbol or symbols are connected with the assignment of the enantiomorph, this assignment implies that the range of values to be considered for the symbols is restricted, because the sign of the linear combination is known. If the enantiomorph assignment is ignored, the range of values for the appropriate symbols is increased, giving two final solutions, the phase values appropriate to each of the enantiomorphs [*cf.* structure determination of panamine (Karle & Karle, 1966)].

After the specifications which determine the origin and enantiomorph have been made, some additional symbols are assigned to other large $|E_\mathbf{h}|$ one at a time as needed, whose $\mathbf{h}$ enter into many combinations as required by formula (4.3). This formula may now be employed to determine the phases of the remaining large $|E_\mathbf{h}|$ in terms of the phase specifications and unknown symbols.

(d) Phase determination

We describe here a procedure for phase determination, which involves hand computation employing (4.3) in the initial stages, followed by (4.4) or (4.5) computed by machine. The machine computation extends the number of phases and reiterates the initial determination with more accurate formulas.

The following steps have generally been followed:

1. A listing is made of five to ten of the largest $|E|$ in the various subgroups, as in the case for centrosymmetric crystals.

2. Phases are assigned which specify the origin and in addition one unknown symbol is assigned. The chosen reflections should form many combinations, as required by (4.3). Throughout the phase determination, the phases $\varphi_\mathbf{h}$ are kept within the range $-\pi < \varphi_\mathbf{h} \leq \pi$.

3. Equation (4.3) is employed to define as many phases of the largest $|E_\mathbf{h}|$ as possible in terms of the specified ones and others that have been newly determined. Fig. 2 should be employed to evaluate the variance, V. A working rule is $V \leq 0.5$ for accepting a phase indication. When all three phases are real and pure imaginary, (4.2) can be applied as for centrosymmetric crystals. It should be noted in applying (4.3) that for each contributor sum $\varphi_\mathbf{k} + \varphi_{\mathbf{h}-\mathbf{k}}$, expressed in terms of symbols, there is generally an ambiguity concerning whether zero, $+2\pi$ or -2π should be added to this quantity. The ambiguity arises from the fact that the contributors to the average are expected, from the previously outlined probability considerations, to cluster about the average value. Thus all contributors should be adjusted by 0, $+2\pi$ or -2π so that their deviation from the average is a minimum. Since the correction for a particular contributing sum is generally unknown, there may be a difficulty in averaging the contributions of two or more such sums in formula (4.3) for a particular $\mathbf{h}$. The problem is avoided in practice when there are many sums $\varphi_\mathbf{k} + \varphi_{\mathbf{h}-\mathbf{k}}$ contributing to (4.3) which lead to the same combination of symbols. In that case, the average of the contributors is the same as that of a single contributor. If there are some minor exceptions, these are ignored in order to progress with the determination. Other special circumstances occur which help to circumvent the problem. For example, if the contributor sums $\varphi_\mathbf{k} + \varphi_{\mathbf{h}-\mathbf{k}}$ for a particular $\mathbf{h}$ are expressible in terms of different symbols, a relationship may be indicated among the symbols. If the same relationship recurs several times, for various choices of $\mathbf{h}$, it may be accepted, thus simplifying the averaging process. In those cases for which the ambiguity cannot be resolved or avoided, the average in (4.3) cannot be taken and the particular $\varphi_\mathbf{h}$ must remain unevaluated until numerical values for the unknown symbols are finally introduced. If desired, this $\varphi_\mathbf{h}$ can be carried through the determination by giving it an additional unknown symbol whose value is defined in terms of others.

4. Another unknown symbol is assigned and the determination is continued with the restricted list of step 1.

5. The next five to ten largest $|E|$ in each subgroup are now considered and eventually full use is made of the listing of all the combinations of $\mathbf{k}$ and $\mathbf{h} - \mathbf{k}$ for a given $\mathbf{h}$.

6. Additional unknown symbols are specified, if required, in order to determine the phases of the majority of the larger $|E_\mathbf{h}|$ in terms of the specified phases and unknown symbols. After about fifty phases have been so determined, it has been found useful to list by machine, and in terms of the symbols, all the combinations of $\mathbf{k}$ and $\mathbf{h} - \mathbf{k}$ that this restricted set can contribute to a given $\mathbf{h}$. This is a feature of the Σ_2 listing program mentioned above in I(*b*). Further phase determination by hand is thus facilitated and, of course, the calculation may be repeated and further extended as more phases are obtained. In this way a set of one to two hundred phases may be obtained. This set may be

further extended by the use of (4.4) and (4.5) after specific values are introduced for the unknown symbols.

The number of unknown symbols to be dealt with may be limited in the following ways.

(i) Often, as the phase determination employing (4.3) proceeds, certain of the unknown symbols are found to be definable in terms of others. Relations should generally be accepted only at the end of the procedure.

(ii) Phase determining formulas which define phases in terms of the structure factor magnitudes may be employed, e.g. the Σ_1 formula for noncentrosymmetric crystals (Karle & Hauptman, 1956) or $B_{3,0}$ and $I_{3,0}$ (Karle & Hauptman, 1958). The latter two formulas are in general not sufficiently accurate to determine the values for the phases of complex structure factors but can often be used to distinguish between the special values 0 or π, or between $+\pi/2$ and $-\pi/2$.

The remaining unknown symbols, if any, are now assigned a succession of values covering the range from $-\pi$ to $+\pi$ and differing by about 45°. If a symbol is associated with the specification of an enantiomorph, it would be limited to half this range. Each combination of possible numerical values assigned to the unknown symbols produces, from the set of one to two hundred phases, defined in terms of these symbols, a numerical set which may be extended by use of (4.4) and (4.5).

In the application of the 'weighted sum formula' (4.4) to the sets of numerical phases, for the purpose of extending them previous to the calculation of Fourier maps, the ambiguity discussed in step 3 above must be taken into account. Owing to the fact that the phases have numerical values, a fairly simple method has been devised for resolving this problem, which appears to be sufficiently accurate in application. In this method two calculations are made with (4.4). For the first calculation all the sums, $\varphi_k + \varphi_{h-k}$, contributing to a particular h are placed in the range $-\pi < \varphi_k + \varphi_{h-k} \leq \pi$, and the value is computed for φ_h. In the second calculation all the sums, $\varphi_k + \varphi_{h-k}$, are placed in the range $0 \leq \varphi_k + \varphi_{h-k} < 2\pi$ and a second value is computed for φ_h. The deviation of each set of contributors from their corresponding average is given in terms of the variance of the contributors. The average value chosen for φ_h is that associated with the smaller variance. If both variances are too large, neither value of φ_h is acceptable. If an accepted φ_h occurs in the range $\pi < \varphi_h \leq 2\pi$, we subtract 2π in order to return it to the standard range.

A test calculation of (4.3) and (4.4) has been made using the known structure of L-arginine dihydrate (Karle & Karle, 1964a). Eighty-two reflections with $|E_h| > 1.5$ and $hkl \neq 0$ were used as a basic deck for this computation in space group $P2_12_12_1$. The results for twenty of these reflections are shown in Table 1. The phases φ_h in radians were computed from the known structure. The phases $(\varphi_h)_0$ and $(\varphi_h)_\pi$ were computed from (4.3), having n terms in the average, where the

individual terms composed of sums of phases, $\varphi_k + \varphi_{h-k}$, were held in the ranges from $-\pi$ to $+\pi$ and 0 to 2π, respectively. The phases $(\varphi_h)_{0,w}$ and $(\varphi_h)_{\pi,w}$ were similarly calculated from the weighted formula (4.4). The spread of the contributors in (4.3) and (4.4) was evaluated by computing their variances, V_0, V_π, $V_{0,w}$, $V_{\pi,w}$, about the corresponding average values. It is seen that there is little difference between the values computed from (4.3) and (4.4) in the range of $|E|$ values above 1.5.

The variances can be employed as a basis for choosing between the two alternative calculations of the average, one with contributing terms in the range $-\pi$ to π and the other in the range 0 to 2π. Obviously the smaller of the two variances V_0 or V_π implies greater clustering of the contributors and suggests which average to choose. As pointed out above, this resolves the 2π ambiguity associated with each term in the average. If, for example, we examine the values for the phases computed from (4.3) or (4.4), we would choose $(\varphi_h)_0$ or $(\varphi_h)_{0,w}$ on the basis of the variances for the phase of (4,11,1), but $(\varphi_h)_\pi$ or $(\varphi_h)_{\pi,w}$ for the phase of (3,1,10).

Restricting our attention to the calculation from (4.4), the average deviation from the known φ_h of the twenty phases computed in Table 1 and chosen according to smallest variance is 0.33 radian. If a rejection criterion based on variance were introduced to the effect that at least one of $V_{0,w}$ and $V_{\pi,w}$ should be less than 1.4, then the phases computed for 1,12,6, 6,2,8, 4,12,5 and 3,2,16 would not be accepted. This would change the average deviation of the sixteen remaining computed phases from the known values to 0.23 radian. The addition of fifty-five one- and two-

Table 1. *Test calculation of (4.3) and (4.4) using the known structure of* L-*arginine dihydrate*

A basic deck of eighty two reflections with $|Eh| > 1.5$ and $hkl \neq 0$ was used. Known phases φh are compared to those computed with (4.3), $(\varphi h)_0$ and $(\varphi h)_\pi$, and with (4.4), $(\varphi h)_{0,\omega}$ and $(\varphi h)_{\pi,\omega}$, where the contributors are first restricted to the range $-\pi < \varphi k + \varphi_{h-k} \leq \pi$ and then to the range $0 \leq \varphi k + \varphi_{h-k} < 2\pi$ respectively, in order to approximate optimum clustering in at least one of the ranges. A measure of the clustering, the corresponding variances about the average value, V (in square radians), are also included. The total number of terms contributing to an average is given in the last column.

h	k	l	$|E_h|$	$(\varphi_h)_0$	V_0	$(\varphi_h)_\pi$	V_π	$(\varphi_h)_{0,w}$	$V_{0,w}$	$(\varphi_h)_{\pi,w}$	$V_{\pi,w}$	n
4	11	1	1.73	0.53	0.37	1.18	1.77	1.88	0.41	1.16	1.64	1.59	9
3	1	10	1.63	2.44	1.94	1.66	2.39	0.91	2.03	1.59	2.40	0.94	14
3	11	4	2.08	2.18	1.83	1.68	2.46	0.53	1.87	1.68	2.45	0.67	10
3	11	10	1.75	2.37	1.18	2.14	2.75	1.34	1.08	2.20	2.65	1.15	8
2	1	14	1.68	2.93	1.06	2.12	2.63	1.33	1.14	2.10	2.62	1.35	12
1	2	3	1.77	0.39	0.16	0.68	1.88	2.32	0.17	0.68	1.89	2.43	22
1	2	16	1.58	3.11	0.73	2.46	2.82	0.87	0.53	2.57	2.86	1.08	12
1	2	18	1.53	-0.92	-0.30	1.18	-2.39	2.27	-0.34	1.17	-2.26	2.50	9
1	12	1	1.82	-1.42	-0.83	0.89	-2.08	2.08	-0.86	0.95	-2.08	2.34	5
1	12	2	1.73	0.21	-0.02	0.48	-2.87	2.95	-0.04	0.46	-2.75	3.26	11
1	12	4	1.92	2.83	1.02	2.57	2.96	0.75	1.05	2.54	2.95	0.82	13
1	12	6	1.76	-0.10	0.69	1.26	2.26	2.40	0.73	1.42	2.43	2.73	12
6	2	8	1.83	0.22	0.53	1.41	1.43	1.64	0.46	1.60	1.63	2.10	7
5	2	12	1.52	-0.07	0.07	1.11	-3.07	2.43	0.04	1.07	-2.92	2.80	6
4	2	16	1.69	0.30	0.27	0.74	1.84	2.52	0.24	0.75	1.93	2.72	4
4	12	5	1.69	-1.16	0.00	1.99	3.14	2.01	0.00	1.85	3.14	2.36	6
3	2	4	1.57	0.22	0.21	0.62	-2.93	2.71	0.16	0.61	-2.75	3.02	12
3	2	9	1.67	2.64	2.29	1.34	2.92	1.07	2.35	1.44	2.94	1.10	10
3	2	10	1.64	-0.18	-0.05	0.73	-2.56	2.71	-0.07	0.70	-2.52	2.88	10
3	2	16	1.53	-0.66	0.16	1.68	-1.96	1.77	0.14	1.51	-1.98	1.92	6

dimensional data to the original eighty-two lowered this average deviation slightly to 0·21 radian. In this case all phases except that for the 4,12,5 would be accepted on the basis of the variance criterion and the three additionally accepted phases would have an average deviation of 0·46 radian. Evidently, a rejection criterion could also be based on the number of contributors to the average in (4.3) and (4.4).

The terms contributing to (4.3) and (4.4) are associated with the products $|E_h E_k E_{h-k}|$ which do not vary greatly from an average value of about 5·5. This leads to an average value of approximately 1·5 for κ, and assuming $q = 9$ contributors and $\alpha \sim q^{\frac{1}{2}} \langle \kappa \rangle$, we find $\alpha \sim 4·5$. As Fig. 2 shows, a value of $\alpha = 4·5$ gives 0·25 for the variance. The experimental variances in Table 1 may be compared with this value. On the basis of the theoretical estimate of 0·25, the cut-off value of 1·4 mentioned above is reasonable, since it corresponds to about 2·4 standard deviations. It should be recalled also that the clustering of the contributors to (4.3) and (4.4) was only approximately obtained in the calculation.

It may be preferable to use the tangent formula (4.5) with the sets of numerical phases in order to extend them. This formula is valid for the entire range of values for the $|E_h|$. Since the signs of $\sin \varphi_h$ and $\cos \varphi_h$ are obtained in the calculation, there is no ambiguity in obtaining φ_h from $\tan \varphi_h$. If we calculate (3.9) and (3.10), employing $|E|$ instead of $|\mathscr{E}|$ over a restricted range k_r for a set of h, we will obtain unscaled values for $|E_h| \cos \varphi_h$ and $|E_h| \sin \varphi_h$. If we take the sum of the squares of these quantities and rescale them by matching their average to the average of the corresponding set of observed $|E_h|^2_{obs}$, we will obtain a set of calculated $|E_h|^2_{calc}$ based on the particular set of phases under consideration. An R index, defined by

$$ R = \frac{\sum\limits_{k_r} ||E_h|_{obs} - |E_h|_{calc}|}{\sum\limits_{k_r} |E_h|_{obs}} \qquad (5.2) $$

may now be computed. We thus have the following rejection criteria in the application of the tangent formula. If a structure factor magnitude $|E_h|_{calc}$ is calculated to be quite small, e.g. < 0·3–0·5, or if a phase changes value greatly on successive reiterations, the phase is rejected. If some assignments of value to the unknown symbols lead to R values in (5.2) which are considerably greater than those for other assignments, they are considered to have much less probability of being correct and are not carried through unless those assignments with lower R values do not lead to an acceptable structure.

In summary, formulas (4.4) and (4.5) serve many purposes. They are used to extend the number of phases initially determined by hand. By reiteration they can effect a convergence of the values of the phases to a more accurate set of values. These formulas also facilitate the application of criteria for the rejection of poorly determined phases. If there are a great many rejections for a particular numerical specification of

the unknown symbols, the values given the symbols should be suspect. The calculations involved are too extensive to be done by hand. We have been using a program for computing (4.4) and (4.5) including the rejection criteria which is written in FORTRAN and has been prepared by P. Gum and S. Brenner of this laboratory. In the application of this calculation, about twenty to thirty phases per atom in the asymmetric unit have been computed. In our experience to date, phases are obtained from these formulas with an average deviation of about 20° to 25°.

7. From the alternative set of phases, determined in II(d) 6 from the various assignments of values for the unknown symbols, E maps are computed which are based on the E_h as Fourier coefficients.

Generally, the three-dimensional E maps will be computed with the largest $|E_h|$ values comprising about thirty per cent of the data obtained from the sphere of reflection from copper radiation. The criteria for a correct map are the same as those mentioned in I(d) 6 for the case of centrosymmetric crystals.

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