The Application of Direct Methods to Difference Structures. Non-Centrosymmetric Structures Containing Heavy Atoms.
III. Enantiomorph and Origin Fixation

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Abstract

Direct methods are applied to the difference structure factors for a non-centrosymmetric structure containing one or more heavy atoms in known positions, such that the known atoms form either a centrosymmetric arrangement, or a translational subcell, or both. The present procedure is initiated by subtracting the known heavy-atom contribution from the observed structure factor (assuming that the observed and calculated structure factors have the same phase) to obtain approximate values of the magnitude and phase of the light-atom contribution. Either about ten reflections, which are most *inconsistent* with respect to the Σ_2 formula, are selected as 'enantiomorph discriminating' reflections, or about ten reflections which are 'subcell' extinct are selected as (enantiomorph and) origin choices and symbols are assigned to these reflections. The Σ_2 phase relationship is used to find relations between the symbols. The analysis of the symbols, together with one or more arbitrary choices to fix the enantiomorph and/or the origin, will lead to a unique solution of the symbols in terms of numerical values. Further refinement of the difference structure factors by the conventional *DIRDIF* procedure followed by a Fourier synthesis leads to an electron density map where the additional heavy-atom symmetry has been destroyed.

Introduction

In our *DIRDIF* procedures (see part I: Van den Hark, Prick & Beurskens, 1976, and references therein), direct methods are applied to the solution of partially known structures, usually containing heavy atoms. Difference structure factors are calculated, making the usual assumption that the observed and calculated structure factors have the same phase. These are then 'normalized', and both amplitudes and phases are refined by a weighted tangent procedure. This approach provides a very powerful tool for the solution of those structures where the known heavy atoms are in special or pseudo-special positions, or otherwise form a structure with higher symmetry than required by the space-group symmetry. Two causes which may result in this higher symmetry are treated in this paper:

(i) The *enantiomorph* problem: the known heavy atoms form a centrosymmetric arrangement. A conventional Fourier synthesis will lead to double image, *i.e.* a superposition of the structure and its enantiomorph.

(ii) The *origin* problem: the known atoms form a subcell. A conventional Fourier synthesis will lead to a multiple image, *i.e.* a superposition of the true supercell with its translation images.

In the preceding paper (part II: Prick, Beurskens & Gould, 1978) we discussed the principles of enantiomorph fixation for the unknown part of the structure. In the present paper we describe the enantiomorph- and origin-fixation procedure for all possible cases where the known heavy atoms do not, at least in principle, completely determine the structure.

Notation

For reflection **h** (meaning *hkl*) we define:

$|F_{obs}|$	observed structure-factor amplitude on absolute scale
F_H	calculated contribution of the known part of the structure ('heavy' atoms)
φ_H	phase of F_H
F_L	contribution of the remaining part of the structure ('light' atoms), or the most probable estimate for this contribution
φ_L	phase of F_L

ΔF_1 $= (|F_{obs}| - |F_H|)\exp(i\varphi_H)$, the conventional difference Fourier coefficient

φ_1 phase of ΔF_1

E_1 'normalized' analogue of ΔF_1

W_1 weight associated with the reliability of ΔF_1 and E_1 [see part I; for a comparison with the weight given by Sim (1960) see Beurskens, Prick, Doesburg & Gould, 1979]; $0 \le W_1 \le 1$.

Methods

The principles of enantiomorph discrimination are described in § (i), and of origin fixation in § (ii); the case where both enantiomorph and origin fixation are needed is discussed in § (iii).

(i) Enantiomorph fixation

For the crystallographic problem at hand, let us assume a non-centrosymmetric structure for which we have found (for instance by inspection of the Patterson synthesis) a centrosymmetric arrangement of heavy atoms (ia). The case where we have only one heavy atom per unit cell is given in (ib).

(ia) Two or more atoms

For each reflection $\mathbf{h}$ there are two possible values for the calculated phase: $\varphi_H = 2\pi\mathbf{h}.\mathbf{r}_0$ or $\varphi_H = 2\pi\mathbf{h}.\mathbf{r}_0 + \pi$, where $\mathbf{r}_0$ is the position of the centre of symmetry. The origin is shifted to this point, and the translational part of each symmetry element is modified accordingly. Then all calculated phases are either $\varphi_H = 0$ or $\varphi_H = \pi$. Reflections selected on the basis of values for $|E_1|$ and weight W_1 are used to initiate the procedure to be described. However, we cannot solve the enantiomorph problem until we insert phases which substantially deviate from the values 0 or π.

Enantiomorph-discriminating reflections. In some space groups it is possible to choose projection reflections which must have $\varphi_L = \pm\frac{1}{2}\pi$ by symmetry; these reflections must have $|F_H| = 0$. We do not use these reflections, as it is not considered advisable to rely entirely on a small number of special reflections.

We determine enantiomorph-sensitive reflections by inspecting Σ_2 interactions and by selecting the reflections that are most inconsistent with respect to the Σ_2 relationship. That is, when φ_L is found as 0 and also as π, the true value is expected to be neither 0 nor π, but in between, which can be about $+\frac{1}{2}\pi$ or $-\frac{1}{2}\pi$. The assignment of a phase $\frac{1}{2}\pi$ to a symbol for which values 0 and π were found has also been used by Karle (1970).

In this paper we make use of the numerical results obtained for a number of test structures as described by Prick (1979). Various executional parameters to be quoted below are based upon the results of practical applications.

We select two sets of reflections:

num: about 100 reflections with $|E_1| > 1.0$ and $W_1 > 0.9$; *i.e.* reflections for which a sufficiently accurate value of the numerical phase φ_L is known: for φ_L^{num} a value equal to φ_1 (0 or 180°) is assumed;

ena: a large number of reflections with $|E_1| > 1.0$ and $W_1 < 0.9$; *i.e.* reflections for which the phase φ_L is not known, and which can be used for enantiomorph discrimination, φ_L^{ena} can have any value.

Using the set *num* as input to a Σ_2 generation procedure, all contributions to reflections of the set *ena* are collected. One Σ_2 term is

$$\varphi_L^{ena}(\mathbf{h}) \simeq \varphi_1^{num}(\mathbf{k}) + \varphi_1^{num}(\mathbf{h} - \mathbf{k}). \tag{1}$$

Such a term is weighted by

$$K_{hk} = 2\sigma_3\sigma_2^{-3/2}|E_1(\mathbf{h})E_1(\mathbf{k})E_1(\mathbf{k} - \mathbf{h})|W_1(\mathbf{h})W_1(\mathbf{k} - \mathbf{h}) \tag{2}$$

with $\sigma_n = \sum_{j=1}^{N_L} Z_j^n$, N_L is the number of unkown ('light') atoms. The weighted average for $\varphi_L^{ena}(\mathbf{h})$ is obtained (by tangent formula) and the conventional measure for the reliability of the result is given by α_h (Karle & Karle, 1966), with

$$\alpha_h^2 = \left\{\sum_k K_{hk}\cos[\varphi(\mathbf{k}) + \varphi(\mathbf{h} - \mathbf{k})]\right\}^2 + \left\{\sum_k K_{hk}\sin[\varphi(\mathbf{k}) + \varphi(\mathbf{h} - \mathbf{k})]\right\}^2. \tag{3}$$

The maximum possible result of (3) obtained when there are no inconsistencies is defined by

$$\beta_h = \sum_k K_{hk}. \tag{4}$$

The enantiomorph-discriminating reflection should have small α_h (inconsistent contributions) and large β_h (many terms involved). Therefore we define the following enantiomorph discriminator:

$$C_h = \frac{\beta_h}{\alpha_h}(\beta_h - \alpha_h) \tag{5a}$$

unless $5\alpha_h < \beta_h$; then

$$C_h = 5(\beta_h - \alpha_h). \tag{5b}$$

The numerical value of C_h measures the degree of inconsistency in the Σ_2 terms for the reflection $\mathbf{h}$.

Reflections to be used in the following symbolic-phase expansion procedure should have large $|E|$ values as well. Therefore we use $|E_1(\mathbf{h})|C_h$ as sorting key for the selection of enantiomorph-discriminating reflections.

In Table 2 some results are given for four test

structures. For each of these structures the ten highest values of $|E_1(\mathbf{h})|\,C_h$ are listed; most of these correspond to reflections with phases $45 < |\varphi_L| < 135°$, which is close enough to $|\varphi_L| = 90°$. Fortunately, the following symbolic phase-expansion procedure is not adversely affected by individual phase errors!

Symbolic-phase correlation. The ten reflections with the highest values of $|E_1(\mathbf{h})|\,C_h$ and without internal $\sum_2$ interactions ($\mathbf{h} + \mathbf{h}' + \mathbf{h}'' = 0$) are chosen, and symbols are assigned to the reflections. The symbols, denoted X, X', ..., represent the phase values 90 or $-90°$. The assignment $\varphi_L^{ena} = X$ implies a possible error which is less than $45°$ for most of the ten assignments.

These ten reflections, together with all reflections of the set *num*, are input to a symbolic-phase generation procedure in order to find symbolic phases for as many reflections as possible. In addition to the interactions (1), which already were calculated, we now have interactions of the types:

$$\varphi_L(\mathbf{h}) \simeq \varphi_1^{num}(\mathbf{k}) + X(\mathbf{h} - \mathbf{k}) \qquad (6)$$

and

$$\varphi_L(\mathbf{h}) \simeq X(\mathbf{k}) + X'(\mathbf{h} - \mathbf{k}) \qquad (7)$$

with weights K_{hk} (equation 2, W_1 replaced by 1). The 60 most probable results of (6) and (7) are used as a secondary set (Beurskens, 1964; Beurskens, Prick, Van den Hark & Gould, 1980) and used to generate many more symbolic phases.

Multiple phase indications for one reflection then lead to relations between the symbols, which can be of the following types (all mod 360°):

$$X = 0 \text{ or } 180° \qquad (8a)$$

$$X \pm X' = 0 \text{ or } 180° \qquad (8b)$$

$$2X = 0° \qquad (8c)$$

$$2X = 180° \qquad (8d)$$

$$X \pm X' \pm X'' = 0 \text{ or } 180° \qquad (8e)$$

$$X \pm X' \pm X'' \pm X''' = 0 \text{ or } 180°. \qquad (8f)$$

The relation $(8d)$ is a trivial identity. The relations $(8a)$, $(8c)$ and $(8e)$ are contradictions to the assumption that X is either 90 or $-90°$. These contradictions cannot be used to determine the value of the symbols, but they are interpreted as indications that the true value of the original phase is rather close to 0 or $180°$, and that symbols which are involved with many of these contradictions are less useful and will be weighted down. The relations $(8f)$ are very weak, and are not used.

Thus we are left with the relations $(8b)$. This is a set of symbol relations that can be coded in a binary way ($X + X' = 180°$ or $X - X' = 0°$ means: X and X' are equal; $X + X' = 0°$ or $X - X' = 180°$ means: X and X' differ in phase by $180°$).

The equations are easily solved by the procedure *SYMAN* (Beurskens & Prick, 1981), using the antisymmetric mode. The enantiomorph is fixed by arbitrarily assigning one numerical value (either $+90$ or $-90°$) to one of the symbols.

Note: if the input atoms have only an approximate centre of symmetry, the calculated phases are not exactly 0 or $180°$, and the enantiomorph is very weakly fixed by the intput atoms. In this case the arbitrary phase assignment to one of the symbols is not allowed, and a unique solution of the symbol equations (8) is obtained. As the calculated phases (φ_1) can have any value, the right-hand sides of $(8a)$–$(8f)$ can also have any value; these equations are treated as complex vector equations and both the real and the imaginary parts will be used. Thus $(8a)$ and $(8e)$ may be given as

$$\sin(X) = \sin(\varphi) \qquad (9a)$$

$$\sin(X \pm X' \pm X'') = \sin(\varphi). \qquad (9e)$$

Most of the phases φ will be close to 0 or $180°$, but a large number of small deviations is sufficient to fix the absolute phase values of the symbols (without any arbitrary phase assignment). Thus the present enantiomorph-fixation procedure can be used and has proved to be very useful in the enhancement of the antisymmetric part of the phase distribution.

Finally, the numerical values for the symbols are substituted in (6) and (7), and all contributors to the phase of one reflection are added as follows: (a) the original numerical phase and all purely numerical terms are added with their proper weights; (b) all terms with symbols are added with their proper weights; (c) the results for (a) and for (b) are added with equal weight, or with double weight for φ_1^{num}. The resulting phases no longer have a centric distribution.

Refinement of the difference structure factors. The majority of phases will have deviations from 0 or $180°$ in the correct direction, but many results will not be accurate. Therefore, the phases are subjected to *DIRDIF* tangent refinement, as described previously (part I). Only one or two cycles are sufficient, and there is no severe danger that the phases turn back to 0 or $180°$ within one or two cycles. A change of phase is accompanied by an adjustment of the amplitude $|F_L|$ in order to satisfy the vector equation $|F_{obs}| = |F_H + F_L|$. The final results for $F_H + F_L$ or for F_L are used as input to a Fourier computer program for the calculation of an electron density map or a difference electron density map, respectively, to be referred to as '*DIRDIF–Fourier*' map.

(ib) One atom only

The known heavy atom is situated at the origin and all calculated phases φ_H are $0°$. The majority of the reflections will have $\varphi_1 = 0°$. Very few weak reflections

(with $|F_H| > |F_{obs}|$) will have $|E_1| > 1\cdot0$. These reflections have $\varphi_1 = 180°$ and $W_1 = 1\cdot0$; if these few reflections participate in the $\sum_2$-generation procedure, inconsistent contributions are encountered and the procedure described in (*ia*) will work. In cases where the heavy atoms do not dominate the intensity data, it is impossible to predict any $\varphi_1 = 180°$. The phases $\varphi_1 = 0°$ will lead to a trivial consistency of all $\sum_2$ interactions; all C_h values (equation 5) are zero, and the procedure described in (*ia*) fails. We then choose the ten reflections with the lowest W_1 (large $|E_1|$) to be used as 'enantiomorph discriminating' reflections. The assignment of symbols, and the subsequent symbol analysis is as described in (*ia*), resulting in symbol phases +45 or −45° (not ±135°, which is too far from 0°). The following tangent refinement and Fourier synthesis will lead to an asymmetric *DIRDIF*–Fourier map.

This procedure is not as strong as the one described in (*ia*), but it works. Firstly, the phases φ_1 (= 0°) have large standard deviations, so the true phases (φ_L) will probably deviate substantially from 0°. Secondly, we have observed that arbitrary phase deviations from 0° will, upon weighted tangent refinement, lead to an asymmetric structural model in which one of the enantiomers is more pronounced than its mirror image. This simply means that physical significance can be attached to the results of the tangent refinement procedure. (This lemma is suggested by experiment; a similar experience was reported by Pontenagel, 1980).

(ii) *Origin fixation*

If the known part of the structure forms an arrangement of *n* identical subcells per unit cell, then only a fraction $1/n$ of all reflections will have non-zero values for F_H. Thus we have an *n*-fold origin ambiguity, which can be solved by assignment of phases to one or more 'subcell extinctions' (with $|E_1| > 1\cdot0$, $W_1 = 0\cdot0$). The centrosymmetric analogue has been treated by Beurskens *et al.* (1980). In the centrosymmetric case, symbols are assigned to ten reflections of the 'weak' parity groups: the symbols represent phases 0 or 180°; after symbol analysis (procedure *SYMAN*, symmetric mode), the origin is fixed by arbitrarily assigning 0 or 180° to one or more symbols. In the non-centrosymmetric case the same procedure is used; a phase, however, can have any value; and the procedure *SYMAN* is used both in symmetric and in anti-symmetric mode. [The right-hand sides of (8*a*)–(8*f*) can have any value; they are treated as complex vector equations]. The mean values of the symmetric (0 or 180°) and anti-symmetric (90 or −90°) solutions give the values ±45, ±135°, which cover all possible phases with a maximum error of 45°. At this point phase refinement and a subsequent Fourier synthesis will lead to a *DIRDIF*–Fourier map where the extra translational symmetry is destroyed.

[Note that in (8*a*)–(8*f*) the symmetric and anti-symmetric modes are not identical: for instance the two equations $X = X'$ and $X = -X'$ are identical in the symmetric mode, and they are contradictions in the anti-symmetric mode (Beurskens & Prick, 1981)].

In the above description of the origin-fixation procedure we have assumed that the problem at hand was a 'true' origin problem: *i.e.* a shift of origin from one of the heavy-atom subcells to any of the other subcells is equivalent to a shift from one 'permissible' origin to another 'permissible' origin (Hauptman, 1972). Such a shift will not affect the phases of the structure seminvariants and it is only these reflections that are phased by the heavy atoms. In this case origin fixation is an arbitrary choice, and the use of two-symbol relations (equation 8*b*) is sufficient for the solution of the origin problem.

On the other hand, the problem at hand may involve a superstructure where the subcell does not necessarily relate to parity classes. In this case the origin is restricted by the known atoms, but there is a translational ambiguity. The possible origin shifts, however, are different from the 'permissible' origin shifts. We are not allowed to assign arbitrary phase values to any of the symbols. As the set of two-symbol relations now has no solution, we must use one- or three-symbol reations, (8*a*) and (8*e*) (see Beurskens & Bosman, 1982).

(iii) *Origin and enantiomorph fixation*

Another special case is the combination of (i) and (ii): the known part, usually a heavy atom, forms a centrosymmetric subcell. This situation is simply treated as described under (ii). The introduction of phase values ±45, ±135° to the symbols will define the origin as well as fix the enantiomorph.

In the *DIRDIF*–Fourier map both the centre of symmetry and the extra translational symmetry are destroyed.

Applications and test results

The procedures described in this paper have been automated and implemented in the *DIRDIF* program system (Beurskens *et al.*, 1981); they have been tested and used on more than 25 known (test) and unknown structures. In this section some typical results are presented. A review of the structures, used in this section, is given in Table 1.

In Table 2 we present the results of the selection procedure for enantiomorph-discriminating reflections. We define Δ as the smallest absolute deviation of the true phase from 0 or 180°. [The maximum value of Δ is 90°, the average value for random phases is 45°.] Enantiomorph-discriminating reflections should have Δ

Table 1. *Some examples of structures used as test cases or solved by the present method*

Structure			Input atoms	References
SEZI	Bis(L-serinato)zinc	$P2_1$		Van der Helm, Nicholas
	$C_6H_{12}N_2O_6Zn$	$Z = 2$	1Zn	& Fisher (1970)
OXYL	2'-Deoxycitidine HCl	$P2_1$		Subramanian & Hunt
	$C_9H_{14}ClN_3O_4$	$Z = 2$	1Cl	(1970)
MONOS	A thio-indol derivative	$P2_12_12_1$		Noordik *et al.* (1978)
	$C_{15}H_{16}N_2O_2S$	$Z = 4$	1S	
DIBFOM	4,4'-Diiodobenzophenone	$Ccc2$		Van der Velden &
	$C_{13}H_8I_2O$	$Z = 4$	1I	Noordik (1979)
ALB	Alborixin	$P2_1$		Busetta (1976)
	$C_{48}H_{84}O_{14}K$	$Z = 2$	1K	
CaLACT	Ca trilactate.$3H_2O$	$P1$		Pontenagel &
	$C_9H_{22}CaO_{12}$	$Z = 1$	1Ca	Kanters (1983)
MADRAS	A nickel(II) complex	$P2_12_12$		Parthasarathi,
	$C_{76}H_{64}BBrNiP_4$	$Z = 8$	2Ni + 2Br	Noordik &
				Monoharan (1982)

Table 2. *Deviations (Δ) from centric phases for enantiomorph-discriminating choices*

The test structures are defined in Table 1.

SESI		OXYL		MONOS		ALB	
$\|E_1\|C_h$	$\Delta(°)$	$\|E_1\|C_h$	$\Delta(°)$	$\|E_1\|C_h$	$\Delta(°)$	$\|E_1\|C_h$	$\Delta(°)$
615	78	1755	69	562	56	1352	6
428	67	286	77	506	47	1128	30
174	77	207	62	396	82	1040	55
96	69	202	81	380	80	1037	72
79	90	199	35	361	41	950	80
60	54	193	31	310	42	928	60
50	79	185	70	292	88	880	52
50	41	166	60	289	31	858	80
49	67	142	31	256	6	810	21
38	75	130	71	246	60	809	64
$\langle\Delta\rangle°$	70		59		53		52
$\langle\|E_1\|\rangle$	1·71		2·02		1·93		1·98

Table 3. *Averaged Δ (°) for ten enantiomorph-discriminating choices, for two different weight limitations*

Limitation	SEZI	OXYL	MONOS
$W_1 < 0.9$	70	59	53
$W_1 < 0.4$	66	53	47
N(changes)*	3	1	2

* N(changes) is the number of changes in the list of ten reflections when the W_1 limitation is reduced.

Table 4. *Final results for four test structures*

	SESI	OXYL	MONOS	ALB
Number of independent heavy atoms	1	1	1	1
remaining non-hydrogen atoms	14	16	19	62
Sequence number of first error peak	6	13	15	8
second error peak	11	16	16	11

as large as possible. As we can see from the table, the procedure gives good results for few reflections. The largest $\|E\|C_h$ values lead to reliable selections, but some low $\|E\|C_h$ values lead to the selection of reflections (with small Δ) which should not have been selected. Fortunately, the symbolic-phasing procedure is not hampered by one or two bad choices (reflections with small Δ) because of the large number of symbolic-phase relationships that are used. The choice of ten for the number of enantiomorph-discriminating reflections is based on practical considerations (see below). Also, experience shows it is not advisable to reduce the weight limitation ($W_1 < 0.9$) as it will reduce the number of reflections from which good enantiomorph-fixation choices can be selected. This is shown in Table 3. When we use $W_1 < 0.4$ instead of $W_1 < 0.9$, the averaged Δ is reduced, showing that some of the best choices are discarded.

The final results of the application of the present procedure to these three test cases are summarized in Table 4. Some comments on these tests and on the examples listed in Table 1 follow.

SEZI and OXYL

These rather small structures are typical cases, with one independent heavy atom in space group $P2_1$. The enantiomorph problem is solved by the present procedure. In a conventional difference Fourier syntheses the first erroneous peak will be peak number 2 which is an atom of the enantiomer, while in our procedure the first erroneous peak is significantly lower (see Table 4).

MONOS

One sulphur atom can be located by inspection of the Patterson map: the result $x = 0.00$ (in space group $P2_12_12_1$) implies a mirror plane (space group of the sulphur structure is $Pnma$). The structure was originally solved by using $x = 0.02$, thereby destroying the mirror symmetry: the remaining atoms were found

by an older version of the program *DIRDIF*. The present procedure does not depend on such personal intervention: with $x = 0.00$, the program will detect the presence of a centre of symmetry and automatically apply the present procedure.

DIBFOM

This was the first structure solved by the present procedure for enantiomorph fixation (i*a*). The iodine atom was found from the Patterson synthesis: $x = 0.049$, $y = 0.25$; $z = 0.0$, chosen so as to fix the origin in the *c* direction. This heavy-atom position constitutes an enantiomorph and origin problem: the iodine structure has space group *Fmmm*. We moved the atom to $y = 0.23$ to eliminate the additional translation symmetry; this corresponds to fixing the origin with respect to the $\frac{1}{2}0\frac{1}{2}$ ambiguity. The resulting iodine structure still has a centre of symmetry, its space group is *Cmmm*. The centric phase distribution was destroyed by the method described above. The complete rest structure (eight non-hydrogen atoms) was found from the first ten peaks of the *DIRDIF*—Fourier synthesis. (*Note*: we did not use procedure (iii) in this case, because it was not yet developed.)

ALB

This 'problem' structure was solved by Busetta (1976) using unconventional techniques. It was used as a test structure by Hull & Irwin (1978), where 50 phase sets had to be generated. With the present procedure (i*a*), using the potassium atom as input, the resulting collection of peaks was not easily interpretable; when, however, the 16 top peaks are used as input to a second run of the program (without enantiomorph discrimination) the complete structure was obtained. (A subsequent check showed that three of the initial 16 peaks were wrong.)

CaLACT

This 'problem' structure was solved by Pontenagel & Kanters (1983) using unconventional techniques. The calcium atom ('one atom only') was placed at the origin, and the method (i*b*) resulted in a *DIRDIF*–Fourier map of which the six highest peaks are oxygens; the seventh peak has bad 'bond' angles and is not an atom. The rest of the structure is found if *DIRDIF* is restarted with one calcium and two or more oxygen atoms.

MADRAS

This was the first structure solved by the present procedure for enantiomorph *and* origin fixation (iii). The positions of the nickel and bromine atoms were obtained from the Patterson synthesis, but nickel and bromine atoms could not be distinguished. The corresponding heavy-atom structure, in space group *Pbma* with subcell $a \times b \times \frac{1}{2}c$, is compatible with the space

groups $P2_12_12_1$ and $P2_12_12$. Application of *DIRDIF* in space group $P2_12_12$ resolved the fourfold ambiguity of the eight phosphorous atoms.

Some practical notes

1. The reflections to be selected with numerical phase (set *num*) must have large weights, as the procedure relies upon their phases being 0 or 180°.

2. The number of reflections to be selected as enantiomorph-discriminating reflections is limited to about ten; if more are chosen, the number of incorrect choices increases; if less, the number of symbolic-phase relationships may be too small.

3. Before the subsequent symbolic-phase expansion, the set *num* (the starting set of reflections with numerical phases) is reduced by removing all reflections which have an enantiomorph discriminator larger than the average value. This increases the reliability of the set.

4. The secondary set of reflections with symbolic phases should contain several reflections to each of the symbols. For ten symbols a secondary set should contain at least 30 reflections. If more than 60 are used the computer time and storage requirements increase rapidly.

5. The symbolic-phase expansion is normally stopped when 4000 symbolic phases have been stored. This number of symbols is sufficient for small and medium structures; it may be increased for larger structures, but then the computer time also increases.

6. After the enantiomorph-fixation procedure, each phase-refinement cycle is followed by a phase-resetting routine to counteract any drift of phases towards a centrosymmetric distribution.

7. The phases resulting from the tangent refinement procedure are modified to enhance the asymmetry of the electron density map by doubling the anti-symmetric part of the electron density function. This is done by doubling the imaginary component of the structure factor.

8. The unrefined reflections (*i.e.* reflections with, say, $|E_1| < 0.9$) are included in the final (difference) electron density function, using Sim's weights (Sim, 1960), but multiplied by 0.5 after the enantiomorph-fixation procedure [(i) or (iii)].

Final comment

The procedure described in this paper can certainly be used when the known part of the structure consists of a molecular fragment (instead of one or more heavy atoms); investigations regarding adjustment of programming parameters for this case are in progress.

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Time-Like Perturbation Method in High-Energy Electron Diffraction

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Abstract

The small-angle approximation usually encountered in dynamical theories of fast electrons essentially leads to a transformation of the propagation-direction variable z into a time-like parameter [Berry (1971). *J. Phys. C,* 4, 697–722]. The three-dimensional stationary Schrödinger equation is then approximated by a two-dimensional 'time'-dependent equation which may be solved by using the standard time-perturbation techniques encountered in quantum mechanics. The basic idea of the present approach consists in studying the evolution operator $U(z,z_0)$ instead of the wave function. Depending on the choice of bases, the matrix elements of $U(z,z_0)$ represent either the transition probabilities of diffraction or the kernel function of the propagation issued from Feynman-path integral theory [Berry & Mount (1972). *Rep. Prog. Phys.* 35, 315–397; Van Dyck (1975). *Phys. Status Solidi,* 72, 321–336;
Jap & Glaeser (1978). *Acta Cryst.* A34, 94–102]. Special attention is devoted to the so-called 'Bloch waves' and 'physical-optics' formulations which both correspond to the same perturbation expansion but with two different unperturbed 'Hamiltonians'.

I. Introduction

The dynamical theory of elastic scattering of fast electrons is of great importance for the understanding of contrast formation in electron microscopy and diffraction images. The methods which have been derived in the past twenty years may be classified in two general classes, those formally considering the crystal as an infinite three-dimensional medium (Bethe, 1928; Darwin, 1914) and those considering the crystal as an infinite number of successive planes of infinitesimal thickness (Cowley & Moodie, 1957a,b).