

Fig. 6. Liaisons hydrogènes intermoléculaires autour de l'axe z situé à $x=0,5$ et $y=0,5$. Les courbes de niveau dessinées correspondent à la section parallèle à a, c , à la cote $z=0,450$ d'une série de différences destinée à localiser les hydrogènes. La première courbe correspond à une densité électronique de $0,1 \text{ e.}\text{\AA}^{-3}$ et la deuxième à $0,2 \text{ e.}\text{\AA}^{-3}$.

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Acta Cryst. (1972). **B28**, 3331

Application of the Pair Relationships to the Structure Determination of 9 α -Fluorocortisol

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(Received 12 May 1972)

The crystal structure of 9 α -fluorocortisol ($C_{21}H_{29}FO_5$; space group $P2_12_12_1$) has been solved by a procedure which incorporates a number of direct-method techniques including, in particular, the recently derived formulas for the cosines of those structure seminvariants, $\varphi_1 + \varphi_2$, which are linear combinations of two phases. These techniques yielded, with perfect accuracy, the values of 49 two-dimensional phases which were used as input to the tangent formula. The initial E map, based on the 250 tangent formula phases, revealed 26 of the 27 nonhydrogen atoms in the structure.

1. Introduction

The values of the cosine invariants, as calculated from normalized structure-factor amplitudes, may serve as the basis for a program of phase determination. The most widely used cosine invariants, $\cos(\varphi_{h_1} + \varphi_{h_2} + \varphi_{h_3})$,

involve a linear combination of three phases subject to the restriction that $\mathbf{h}_1 + \mathbf{h}_2 + \mathbf{h}_3 = 0$, and their values are independent of the choice of origin and enantiomorph and are uniquely determined by observed structure-factor magnitudes alone. These cosine invariants, as computed by the modified triple product

(Hauptman, Fisher, Hancock & Norton, 1969) and MDKS formulas (Fisher, Hancock & Hauptman, 1970*a,b*; Hauptman, 1972*a*), have been used to solve a number of structures (*e.g.* Weeks, Cooper, Norton, Hauptman & Fisher, 1971; Duax, Weeks & Hauptman, 1972).

Although the values of all phases are fixed once the origin and enantiomorph have been selected, it is not always true that all phases are accessible through the universal invariants, $\cos(\varphi_1 + \varphi_2 + \varphi_3)$, alone (Hauptman, 1972*a*, Chapter I). In addition, the situation often arises in which a given phase can be related to the origin-specifying reflections, but one or more of the intervening cosine invariants cannot be accurately computed, and the phase in question cannot be found reliably. In such cases, it is necessary to use certain types of cosine seminvariants in order to find the unknown phase. In contrast to the cosine invariants, the values of the cosine seminvariants are uniquely determined by the observed structure factor magnitudes provided that the functional form of the geometric structure factor has been specified. Thus, the \cos ies of individual phases which are structure seminvariants may be computed using the space-group specific \sum_1 formulas (Hauptman & Karle, 1953). If these auxiliary formulas also fail to provide a path to an important unknown phase, the latter may be assigned two or more possible values and introduced into the set of known phases as an ambiguity (Germain & Woolfson, 1968). The structure will, presumably be found on a Fourier map computed for a set of phases based on one of the values of the ambiguous phase.

The coincidence method of Grant, Howells & Rogers (1957) provided a means of relating the signs of pairs of structure factors in centrosymmetric space groups by utilizing suitable combinations of triple-product sign relationships, each of which was known with high probability. For example, if

$$S(\mathbf{h})S(\mathbf{h}') \simeq S(\mathbf{h} + \mathbf{h}') \quad (1.1a)$$

with probability P_1 , and

$$S(\mathbf{h})S(\mathbf{h}') \simeq S(\mathbf{h} - \mathbf{h}') \quad (1.1b)$$

with probability P_2 , then

$$S(\mathbf{h} + \mathbf{h}') \simeq S(\mathbf{h} - \mathbf{h}') \quad (1.2)$$

with probability

$$P = 2P_1P_2 - P_1 - P_2 + 1, \quad (1.3)$$

and no knowledge of $S(\mathbf{h})$ or $S(\mathbf{h}')$ is required. Recently (Hauptman, 1971, 1972*b*) it has been found that the relationships among pairs of phases which are related as in equation (1.2) may be expressed in terms of formulas for the space-group dependent cosine seminvariants, $\cos(\varphi_1 + \varphi_2)$. In these (so-called pair) formulas, the cosine seminvariants are computed in terms of a summation of the products of pairs of $(|E|^2 - 1)$ for all pairs of reflections which are related to each of the paired reflections in \sum_2 triples. The resulting summa-

tions provide a stronger measure of the relationship among such phases than can be obtained from the single pair of relationships given in equations (1.1).

The pair formulas, like the \sum_1 formulas, may provide a means of obtaining necessary phases which cannot be reached through an analysis of the universal invariants $\cos(\varphi_1 + \varphi_2 + \varphi_3)$ alone or through those phase-determining formulas which relate triples of reflections for which $\mathbf{h}_1 + \mathbf{h}_2 + \mathbf{h}_3 = 0$. Thus, they may be useful in reducing the number of ambiguities which must be introduced at the beginning of the phasing procedure for an unknown structure. The use of the pair formulas in this way is illustrated in this communication by their application to the unknown structure of 9 α -fluorocortisol. It is not the intention of the authors to claim that this structure could not have been solved by some other direct-method approach, without consideration of the pair formulas. However, use of the pair formulas did eliminate the need for any ambiguities, and such procedures may become increasingly important as the size of structures under consideration and the resulting number of ambiguities necessary to insure the solution of the structure increase.

2. Pair formulas

In space group $P2_12_12_1$, two types of formulas exist which allow the cosine seminvariants, $\cos(\varphi_1 + \varphi_2)$, where the phases φ_1 and φ_2 are both restricted to be either 0 or π or both restricted to be $\pm\pi/2$, to be computed from normalized structure-factor magnitudes alone. The detailed derivation of such formulas has been presented elsewhere (Hauptman, 1972*b*), and only the results are summarized here. The first type of formula, in the form applicable to $0kl$ reflections, is

$$\begin{aligned} E_{0k_1l_1}E_{0k_2l_2} &= |E_{0k_1l_1}E_{0k_2l_2}| \cos(\varphi_{0k_1l_1} + \varphi_{0k_2l_2}) \\ &\simeq \frac{N}{2} \langle (-1)^{h + \frac{1}{2}(k_1+k_2)} (|E_{h, \frac{1}{2}(k_1+k_2), \frac{1}{2}(l_1+l_2)}|^2 - 1) \\ &\quad \times (|E_{h, \frac{1}{2}(k_1-k_2), \frac{1}{2}(l_1-l_2)}|^2 - 1) \rangle_h \\ &\simeq \frac{N}{2} \langle (-1)^{h + \frac{1}{2}(k_1-k_2) + l_1} (|E_{h, \frac{1}{2}(k_1+k_2), \frac{1}{2}(l_1-l_1)}|^2 - 1) \\ &\quad \times (|E_{h, \frac{1}{2}(k_1-k_2), \frac{1}{2}(l_1+l_2)}|^2 - 1) \rangle_h \end{aligned} \quad (2.1)$$

where $k_1 \pm k_2$ and $l_1 \pm l_2$ are even (*i.e.* k_1 and k_2 have the same parity, and l_1 and l_2 have the same parity) and N is the number of atoms, assumed identical to each other, in the unit cell. Clearly, the contributions from the two parts of this formula may be combined. Analogous formulas for the $h0l$ and $hk0$ reflections may be found through a cyclic permutation of the indices. Because of the cumbersome notation occurring in formulas of this sort, it is convenient to introduce the notation $\mathbf{h}_1 = (0k_1l_1)$, $\mathbf{h}_2 = (0k_2l_2)$, $\mathbf{h}_3 = [h, \frac{1}{2}(k_1+k_2), \frac{1}{2}(l_1+l_2)]$ or $[h, \frac{1}{2}(k_1+k_2), \frac{1}{2}(l_1-l_2)]$, $\mathbf{h}_4 = [h, \frac{1}{2}(k_1-k_2), \frac{1}{2}(l_1-l_2)]$ or $[h, \frac{1}{2}(k_1-k_2), \frac{1}{2}(l_1+l_2)]$, and $E_{\mathbf{h}_1} = E_1$, *etc.* In the Type I formulas [equation (2.1)], reflections \mathbf{h}_3 and \mathbf{h}_4 may be, and generally are, three-dimensional, but

in the Type II formulas, of which

$$E_{0k_1l_1}E_{0k_1l_2} = |E_{0k_1l_1}E_{0k_1l_2}| \cos(\varphi_{0k_1l_1} + \varphi_{0k_1l_2})$$

$$\simeq \frac{N}{2} \langle (-1)^{k+\frac{1}{2}(l_1-l_2)} (|E_{0,k,\frac{1}{2}(l_1+l_2)}|^2 - 1) \times (|E_{0,k+k_1,\frac{1}{2}(l_1-l_2)}|^2 - 1) \rangle_k \quad (2.2)$$

is an example, reflections $\mathbf{h}_3 = [0, k, \frac{1}{2}(l_1 + l_2)]$ and $\mathbf{h}_4 = [0, k + k_1, \frac{1}{2}(l_1 - l_2)]$ [not to be confused with the \mathbf{h}_3 and \mathbf{h}_4 used in (2.1)] always have at least one zero index. It is apparent that formulas of the second type are applicable only to pairs, \mathbf{h}_1 and \mathbf{h}_2 , having a common nonzero component.

Table 1. Pairing of the two-dimensional reflections having $|E|_{\text{obs}} > 1.4$

Reflection 1	Reflection 2	Obs $ E_1E_2 $ *cos $(\varphi_1 - \varphi_2)$	Calc $ E_1E_2 $ *cos $(\varphi_1 - \varphi_2)$	No. ctr.	s
0 16 2	0 18 2	-7.7	-144	18	11.8
0 16 2	0 16 4	-5.3	-74	17	6.1
0 16 2	0 16 4	-5.3	-30	36	4.0*
0 18 2	0 16 4	4.5	68	19	5.9
0 22 1	0 8 7	-3.9	-147	19	12.1
0 4 3	0 6 3	-3.9	-107	21	9.4
0 4 3	0 8 3	2.9	89	12	5.8*
0 4 3	0 26 3	4.4	-92†	11	5.9*
0 6 3	0 8 3	-2.6	-71	21	6.3
0 6 3	0 8 3	-2.6	74†	12	4.9*
0 8 3	0 8 5	-3.0	-36	43	4.8*
0 8 3	0 8 7	2.8	37	41	4.7*
0 8 5	0 8 7	-4.4	-52	17	4.3
0 8 5	0 10 7	3.4	56	17	4.5
0 8 7	0 10 7	-3.2	-76	13	5.3
0 17 2	0 19 2	-3.6	-183	18	14.6
0 1 4	0 23 4	-3.0	-81	19	6.8
0 15 4	0 23 4	5.5	-55†	15	4.3
0 1 6	0 3 6	-4.8	-133	17	10.5
0 9 1	0 23 5	-2.4	-102	19	8.4
0 7 3	0 23 3	5.8	-148†	11	9.4*
0 11 5	0 13 5	3.0	145	10	8.6*
4 0 0	8 0 0	-2.7	-268	25	25.0
5 0 1	7 0 1	-2.8	-66	48	8.9
7 0 1	9 0 1	-2.5	-33	41	4.2
3 0 3	5 0 3	-3.3	-41	51	5.8
4 0 0	4 20 0	2.6	131	9	7.4*
2 6 0	2 8 0	2.5	107	19	8.8*
2 6 0	2 18 0	-2.6	-65	18	5.3*
2 10 0	10 10 0	3.6	32	39	4.1*
6 10 0	10 10 0	-3.5	-235	36	26.5*
6 10 0	6 12 0	-2.9	-600	14	41.7*
6 10 0	10 12 0	2.8	633	13	42.4
10 10 0	6 12 0	2.8	633	13	42.4
10 10 0	10 12 0	-2.6	-785	10	46.0*
6 12 0	10 12 0	-2.2	-246	34	26.8*
6 12 0	6 14 0	2.4	80	13	5.5
4 20 0	6 20 0	2.2	86	11	5.4
2 1 0	6 1 0	-12.6	-76	18	6.9
6 1 0	10 9 0	6.6	86	14	6.4
6 1 0	4 17 0	8.6	58	16	4.9
6 1 0	6 21 0	6.8	149	14	10.8*
8 9 0	8 11 0	-7.3	-360	13	24.5*
8 11 0	8 19 0	10.6	-121†	11	8.1
4 17 0	6 17 0	-5.2	-165	13	11.3
4 17 0	8 19 0	-5.3	-98	13	6.9
6 17 0	6 19 0	5.1	81	12	5.5
6 17 0	6 19 0	5.1	75	13	5.3*
7 4 0	5 6 0	3.0	-59†	16	4.6
5 6 0	5 10 0	3.1	94	17	7.4
5 10 0	7 12 0	5.9	334	15	24.3
7 20 0	7 22 0	-4.2	-273	10	16.2*
1 11 0	1 13 0	-4.6	-479	19	39.0*
1 11 0	1 21 0	5.1	85	15	6.4
1 11 0	1 23 0	-3.7	-60	15	4.5
1 11 0	1 23 0	-3.7	-73	17	5.8*
1 13 0	1 21 0	-3.5	-104	15	7.7
1 13 0	1 23 0	2.5	74	13	5.1
1 21 0	1 23 0	-2.8	-265	13	17.8*

* Indicates that pair relation of Type II was used.

† Disagreement between observed and calculated $|E_1E_2| \cos(\varphi_1 - \varphi_2)$.

The use of these formulas can be best understood by considering examples, and some data for the pairs between the strongest 9 α -fluorocortisol two-dimensional reflections are presented in Table 1. For example the scaled average of the products of $|E|^2 - 1$ for the pairs of $h, 17, 2$ and $h, 1, 0$ reflections and the pairs of $h, 17, 0$ and $h, 1, 2$ reflections yielded -144 as the calculated value of $E_{0,16,2} E_{0,18,2}$, indicating that $0, 16, 2$ and $0, 18, 2$ have different phases. The quantity $|E_1 E_2|^* \cos(\varphi_1 - \varphi_2)$ is tabulated rather than $E_1 E_2 = |E_1 E_2|^* \cos(\varphi_1 + \varphi_2)$ of (2.1) and (2.2) because the relationship between the two phases is immediately apparent from the sign of the former. If this sign is positive, the phases have the same value, but they differ by π radians if the sign is negative. As can be seen from Table 1, the magnitude of the calculated product of the normalized structure-factor amplitudes is quite different from the observed value. However, this is not a serious problem because it is known that the phase of each of the paired reflections is restricted to one of two possible values, and the pair formula is only used to determine if these values are the same or differ by π radians. The probability that the correct relationship between the phases is the indicated one increases as the absolute value of the calculated product increases, and one measure of the reliability of the relative phase indication is given by the significance level,

$$s = 2n^{\frac{1}{2}}(\text{obs}|E_1 E_2| + \text{calc}|E_1 E_2|)/N, \quad (2.3)$$

where n is the number of contributors to the average in equation (2.1) or (2.2), and N is the number of atoms in the unit cell. From a study of the results of the application of formulas of this type to the data for several structures having 20–30 nonhydrogen atoms in the asymmetric unit, it appears that the indicated phase relationship is normally correct if s is four or greater. Only those pairs having this minimum significance level are included in Table 1. Inspection of the table shows that only six of the fifty-nine pair relations were incorrectly indicated. An asterisk beside the value of s indicates that the figures were obtained from a Type II formula, and Type I formulas were used in those cases where there is no asterisk.

The relationship of the pair formulas to the coincidence method of Grant, Howells & Rogers (1957) may be made clearer by examining the nature of the individual contributors to the pair summations, and an analysis of this type also helps one to understand how and when the pair formulas will give incorrect relative phase indications. The case of $1, 11, 0$ and $1, 21, 0$ will be considered as an illustration. The Type I summation for these two reflections is over the products of $(|E|^2 - 1)$'s for the pairs of $1, 5, l$ and $0, 16, l$ reflections and the pairs of $0, 5, l$ and $1, 16, l$ reflections. The paired reflections $1, 11, 0$ and $1, 21, 0$ each form a triple of the Σ_2 type with some symmetry variant of each $1, 5, l$ and $0, 16, l$ and with each $0, 5, l$ and $1, 16, l$. The largest contributor to the summation occurs when $h_3 = 152$ and

$h_4 = 0, 16, 2$, and the Σ_2 triples corresponding to this contributor are given in Table 2.

Table 2. Σ_2 triples corresponding to a large contributor to the summation for the pair $(1, 11, 0; 1, 21, 0)$

$h(h_1 \text{ or } h_2)$	$k(h_3 \text{ variant})$	$-h-k(h_4 \text{ variant})$	A^*
1 21 0	$\bar{1} \bar{5} \bar{2}$	0 $\bar{16}$ 2	2.17
1 11 0	$\bar{1}$ 5 2	0 $\bar{16}$ $\bar{2}$	2.86

$$* A = (2/N^{1/2}) |E_h E_k E_{-h-k}|.$$

It is convenient to introduce the notation $\cos(134) = \cos(\varphi_{h_1} + \varphi_{h^*_3} + \varphi_{h^*_4})$ and $\cos(234) = \cos(\varphi_{h_2} + \varphi_{h^*_3} + \varphi_{h^*_4})$ where the asterisk indicates that symmetry variant of the associated reflection needed to yield a structure invariant. Owing to the space-group symmetries, $\cos(134) = \pm \cos(234)$. If $\varphi_{\bar{1} \bar{5} \bar{2}} = \alpha$, $\varphi_{0 \bar{16} 2} = \beta$, $\varphi_{1 11 0} = \varphi_1$, and $\varphi_{1 21 0} = \varphi_2$, then

$$\Phi_1 = \varphi_{1 11 0} + \varphi_{\bar{1} 5 2} + \varphi_{0 \bar{16} 2} = \varphi_1 + \alpha + \beta \quad (2.4)$$

and

$$\Phi_2 = \varphi_{1 21 0} + \varphi_{\bar{1} 5 \bar{2}} + \varphi_{0 \bar{16} 2} = \varphi_2 + \alpha + \beta. \quad (2.5)$$

It follows that

$$\Phi_1 = \Phi_2 \text{ if } \varphi_1 = \varphi_2 \quad (2.6)$$

and

$$\Phi_1 = \pi + \Phi_2 \text{ if } \varphi_1 = \pi + \varphi_2. \quad (2.7)$$

Hence $\varphi_1 = \varphi_2$ or $\varphi_1 = \pi + \varphi_2$ according as $\cos \Phi_1 = \cos \Phi_2$ or $\cos \Phi_1 = -\cos \Phi_2$. (If $\cos \Phi_1 = \pm \cos \Phi_2 \approx 0$, no information is available.) If the A values for the two triples are both large, as is true in this example, then it is probable that both cosine seminvariants will have positive values and that the phase relationship as indicated by equation (2.6), which agrees with the overall indication from equation (2.1), will be correct. Consistent with the pair equations (2.1) and (2.2) is the assumption that the two cosine seminvariants related to a single dominant contributor have the same sign.† It is apparent then that the pair relationship will fail in those cases where there is a single dominant contributor, and that contributor has one positive and one negative associated cosine seminvariant. Thus, erroneous conclusions based on the pair formulas can be avoided in large part by examining the large contributors and checking the calculated values of their cosines which are predicted by the modified triple-product and MDKS formulas.

3. Application to 9 α -fluorocortisol

9 α -Fluorocortisol is a steroid containing 27 nonhydrogen atoms which crystallizes in space group

† The same relationship between the paired phases is not obtained from the sign of the individual contribution to the pair summations [equations (2.1) and (2.2)] as is obtained from the assumption of equal cosine seminvariants for the two related Σ_2 triples in the case that either, but not both, of $|E_{h_3}|$, $|E_{h_4}|$ is less than unity. As an example, consider the contribution of $6, 17, 0$ and $6, 1, 2$ to the $(0, 16, 2; 0, 18, 2)$ pair as given in Table 4.

$P2_12_12_1$ with one molecule per asymmetric unit in a cell having the dimensions $a=10.087$, $b=23.710$, and $c=7.660$ Å. The details of the structure refinement and molecular geometry will be given elsewhere (Weeks & Duax, to be published). In space group $P2_12_12_1$, the reflections in the three centrosymmetric projections are especially easy to work with because their phases have restricted values, and analysis of the computed cosine seminvariants is facilitated (Duax, Weeks & Hauptman, 1972). In the case of 9 α -fluorocortisol, the cosine seminvariants, $\cos(\varphi_1 + \varphi_2 + \varphi_3)$, corresponding to each of the \sum_2 triples involving three two-dimensional reflections having $|E|_{\text{obs}}$ greater than 1.3, were computed by means of both the modified triple product and MDKS formulas. After selection of the origin and the enantiomorph, the values of these cosine seminvariants, along with the values for the cosines of single phases which are structure seminvariants [computed by the \sum_1 formulas, Karle & Hauptman, 1956, equations (5.89)–(5.91)] and the cosines of seminvariant linear combinations of two phases computed by the pair formulas and displayed in Table 1,

were used to find phases for 49 two-dimensional reflections having large normalized structure-factor amplitudes and these were all later shown to be correct. This set of 49 phases was input to the tangent formula which was used to determine 201 additional phases, and 26 of the nonhydrogen atoms were found among the highest 35 peaks on the E map based on all 250 phases. The strength of the particular set of base phases which were used is demonstrated by the fact that, throughout the tangent cycles, multiple minima were encountered in the modified tangent minimization function only twice (Hauptman & Weeks, 1972). Although it is undoubtedly true that alternative methods of phasing this structure would have been ultimately successful, the merit of an approach which requires inspection of but a single Fourier map, in which nearly the entire structure was to be found among the strongest peaks, is obvious.

The two-dimensional reflections for which $|E|_{\text{obs}}$ is greater than 1.3 are presented in Table 3. A partial selection of the origin (Hauptman & Karle, 1956) was made by assigning phases to 610 and 7,12,0 because

Table 3. Two-dimensional reflections having $|E|_{\text{obs}} > 1.3$

The phases, in radians, are expressed relative to the origin and enantiomorph selection $\varphi_{610}=0$, $\varphi_{7,12,0}=\pi/2$, $\varphi_{0,12,1}=0$, and $\varphi_{0,15,4}=\pi/2$.

Ogg	E	Phase	Ogu	E	Phase	Oug	E	Phase	Ouu	E	Phase
0 16 2	3.02	0*	0 8 5	2.17	0*	0 15 4	3.47	$\pi/2^*$	0 23 3	2.67	$-\pi/2$
0 2 6	2.90	0*	0 26 3	2.12	π^*	0 1 6	2.42	$\pi/2^*$	0 7 3	2.19	$-\pi/2^*$
0 18 2	2.55	π^*	0 12 1	2.11	0*	0 25 2	2.38	$-\pi/2$	0 11 1	1.93	$-\pi/2$
0 14 4	2.11	0*	0 4 3	2.08	π^*	0 19 2	2.10	$\pi/2^*$	0 13 5	1.76	$-\pi/2$
0 16 4	1.77	π^*	0 8 7	2.03	π^*	0 3 6	2.00	$-\pi/2^*$	0 11 5	1.71	$-\pi/2$
0 4 6	1.42	π^*	0 22 1	1.94	0*	0 1 4	1.90	$-\pi/2$	0 23 5	1.68	$-\pi/2^*$
0 24 2	1.41	0	0 6 3	1.91	0*	0 17 2	1.71	$-\pi/2^*$	0 27 1	1.63	$-\pi/2$
0 12 2	1.39	0	0 10 7	1.60	0*	0 23 4	1.59	$\pi/2$	0 9 1	1.44	$\pi/2$
0 0 4	1.37	0	0 8 3	1.40	π^*	0 15 6	1.36	$\pi/2$	0 15 1	1.36	$-\pi/2$
			0 24 3	1.31	0*						
g0g	E	Phase	g0u	E	Phase	u0g	E	Phase	u0u	E	Phase
10 0 4	2.08	0	8 0 5	1.46	$-\pi/2$	1 0 4	1.56	0	5 0 7	2.39	$-\pi/2$
4 0 0	1.88	π^*	4 0 1	1.36	$-\pi/2$	1 0 6	1.50	0	1 0 1	2.24	$-\pi/2^*$
4 0 6	1.61	0				5 0 6	1.41	π	5 0 3	2.16	$-\pi/2$
8 0 0	1.44	0*				7 0 6	1.39	π	5 0 1	1.75	$\pi/2^*$
6 0 6	1.38	0							7 0 1	1.61	$-\pi/2^*$
0 0 4	1.37	0							9 0 1	1.55	$\pi/2$
4 0 2	1.33	π							3 0 3	1.53	$\pi/2$
gg0	E	Phase	gu0	E	Phase	ug0	E	Phase	uu0	E	Phase
4 6 0	2.18	π	8 11 0	4.25	π^*	7 12 0	3.48	$\pi/2^*$	1 11 0	2.60	$\pi/2^*$
2 10 0	1.98	π^*	6 1 0	4.05	0*	7 22 0	2.54	$\pi/2^*$	1 15 0	2.13	$-\pi/2$
6 10 0	1.92	0*	2 1 0	3.12	π^*	5 6 0	1.85	$\pi/2^*$	1 21 0	1.98	$\pi/2^*$
4 0 0	1.88	π^*	8 19 0	2.49	π	5 10 0	1.70	$\pi/2^*$	5 7 0	1.91	$\pi/2$
10 10 0	1.83	π^*	6 17 0	2.47	π^*	7 20 0	1.66	$-\pi/2^*$	1 13 0	1.79	$-\pi/2^*$
8 4 0	1.76	0	4 17 0	2.12	0*	7 4 0	1.65	$\pi/2$	7 17 0	1.49	$-\pi/2$
2 18 0	1.74	π	6 19 0	2.07	π	1 12 0	1.60	$\pi/2^*$	1 23 0	1.43	$-\pi/2^*$
2 8 0	1.68	0	8 9 0	1.73	0*	3 22 0	1.37	$-\pi/2$	3 1 0	1.37	$\pi/2$
6 20 0	1.62	π	6 21 0	1.68	0	9 10 0	1.36	$\pi/2$	5 21 0	1.33	$-\pi/2$
6 14 0	1.60	π	10 9 0	1.64	0	3 6 0	1.31	$-\pi/2$	11 9 0	1.31	$\pi/2$
6 12 0	1.55	π^*	4 21 0	1.54	π	5 24 0	1.30	$\pi/2$			
2 6 0	1.49	0	2 19 0	1.41	0						
10 12 0	1.47	0*	2 23 0	1.30	0						
8 0 0	1.44	0*									
4 20 0	1.41	π									
2 20 0	1.34	0									

* This phase was among the 49 phases input to the tangent formula.

examination of Table 3 and the list of Σ_2 triples revealed that not only did these reflections have large normalized structure factor magnitudes, but they also occurred in many triples which had large A values and well-determined cosines. Throughout the phasing procedure, new phases were not determined from single Σ_2 triples unless the triples passed certain restrictions placed on the values of their cosine seminvariants as calculated by the modified triple product and MDKS formulas. If A was greater than 3, both calculated cosine values were required to be greater than 0.5. If A was in the range 2–3, both calculated cosines were required to be greater than 0.75, and if A was in the range 1.5–2, both calculated cosines were required to be greater than unity. A *post mortem* analysis revealed

that, with such conservative acceptance criteria, no cosine was assigned an incorrect value, and the use of three of these cosines allowed the phases of 1,11,0, 1,13,0 and 5,10,0 to be related to the phases of the origin limiting reflections.

Although the phases of all $hk0$ reflections are fixed by the assignment of phases to 610 and 7,12,0, it was not possible, at this point, to determine any more of these phases solely on the basis of Σ_2 triples having well-calculated cosines. However, the pair relationships [$hk0$ analogs of equations (2.1) and (2.2)] did provide a means for finding the phases of several other important $hk0$ reflections, thereby eliminating the necessity of introducing the phases of any of these reflections as ambiguities. The pairings among the $uu0$ re-

Table 4. Σ_2 triples for large contributors (both $A > 1$) to some selected pairs

h_1		h_2		h_3		h_4		$A(134)$	cos (134)			$A(234)$	cos (234)			calc $ E_1 E_2 $		
									TPROD	TRUE		TPROD	TRUE		$^* \cos(\varphi_1 - \varphi_2)$			
1	11	0	1	13	0	1	1	1	2.14	0.69	0.99	1.48	0.67	0.99	-583			
						7	12	0	6	1	0	7.06	0.84	1.00	4.87	0.84	1.00	-9262
						1	12	0	2	1	0	2.50	0.81	1.00	1.73	0.81	1.00	-744
1	11	0	1	21	0	1	5	2	2.86	0.71	0.92	2.17	0.63	0.92	1133			
						1	17	3	0	6	3	2.95	0.76	0.93	1.62	1.05	0.93	-1223
						6	17	0	5	6	0	2.29	0.97	1.00	1.26	1.34	1.00	-674
						4	17	0	5	6	0	1.97	1.19	1.00	-464			
1	13	0	1	21	0	1	17	3	2.21	0.58	0.93	2.43	0.54	0.93	-1525			
						6	17	0	7	4	0	1.41	0.68	1.00	1.56	1.19	1.00	-484
1	13	0	1	23	0	1	5	2	1.66	0.76	0.92	1.32	0.93	0.92	767			
						1	1	1	0	22	1	1.49	0.78	0.99	1.08	1.31	0.99	-466
						7	22	0	6	1	0	3.92	1.03	1.00	2.83	1.29	1.00	-4558
						3	22	0	2	1	0	1.63	1.01	1.00	-422			
0	6	3	0	26	3	5	16	3	1.22	0.79	0.89	1.35	0.70	0.89	-285			
						0	16	4	0	10	7	1.05	1.77	1.00	1.16	1.38	1.00	-185
0	4	3	0	26	3	0	15	4	2.68	1.09	1.00	2.73	0.70	-1.00	-1631			
						8	15	3	8	11	0	2.04	0.55	-0.96	2.08	0.81	0.96	-409
						1	15	3	1	11	0	1.71	0.85	0.99	1.75	0.87	0.99	534
0	6	3	0	24	3	0	15	4	1.84	0.75	1.00	1.26	0.56	-1.00	-645			
						6	7	3	6	1	0	2.43	0.67	0.95	1.78	0.68	0.95	-1391
						0	7	3	0	1	6	1.95	1.14	1.00	1.43	0.43	-1.00	1002
0	17	2	0	19	2	2	18	2	2.07	0.70	0.82	2.54	0.47	0.82	-1437			
						6	18	2	6	1	0	2.42	0.75	0.99	2.96	0.60	0.99	-1893
						0	18	2	0	1	4	1.60	0.12	-1.00	1.97	0.78	1.00	785
0	16	2	0	18	2	2	17	2	2.28	0.66	0.71	1.92	0.78	0.71	-273			
						6	17	2	6	1	0	4.78	0.67	0.99	4.03	0.75	0.99	-2589
						6	17	0	6	1	2*	1.28	0.81	0.92	1.08	0.87	0.92	57
						0	17	2	0	1	4	1.90	0.53	1.00	1.60	0.12	-1.00	277
0	8	5	0	8	7	1	8	6	1.18	0.66	0.97	1.11	0.55	0.97	-131			
						5	8	6	5	0	1	1.69	0.89	0.76	1.58	0.60	0.76	-485
						0	1	6	0	9	1	1.46	0.86	-1.00	1.36	1.01	1.00	283
						0	3	6	0	11	1	1.61	1.17	-1.00	1.51	1.75	1.00	442
						0	4	6	0	12	1	1.26	1.43	1.00	1.18	1.31	1.00	-194
0	8	5	0	10	7	1	9	6	1.89	1.46	0.96	1.40	1.37	0.96	674			
						0	9	1	0	1	6	1.46	0.86	-1.00	1.07	0.56	-1.00	283
0	8	7	0	10	7	6	9	7	2.59	0.80	0.99	2.04	0.95	0.99	-1399			
						0	9	1	0	1	6	1.36	1.01	1.00	1.07	0.56	-1.00	283

* $|E_{612}| = 0.89 < 1.00$. See footnote in §2.

flections proved to be particularly useful. Fig. 1(a) shows that not only were the signs of all possible pairings among four of the reflections of this type strongly determined, but they were also all internally consistent. Since the phases of two of these reflections, 1,11,0 and 1,13,0, were already known, the symbol α was assigned the value $\pi/2$, and 1,21,0 and 1,23,0 could be added to the set of reflections with known phase. Reflection 560 was also strongly paired to the known 5,10,0, and knowledge of the value of its phase and of the two $uu0$ phases made seven additional phases accessible from the Σ_2 triples, resulting in a total number of 15 known $hk0$ phases. The contributors to the set of strongly paired $uu0$ reflections of 9α -fluorocortisol for which both of the related Σ_2 triples have A values greater than 1 are presented in Table 4, each entry in the last column of which is the contributor to (2.1) or (2.2) corresponding to the pair of triples in that row, and it can be verified that not only are all of these individual contributions internally consistent, but the predicted cosine seminvariants for the Σ_2 triples are all strongly indicated to be positive. In order that the phase assignments which were made for 1,21,0

and 1,23,0 be incorrect, the cosine seminvariants for several of the triples in this group would have to be negative, contrary to the entries in Table 4.

After the values of the phases for eight additional $hk0$ reflections were determined by means of calculated cosines, $\cos(\varphi_1 + \varphi_2 + \varphi_3)$, the third origin-specifying phase was assigned. Any reflection with l odd (Hauptman & Karle, 1956) would have served this purpose, but the 0,12,1 reflection was chosen because it was noticed that it would interact well with the $hk0$ phases which were already known. Four more phases could then be found, and they included the 0,22,1 phase which formed part of a set of paired Ogu reflections as shown in Table 4 and Fig. 1(b). Five of these Ogu reflections (0,10,7; 0,8,3; 0,8,5; 0,8,7; 0,24,3) were strongly inter-related and were immediately added to the set of reflections with known phase, but conflicts were encountered when three additional reflections (0,26,3; 0,6,3; 0,4,3) were considered. For this reason, phases were first found for three related Ogg reflections because one of these phases, 0,16,2, could be consistently obtained from three Σ_2 triples each of which was strongly indicated to have a cosine seminvariant equal to unity. After these Ogg phases had been found, the remainder of the Ogu reflections under consideration were accessible from triples, and their phases, relative to the remainder of the Ogu reflections were found to be as shown in Fig. 1(b). This resulted in contradiction of three of the Ogu pair averages [circled in Fig. 1(b)] of which the most serious violation involved the (0,4,3; 0,26,3) pair. However, the two largest contributors to the mildly discrepant (0,6,3; 0,26,3) pair disagreed with the overall sum, and the positive calculated cosines associated with these contributors, listed in Table 4, clearly gave the correct relationship between these phases. In addition to the three pair averages which are incorrect, two large contributors to the (0,4,3; 0,26,3) pair and a large contributor to each of the pairs (0,6,3; 0,24,3) and (0,6,3; 0,8,3) are wrong, and these contributors are also shown in Table 4. It can be seen that in each case that a cosine seminvariant should have been negative, the calculated value, although positive, was small, so that there was in fact some doubt that the indicated pair relationship (2.1) or (2.2) was valid. Furthermore, the evidence for the relative Ogu phases being as shown in Fig. 1(b) was quite strong, and any changes in these phases would have resulted in a greater number of violations.

It may be verified from a consideration of the rules for space group $P2_12_12_1$ given by Hauptman & Karle (1956) that, given the choice of origin-defining reflections used in this structure determination ($gu0$, $ug0$ and Ogu reflections were used), the enantiomorph can be chosen by selecting one of the two possible values for a phase of one of the following types: Oug , $u0g$, $g0u$, and Ouu [e.g. $\cos(\varphi_{gu0} + \varphi_{0ug}) = 0$]. Inspection of Table 3 reveals that 0,15,4 has the highest normalized structure factor amplitude of all the reflections in these four classes and, in addition, it interacted with many

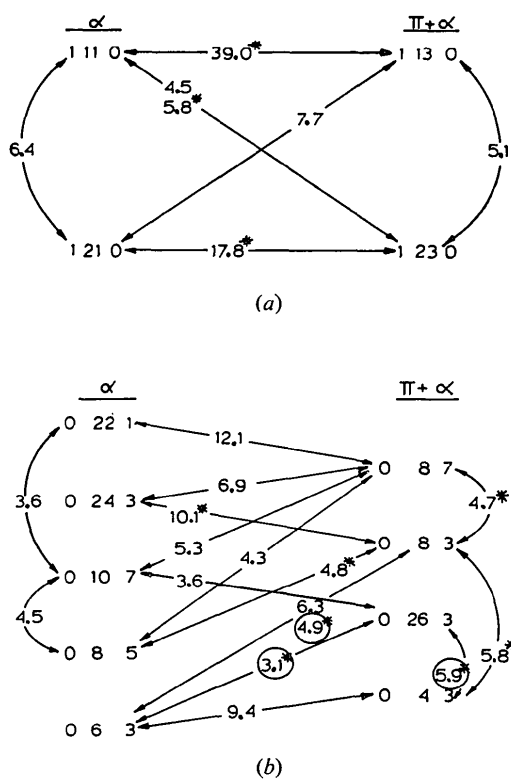


Fig. 1. Pairings among two groups of 9α -fluorocortisol reflections. Values of s [equation (2.3)] are indicated on the arrows, and an asterisk indicates that a pair relationship of Type II was used. In those cases where the pair formula gave the opposite relationship from the one shown, the s values are circled. (a) Pairings among the $uu0$ reflections. (b) Pairings among the Ogu reflections.

reflections whose phases were already known in triples having well-determined cosines. Consequently, the enantiomorph was fixed by assigning a value of $\pi/2$ to φ_{0154} , and the phases for an interrelated set of seven additional reflections were found from the Σ_2 triples, and thus the set of 49 two-dimensional reflections which were input to the tangent formula was completed.

Although the phases of reflections 0,11,1, 014, and 091 were not included among the 49 phases input to the tangent formula, consideration of the information concerning these phases which was available before tangent extension and refinement of the basis set is instructive because the Σ_2 triples involving these reflections had an interesting relationship to some of the pairs. During the phasing of 9 α -fluorocortisol, an attempt was made to determine phases for blocks of related reflections so that there would be internal checks on virtually all phase assignments. Since it was possible to obtain an adequate starting set without great difficulty, it was not necessary to include less reliable phases or phases which did not help to make other phases accessible. The two-dimensional triples involving 0,11,1, 014, and 091, which have $A > 1$ and $|E_h|, |E_k|, |E_{-h-k}| > 1.3$ are listed in Table 5. Although φ_{0111} could have been found from triple 2, the opposite indication was given for this phase by triple 1

if it were assumed that the cosine seminvariant for this triple has a value of unity. The values of 0.70 and 0.59, calculated for this cosine by the triple-product and MDKS formulas respectively, are only slightly less than the acceptance limit of 0.75 used for triples with A values in the range 2–3. Consequently, there was uncertainty as to the true phase for 0,11,1. Inspection of Table 5 reveals that two of the four triples involving 0,11,1 which have A values greater than 1.5, and which have known phases for the other two reflections, have negative cosines. Three triples with A values between 1.0 and 1.5 agree with triples 2 and 5 assuming that these triples with lower A values have cosine seminvariant values of unity. However, confusion arises because the negative cosines belong to two of the triples with higher A values, and neither formula gives a definitive negative indication for either of these cosines. Under such circumstances, consideration of the internal relationships among the triples may be helpful. Table 4 shows that triples 1 and 2 form a large contributor to the (043; 0,26,3) pair, and triples 4 and 5 form a contributor to the (085; 087) pair. In both cases, the accepted relationship between the paired reflections requires that the cosines for these particular contributors have opposite signs, and in both sets of contributing triples, the triple with a negative cosine had a lower cosine value as calculated by both

Table 5. Two-dimensional triples involving 0,11,1, 014 or 091 which have $A > 1$

Serial	h	k	-h-k	A	cos ($\varphi_h + \varphi_k + \varphi_{-h-k}$)		
					TPROD	MDKS	TRUE
1	0 11 1	0 $\overline{26}$ 3	0 15 $\overline{4}$	2.73*	0.70	0.59	-1
2	0 11 1	0 4 3	0 $\overline{15}$ $\overline{4}$	2.68*	1.09	1.77	1
3	0 11 1	0 $\overline{27}$ 1	0 16 $\overline{2}$	1.83	0.62	0.14	1
4	0 11 1	0 $\overline{8}$ 5	0 $\overline{3}$ $\overline{6}$	1.61*	1.17	0.90	-1
5	0 11 1	0 $\overline{3}$ 6	0 $\overline{8}$ 7	1.51*	1.75	1.29	1
6	0 11 1	0 $\overline{1}$ 6	0 $\overline{10}$ $\overline{7}$	1.44*	1.07	0.72	1
7	0 11 1	0 $\overline{17}$ 2	0 6 $\overline{3}$	1.22*	1.57	1.84	1
8	0 11 1	0 $\overline{19}$ 2	0 8 $\overline{3}$	1.09*	0.82	1.27	1
9	0 1 4	0 18 $\overline{2}$	0 $\overline{19}$ $\overline{2}$	1.97*	0.78	0.71	1
10	0 1 4	0 22 $\overline{1}$	0 $\overline{23}$ $\overline{3}$	1.90	0.41	-0.07	-1
11	0 1 4	0 16 $\overline{2}$	0 $\overline{17}$ $\overline{2}$	1.90*	0.52	0.01	1
12	0 1 4	0 7 3	0 $\overline{8}$ 7	1.63*	0.77	0.97	1
13	0 1 4	0 17 $\overline{2}$	0 $\overline{18}$ $\overline{2}$	1.60*	0.12	0.05	-1
14	0 1 4	0 $\overline{16}$ 2	0 15 $\overline{6}$	1.51	-0.01	-0.14	-1
15	0 1 4	0 12 1	0 $\overline{13}$ $\overline{5}$	1.36	1.11	1.29	1
16	0 1 4	0 $\overline{12}$ 1	0 11 $\overline{5}$	1.32	0.64	0.89	1
17	0 1 4	0 $\overline{27}$ $\overline{1}$	0 26 $\overline{3}$	1.26	0.23	-0.69	1
18	0 1 4	0 24 $\overline{2}$	0 $\overline{25}$ $\overline{2}$	1.23	0.58	0.35	1
19	0 1 4	0 22 1	0 $\overline{23}$ $\overline{5}$	1.20*	0.81	1.25	1
20	0 1 4	0 9 1	0 8 $\overline{5}$	1.14	0.87	1.28	1
21	0 9 1	0 6 3	0 $\overline{15}$ $\overline{4}$	1.84*	0.75	0.53	1
22	0 9 1	0 $\overline{16}$ 2	0 7 $\overline{3}$	1.84*	0.95	0.95	1
23	0 9 1	0 $\overline{23}$ 3	0 14 $\overline{4}$	1.57	0.51	0.09	-1
24	0 9 1	0 $\overline{8}$ 5	0 $\overline{1}$ $\overline{6}$	1.46*	0.86	0.27	-1
25	0 9 1	0 $\overline{11}$ 5	0 2 $\overline{6}$	1.37	0.99	0.35	-1
26	0 9 1	0 $\overline{1}$ 6	0 $\overline{8}$ 7	1.36*	1.01	0.47	1
27	0 9 1	0 $\overline{24}$ 3	0 15 $\overline{4}$	1.26*	0.56	0.32	-1
28	0 9 1	0 $\overline{27}$ 1	0 18 $\overline{2}$	1.15	0.81	1.89	1
29	0 9 1	0 $\overline{1}$ 4	0 $\overline{8}$ $\overline{5}$	1.14	0.87	1.28	1
30	0 9 1	0 7 3	0 $\overline{16}$ $\overline{4}$	1.08*	0.57	0.20	-1
31	0 9 1	0 1 6	0 $\overline{10}$ 7	1.07*	0.56	-0.45	-1
32	0 9 1	0 17 2	0 $\overline{26}$ $\overline{3}$	1.01*	-0.55	0.08	-1

* φ_k and φ_{-h-k} were both among the set of 49 two-dimensional phases input to the tangent formula.

formulas. However, despite the fact that it now seems apparent that the bulk of the evidence indicated that $\varphi_{0111} = -\pi/2$, hindsight is always clearer than foresight, and at the time the initial phases were derived, it did not seem as if it was necessary to introduce this phase when there was a chance that it might be wrong.

The relationship of the triples involving 014 to the pairs is relatively straightforward. The (0,17,2; 0,19,2) pair requires that the cosine seminvariants for triples 9 and 13 have opposite sign, and the (0,16,2; 0,18,2) pair places the same requirement on triples 11 and 13. Thus, triple 13 probably has a negative cosine since the conflicting contributors to both pairs would then be resolved, and this conclusion is also favored by the triple product and MDKS cosine seminvariant values. The pair relationships among the 091 triples are more complex and are summarized in Table 6. Here, as in the case of the 0,11,1 triples, the triples with cosine seminvariant values of unity do have higher calculated values from both formulas although the distinction is not definitive. Triples 24 and 31 constitute an example of the relatively infrequent type of pair contributor which gives a correct indication of the relationship among the paired phases because both cosine seminvariants are negative. Reflection 091 occurs in many more triples having negative cosines than predicted by probability theory when the A values are greater than unity. A few reflections of this type occasionally occur, but it is wise to verify the intensity of such a reflection since it might have been mis-measured. In this case, however, the amplitude of the 091 reflection had been, in fact, correctly measured.

Table 6. Relationships among the cosine seminvariants for triples involving 091 as indicated by pairs

Triple 1	Triple 2	$\cos_1 \cdot \cos_2$	Paired reflections
24	26	-1	0,8,5; 0,8,7
24	29	-1	0,1,4; 0,1,6
24	31	+1	0,8,5; 0,10,7
26	31	-1	0,8,7; 0,10,7

4. Conclusion

The procedures used to determine an initial set of 49 phases for the structure of 9 α -fluorocortisol have been described in detail, and the role in phase determination played by the cosines of those structure seminvariants, $\varphi_1 + \varphi_2$, which are linear combinations of two phases, has been emphasized. These cosines were computed by the recently derived pair formulas

(Hauptman, 1972*b*), and these formulas, like the Σ_1 formulas, may provide a means for finding the phases of one or more reflections which occur in blocks which cannot be related to the origin and enantiomorph fixing reflections by Σ_2 type relationships alone. In this way, the need for some of the ambiguities which are deliberately introduced in the multiple solution approach to direct methods may be avoided, and in the case of 9 α -fluorocortisol no ambiguities were necessary.

The mechanics of the use of the pair formulas have been illustrated, and the relationship of these formulas to the coincidence method of Grant, Howells & Rogers (1957) and to certain Σ_2 triples has been demonstrated. Examination of the values computed by the modified triple-product and MDKS formulas for the cosine seminvariants, $\cos(\varphi_1 + \varphi_2 + \varphi_3)$, of Σ_2 triples in these related groups may help to detect cases when the phase relationships indicated by the pair formulas are incorrect.

The authors are grateful to Dr W. L. Duax for many helpful discussions concerning the application of the pair formulas. This research was supported in part by U.S.P.H. Grant No. CA 10906.

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