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Destruction of Pseudo-Centrosymmetry with Direct Methods

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Phase refinement based on minimization of $C = \Sigma_{\mathbf{h},\mathbf{k}}|E_{\mathbf{h}}E_{\mathbf{k}}E_{-\mathbf{h}-\mathbf{k}}|[1 - \cos(\varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} + \varphi_{-\mathbf{h}-\mathbf{k}})]^2$ has been tested on several known structures (space group $P2_1$) containing elements of pseudo-centrosymmetry. C always has a maximum for a consistent centric phase set provided that some invariants have a phase of 180°. Thus C will have a minimum for a noncentric phase set, and the phases do not turn centric during the refinement as often is the case when the ordinary tangent formula is applied. The hydrochloride of the insect alkaloid adaline (space group $P2_1$), whose cell constants and hitherto unpublished atomic positions are given, is one of the examples upon which the destruction of centrosymmetry is demonstrated. The destruction of centrosymmetry was indicated by the largest maximum of a one-dimensional modified F^2 synthesis along the unique axis.

Introduction

A non-centrosymmetric structure containing a centrosymmetric arrangement of atoms in the unit cell, such as one or two Br atoms among several C and O atoms, represents a problem of pseudo-centrosymmetry. It is a common experience that the tangent formula has difficulties in refining phases of such structures, especially if there are no reflexions with phase restrictions, and it often ends up with centric phases even if the refinement starts with known phases. Normally the centrosymmetry is broken by the extraction of a part of the structure from the Fourier map based for instance on centric heavy-atom phases. The full structure is then obtained by successive Fourier synthesis. This process is automatically carried out in the phase-correction method (Hoppe & Gassman, 1968). Karle & Karle (1969) showed how the difficulties with the tangent formula were met in the structure solution of an alkaloid $C_{31}H_{38}NO_6Br$, in space group $P2_12_12_1$ with Br at x,0,0. Keeping phases computed from the bromobenzoate group fixed, phases for additional reflexions were obtained by the tangent formula. The E map computed from these phases was claimed to be better resolved than that based on bromobenzoate phases alone. Busetta (1976) tested a modification of the tangent formula to meet this problem with alborixin, $C_{48}H_{84}O_{14}K$ (space group $P2_1$; $Z = 2$) for which two thirds of the 406 phases with $|E| > 1{\cdot}60$ differed by less than 30° from the most similar centric solution. This article will describe an alternative method to solve such problems.

Phase refinement

The tangent formula, which is normally used for phase refinement with direct methods, implies (Lesk, 1976) the minimization of

$$G = -\sum_{\mathbf{h},\mathbf{k}} P_{\mathbf{h},\mathbf{k}} \cos Y_{\mathbf{h},\mathbf{k}} \tag{1}$$

where $P_{\mathbf{h},\mathbf{k}} = |E_{\mathbf{h}}E_{\mathbf{k}}E_{-\mathbf{h}-\mathbf{k}}|$ and $Y_{\mathbf{h},\mathbf{k}} = \varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} + \varphi_{-\mathbf{h}-\mathbf{k}}$. The same results are of course obtained by minimization of

$$S = \sum_{\mathbf{h},\mathbf{k}} P_{\mathbf{h},\mathbf{k}} \sin(Y_{\mathbf{h},\mathbf{k}}/2)^2$$

since $S = G/2$ + constant. The conditions for extrema of G are given by the equation set

$$G'_{\mathbf{h}} = \delta G/\delta\varphi_{\mathbf{h}} = \sum_{\mathbf{k}} P_{\mathbf{h},\mathbf{k}} \sin Y_{\mathbf{h},\mathbf{k}} = 0, \tag{2}$$

which can be rearranged to the tangent formula by standard trigonometry. Both $\varphi_{\mathbf{h}} = 0$ and $180°$ are solutions of (2) but only that solution for which

$$G''_{\mathbf{h}} = \sum_{\mathbf{k}} P_{\mathbf{h},\mathbf{k}} \cos Y_{\mathbf{h},\mathbf{k}} > 0 \tag{3}$$

gives a minimum of G, *i.e.* G or S, always has a minimum for a consistent centric phase set. The tangent formula is therefore not well suited to refine the phases of structures with strong features of pseudo-centrosymmetry, especially in cases where centric phase sets have to be turned into noncentric ones. Moreover, the value of S may even be higher for the correct phases than for the closest centric phases (Table 1).

On the other hand, minimization of

$$C = \sum_{\mathbf{h},\mathbf{k}} P_{\mathbf{h},\mathbf{k}} (1 - \cos Y_{\mathbf{h},\mathbf{k}})^2 \tag{4}$$

would be more suitable in case of pseudo-centrosymmetry, since C always has a maximum for a centric phase set provided that some Y's are 180°. In order to prove this let us consider that all phases have centric values. Extrema of C are obtained from

$$C'_{\mathbf{h}} = \delta C/\delta\varphi_{\mathbf{h}} = \sum_{\mathbf{k}} P_{\mathbf{h},\mathbf{k}} (2 \sin Y_{\mathbf{h},\mathbf{k}} - \sin 2Y_{\mathbf{h},\mathbf{k}}) = 0. \tag{5}$$

Let us consider one equation in set (5) and write $C'_{\mathbf{h}}$ and $C''_{\mathbf{h}}$ as

$$C'_{\mathbf{h}}(\varphi) = 2A \sin \varphi - B \sin 2\varphi = 0 \tag{6}$$

$$C''_{\mathbf{h}}(\varphi) = 2A \cos \varphi - 2B \cos 2\varphi. \tag{7}$$

Here

$$B = \sum_{\mathbf{k}} P_{\mathbf{h},\mathbf{k}} \text{ and } A = \sum_{\mathbf{k}} \varepsilon_{\mathbf{h},\mathbf{k}} P_{\mathbf{h},\mathbf{k}}$$

($\varepsilon = 1$ if $Y = 0°$, $\varepsilon = -1$ if $Y = 180°$). Thus $A < B$ if at least one Y is 180°. The two centric solutions of (6), $\varphi = 0$ and $180°$, give $C''_{\mathbf{h}} = 2(A - B) < 0$, *i.e.* maxima of C. Division of (6) by $\sin\varphi$ results in $\cos\varphi = A/B$, which yields the two other solutions, $\varphi = \alpha$ and $-\alpha$, with $C''_{\mathbf{h}} = 2(B^2 - A^2)/B > 0$, *i.e.* minima of C. A large number of inconsistencies among the Y values gives a small value of A/B, *i.e.* α close to 90 or 270°. The centrosymmetry can then be broken and the enantiomer selected by assigning a phase of α to one reflexion which should preferentially have a small value of A and a large value of B.

Set (5) also corresponds to extrema of

$$C_{\mathbf{h}} = \sum_{\mathbf{k}} P_{\mathbf{h},\mathbf{k}} (1 - \cos Y_{\mathbf{h},\mathbf{k}})^2 \tag{8}$$

which is a special case of

$$Q_{\mathbf{h}} = \sum_{\mathbf{k}} w_{\mathbf{h},\mathbf{k}} (c_{\mathbf{h},\mathbf{k}} - \cos Y_{\mathbf{h},\mathbf{k}})^2, \tag{9}$$

where w is a statistical weight and c is an estimated or calculated value of the cosine invariant. The equation set (9) was given by Hauptman, Fisher, Hancock & Norton (1969) who used $Q_{\mathbf{h}}$ for the least-squares refinement of structure invariants. Hauptman & Weeks (1972) used $Q_{\mathbf{h}}$ in connexion with their modified tangent formula.

Phase refinement by minimization of C has disadvantages compared with the employment of the tangent formula. The phase, for instance, cannot be explicitly given by (5). Moreover, if $C_{\mathbf{h}}$ has two minima the question arises whether one should choose the phase corresponding to the deepest minimum or some kind of weighted mean. In the author's experience, however, the occurrence of two minima for $C_{\mathbf{h}}$ is rare, except when the destruction of pseudo-centrosymmetry begins.

Table 1. *Evolution of the least-squares sums S ($\times 10^{-2}$) and C ($\times 10^{-2}$) during the minimization of C*

Values for cycle 0 correspond to a consistent centric phase set.

Capnellenetriol			The pregnadiene derivative			Ascorbic acid		
Cycle	S	C	Cycle	S	C	Cycle	S	C
0	38·8	74·4	0	19·0	38·9	0	22·9	45·9
1	46·4	64·1	1	24·3	34·5	1	33·0	39·0
2	42·2	44·6	2	26·6	27·0	2	33·9	32·7
3	33·9	32·3	3	21·9	20·7	3	31·3	30·9
4	31·8	27·8				5	32·9	29·9
5	31·1	26·3						

Location and estimation of pseudo-centrosymmetry

The refinement of phases of a structure with pseudo-centrosymmetry may consist of the conversion of a centric phase set into a noncentric one. It would then be of interest to estimate and locate the pseudo-centrosymmetry during the cycles of refinement. Pseudo-centres can be located by the maxima of an F^2 synthesis (Patterson, 1949):

$$X(\mathbf{u}) = 1/V \sum_{\mathbf{h}} F_{\mathbf{h}}^2 \exp(-2\pi i\mathbf{h}.\mathbf{u}).$$

$X(\mathbf{u})$ is a measure of the extent to which the electron density approximates to centrosymmetry about a point at $\frac{1}{2}\mathbf{u}$. The peaks of $X(\mathbf{u})$ are positioned at $\mathbf{u} = \mathbf{r}_j + \mathbf{r}_k$ with a height of $\sum_j^m f_j f_k$, where m is the number of atoms related by a centre of symmetry at $\frac{1}{2}\mathbf{u}$. For instance, in space groups $P2_1$ and $C2$ atoms related by a mirror plane and atoms lying in that plane, which is perpendicular to the unique axis, are related to their equivalent atoms by a centre of symmetry on the unique axis. Thus only the calculation of a one-dimensional F^2 synthesis is required in these two space groups. For this purpose it is convenient to modify $X(\mathbf{u})$ into

$$W(\mathbf{u}) = \sum_{\mathbf{h}} |E_{\mathbf{h}}|^2 \cos(2\varphi_{\mathbf{h}} - 2\pi\mathbf{h}.\mathbf{u}) / \sum_{\mathbf{h}} |E_{\mathbf{h}}|^2 \qquad (10)$$

where F has been substituted by $|E_{\mathbf{h}}| \exp(\varphi_{\mathbf{h}})$, terms for $\mathbf{h}$ and $-\mathbf{h}$ combined, and $X(\mathbf{u})$ divided by a constant. The largest maximum of W, $W_{\max}$, will then be unity for a centrosymmetric structure. $W_{\max}$ must be small for the correct phase solution of an equal-atom structure which does not contain a centrosymmetric arrangement of a part of the structure.

Applications

The minimization of C by the equation set (5) has been successfully tested on five known structures (all in space group $P2_1$): $\Delta 9(12)$-capnellene-$3\beta,8\beta,10\alpha$-triol (Karlsson, 1977), 3,20-bis(ethylenedioxy)pregna-5,7-diene (Braun, Hornstra, Knobler, Rutten & Romers, 1973), ascorbic acid (Hvoslef, 1968), adaline hydrochloride (Tursch *et al.*, 1973), convergine hydrochloride (Tursch *et al.*, 1974), given as examples.

The phase solution proceeded as follows. A consistent centric phase set was first expanded from a centric starting set. One of the general reflexions was then given a noncentric phase to select the enantiomer and break the centrosymmetry according to the criteria mentioned earlier. Minimization of C could now start with one phase noncentric and the rest centric. The evolution of the least-squares sums S and C during the refinement is given in Table 1. Note that S can be smaller for the centric phase set (cycle 0) than for the correct noncentric one.

The starting set for phase expansion was generated by the convergence procedure (Germain, Main & Woolfson, 1971) using $\alpha_{\mathbf{h}} = |\sum_{\mathbf{k}} E_{\mathbf{h}} E_{\mathbf{k}} E_{-\mathbf{h}-\mathbf{k}}|^2$ as the elimination criterion. Closest centric values of the correct phases were used as known phases in the starting set. The correct phases (given in parentheses later in the text) correspond to an origin position coinciding with the largest maximum of W (the published coordinates may be related to a different origin).

Capnellenetriol

The asymmetric unit contains two molecules of the triol ($C_{15}H_{24}O_3$) and one water molecule. The phase expansion was done according to the convergence map from a starting set consisting of $3\bar{6}4$ (20°), 3,10, 4 (352°), 127 (322°), 4,14,6 (185°), 450 (0°), 2,17,2 (190°) and 12,11,3 (39°). The first inconsistency appeared when 28 phases had been determined with centric values. 252 consistent centric phases had an average phase error of 42°. The enantiomer was determined by 2,13,2 (109°) which was given the phase 96°. The minimization of C resulted in an average phase error of 12°.

$W_{\max}$ is only 0·19 and corresponds to a pseudo-centre at $z = 0{\cdot}18$ which relates nine atoms and their equivalent atoms within 0·55 Å. The second larger maximum ($W = 0{\cdot}16$) corresponds to seven atoms at $z \simeq 0{\cdot}83$.

The value of $W_{\max}$ is small (all the other structures given as examples have $W_{\max} > 0{\cdot}51$). The method could hardly have been expected to work in this case. The average angular deviation from centric phases was 39° for all general E's but only 28° for the 27 first determined general phases. Moreover, it was impossible to expand the base set given any combination of phases, into a correct phase set by the tangent formula.

Ascorbic acid ($C_6H_8O_6$)

The asymmetric unit contains two molecules. $W_{\max}$ is 0·84, and 15 of the 24 C and O atoms have approximately the same y coordinate (b unique). Reflexions 15, 3,$\bar{2}$ (4°), 17,1,$\bar{2}$ (175°), 14,1,$\bar{4}$ (175°), $35\bar{6}$ (191°), $92\bar{3}$ (197°), 10,2,1 (193°) and 11,3,2 (189°) were used for the phase expansion. Reflexion 7,2,$\bar{2}$ (54°) was given the phase 74° to select the enantiomer.

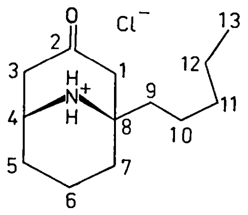

Fig. 1. Adaline hydrochloride, absolute configuration.

The pregnadiene derivative

The plane of the molecule ($C_{25}H_{36}O_4$) is almost perpendicular to the unique b axis (6·02 Å), so that 12 of the 29 C and O atoms have almost the same y coordinate. $W_{\max}$ is 0·59. The average deviation from centrosymmetry is 26° for the general phases among 200 E values larger than 1·52. The initial reflexions were $6,3,\overline{12}$ (187°), $7,0,\overline{12}$ (0°), 2,0,10 (0°), 3,1,10 (176°), 11,1,5 (5°), 2,3,10 (16°), $2,2,\overline{14}$ (177°), $2,3,\overline{11}$ (188°) and $9,0,\overline{11}$ (0°). Reflexion $64\bar{5}$ (325°) was given the value 270° to select the enantiomer.

Adaline hydrochloride

The salt, $C_{13}H_{23}NO.HCl$ (Fig. 1), crystallizes in space group $P2_1$ with $a = 11·19$, $b = 8·905$, $c = 7·603$ Å, $\gamma = 109·98°$ and $Z = 2$. The structure was solved by the heavy-atom method and refined anisotropically to $R = 0·07$. Atomic positions are given in Table 2. Atoms C(10) and C(10)* were refined with an occupancy factor of 0·5 each, which is probably due to a disordered hydrocarbon tail as evidenced by large temperature factors for atoms C(9) to C(13). The C(10)* atom is connected to C(9) but not to C(10). The general phases among 110 E values with $|E| > 1·60$ had an average deviation of 20° from centric values. The straightforward minimization of C gave $W_{\max} = 0·79$, $C = 353$, $S = 650$ (S was 428 in the consistent centric solution) and an average phase error of 13°. The collection of real peaks and their mirror-related spurious counterparts in the E map shows centrosymmetric features (Table 2). There was another more consistent but false solution with $C = 320$, $S = 296$ and $W_{\max} = 0·30$, a rather low value.

Table 2. *Final atomic positions* ($\times 10^3$ *for* C, N, O) *and peak heights in the E map for adaline hydrochloride*

P^* denotes mirror-related peak heights.

	x	y	z	P	P^*
Cl	0·0621 (4)	0·7032 (5)	0·25	1083	–
N	114 (1)	419 (2)	67 (2)	306	160
O	383 (1)	444 (2)	437 (2)	336	185
C(1)	337 (2)	547 (3)	160 (3)	319	291
C(2)	302 (3)	445 (3)	326 (3)	312	170
C(3)	163 (2)	366 (3)	377 (3)	320	217
C(4)	83 (2)	296 (2)	208 (3)	334	183
C(5)	92 (2)	138 (2)	145 (3)	299	188
C(6)	231 (3)	171 (3)	78 (4)	183	45
C(7)	268 (2)	301 (3)	−55 (4)	230	145
C(8)	250 (2)	462 (3)	5 (3)	343	209
C(9)	264 (3)	578 (5)	−148 (3)		
C(10)	384 (5)	686 (6)	−206 (8)		
C(10)*	275 (4)	722 (6)	−126 (9)		
C(11)	333 (4)	791 (4)	−357 (5)		
C(12)	335 (3)	941 (4)	−311 (5)		
C(13)	329 (3)	38 (3)	−478 (6)		

Convergine hydrochloride

The salt, $C_{13}H_{23}NO.HCl$, has the Cl ion at $y = 0·5800$ (b unique), atoms C(1), C(9a), N, C(6a), C(6) at $y \simeq 0·65$, atoms C(2), C(3), C(3a), C(4), C(5), C(10) at $y \simeq 0·47$, atoms C(7), C(8), C(9) at $y \simeq 0·53$ and the O atom at $y = 0·7681$. The above y values correspond to pseudo-centres at $y = 0·33$, 0·40, 0·22, 0·38, 0·518 with $W(y)$ maxima of 0·40, 0·51, 0·17, 0·12 and 0·03 respectively. The calculation was based on known phases for 110 E values with $|E| > 1·60$. The pseudo-centre at the largest maximum also relates the O atom to the equivalent of C(3a), since these atoms have almost the same x and z coordinates. The minimization of C with (5), starting from the centric phase set which was related to $W_{\max}$, was straightforward and gave $C = 265$. It was also possible to solve the structure from Cl phases, although the Cl position is related to the second largest maximum of W. The 80 best determined Cl phases were expanded to a consistent centric phase set, and reflexion $43\bar{4}$ was chosen to select the enantiomer. The refinement gave $C = 711$, a larger value than before, but the E map clearly showed the structure almost without mirror symmetry. The maximum of W at $y = 0·40$ gradually became larger than that related to the Cl ion during the refinement with (5).

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