

nitudes in the matrix. This extra information can only be used if a function based on a Fourier summation is employed instead of a determinant to derive positions in (x,y) space. Tests are now being made using a 2D FFT summation that includes contributions from these omitted triple-phase invariants.

In conclusion, although the value of a Karle-Hauptman determinant is a discriminating figure of merit for selecting good phase sets, when used in conjunction with magic integers in a phase-determining role, it is not of sufficient power to justify the amount of computer time required to evaluate the very large number of determinants involved.

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On the Application of Phase Relationships to Complex Structures. XVI. A Random Approach to Structure Determination

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With triple-phase relationships treated as linear equations it is possible to refine a set of phases from given initial values. Phases so obtained are better than those found by refining to self-consistency with the tangent formula. An investigation of the radius of convergence of the least-squares refinement process showed that a substantially correct solution may often be found even starting with random phases. Systems containing up to 300 phases have been investigated and the results and their implications are discussed. It is concluded that the random approach can, at the very least, be used to obtain 70–100 phases as a good starting point for phase development. There is also the possibility of obtaining a sufficient number of phases directly to define a reasonably complex structure, especially with a computer augmented by an array processor. A problem which can arise with linear equations, as with the tangent formula, is that the phases obtained do not adequately define the enantiomorph and give an *E* map with a pseudo centre of symmetry. Two methods of overcoming this problem are described.

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Introduction

In describing *MAGLIN*, a new approach to structure determination, Woolfson (1977) proposed an alternative to the tangent formula as a means of refining phases. The basic idea is quite simple. A triple-phase relationship, as given by the *MULTAN* \sum_2 routine, is represented by

$$\varphi_p \pm \varphi_q \pm \varphi_r + b \simeq 0 \pmod{2\pi}. \quad (1)$$

Expressing phases in cycles and using the appropriate value of κ as a weight this may be transformed to

$$\kappa\varphi_p \pm \kappa\varphi_q \pm \kappa\varphi_r \simeq \kappa(n - b), \quad (2)$$

where n is some, generally unknown, integer. If the integers are known then the whole system of such equations, normally far more numerous than the constituent phases, may be written in matrix-algebra notation as

$$\mathbf{A}\varphi = \mathbf{c} \quad (3)$$

to give a least-squares solution

$$\varphi = (\mathbf{A}^T\mathbf{A})^{-1}\mathbf{A}^T\mathbf{c}. \quad (4)$$

If an approximate set of phases is available then nearest integers may be found for the right-hand sides of the equations and a process of cyclic refinement of phases may be carried out.

The effectiveness of this technique of phase refinement has been tested for several structures by refining from an initially correct set of phases. The results of so doing are shown in Table 1 compared with tangent-formula refinement starting from the same point with the same data set. These results, and others, show that the linear-equations refinement is always at least as good as that by the tangent formula and often is far better. The ergocalciferol results are of some interest here. As the system being treated becomes larger so the least-squares solution steadily improves while the tangent-formula solution just as steadily deteriorates. The rather perverse behaviour of the tangent formula for this structure is the probable reason for the difficulty experienced in solving it with *MULTAN* (Hull, Leban, Main, White & Woolfson, 1976).

It is the combination of a magic-integer technique for determining trial phases (White & Woolfson, 1975;

Declercq, Germain & Woolfson, 1975) and of the linear equations for refining phases that constitutes the proposed *MAGLIN* system.

Weighting the equations

The equations were found to work well in the 'refinement' of correct phases. When refinement was started from phases of rather mediocre quality then the need for extra weighting of the equations, other than κ weighting, became evident. For example, supposing that when the current phase estimates (in cycles) were inserted into a relationship its value was exactly 1.5. What nearest integer should be used? Clearly in this case the relationship is of no value in the refinement process and should be eliminated from the system. It could be brought back later when the new phase estimates gave a value for the relationship which was not half-integral. But then let us suppose that the current phases gave the relationship the value 1.48 – should we wish to trust completely the indicated value of the nearest integer? The sensible thing here would be to retain the equation with a nearest integer of unity but to give it rather low weight. Thus we could end up with a weighting scheme where the complete weight given to an equation was $\kappa w(\alpha)$, where α is the departure from nearest integer and satisfies

$$-0.5 < \alpha < 0.5 \quad (5)$$

and $w(\alpha)$ is close to unity for small values of α but approaches zero as $|\alpha|$ approaches 0.5. There is no doubt that a sensible function $w(\alpha)$ could easily be found and that it would work splendidly but such a weighting scheme would be entirely impracticable. In every cycle of refinement the weights would change and so would the elements of the matrix \mathbf{A} in equations (3) and (4). The most expensive part of the phase-refinement process is the matrix inversion of equation (4) and to do this once every cycle is unthinkable – at least in the present state of computer technology.

A device for achieving what we want, but at little expense, is implicit in an idea explained in the *MAGLIN* paper (Woolfson, 1977). Originally it was used to refine for some phases with a system which included a number of other phases for which phase

Table 1. *A comparison of the linear-equations and tangent-formula techniques of phase refinement*

Structure	Number of phases	Number of relationships	Mean phase error	
			Linear equations	Tangent formula
Lithocholic acid ($\text{C}_{24}\text{H}_{40}\text{O}_3$, $P2_12_12_1$, $Z = 4$)	35	65	20°	27°
Cortisone ($\text{C}_{21}\text{H}_{28}\text{O}_5$, $P2_12_12_1$, $Z = 4$)	50	209	21.8	22.4
Ergocalciferol ($\text{C}_{28}\text{H}_{44}\text{O}$, $P2_12_12_1$, $Z = 8$)	50	230	33.6	35.0
	70	435	32.0	37.2
	146	1267	27.8	43.5

estimates were not available. The idea will be re-explained in terms of the present context.

In what follows, to keep the discussion simple, we shall disregard the κ weighting. Let us consider a typical relationship of the form

$$\varphi_3 - \varphi_5 + \varphi_9 \simeq n \quad (6)$$

with current phase estimates $\varphi_3 = 0.6$, $\varphi_5 = 0.1$, $\varphi_9 = 0.7$. Substituting these values into the left-hand side gives 1.2 and in the total set of equations this appears as

$$\varphi_3 - \varphi_5 + \varphi_9 = 1. \quad (7)$$

This equation alone, with 1 on the right-hand side, will introduce a tendency in the least-squares solution to reduce the value of φ_3 and φ_9 and increase the value of φ_5 . What actually happens to these phases will depend on the aggregate effect of all the equations. However, let us now suppose that the equation is used in the form

$$\varphi_3 - \varphi_5 + \varphi_9 = 1.2, \quad (8)$$

that is we use the calculated value of the left-hand side on the right-hand side. A moment's thought will show that, to a first approximation, the equation has been effectively eliminated for it will introduce no tendency to change any of the constituent phases. Of course the equation is still there and it will have some effect but this will be mainly as a damping effect on changes of the involved phases.

Equations (7) and (8) may both be written in the form

$$\varphi_3 - \varphi_5 + \varphi_9 = 1 + f, \quad (9)$$

where $f = 0$ gives equation (7) and corresponds to giving the equation full weight while $f = 0.2$ gives equation (8) and the virtual elimination of the equation.

The weight we actually wish to use depends on the value of α . If $|\alpha| = 0.5$ then we require $f(\alpha) = 0.5$ while if α is small then $f(\alpha)$ can be close to zero. In fact we have found a convenient form of weight

$$f(\alpha) = 2^{m-1} \alpha^m \quad (10)$$

with $m > 1$. The form of this function with various values of m is shown in Fig. 1. For $m = 1$, $f(\alpha) = \alpha$ which is equivalent to neutralizing all the equations so that no refinement takes place at all and $m = \infty$ corresponds to always accepting the nearest integer except when $\alpha = \frac{1}{2}$.

The advantage of this type of weighting procedure is that, with κ reintroduced, a typical linear equation is of the form

$$\kappa\varphi_p \pm \kappa\varphi_q \pm \kappa\varphi_r = \kappa[n - b + f(\alpha)] \quad (11)$$

and hence, in terms of equation (3), only the vector \mathbf{c} is modified at each cycle of refinement.

As a result of many experiments it seems that a good weighting function to use is $4\alpha^3$. Some results of using this and other weighting functions will be given later.

The termination of refinement

When integers are used on the right-hand sides of the equations the refinement process reaches a natural termination – when the integers do not change. This is rather like the refinement of a centrosymmetric structure by a Fourier method which is stopped when the structure factors no longer change in sign. When the weighting function $f(\alpha)$ is used the completion stage is not so clear. As one cycle succeeds another so do the phases gradually drift and the analogy of Fourier refinement of a noncentrosymmetric structure suggests itself, where the calculated phases and the atomic coordinates constantly change.

On the basis of experience a number of criteria have been used to terminate the refinement: (i) $|\Delta\varphi|_{\max.} < 0.003$ ($\approx 1^\circ$); (ii) $|\Delta\alpha|_{\max.} < 0.005$; (iii) $[\Delta f(\alpha)^2]^{1/2} < 0.01$; (iv) fixed number of refinement cycles; (v) $(\alpha^2)^{1/2} < 0.01$. These all work reasonably well and one finishes the refinement process with substantially better phases than one started with. However, an examination of intermediate stages shows that very frequently the phases do not steadily improve as the refinement progresses but that the system goes through a set of phases much closer to the correct ones than those finally obtained. Obviously there is a great incentive to try to detect this situation; not only could one get a better answer but also one would do less work! What is needed is an effective figure of merit which would recognize a good set of phases even when there were not too many of them, say 100 or less. Testing for the relationships to be as close to zero as possible is not satisfactory; the refinement is one that drives the α 's towards zero and, statistically, the α 's end up much closer to zero than they would with correct phases.

Consequently it was decided to test the distribution of the values of α , and quantities related to α , obtained after each refinement cycle in terms of the theoretical distributions available from the work of Cochran

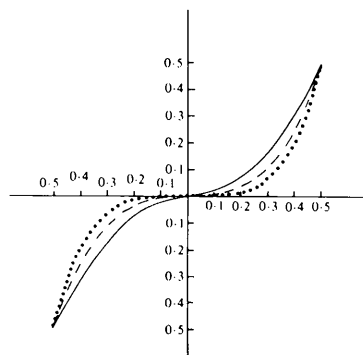


Fig. 1. The weighting function $2^{m-1} \alpha^m$ for $m = 2$ (full line), $m = 3$ (dashed line) and $m = 4$ (dotted line).

(1955) and Karle & Karle (1966). Five figures of merit were explored:

$$\eta_s = \sum_j |\alpha_j^s| - \langle |\alpha_j^s| \rangle, s = 1, 2, 3, 4 \quad (12)$$

and

$$\eta_5 = \sum_j |\cos \alpha_j - I_1(\kappa_j)/I_0(\kappa_j)|, \quad (13)$$

where $\langle |\alpha_j^s| \rangle$ is the theoretical mean value of $|\alpha_j^s|$ for the j th invariant and $I_1(\kappa_j)/I_0(\kappa_j)$ is the theoretical mean value of $\cos \alpha_j$. The results were somewhat disappointing and the minimum value of η was often at a cycle which was far from the minimum mean phase error. Two examples are given for the η_5 test in Fig. 2. It will be seen that in neither is predicted the point at which the mean phase error is a minimum.

It is concluded that the values of η are not really useful as an indication of when to stop and the rather *ad hoc* criteria (i)–(v) are used instead.

Acceleration of convergence

If the value of a refining phase is followed from one cycle to the next it is found that the path of the variation is quite smooth and well behaved. In Fig. 3 there are shown the refinement paths of eight different phases during 33 cycles of refinement and it can be seen that there are some quite large changes between the beginning and the end. Nevertheless, the general form of these refinement curves suggests that from a particular point during the refinement it might be possible successfully to extrapolate forward by the equivalent of a few cycles.

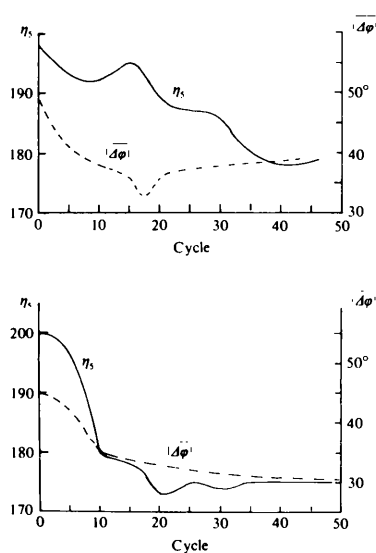


Fig. 2. Two examples of the variation of the figure of merit, η_5 , and the mean phase error over 50 cycles of least-squares refinement.

This was tried in the following way. The phases were found for m iterations of the least-squares linear-equations process. Let these be $\varphi_{i+1} \dots \varphi_{i+s} \dots \varphi_{i+m}$. These values were fitted to a low-order polynomial $p(s)$ of degree $n < m - 1$. The value of $p(t)$ for $t > m$ then gave the required extrapolated value, equivalent to moving forward $t - m$ iterations. Then one may calculate by least-squares iteration m more values and repeat the extrapolation. Good success with this method has been obtained with $m = 3, t = 6; m = 4, t = 8$ with a second-degree polynomial but attempts to carry the extrapolation too far, e.g. $m = 4, t = 10$, have been unsuccessful, giving phases which fluctuate wildly in value.

The general conclusion is that a moderate use of extrapolation is safe and profitable with a saving in computing time approaching 50%. One difficulty introduced by extrapolation is that although the extrapolated phases are a reasonable approximation to those which would be found by $t - m$ iterations, they are not the same and the convergence criterion shows a sudden jump in value. Consequently it becomes more difficult to know when to stop refining and this wipes out some of the gain in computing time.

The radius of convergence – a surprise result

A quantity of interest in any refinement technique is its radius of convergence – that is to say the distance in parameter space from which it is possible to converge to the correct solution. For our purpose the term ‘correct solution’ needs to be qualified for, as we have seen, even starting from correct phases one may refine to a point giving a mean phase error typically in the range 20–30°. We shall therefore use as our criterion for a successful convergence that the final mean phase error shall not be greater than 30°.

A series of trials were carried out with data from the known structure of 3-chloro-1,3,4-triphenylazetid-2-one (AZET) (Colens, Declercq, Germain, Putzeys & Van Meerssche, 1974). The data set consisted of 70 large E 's, taken from the end of a *MULTAN* convergence map, which were interrelated by 405 triple-phase relationships. To the true phases there were added random errors with a normal distribution and

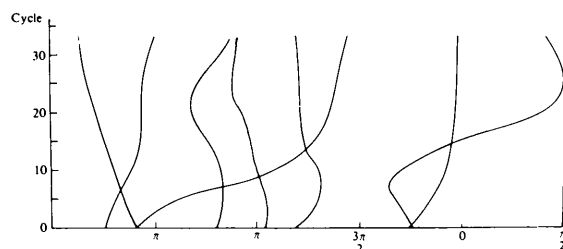


Fig. 3. The variation of eight phases over 33 cycles of refinement.

Table 2. Number of successes with 40 trials for initial phase errors with standard deviation σ and refinement weighting function $2^{m-1}\alpha^m$

σ	m	2	3	4	∞
30	40	40	40	40	40
45	40	40	40	40	40
60	25	40	27	30	30
75	23	38	20	19	19
90	16	34	17	5	5

standard deviation σ . These initial phases were then refined and any final set of phases with mean error less than 30° was designated as successful. For each value of σ , 40 runs were made and the proportion of successes found is recorded in Table 2 where the weight function, as defined in equation (10), was used with $m = 2, 3, 4$ and ∞ (i.e. integers were taken). The results were rather surprising and, indeed, in initial trials the maximum σ was taken at 60° since it was felt that it would be unreasonable to expect to reach a correct solution from any greater r.m.s. error. In fact, as can be seen, even with $\sigma = 90^\circ$ for $f(\alpha) = 4\alpha^3$ there is a very high probability of success. These results naturally raised the question of what would be the outcome if one started with truly random phases. As one might expect from Table 2, with $f(\alpha) = 4\alpha^3$ there is still a high success rate; a run of 15 trials gave six outcomes for which the mean error for the 70 phases was between 20 and 25° .

It should be stressed that the investigation reported

here was not a computational tour de force achieved by some prodigious use of computer time. For the AZET phases the complete refinement time with a random start took about ten seconds so that in a period of a minute or two one could be quite sure of having at least one set of 70 phases with mean error less than 25° .

Further investigations of random starting points

With a starting point of 70 phases with low mean error it should be possible to develop further phases either by the tangent formula or by the *MAGLIN* ψ -map process. The possibility also presents itself that starting with random phases it may be possible to generate enough phase information directly to define the structure without the need for determining additional phases. But then again, even if this objective could be achieved there is the question of how long it would take and whether in practical terms structures could be solved this way.

In Table 3 there are shown the results of experiments with a number of different structures with varying numbers of phases and relationships. The main observations are:

(i) In general, as the size of the system increases so are good solutions harder to find.

(ii) Although refining from correct phases for ergocalciferol gives a lower mean error for a larger system (Table 1), in the experiments with random starts the solutions found for the largest system were not only fewer but also had a greater mean phase error. This means that in 100 trials one had not stumbled upon the

Table 3. Tests of random-start method with ergocalciferol, cortisone, R2, AZET and cinobufagin

Experimental parameters (N, M, T) give the number of phases (N), the number of relationships (M) and the number of trials (T). The results column gives the mean phase error for the best solutions with the number of times that solution is found in parentheses.

Structure	N, M, T	Results	Time per trial(s)
Ergocalciferol	33,110,100	26.9 (4) 31.2 (1) 33.4 (3)	1.3*
	50,230,50	33.6 (2) 33.9 (1) 36.7 (5) 37.0 (2) 38.3 (1)	
	66,382,50	44.1 (2) 47.0 (1) 47.6 (1)	7*
	150,1326,100	42.3 (1) 48.0 (1) 48.5 (1)	
Cortisone	50,209,150	15.9 (1) 21.8 (4) 22.3 (8) 26.2 (1) 31.4 (1)	
R2	40,104,50	20.5 (1) 21.9 (1) 28.2 (1) 32.8 (1)	
	50,173,50	15.8 (2) 20.0 (1) 34.5 (1)	
	60,217,50	18.4 (1) 38.9 (1)	3†
	80,362,50	23.4 (1)	6†
AZET	50,212,50	17.0 (3) 20.9 (2) 26.0 (2)	
	100,844,10	22.9 (1) 23.8 (1) 24.1 (2)	
	200,3201,27	30.0 (2) 30.5 (1) 31.0 (1) 31.7 (1) 32.4 (2)	100*
Cinobufagin	100,892,50	33.4 (1) 35.3 (1) 38.5 (1)	15†
	300,4725,500	19.4 (1) 20.6 (1) + 4 below 45°	108†

* Times at York.

† Times at Louvain.

Table 4. Phases from a random starting point for 60 phases of cinobufagin

 φ_R = refined phase, and φ_1, φ_2 are the correct phase referred to two different choices of origin and enantiomorph.

<i>h k l</i>	φ_R	φ_1	φ_2	φ'_R	<i>h k l</i>	φ_R	φ_1	φ_2	φ'_R	<i>h k l</i>	φ_R	φ_1	φ_2	φ'_R
0 12 1	0	0	0	0	1 1 2	88	62	118	60	1 5 15	270	279	261	270
5 12 0	90	90	90	90	1 7 16	91	119	61	120	5 7 12	270	252	288	270
2 7 13	357	321	39	330	0 6 17	180	180	180	180	3 12 4	270	322	218	270
1 13 3	91	75	105	120	2 13 4	358	302	58	330	2 7 15	178	157	203	150
2 9 13	2	108	252	30	1 3 1	90	138	42	90	7 1 2	88	358	182	60
2 0 2	0	0	0	0	5 5 11	91	57	123	120	2 1 1	179	173	187	150
3 0 1	90	90	90	90	0 8 16	180	180	180	180	5 1 4	87	51	129	60
1 15 0	270	270	270	270	2 1 2	2	97	263	30	3 13 1	99	141	39	120
6 0 6	180	180	180	180	2 0 0	180	180	180	180	1 5 17	90	48	132	90
1 6 18	90	165	15	90	4 1 1	0	323	37	0	5 6 12	264	242	298	240
0 7 17	90	90	270	90	5 0 1	270	270	270	270	1 8 15	270	296	244	270
4 7 13	181	161	199	210	1 6 12	276	326	214	300	2 5 16	175	207	153	150
0 8 14	0	0	0	0	2 5 12	181	204	156	210	5 8 15	270	249	291	270
3 6 14	271	299	241	300	6 6 11	3	67	293	30	3 12 2	90	108	72	90
4 7 15	0	4	356	0	4 5 14	179	157	203	150	2 13 2	178	128	232	150
1 15 2	93	148	32	120	2 6 14	183	193	167	210	4 15 1	0	20	340	0
4 13 2	0	321	39	0	3 14 4	268	163	17	240	2 2 1	2	327	33	30
1 13 1	268	256	284	240	3 6 13	268	162	18	240	3 8 13	271	320	220	300
3 12 0	270	270	270	270	5 13 5	82	85	95	60	2 1 3	356	263	97	330
1 7 14	270	256	284	270	3 5 15	97	100	80	120	3 2 2	269	282	258	240

minimum corresponding to refining from correct phases.

(iii) The single very good solution for cortisone with $|\Delta\varphi| = 15.9^\circ$ was obtained accidentally when the program exceeded the present maximum number of cycles of refinement. This underlines the unsatisfactory nature of the present criterion for terminating the refinement.

(iv) A massive trial on cinobufagin found two solutions for 300 phases with a mean phase error of about 20° . Any optimism that this result might induce must be tempered by the fact that the total computer time was 15 h.

(v) The time of refinement for a single random start has been found from experience to vary as $(NM)^{3/4}$ where N is the number of phases and M the number of relationships. This formula works extremely well over the complete range of size of system which has been investigated.

(vi) The combination of time per random start with number of starts required to find a good solution gives a practical limit of size of system which can be investigated with a DEC 10 computer corresponding to 100–150 phases.

It should be pointed out that the ability to reach a good solution from a random start is not confined to refinement with linear equations. The tangent formula is almost as successful and takes a comparable amount of computer time. With a limited number of trials the results obtained by the two methods of refinement may be similar in quality. However, as can be seen from Table 1, better solutions are accessible with the linear-equations refinement technique and for this reason it is much to be preferred.

The enantiomorph problem

The examination of the linear equations and the random approach was undertaken with known structures. Since the initial phases were completely random then in order to test the outcome of a refinement process it was necessary to check the phases against known phases with all possible choices of origin and enantiomorph.

It soon became clear that there were some solutions, apparently satisfactory from the point of view of mean phase error, which were entirely unsatisfactory in that they did not adequately define a single enantiomorph. This is illustrated in Table 4 which shows the results of one run with cinobufagin. The refined phases have a mean error of 30° with respect to the phases φ_1 and 34° with respect to phases φ_2 , corresponding to a different origin and enantiomorph. The refined phases used as a starting point with the tangent formula do not solve the structure – which is not really surprising since the phases do not clearly define the enantiomorph.

A method was found whereby the set of phases φ_R could be modified so as to improve the enantiomorph discrimination. All the phases φ_R came out close to special values $0, 90, 180$ or 270° and, with the noteworthy exception of reflexion 0.7.17, the refined phase is almost an average of that from φ_1 and φ_2 . However, the values of φ_R are not exact averages of the two solutions; there are small but significant deviations. What can be found is that, where deviations from exact values are present, then in 27 out of 33 cases the deviation is in a direction which is consistent with column φ_1 , which is the column giving agreement with 0.7.17. The phases are now modified in the following way. Where

Table 5. The Δ -shift method ($\Delta = 30^\circ$) applied to an AZET data set with 200 phases and 3201 relationships

	Correct phases	Random starts				
	$\{0^\circ, 60.6^\circ\}$	1	2	3	4	5
Phase errors for two enantiomorphs after refinements with $f(\alpha) = 4\alpha^3$	$\{30.2, 42.6\}$	$\{30.7, 42.5\}$	$\{31.0, 43.9\}$	$\{33.0, 40.7\}$	$\{34.6, 38.7\}$	$\{31.6, 44.3\}$
Mean phase departure from special values	19.5	20.0	19.2	17.3	17.6	20.0
Phase errors after Δ shift	$\{29.9, 50.3\}$	$\{33.6, 51.4\}$	$\{32.3, 56.2\}$	$\{34.6, 48.9\}$	$\{38.9, 41.5\}$	$\{33.0, 50.4\}$

there is a deviation, δ , from a special value, S , then the phase is changed to $S + \text{sign}(\delta)\Delta$, where Δ is a fixed phase shift, usually taken as 30° . The effect of the modification is shown in column ϕ'_R of Table 4 and these phases have a mean error of 25° when compared with ϕ_1 and 47° with ϕ_2 . However, these modified phases fed into the linear-equations refinement process will regress back to their original ϕ_1 values. In addition, if they are used as a starting point for phase development by the tangent formula then they are no more successful than the original unmodified ones.

Actually for cinobufagin the enantiomorph problem disappears if one takes a larger data set. In Table 3 there are three solutions shown for 100 phases. The best agreement with another origin and enantiomorph choice for these three solutions gave mean phase errors of 70 , 72 and 66° respectively and the enantiomorph has been strongly selected.

The reason for the enantiomorph problem is tied up with the refinement process. Common to both the linear-equations and the tangent-formula methods is a tendency to produce solutions with small values of the triple-phase invariants. The whole basis of the linear-equations method is to find phases which give as small magnitudes as possible for the α 's, the departures of the invariants from integers. Driving the α 's towards zero gives a pseudo centre of symmetry in the structure they represent. A representation of the situation may be seen in Fig. 4 where OA represents an invariant in the complex plane, OB an invariant for an enantiomorph

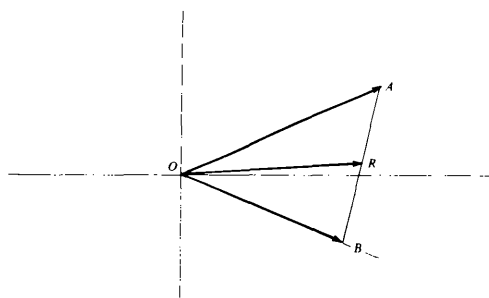


Fig. 4. Small values of α correspond to admixtures of two enantiomorphs (see text).

structure of lesser weight and OR represents the average of the two structures. With the phases from the linear-equations method, and from the tangent formula, the enantiomorph problem presents itself in an electron-density or an E map in the form of a pseudo centre of symmetry with two enantiomorphic images of the structure with slightly different weights.

It is this mechanism which is probably responsible for most *MULTAN* failures. For some structures it is possible to start with 200 correct phases and to refine them to self-consistency with the tangent formula (and with linear equations) in such a way as to lose the structure because of the enantiomorph problem. An outstanding example of this was with the structure of AZET where the system used contained 200 phases and 3201 relationships. Since the space group is $Pca2_1$ then to compare refined phases with observed it was necessary to consider the calculated phases for all possible origins on the 2_1 axes. The method of doing this was straightforward and will not be further considered.

The results of refinement experiments with the AZET data are shown in Table 5.

Starting with true phases the agreements with two different origins and enantiomorphs were $\{0, 60.6^\circ\}$. After refinement with $f(\alpha) = 4\alpha^3$ these became $\{30.2, 42.6^\circ\}$ and it is evident that the phases are not distinguishing the enantiomorph very clearly. At this stage the pseudo centre of symmetry was detected by moving to all possible origins along one 2_1 axis and calculating

$$Z = \sum_{j=1}^{200} |\cos \varphi_j| \quad (14)$$

which is a measure of the closeness of the phases to the special values 0 and π . The highest value of Z indicated the pseudo centre of symmetry and the mean departure of the refined phases from special values was 19.5° . The corresponding value for the true phases was 38° .

The Δ -shift phase modification was made in a fairly arbitrary way; for any phase differing by less than 30° from a special value a shift of 30° from the special value was made in the indicated direction. For the 200-phase AZET example this then gave $\{29.9, 50.3^\circ\}$ and

Table 6. Refinement of 200 phases with 3201 relationships for AZET with $f(\alpha) = 2^{0.3\alpha^{1.3}}$ followed by several cycles with $f(\alpha) = \cos^{-1}[I_1(\kappa)/I_0(\kappa)] \text{ sign } (\alpha)$

	Correct phases	Random starts				
	{0°, 60.6°}	1	2	3	4	5
Phase errors for two enantiomorphs after refinement with $f(\alpha) = 2^{0.3\alpha^{1.3}}$	{33.3, 35.8}	{33.5°, 41.2°}	{36.5°, 34.5°}	{36.1°, 35.5°}	{39.3°, 40.3°}	{35.4°, 37.7°}
Phase errors after further refinement	{34.8, 54.3}	{30.9, 56.2}	{52.9, 34.8}	{41.2, 38.6}	{40.6, 51.7}	{37.3, 50.7}

the enantiomorph discrimination was much improved. So far the description has been restricted to beginning with correct phases and this corresponds to the first column of Table 5. The remaining columns are for random starts and it will be seen that some of them correspond to good enantiomorph discrimination – particularly starting set 2.

Defining the enantiomorph

The weighting function, $4\alpha^3$, which has generally been found to be most efficient does have a drawback when the enantiomorph problem arises. This function allows for a gradual drift of each invariant towards a zero value as the refinement proceeds. For this reason, when the enantiomorph problem arises, an alternative function may be used.

For any invariant, α , there exists an estimate for $\cos \alpha$ based on the associated κ value. This is (Germain, Main & Woolfson, 1970)

$$\langle \cos \alpha \rangle = I_1(\kappa)/I_0(\kappa). \quad (15)$$

The technique we have used to enhance enantiomorph information is to complete the refinement with $f(\alpha) = 4\alpha^3$ by a few cycles for which

$$f(\alpha) = \text{sign } (\alpha) \cos^{-1}[I_1(\kappa)/I_0(\kappa)]. \quad (16)$$

This form of function gives an estimate of the magnitude of α (approximately) with an estimate of its sign based on α itself.

The results of this procedure are shown in Table 6. In order to make the test as stringent as possible the initial refinement was carried out not with function $4\alpha^3$ but with $2^{0.3\alpha^{1.3}}$ which gives distinctly inferior results from the enantiomorph-defining point of view. This may be seen by comparing the top rows in Tables 5 and 6 which correspond to refinement from the same original phase set.

The idea works quite well and is capable of giving good enantiomorph discrimination (see column 2, Table 6). However, a proper test of any set of phases is a Fourier map. E maps were calculated with the initial

phases {33.3, 35.8°} and with the final phases {34.8, 54.3°}. The first map showed a clear centre of symmetry along the 2_1 axis with related peaks differing in height by less than 10%. The second map, by contrast, gave a much clearer picture with the almost complete removal of the pseudo centre of symmetry and a large proportion of the molecule could clearly be distinguished.

It appears from this work that the enantiomorph problem has essentially been solved. The ideas for solving it, as described here, represent the very first to be thought of and tried and it seems likely that with trials of other ideas an even better process for enantiomorph discrimination may be found.

The need for a figure of merit

With the random approach, especially for moderate-sized systems, obtaining a phase set with low mean phase error is straightforward – at least in all cases tried so far. The problem is to know how to recognize a good phase set. The figures of merit used in *MULTAN* are of very little use for medium-sized systems (80 phases, say) and some more reliable figure of merit is required.

This is not a problem we can claim to have solved, although we do have a partial solution. It was noticed that the values of η , defined in equation (12), although they did not reliably indicate when to cease refinement, did correlate to some extent with the final mean error. We devised a combined figure of merit

$$q = \frac{\eta_1}{\bar{\eta}_1} + \frac{\eta_2}{\bar{\eta}_2} + \frac{\eta_3}{\bar{\eta}_3} + \frac{\eta_4}{\bar{\eta}_4} \quad (17)$$

which has a mean value of 4 and which is such that low values of q are a favourable indication for the phases. When values of q are plotted against the mean phase error, as shown in Fig. 5, it is seen that solutions with $q < 4$ tend to include most of those with lowest mean phase error. For the 30-phase example (Fig. 5a) the two best solutions have $q > 4$ but it is interesting to note that these sets of phases are abnormal in the sense

that they are better than phases obtained by refining true phases to self consistency.

The search for a better figure of merit, applicable to moderate-sized systems, continues.

Use of the random approach

Basically there are two possible ways of exploiting the random approach. One is to attempt to find a good set of phases for a sufficient number of reflexions completely to define the structure in an E map. That this is possible there can be no doubt but it may be a very costly exercise. As a generalization it seems that to solve a 40–50 atom structure in this way could take about 2 h on a DEC 10 computer. While this is not a cost one is prepared to pay if a more economical approach is available, it is a cost which modern technology can reduce. By the use of an array processor it is possible to reduce the time of matrix operations by a factor of ten or so and then first-time solutions of structures should be possible in times of the order of 10–15 min.

The approach which seems more attractive and economical at the present time is to start by developing sets of phases for 70–80 reflexions which, with extrapolation, should take 4 s or so per set. Even for obdurate structures no more than 100 should need to be developed and then, with a suitable figure of merit, one would hope to isolate 20 or so sets, at least one of which should be a good one. These sets can then be developed as described for the *MAGLIN* process (Woolfson, 1977) where ten or twelve new phases are represented by magic integers and a ψ map is calculated

to find probable values for them. Once a base of 70 or more phases is established it seems likely that only one set of probable values for the new phases will present itself, and this will be that which would have been obtained by applying the tangent formula. However, it should be noted that if two or more large peaks are found in the ψ map and these lead to different but plausible phases for the additional reflexions then a weakness in the tangent-formula approach will be revealed. The tangent formula can only give *one* solution in developing the new phases and this solution is not necessarily the correct one.

Experiments on how best to use the random approach will be made but one thing is already clear. Since it is so cheap and easy to produce good sets of phases for 40 or even more reflexions the phase-permutation approach, even improved by magic integers (Main, 1978), ought no longer to be used to initiate phase development, no matter how that development is done.

Conclusion

Consideration of the random approach gives a valuable insight into fundamental aspects of structure solving by direct methods. If, for example, one begins with 150 phases and 1500 relationships then it turns out that one is likely to get a good solution in 50–100 trials. What does this mean?

It means that in the 150-dimensional space in which the refinement takes place the number of minima towards which one may converge is moderately small, say 100, and so one is likely to stumble on the correct solution in about that number of random trials. That is a surprising and an important result; the number of minima is not something impossibly large, like 10^6 , as might be thought.

We venture to suggest that many apparently systematic and theoretically intricate direct methods actually solve complicated structures by a random approach! Certainly this is true of *MULTAN*. It has been frequently observed that the correct solution is obtained from a starting point which is not the one with smallest phase errors. For complicated structures, where the initial phase-development pathway is *via* relationships of doubtful validity, the 32 or 64 pathways may merely be that number of differing random phase developments which are subsequently refined to self-consistency by the tangent formula. This explains one other phenomenon we have observed. When *MULTAN* has failed to solve a structure then a solution will sometimes come about by the haphazard process of artificially halving the temperature factor or telling the program that there are twice as many atoms as there really are. All this does is to disturb the system so that it attempts a solution *via* a different route with a new

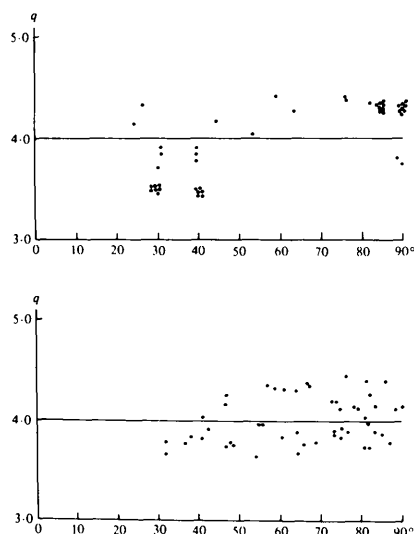


Fig. 5. The combined figure of merit, q , plotted against mean phase error for ergosterol with (a) 30 phases, 90 relationships and (b) 70 phases, 435 relationships.

selection of E 's. The more random starts one makes the better the chance of finding the solution!

Another characteristic of phase developing and refining methods, such as the tangent formula or linear equations, is that even when wrong phase sets are obtained, an E map from the phases will reveal a molecular fragment. Particular sets of E 's may relate most strongly to particular parts of the structure and if the relative phases of the E 's are correctly deduced then the corresponding portion of the molecule will be seen although it may be incorrectly positioned.

This is probably the basis of the success of the symbolic addition method. If one is prepared to make several starts then within a few trials a set of phases giving a fragment may be found. With such a fragment an extremely efficient process of structure development may be initiated (e.g. Karle, 1968).

It should not be thought that we are saying that *all* structures are solved by a pseudo random approach. For simple structures the *MULTAN* development process can start from a best set of phases such that as the phase development proceeds so the phases being developed are close to their correct values. Again, if techniques are employed which can give reliable estimates for the values of structure-invariant quantities, then the complexity of structure for which a solution is obtained by a 'non-random' pathway may well be greater.

The question does nevertheless present itself – with large and fast computers available and with hardware

such as array processors becoming ever more common – how worthwhile is it to develop intricate and subtle techniques when a bull-at-the-fence process may be enough?

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The Use of Karle–Hauptman Determinants in Small-Structure Determinations

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This paper illustrates the potential of Karle–Hauptman determinants for the solution of the phase problem in a 'difficult' small structure. An outline of the procedure followed is given. Suggestions for the future are presented, together with a discussion of the results obtained.

Introduction

Efforts to solve small and medium structures (as opposed to large protein structures) by direct methods have centred on the Σ_2 relation. Attempts to include relations among more than three phases have met with some initial success (Gilmore, 1977; Gilmore, Hardy, MacNicol & Wilson, 1977; Blank, Rodrigues, Pletcher

& Sax, 1976; Sax, Rodrigues, Blank, Wood & Pletcher, 1976). Quartets and quintets have yielded efficient criteria for discriminating between solutions obtained by Σ_2 -based processes (Schenk, 1973*a,b*). The empirical formulae obtained by Schenk have been supplemented by theory (Hauptman, 1974*a,b*, 1975*a,b*; Giacovazzo, 1974, 1975; Heinerman, 1975).

A totally different approach to the problem was