Precision of the numerical values

The quantities calculated, the crystallographic program systems which produced them, and the precision referred to the least significant digit quoted in each case, are as follows:

Quantities	Program systems	Precision
$V, a^*, b^*, c^*, \alpha^*, \beta^*, \gamma^*, V^*$	XRAY, NRC	± 0
$\sin \theta/\lambda$	XRAY, NRC, LASL	± 1
Interpolated f-values	XRAY, NRC, LASL	± 3
F_c, A_c, B_c	XRAY, NRC, LASL	± 7
$\sum \lvert F_o \rvert$	XRAY, NRC, LASL	± 0
$\sum \lvert F_c \rvert$	XRAY, NRC, LASL	± 18
$\sum \lvert \Delta F \rvert$	XRAY, NRC, LASL	± 6
R	XRAY, NRC, LASL	± 1
$\sum w(\Delta F)^2$	XRAY, NRC	± 1
Interatomic distances	XRAY, NRC, LASL	± 0
E.s.d.'s of distances	XRAY, NRC, LASL	± 5
Valence angles	XRAY, NRC, LASL	± 1
E.s.d.'s of angles	XRAY, NRC, LASL	± 17
Electron densities	XRAY, NRC, LASL	± 1
Least-squares matrices	XRAY, NRC, LASL	± 15
Inverse matrices	NRC	–
L.S. shifts and e.s.d.'s		
(*a*) full matrix	XRAY, LASL	± 15
(*b*) 9×9 block-diagonal	XRAY, NRC	± 2
(*c*) 3×3 and 6×6 block-diagonal	NRC	–
(*d*) 4×4 and 5×5 block-diagonal	XRAY, NRC	± 5

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Strong Enantiomorph Discrimination *via* Calculated Cosine Invariants

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Using calculated values of the cosine invariants and the concept of orthogonal classes of phases, a procedure for decisive enantiomorph selection is described. The method, which is strongly dependent on a study of invariants of special type, facilitates the evaluation of an initial set of phases and provides a broad base for subsequent phase extension by one of the tangent techniques. Three applications of this new procedure are cited.

1. Introduction

If a structure invariant L has the value s for a crystal structure S then the value of the same structure invariant for the enantiomorphous structure S' is $-s$ (Hauptman & Karle, 1956). Thus if $s=0$ or π then L has the same value (0 or π) for both enantiomorphs and is not suitable for enantiomorph discrimination. If, on the other hand, $s \neq 0$ or π then, since the magnitude of s (or, equivalently, $\cos s$) is determined by the known magnitudes of the structure factors, the enantiomorph may be chosen by specifying arbitrarily the sign of s. This observation forms the basis for enantiomorph selection in crystal structure determination by direct methods.

In practice one attempts to employ a structure invariant L whose value is approximately equal to $\pm\pi/2$ in order to insure strong enantiomorph discrimination. Even so, for complex structures, a single structure invariant constitutes a very narrow foundation on which to base a technique for phase determination. For this reason one has often found, in practice, that enantiomorph specification has not been decisively made and has led to an initial E map which contains fragments of both enantiomorphs and presents great difficulties of interpretation. In the present paper a technique for enantiomorph specification is described which employs, instead of just a single invariant, a class of several structure invariants, each member of which approximately equals $\pm\pi/2$. In this way the base of the phase determination process is considerably broadened with resultant unambiguous enantiomorph discrimination.

Only the space group $P2_1$ is considered here but the same technique may be used in most of the other non-centrosymmetric space groups. It is assumed finally that the values of the cosine invariants, $\cos(\varphi_{\mathbf{h}}+\varphi_{\mathbf{k}}+\varphi_{-\mathbf{h}-\mathbf{k}})$, where φ is the phase of the normalized structure factor E, have been calculated from known magnitudes $|E|$, at least approximately, by methods recently described (Hauptman, Fisher, Hancock & Norton, 1969; Hauptman, 1970; Hauptman, Fisher & Weeks, 1971).

2. Motivation

If the integer k is fixed, then, as h and l range over those integers for which the normalized structure factor magnitudes, $|E_{hkl}|$, are large, it is known that the corresponding phases φ_{hkl} will, in general (provided that $|E_{0\,2k\,0}|$ is not too large), take on values distributed over the range 0 to 2π. If the origin is fixed so that $\varphi_{0\,2k\,0}=0$ (which may always be done in $P2_1$), then some of the φ_{hkl}'s are expected to have values in the neighborhood of 0 or π and others in the neighborhood of $\pm\pi/2$. In view of the relationship

$$\varphi_{\bar{h}\bar{k}\bar{l}}=\varphi_{h\bar{k}l}, \text{ if } k \text{ is even}, \tag{2·1}$$

or

$$\varphi_{\bar{h}\bar{k}\bar{l}}=\pi+\varphi_{h\bar{k}l}, \text{ if } k \text{ is odd}, \tag{2·2}$$

it follows that, if k is even

$$\cos(\varphi_{h\bar{k}l}+\varphi_{\bar{h}\bar{k}\bar{l}}+\varphi_{0\,2k\,0})=\cos 2\varphi_{h\bar{k}l} \tag{2·3}$$

$$\simeq \pm 1 \tag{2·4}$$

according as

$$\varphi_{h\bar{k}l}\simeq 0 \text{ or } \pi \tag{2·5}$$

or

$$\varphi_{h\bar{k}l}\simeq \pm\pi/2 \tag{2·6}$$

respectively. If, on the other hand, k is odd, then

$$\cos(\varphi_{h\bar{k}l}+\varphi_{\bar{h}\bar{k}\bar{l}}+\varphi_{0\,2k\,0})=-\cos 2\varphi_{h\bar{k}l} \tag{2·7}$$

$$\simeq \mp 1 \tag{2·8}$$

according as

$$\varphi_{h\bar{k}l}\simeq 0 \text{ or } \pi \tag{2·9}$$

or

$$\varphi_{h\bar{k}l}\simeq \pm\pi/2 \tag{2·10}$$

respectively. In other words the special cosine invariants (2·3), (2·7), by doubling the phase $\varphi_{h\bar{k}l}$, exaggerate, for fixed k, the deviations in the values of the φ_{hkl}. Thus, differences of $\pi/2$ among the φ_{hkl} (permitting strong enantiomorph discrimination) imply, *via* (2·3)–(2·10), that the values of some cosine invariants are approximately -1 so that the identification of these cosines, by means of their calculated values, is feasible. This observation is the motivation for the method of strong enantiomorph discrimination which is described here, and already clearly shows the strong dependence of the method on the calculated cosine invariants, in particular those calculated to be negative. (It should be noted that $|E_{0\,2k\,0}|$ must not be too large; otherwise, as the probability distribution of cosine invariants shows (Cochran, 1955; Hauptman, Fisher, Hancock & Norton, 1969), the values of most of the cosines (2·3) or (2·7) will be approximately unity, and the possibility of constructing two 'orthogonal' classes of phases as described in the sequel is greatly reduced.)

3. Analysis

In accordance with section 2, the basic idea is to find an integer k and two ('orthogonal') classes, I and II, of phases φ_{hkl} having the properties:

1. $|E_{0\,2k\,0}|$ is moderately large (say $\simeq 2$);
2. every $|E_{hkl}|$ corresponding to any phase φ_{hkl} in Class I or II is large (say >1);
3. any two phases in Class I differ from each other by 0 or π, approximately;
4. any two phases in Class II differ from each other by 0 or π, approximately;
5. any phase in Class I differs from any phase in Class II by $\pi/2$ approximately.

It will be seen in the sequel that while it is highly desirable to have Property 1, this requirement may not be essential.

In order to identify two classes, I and II, with the stated properties, determine first an integer k such that $|E_{0\,2k\,0}|$ is large. Place tentatively in Class I those phases φ_{hkl} for which the $|E_{hkl}|$ are large (so that Property 2 is satisfied) and the calculated values of the cosine invariants $\cos(\varphi_{h\bar{k}l}+\varphi_{\bar{h}\bar{k}\bar{l}}+\varphi_{0\,2k\,0})$ are large:

$$\cos(\varphi_{h\bar{k}l}+\varphi_{\bar{h}\bar{k}\bar{l}}+\varphi_{0\,2k\,0})\simeq +1\,. \tag{3·1}$$

Then

$$2\varphi_{hkl}\simeq\varphi_{0\,2k\,0} \text{ or } \pi+\varphi_{0\,2k\,0} \tag{3·2}$$

according as k is even or odd. Hence

$$\varphi_{hkl}\simeq\tfrac{1}{2}\varphi_{0\,2k\,0} \text{ or } \tfrac{1}{2}\varphi_{0\,2k\,0}+\pi \text{ if } k \text{ is even}, \tag{3·3}$$

$$\varphi_{hkl} \simeq \tfrac{1}{2}\varphi_{0\,2k\,0} \pm \pi/2 \text{ if } k \text{ is odd}, \tag{3·4}$$

and in either case Property 3 is presumably satisfied for these members of Class I ['presumably' because calculated cosines (3·1) are subject to some error]. In order to insure that Property 3 hold with at most minor exception for the elements of Class I, retain only those phases φ_{hkl} which 'interact' strongly with one or several others, $\varphi_{h'kl'}$, *i.e.* those φ_{hkl} such that at least one of

$$A = \frac{2}{N^{1/2}} |E_{hkl}E_{h'kl'}E_{h\pm h',\,0,\,l\pm l'}| \tag{3·5}$$

is large and for which calculated cosine invariants satisfy at least one of

$$\cos(\varphi_{\bar{h}k\bar{l}} + \varphi_{\bar{h}'\bar{k}\bar{l}'} + \varphi_{h+h',\,0,\,l+l'}) = \pm 1\,, \tag{3·6}$$

$$\cos(\varphi_{\bar{h}k\bar{l}} + \varphi_{h'\bar{k}l'} + \varphi_{h-h',\,0,\,l-l'}) = \pm 1\,. \tag{3·7}$$

It is clear from (3·6) and (3·7) that in this case, since $\varphi_{h\pm h',\,0,\,l\pm l'} = 0$ or π, only those phases will be retained in Class I for which Property 3 must almost surely hold.

Next, Class II consists tentatively of those phases φ_{hkl} for which the $|E_{hkl}|$ are large (so that Property 2 is satisfied) and the calculated values of the cosine invariants $\cos(\varphi_{h\bar{k}l} + \varphi_{\bar{h}\bar{k}\bar{l}} + \varphi_{0\,2k\,0})$ are small:

$$\cos(\varphi_{h\bar{k}l} + \varphi_{\bar{h}\bar{k}\bar{l}} + \varphi_{0\,2k\,0}) \simeq -1\,. \tag{3·8}$$

Then

$$2\varphi_{hkl} \simeq \pi + \varphi_{0\,2k\,0} \text{ or } \varphi_{0\,2k\,0} \tag{3·9}$$

according as k is even or odd. Hence

$$\varphi_{hkl} \simeq \tfrac{1}{2}\varphi_{0\,2k\,0} \pm \frac{\pi}{2} \text{ if } k \text{ is even}, \tag{3·10}$$

$$\varphi_{hkl} \simeq \tfrac{1}{2}\varphi_{0\,2k\,0} \text{ or } \tfrac{1}{2}\varphi_{0\,2k\,0} + \pi \text{ if } k \text{ is odd}, \tag{3·11}$$

and, in either case, Property 4 is presumably satisfied for these members of Class II. As before, in order to insure that Property 4 holds with negligible exception, retain only those phases φ_{hkl} in Class II with interact strongly with one another in the sense defined earlier.

Next, if k is even, compare (3·3) with (3·10) in order to verify that Property 5 holds. If k is odd, compare (3·4) and (3·11).

In order to secure Property 5 with at most minor exceptions, only those phases are retained such that no phase in Class II interacts strongly with any phase in Class I, *i.e.* if $\varphi_{h_1kl_1}$ is in Class I and $\varphi_{h_2kl_2}$ is in Class II then either

$$A = \frac{2}{N^{1/2}} |E_{h_1kl_1} E_{h_2kl_2} E_{h_2\pm h_2,\,0,\,l_2\pm l_2}| \simeq 0 \tag{3·12}$$

or, if A of (3·12) is large, then calculated cosine invariants satisfy

$$\cos(\varphi_{h_1kl_1} + \varphi_{h_2\bar{k}l_2} + \varphi_{-h_1-h_2,\,0,\,-l_1-l_2}) \simeq 0 \tag{3·13}$$

or

$$\cos(\varphi_{h_1kl_1} + \varphi_{\bar{h}_2\bar{k}\bar{l}_2} + \varphi_{-h_1+h_2,\,0,\,-l_1+l_2}) \simeq 0\,. \tag{3·14}$$

Clearly, (3·12)–(3·14) are consistent with the previously derived

$$\varphi_{h_1kl_1} + \varphi_{h_2\bar{k}l_2} + \varphi_{-h_1-h_2,\,0,\,-l_2-l_2} \simeq \pm\frac{\pi}{2} \tag{3·15}$$

and

$$\varphi_{h_1kl_1} + \varphi_{\bar{h}_2\bar{k}\bar{l}_2} + \varphi_{-h_1+h_2,\,0,\,-l_1+l_2} \simeq \frac{\pm\pi}{2} \tag{3·16}$$

for all phases $\varphi_{h_1kl_1}$ in Class I and for all phases $\varphi_{h_2kl_2}$ in Class II, *i.e.* Property 5.

Since each structure invariant (3·15) or (3·16) is approximately $\pm\pi/2$, it is clear that the class consisting of all of them constitutes a collection of structure invariants each approximately $\pm\pi/2$ and therefore appropriate for decisive enantiomorph discrimination. Clearly too, owing to the built-in redundancy in defining Classes I and II, a modified procedure suggests itself. Thus Property 1, while highly desirable, may possibly be dispensed with and only the notions of strongly and weakly interacting classes of phases employed. It should, however, be emphasized that in the three applications of this method actually made thus far, Property 1 has in fact been satisfied. In any event the method is strongly dependent on the ability to calculate cosine invariants, at least approximately, and, in view of (3·8), (3·13), (3·14), the identity of the small or negative cosines is seen to be of crucial importance.

Once the values of an initial set of phases have been obtained, *via* origin fixation and the method of strong enantiomorph selection as described here, then the usual tangent techniques (*e.g.* Karle & Hauptman, 1956) are used to expand this basic set.

4. Applications

The technique for strong enantiomorph selection described in this paper has been integrated into the previously secured direct methods for determination of initial phases (Hauptman, Fisher, Hancock & Norton, 1969; Hauptman, 1970; Hauptman, Fisher & Weeks, 1971; Duax, Weeks & Hauptman, 1972) and used to solve the following structures in space group $P2_1$: 17β-acetoxy-2,4-dioxa-3-thia-5α-androstan-3-one ($C_{21}O_5SH_{28}$), the aldosterone–water complex ($C_{21}O_5H_{28}.H_2O$), and valinomycin ($C_{54}N_6O_{18}H_{90}$).

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