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Direct Phase Determination of Triple Products from Bijvoet Inequalities

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The classical method of phase determination from Bijvoet inequalities is applied to the phase $\bar{\varphi}_{\mathbf{hk}}=\frac{1}{2}(\varphi_{\mathbf{hk}}-\varphi_{\bar{\mathbf{h}}\bar{\mathbf{k}}})$ of the triple product $\tau_{\mathbf{hk}}\equiv F_{\mathbf{h}}F_{\mathbf{k}}F_{\overline{\mathbf{h}+\mathbf{k}}}$. The phase-determining formula is then (in the case of a centrosymmetric configuration of anomalous scatterers):

$$\sin\bar{\varphi}_{\mathbf{hk}}=\frac{|\tau_{\mathbf{hk}}|^2-|\tau_{\bar{\mathbf{h}}\bar{\mathbf{k}}}|^2}{4\tau''_{\mathbf{hk}}|\tau^0_{\mathbf{hk}}|}$$

in which $\tau''_{\mathbf{hk}}$ is the contribution from the imaginary part of the complex double Patterson function to $\tau_{\mathbf{hk}}$, and $|\tau^0_{\mathbf{hk}}|^2=\frac{1}{2}(|\tau_{\mathbf{hk}}|^2+|\tau_{\bar{\mathbf{h}}\bar{\mathbf{k}}}|^2)-|\tau''_{\mathbf{hk}}|^2$. It is shown that $\tau''_{\mathbf{hk}}$ contains an important term, *i.e.* the contribution from the origin peak of the double Patterson function, which is independent of the positions of the anomalous scatterers. A test calculation on a structure in $P1$, containing two Br ions, shows that, in fact, the phases of the triple products can be determined without introducing any *a priori* knowledge about the positions of the anomalous scatterers, provided an appropriate scaling procedure is applied.

Introduction

If a structure contains anomalous scatterers, and their contribution to the structure factor is known, then the average phase $\bar{\varphi}_{\mathbf{h}}=\frac{1}{2}(\varphi_{\mathbf{h}}-\varphi_{\bar{\mathbf{h}}})$ of $F_{\mathbf{h}}$ can be found by a method that was proposed simultaneously by Peerdeman & Bijvoet (1956), Ramachandran & Raman (1956) and Okaya & Pepinsky (1956). According to this method, for the case that the configuration of the anomalous scatterers is centrosymmetric, $\bar{\varphi}_{\mathbf{h}}$ is given by the following expression:

$$\sin\bar{\varphi}_{\mathbf{h}}=\frac{|F_{\mathbf{h}}|^2-|F_{\bar{\mathbf{h}}}|^2}{4F''_{\mathbf{h}}[\frac{1}{2}(|F_{\mathbf{h}}|^2+|F_{\bar{\mathbf{h}}}|^2)-|F''_{\mathbf{h}}|^2]^{1/2}} \tag{1}$$

in which $F''_{\mathbf{h}}=2\sum_j f''_j\cos 2\pi\mathbf{h}\,.\,\mathbf{r}_j$, while f''_j is the imaginary component in the form factor of atom j. From (1) the phase φ of the structure factor is found, apart from an ambiguity between φ and $\pi-\varphi$. In practice the phase angle nearest to that of the heavy-atom contribution is accepted. If the configuration of the anomalous scatterers is non-centrosymmetric then the formulation is slightly more complicated, but not fundamentally different.

In this paper we shall show that this method can be generalized to obtain the phase of a triple product from the 'Bijvoet difference' between $|F_{\mathbf{h}}F_{\mathbf{k}}F_{\overline{\mathbf{h}+\mathbf{k}}}|^2$ and $|F_{\bar{\mathbf{h}}}F_{\bar{\mathbf{k}}}F_{\mathbf{h}+\mathbf{k}}|^2$, with a formula closely analogous to (1). The basis for this approach is that the complex double Patterson function $\int\varrho(\mathbf{r})\varrho(\mathbf{r}+\mathbf{U})\varrho(\mathbf{r}+\mathbf{V})\mathrm{d}\mathbf{r}$, defined with the complex electron density function $\varrho(\mathbf{r})$ and of which, analogous to Sayre (1953), the $F_{\mathbf{h}}F_{\mathbf{k}}F_{\overline{\mathbf{h}+\mathbf{k}}}$ are the Fourier coefficients, can be regarded as a structure containing a number of 'anomalous scatterers'. That the anomalous scatterer with the largest imaginary component of scattering power is situated at the origin of the double Patterson function even makes it feasible to determine the phases of triple products without knowing the positions of the anomalously scattering heavy atoms in the structure.

In this connexion it must be remarked that in principle only origin-invariant phases are accessible to measurement by a physical experiment. Triple-product phases fulfil this requirement, and in this respect there is no need to fix the origin by locating the anomalous scatterers.

Theory

If a structure contains anomalous scatterers the structure-factor equation is

$$F_{\mathbf{h}}=\sum_{j=1}^{N}[f_j(\mathbf{h})+if''_j]\exp 2\pi i\mathbf{h}\,.\,\mathbf{r}_j \tag{2}$$

in which the form factors include temperature factors. The triple product $F_{\mathbf{h}}F_{\mathbf{k}}F_{\overline{\mathbf{h}+\mathbf{k}}}$ can then be written as

$$\begin{aligned}F_{\mathbf{h}}F_{\mathbf{k}}F_{\overline{\mathbf{h}+\mathbf{k}}}=&\sum_{j=1}^{N}f_j(\mathbf{h})f_j(\mathbf{k})f_j(\overline{\mathbf{h}+\mathbf{k}})\\&+i\sum_{j=1}^{N}f''_j[f_j(\mathbf{h})f_j(\mathbf{k})\\&+f_j(\mathbf{h})f_j(\overline{\mathbf{h}+\mathbf{k}})+f_j(\mathbf{k})f_j(\overline{\mathbf{h}+\mathbf{k}})]\\&\sum_{\substack{j1,j2,j3=1\\ \text{not } j1=j2=j3}}^{N}\{f_{j1}(\mathbf{h})f_{j2}(\mathbf{k})f_{j3}(\overline{\mathbf{h}+\mathbf{k}})\\&+i[f_{j1}(\mathbf{h})f_{j2}(\mathbf{k})f''_{j3}+f_{j1}(\mathbf{h})f''_{j2}f_{j3}(\overline{\mathbf{h}+\mathbf{k}})\\&+f''_{j1}f_{j2}(\mathbf{k})f_{j3}(\overline{\mathbf{h}+\mathbf{k}})]\}\\&\times\exp 2\pi i[\mathbf{h}\,.\,(\mathbf{r}_{j_1}-\mathbf{r}_{j3})+\mathbf{k}\,.\,(\mathbf{r}_{j_2}-\mathbf{r}_{j3})]\end{aligned} \tag{3}$$

in which any term containing f''_j more than once has been omitted.

The first two summations of (3) can be regarded as the contribution of the origin peak of the complex double Patterson function, $\int\varrho(\mathbf{r})\varrho(\mathbf{r}+\mathbf{U})\varrho(\mathbf{r}+\mathbf{V})\mathrm{d}\mathbf{r}$, based on the complex electron density function, $\varrho(\mathbf{r})$, to the triple product. The other terms in (3) correspond to contributions from peaks with position vectors ($\mathbf{U}=\mathbf{r}_{j1}-\mathbf{r}_{j3}$, $\mathbf{V}=\mathbf{r}_{j2}-\mathbf{r}_{j3}$). For the sake of argument we consider the case that the structure contains two identical anomalous heavy scatterers in $P1$. Then the imaginary part of (3) can be approximated by

$$\tau''_{\mathbf{hk}}=2f''[f(\mathbf{h})f(\mathbf{k})+f(\mathbf{h})f(\overline{\mathbf{h}+\mathbf{k}})+f(\mathbf{k})f(\overline{\mathbf{h}+\mathbf{k}})] \times[1+\cos 2\pi\mathbf{h}\,.\,\mathbf{U}_1+\cos 2\pi\mathbf{k}\,.\,\mathbf{U}_1+\cos 2\pi(\mathbf{h}+\mathbf{k})\,.\,\mathbf{U}_1] \tag{4}$$

in which $f(\mathbf{h})=f_{j_1}(\mathbf{h})=f_{j_2}(\mathbf{h})$ and $f''=f''_{j1}=f''_{j2}$ are the real and imaginary part of the two anomalous scatterers j_1 and j_2, respectively, and $\mathbf{U}_1$ is the interatomic vector between these atoms. In (4) the contributions from double Patterson peaks with form factors of the shape $f''ff_j$ and $f''f_if_j(i,j\neq j_1,j_2)$ have been neglected. The double Patterson function, with Fourier coefficients $\tau_{\mathbf{hk}}=F_{\mathbf{h}}F_{\mathbf{k}}F_{\overline{\mathbf{h}+\mathbf{k}}}$, can thus be regarded as a 'structure' containing an anomalous scatterer at the origin, whose imaginary part of the form factor is $2f''[f(\mathbf{h})f(\mathbf{k})+f(\mathbf{h})f(\overline{\mathbf{h}+\mathbf{k}})+f(\mathbf{k})f(\overline{\mathbf{h}+\mathbf{k}})]$, and anomalous scatterers on the hyper-axes with positions $(\mathbf{U}_1,\mathbf{0})$, $(\mathbf{U}_1,\mathbf{U}_1)$, $(\mathbf{0},\mathbf{U}_1)$, $(\overline{\mathbf{U}}_1,\mathbf{0})$, $(\overline{\mathbf{U}}_1,\overline{\mathbf{U}}_1)$ and $(\mathbf{0},\overline{\mathbf{U}}_1)$, whose imaginary parts of the form factors are one half of that of the origin peak. Therefore, (1) applies equally well to the phase $\bar{\varphi}_{\mathbf{hk}}$ and reads

$$\sin\bar{\varphi}_{\mathbf{hk}}\simeq\frac{|\tau_{\mathbf{hk}}|^2-|\tau_{\bar{\mathbf{h}}\bar{\mathbf{k}}}|^2}{4\tau''_{\mathbf{hk}}[\frac{1}{2}(|\tau_{\mathbf{hk}}|^2+|\tau_{\bar{\mathbf{h}}\bar{\mathbf{k}}}|^2)-|\tau''_{\mathbf{hk}}|^2]^{1/2}} \tag{5}$$

in which $\tau''_{\mathbf{hk}}$ is given by (4).

If the vector $\mathbf{U}_1$ between the two anomalous scatterers is not known, then, as will be shown below, an omission of the cosine terms in (4):

$$\tau''_{\mathbf{hk}}=2f''[f(\mathbf{h})f(\mathbf{k})+f(\mathbf{h})f(\overline{\mathbf{h}+\mathbf{k}})+f(\mathbf{k})f(\overline{\mathbf{h}+\mathbf{k}})] \tag{6}$$

leads to a good result, providing a scaling procedure is applied. Clearly the basis for the possibility of using (6) instead of (4) in the phase-determining formula (5) is the fact that the complex double Patterson function contains an origin peak with a complex form factor, an anomalous scatterer as it were. This fact makes it feasible to find phase information from Bijvoet inequalities without even knowing the positions of the anomalous scatterers in the unit cell. Of course, the ambiguity between φ and $\pi-\varphi$ as possible values for the phase of the triple product still remains, but it is quite safe, in view of the alleged positivity of the triple product, to choose the one that is nearer to zero. This is especially true if the triple products $F_{\mathbf{h}}F_{\mathbf{k}}F_{\overline{\mathbf{h}+\mathbf{k}}}$ are chosen in such a way that the corresponding value of $A=2\sigma_3|E_{\mathbf{h}}E_{\mathbf{k}}E_{\overline{\mathbf{h}+\mathbf{k}}}|/\sigma_2^{3/2}$ is reasonably large.

In order to keep the argument simple the method was explained in terms of a structure containing two identical anomalous scatterers in the unit cell. However, the formulae may easily be extended to any configuration of anomalous scatterers, even the non-centrosymmetric, by using (3) to derive $\tau''_{\mathbf{hk}}$ and subsequently applying the standard methods of anomalous diffraction as used for ordinary structure factors.

Test calculations

The method was applied to the X-ray data of dexetimide (Spek, 1976). The space group is $P1$; the structure contains two anomalous scatterers (Br^-) in the unit cell. Some relevant data are given in Table 1. In order to reproduce experimental conditions, the scale factor and temperature factor, derived from Wilson's (1942) statistics, were applied throughout the calculations.

Table 1. *X-ray data for the crystal structure of dexetimide*, $\mathrm{C_{23}H_{27}N_2O_2Br.\frac{1}{2}H_2O}$

Space group: $P1$
$Z=2$
$a=7{\cdot}390\ (2)$ Å
$b=9{\cdot}073\ (1)$
$c=17{\cdot}248\ (2)$
$\alpha=96{\cdot}24\ (1)^\circ$
$\beta=101{\cdot}78\ (2)$
$\gamma=81{\cdot}28\ (2)$
$\lambda(\mathrm{Cu}\ K\alpha)=1{\cdot}5418$ Å

$F(000)=478$
$E(000)=3{\cdot}16$
Absorption correction
applied $\mu(\mathrm{Cu}\ K\alpha)=29{\cdot}4\ \mathrm{cm}^{-1}$
$f''(\mathrm{Br})=1{\cdot}46$
Number of observed
reflexions hkl: 2419
$\overline{hkl}$: 2793
$R=0{\cdot}046$
$c_{\mathrm{Wilson}}=1{\cdot}08\ c_{\mathrm{l.s.}}$
$B_{\mathrm{Wilson}}=3{\cdot}94$ Å^2

In a preliminary calculation from 103 reflexions, for which $|F^0_{\mathbf{h}}|>40$ and $|E_{\mathbf{h}}|>1{\cdot}3$, 506 triple products were generated. Calculations performed with (5) gave two sets of $\sin\varphi^{\mathrm{calc}}$ values, one with the Br positions known [$\tau''_{\mathbf{hk}}$ calculated by (4)] and one with them unknown [$\tau''_{\mathbf{hk}}$ calculated by (6)]. Plots of $\sin\varphi^{\mathrm{calc}}$ against $\sin\varphi^{\mathrm{true}}$* indicate a linear relation, with correlation coefficients of 0·86 in both cases and with slopes of 0·97 and 3·20 respectively. Evidently the slope of the second graph, the one that is based on the origin peak of the double Patterson function alone, is far too small; many of the $|\sin\varphi^{\mathrm{calc}}|$ values happen to be larger than one. The reason for this is that, since large structure factors are involved, the values of $\cos 2\pi\mathbf{h}\,.\,\mathbf{U}$, $\cos 2\pi\mathbf{k}\,.\,\mathbf{U}$ and $\cos 2\pi(\mathbf{h}+\mathbf{k})\,.\,\mathbf{U}$ tend to be positive; consequently the value of $\tau''_{\mathbf{hk}}$ calculated by (4) is systematically larger than the value calculated by (6). Therefore a scaling procedure was applied. It is based on the requirement

$$k^{-2}\langle\sin^2\bar{\varphi}^{\mathrm{calc}}_{\mathbf{hk}}\rangle_{\mathbf{h},\mathbf{k}}=\left\langle\int\sin^2\Phi P(\Phi|A)\mathrm{d}\Phi\right\rangle_{\mathbf{h},\mathbf{k}} =\left\langle\frac{I_1(A)}{AI_0(A)}\right\rangle_{\mathbf{h},\mathbf{k}}$$

where k is a scaling factor and $I_1(A)/AI_0(A)$ is the expectation value of $\sin^2\varphi$ given the value of A

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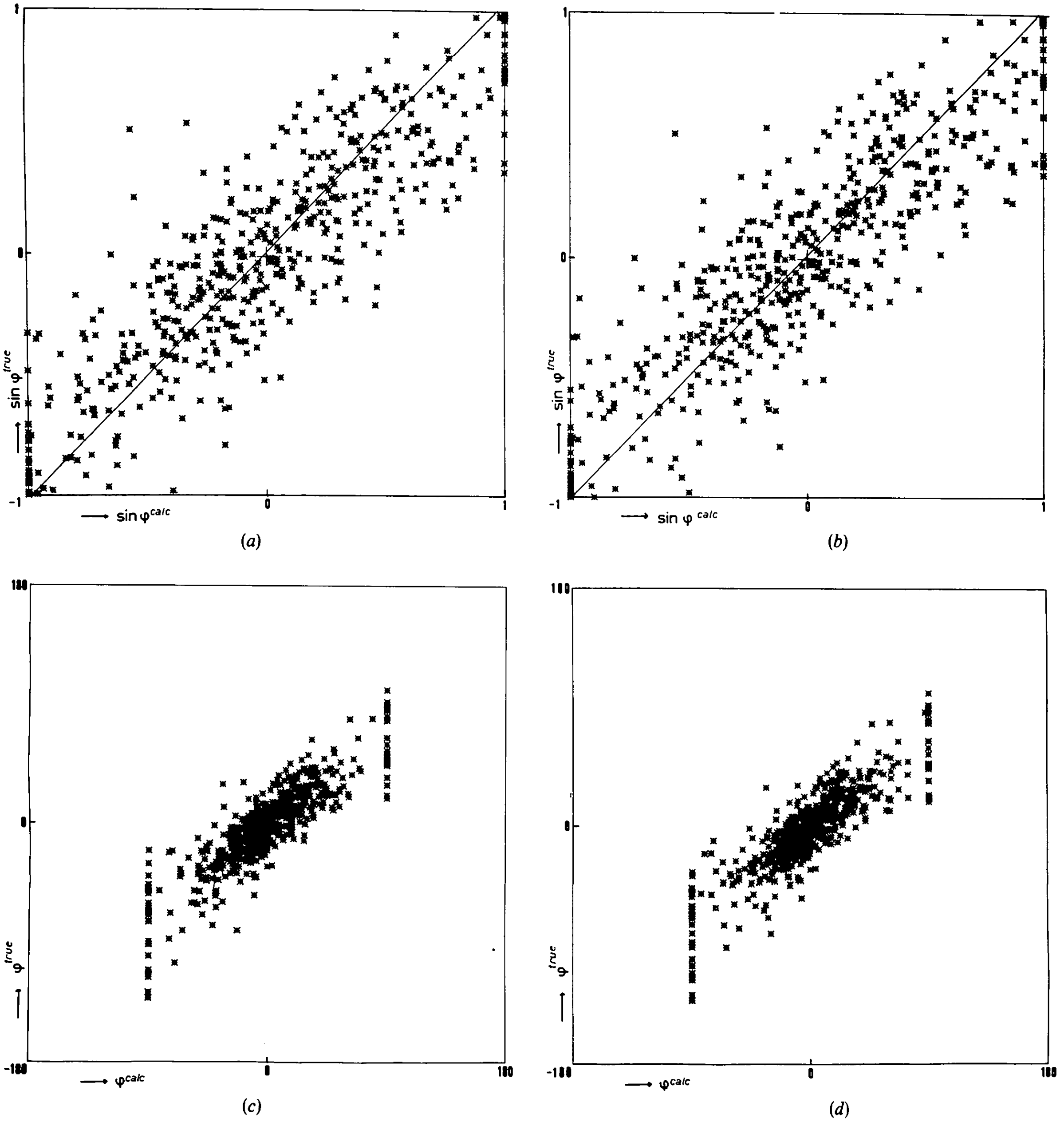
* $\varphi^{\mathrm{true}}_{\mathbf{hk}}$ is the average value of the phases $\varphi_{\mathbf{hk}}$ and $-\varphi_{\bar{\mathbf{h}}\bar{\mathbf{k}}}$, obtained from the refined structure.

(Hauptman, 1972). The scaling procedure was iteratively applied to both curves; in each cycle all values of $|\sin \bar{\varphi}^{\text{calc}}|$ larger than k were set equal to k. The resulting scaling factors were 0·75 and 2·4, respectively, which gave rise to two straight lines with slopes of 0·97 and 0·98 and correlation coefficients of 0·88 and 0·87 respectively [Fig. 1(*a*) and (*b*)]. The resulting graphs of $\bar{\varphi}^{\text{calc}}$ against $\bar{\varphi}^{\text{true}}$ for the two sets are shown in Fig. 1(*c*) and (*d*); the corresponding values of $\langle|\Delta\varphi_{\mathbf{hk}}|\rangle_{\mathbf{h},\mathbf{k}}$ and $\langle|\Delta\varphi_{\mathbf{hk}}|^2\rangle^{1/2}_{\mathbf{h},\mathbf{k}}$ are 14 and 19° for the first set (known Br positions) and 15 and 20° for the second set (unknown Br positions). The gratifying result is that the phases of the triple products can be determined quite accurately without introducing the heavy-atom positions. A knowledge of these positions scarcely improves the accuracy of the results and only influences the scale factor. A number of additional calculations (Table 2) using both $|F^o_{\mathbf{h}}|$ and $|F^c_{\mathbf{h}}|$, with



(*a*) (*b*) (*c*) (*d*)

Fig. 1. Comparison of correct values of sin $\bar{\varphi}$ and $\bar{\varphi}$ with those obtained by (5) and subsequent scaling. (*a*),(*c*) $\tau''_{\mathbf{hk}}$ calculated with known heavy-atom positions. (*b*),(*d*) $\tau''_{\mathbf{hk}}$ calculated with unknown heavy-atom positions.

Table 2. *Results of the phase determination of triple products employing the Bijvoet inequalities with the data of dexetimide*

Set number	F used	Heavy-atom positions included	Minimum $\|F\|$	Minimum $\|E\|$	Number of reflexions	Number of triple products	Scaling factor	Correlation coefficient	$\langle\|\Delta\varphi\|\rangle$	$\langle\Delta^2\varphi\rangle^{1/2}$
1	F^o	no	40	1·3	103	506	2·4	0·87	15°	20°
2	F^o	yes	40	1·3	103	506	0·75	0·88	14	19
3	F^c	no	40	1·3	86	342	2·1	0·95	10	15
4	F^c	yes	40	1·3	86	342	0·65	0·95	10	15
5	F^o	no	50	0·0	87	441	2·0	0·82	22	34
6	F^o	yes	50	0·0	87	441	0·89	0·75	21	37
7	F^c	no	50	0·0	64	342	2·0	0·89	16	30
8	F^c	yes	50	0·0	64	342	0·83	0·87	16	31
9	F^o	no	25	1·2	322	5139	1·8	0·77	21	37
10	F^c	no	25	1·2	258	3832	1·4	0·92	14	19

varying lower limits on $|F_{\mathbf{h}}|$ and $|E_{\mathbf{h}}|$, merely confirm these results and show the influence of observational errors. Especially interesting for practical application is entry No. 9 in this table, where the phases of 5139 triple products were calculated with a mean error in φ of 21°.

Discussion

The method described in the previous section opens the possibility of finding phases of triple products from Bijvoet differences, without needing to find the positions of the anomalous scatterers first. That the phases of the triple products can be determined with reasonable accuracy, at least in a structure containing only a few anomalous scatterers, was shown by a test calculation on a structure in $P1$ containing two Br ions. An inspection of Table 2, where the results are given, shows that, for the chosen example, the accuracy of the phase determination does not even depend on whether or not the heavy-atom positions are introduced, provided that an appropriate scaling procedure, based on the theoretical distribution of the phase of a triple product, is applied.

However, the accuracy does strongly depend on the accuracy of the Bijvoet differences, as is shown by the dramatic decrease in $\langle|\Delta\varphi_{\mathbf{hk}}|\rangle_{\mathbf{h},\mathbf{k}}$ and $\langle|\Delta\varphi_{\mathbf{hk}}|^2\rangle^{1/2}_{\mathbf{h},\mathbf{k}}$ if $|F^c_{\mathbf{h}}|$'s are used instead of $|F^o_{\mathbf{h}}|$'s. In this context it is interesting to note that the anomalous phase-determination methods will certainly receive new impetus if synchrotron radiation becomes of more common use, since high values of f'' are possible by tuning the radiation wavelength near the absorption edge. Our method may then find application in protein phase determination, especially since neither the positions nor the occupancies of the heavy-atom sites need to be known.

A practical qualitative application of the method lies in the possibility of achieving enantiomorph discrimination by selecting those triple products which show large Bijvoet differences.

Extension of the procedure to other structure invariants (*e.g.* quartets, quintets) is straightforward. Also, reasoning along the same lines, the isomorphous replacement method can, in principle, be applied to obtain the phases of structure invariants.

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