Thus, a synthesis with the left hand side of equation (29) as Fourier coefficients yields just the heavy atom Patterson vectors.

Equation (29) has been used for determining the heavy atom positions in the various dyed derivatives of ribonuclease with good results. The maps thus obtained by combining the isomorphous derivative and anomalous scattering information were found to give larger peak to background ratio than the maps obtained by using either of the data separately. It is to be expected that this improvement will be more marked when maps of derivatives containing more than two or three heavy atom replacements are studied at low resolution. The details of the results obtained in the different derivatives of ribonuclease will be published shortly.

The authors are grateful to Prof. David Harker for the many stimulating discussions they had with him and his keen interest in this study. We are thankful to Drs D. R. Harris and H. H. Mills and Miss Elaine De Jarnette for help in collecting and processing the data which were used in testing some of the above methods. The investigation was supported in part by the Public Health Service Research Career Development Program Award GM-K3-16737 from the National Institutes of Health to one of us (G. K.) and research grants NIH-A-3942, NSF-GB-429 and the Dean Langmuir Foundation.

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Combination of Multiple Isomorphous Replacement and Anomalous Dispersion Data for Protein Structure Determination
II. Correlation of the Heavy-Atom Positions in Different Isomorphous Protein Crystals

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As a first step in applying the multiple isomorphous series method for protein structure determination, one has to determine the positions occupied by the heavy atoms in the various heavy atom dyed crystals. Usually this part of the analysis proceeds in two steps. First, the relative arrangement of the heavy atoms in a single derivative is established from vector maps and the second step correlates these different configurations with respect to a common origin. It was shown in part I how combination of isomorphous replacement and anomalous scattering data gives very valuable information for the solution of the first stage of the analysis. In this paper we show how similar methods can be used for establishing the positions of the heavy atoms in the different heavy atom derivatives with respect to the same origin.

Introduction

In the preceding article (part I. Kartha & Parthasarathy, 1964) we have discussed a method for combining multiple isomorphous replacement and anomalous dispersion data for determining the heavy atom positions in protein derivatives. The next problem is to relate the positions of the heavy atoms in the different derivatives to a common origin. This problem of correlating the positions of the heavy atoms in various derivatives becomes serious in certain space groups; for example $P2_1$ or $P4$, where the origin of reference is not fixed by symmetry alone, but can be taken anywhere along the symmetry axis. In these cases, in order to draw the phase circles with correct orientations, we have to refer the coordinates of the heavy atoms in all the derivatives to a common origin. Various methods have been suggested for doing this (Harker, 1956; Bragg, 1958; Perutz, 1956; Blow, 1958; Rossmann, 1960), of which Rossmann's method has been particularly successful. He uses as Fourier coefficients $(|F_{PH1}|-|F_{PH2}|)^2$, where the subscripts 1 and

2 refer to the two heavy atom derivatives*. Another Fourier method has been used (Kartha, 1962) and some of the results obtained in this way have been outlined by Kartha, Bello, Harker & De Jarnette (1963). This is also a Fourier method, but uses as coefficients the quantities $(\Delta|F|_{\text{iso}})_1 \,.\, (\Delta|F|_{\text{iso}})_2$. This same function was also recently suggested by Steinrauf (1963).

All the methods indicated above use only the data from multiple isomorphous replacement. It is also possible to use anomalous dispersion data for correlating the positions of the heavy atoms. When either kind of data is used alone, not only the desired correlation peaks, but also a lot of undesirable background features, are present. By a proper combination of the isomorphous and anomalous dispersion data, it is possible, as shown below, to eliminate almost all the background. In addition, it is also possible to obtain the correlation of the heavy atom vectors in their absolute configuration.

Correlation function (iso-correlation function)

There are two main correlation functions, one due to Rossmann and another due to Kartha, both of which use the isomorphous data to obtain the correlation between the heavy atom positions of the different protein derivatives. In Rossmann's function, in addition to the desired correlation vectors $\pm(\mathbf{r}_{H1}-\mathbf{r}_{H2})$ which appear as holes (*i.e.*, negative peaks), we get also large positive peaks corresponding to the self Pattersons of the heavy atoms in the two derivatives. We shall show that the latter correlation function, which uses the Fourier coefficients $(\Delta|F|_{\text{iso}})_1 \,.\, (\Delta|F|_{\text{iso}})_2$, gives a map which is much simpler to interpret than that of Rossmann.

Denoting the two heavy atom derivatives by 1 and 2, we have from equation (4) of part I

$$(\Delta|F|_{\text{iso}})_1=|F_{H1}|\cos(\alpha_{PH1}-\alpha_{H1}) \tag{1}$$

$$(\Delta|F|_{\text{iso}})_2=|F_{H2}|\cos(\alpha_{PH2}-\alpha_{H2})\,. \tag{2}$$

Then

$$\begin{aligned}&(\Delta|F|_{\text{iso}})_1 \,.\, (\Delta|F|_{\text{iso}})_2\\&\quad=|F_{H1}|\,|F_{H2}|\cos(\alpha_{PH1}-\alpha_{H1})\cos(\alpha_{PH2}-\alpha_{H2}).\end{aligned}$$

Expressing the cosines in the above relation in terms of exponentials, we have

$$\begin{aligned}(\Delta|F|_{\text{iso}})_1 \,.\, (\Delta|F|_{\text{iso}})_2&=\tfrac{1}{4}|F_{H1}|\,|F_{H2}|\\&\times\{\exp[i(\alpha_{PH1}-\alpha_{H1})]+\exp[-i(\alpha_{PH1}-\alpha_{H1})]\}\\&\times\{\exp[i(\alpha_{PH2}-\alpha_{H2})]+\exp[-i(\alpha_{PH2}-\alpha_{H2})]\}\\&=\tfrac{1}{4}F_{H1}F^*_{H2}\exp[-i(\alpha_{PH1}-\alpha_{PH2})]\\&+\tfrac{1}{4}F^*_{H1}F_{H2}\exp[i(\alpha_{PH1}-\alpha_{PH2})]\\&+\tfrac{1}{4}F_{H1}F_{H2}\exp[-i(\alpha_{PH1}+\alpha_{PH2})]\\&+\tfrac{1}{4}F^*_{H1}F^*_{H2}\exp[i(\alpha_{PH1}+\alpha_{PH2})]\,.\end{aligned} \tag{3}$$

To a good approximation, for a majority of reflections, one can write $\alpha_{PH1}\simeq\alpha_{PH2}\simeq\alpha_P$. This assumption may not hold in cases when F_{H1} and F_{H2} are opposite to each other and normal to F_P. Luckily, however, precisely in these cases, the differences $(\Delta|F|_{\text{iso}})_1$ and $(\Delta|F|_{\text{iso}})_2$ would be small, and the corresponding term in the Fourier series would, in any case, be small. Under these assumptions, equation (3) reduces to the following:

$$\begin{aligned}(\Delta|F|_{\text{iso}})_1 \,.\, (\Delta|F|_{\text{iso}})_2&=\underset{\text{(I)}}{\tfrac{1}{4}F_{H1}F^*_{H2}}+\underset{\text{(II)}}{\tfrac{1}{4}F^*_{H1}F_{H2}}\\&+\underset{\text{(III)}}{\tfrac{1}{4}F_{H1}F_{H2}\exp(-2i\alpha_P)}+\underset{\text{(IV)}}{\tfrac{1}{4}F^*_{H1}F^*_{H2}\exp(2i\alpha_P)}\,.\end{aligned} \tag{4}$$

In equation (4), *the first term* (I) *gives the vectors from derivatives* 1 *to* 2, *i.e.* peaks of strength $f_{H1}f_{H2}$ occur at positions $(\mathbf{r}_{H1}-\mathbf{r}_{H2})$. *The second term* (II) *contributes exactly the centrosymmetrical mate peaks* of (I) at positions $-(\mathbf{r}_{H1}-\mathbf{r}_{H2})$. Thus, the first two terms supply the wanted information. The (III) and (IV) terms essentially contribute to the background. These background terms are similar to those occurring in the Fourier map using the coefficients $(\Delta|F|_{\text{iso}})^2$. (See under *Heavy atom vector map from the isomorphous data*, in part I). We shall presently show that the background is eliminated by suitably combining isomorphous and anomalous dispersion data.

Correlation function from anomalous dispersion data (ano-correlation function)

Let us denote by $(\Delta|F|_{\text{ano}})_1$ and $(\Delta|F|_{\text{ano}})_2$ the difference $(|F(+)|-|F(-)|)\,(f'/2f'')$ for the two derivatives, respectively. Then, from equation (26) of part I, we have

$$(\Delta|F|_{\text{ano}})_1=|F_{H1}|\sin(\alpha_{PH1}-\alpha_{H1}) \tag{5}$$

$$(\Delta|F|_{\text{ano}})_2=|F_{H2}|\sin(\alpha_{PH2}-\alpha_{H2})\,. \tag{6}$$

From a comparison of equations (1), (2), (5), (6) and (4), it is clear that a Fourier synthesis with coefficients $(\Delta|F|_{\text{ano}})_1 \,.\, (\Delta|F|_{\text{ano}})_2$ should give peaks at $\pm(\mathbf{r}_{H1}-\mathbf{r}_{H2})$, closely analogous to the synthesis with coefficients $(\Delta|F|_{\text{iso}})_1 \,.\, (\Delta|F|_{\text{iso}})_2$. Following the method used in the preceding section, we have

$$\begin{aligned}(\Delta|F|_{\text{ano}})_1\,(\Delta|F|_{\text{ano}})_2&=\underset{\text{(I)}}{\tfrac{1}{4}F_{H1}F^*_{H2}}+\underset{\text{(II)}}{\tfrac{1}{4}F^*_{H1}F_{H2}}\\&+\underset{\text{(III)}}{\tfrac{1}{4}F_{H1}F_{H2}\exp(-2i\alpha_P)}-\underset{\text{(IV)}}{\tfrac{1}{4}F^*_{H1}F^*_{H2}\exp(2i\alpha_P)}\,.\end{aligned} \tag{7}$$

As in the interpretation of equation (4), *the first two terms* (I) *and* (II) *give the correlation vector* $(\mathbf{r}_{H1}-\mathbf{r}_{H2})$ *and its centrosymmetrical mate*. The (III) and (IV) terms essentially contribute to the background. Note, however, that the (III) and (IV) terms in equations (4) and (7) have opposite signs. Consequently, adding equations (4) and (7), we have

$$\begin{aligned}(\Delta|F|_{\text{iso}})_1\,(\Delta|F|_{\text{iso}})_2+(\Delta|F|_{\text{ano}})_1\,(\Delta|F|_{\text{ano}})_2\\=\tfrac{1}{2}F_{H1}F^*_{H2}+\tfrac{1}{2}F^*_{H1}F_{H2}\,.\end{aligned} \tag{8}$$

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* We shall follow the definitions used in part I.

Thus, *a synthesis with the coefficients on the right hand side of equation* (8) *should give only the correlation vectors.*

It is, however, important to emphasize at this point that the assumption $\alpha_{PH1}\simeq\alpha_{PH2}\simeq\alpha_P$ is less justifiable in the anomalous dispersion correlation function than in the isomorphous case. For a comparison of equations (4) and (7) and the underlying assumptions used in deriving them reveals that, in using the isomorphous data, the error due to the assumptions is small for larger terms in the Fourier coefficient and in the anomalous dispersion case (equation (7)) the error is large for larger terms. Since the assumption $\alpha_{PH1}\simeq\alpha_{PH2}\simeq\alpha_P$ is more nearly true for larger terms in the isomorphous correlation function and only for smaller terms in the anomalous correlation function, one would expect a better result with the former function.

Isomorphous-anomalous dispersion correlation function (iso-ano correlation function)

It is possible to combine the $\Delta|F|_{\rm iso}$ and $\Delta|F|_{\rm ano}$ in another way which removes, in addition to the background, the mate peaks as well. We know that

$$\Delta|F|_{\rm iso}=|F_H|\cos(\alpha_{PH}-\alpha_H)$$
$$\Delta|F|_{\rm ano}=|F_H|\sin(\alpha_{PH}-\alpha_H)\,.$$

Consequently,

$$(\Delta|F|_{\rm iso}+i\Delta|F|_{\rm ano})=|F_H|\{\cos(\alpha_{PH}-\alpha_H)+i\sin(\alpha_{PH}-\alpha_H)\}=F_H^*\exp i\alpha_{PH}\,. \tag{9}$$

Similarly,

$$(\Delta|F|_{\rm iso}-i\Delta|F|_{\rm ano})=F_H\exp(-i\alpha_{PH})\,. \tag{10}$$

Equations (9) and (10) immediately suggest a correlation map between two derivatives 1 and 2 based on the coefficients

$$(\Delta|F|_{\rm iso}+i\Delta|F|_{\rm ano})_1=F_{H1}^*\exp(i\alpha_{PH1})$$

and

$$(\Delta|F|_{\rm iso}-i\Delta|F|_{\rm ano})_2=F_{H2}\exp(-i\alpha_{PH2})\,.$$

Multiplying the above two equations and approximating $\alpha_{PH1}=\alpha_{PH2}$, we have

$$(\Delta|F|_{\rm iso}+i\Delta|F|_{\rm ano})_1\times(\Delta|F|_{\rm iso}-i\Delta|F|_{\rm ano})_2=F_{H1}^*F_{H2}\,. \tag{11}$$

It is obvious from equation (11) *that a map with coefficients, as in the left hand side of equation* (11), *should give peaks at the ends of the vectors* ($\mathbf{r}_{H2}-\mathbf{r}_{H1}$), *but not the inverse peaks.* Consequently, not only the correlation vectors, but also their absolute configuration is determined. A similar map giving peaks at ($\mathbf{r}_{H1}-\mathbf{r}_{H2}$) can be obtained by using as coefficients

$$(\Delta|F|_{\rm iso}-i\Delta|F|_{\rm ano})_1\times(\Delta|F|_{\rm iso}+i\Delta|F|_{\rm ano})_2=F_{H1}F_{H2}^*\,. \tag{12}$$

It is important to note that in preparing coefficients for the above mentioned maps, care should be taken to index the reflections properly. The general procedure for indexing the reflections when anomalous despersion is present has been discussed (Peerdeman & Bijvoet, 1956) and it is not likely to be much of a problem, especially when diffractometers are used for intensity collection. If the same coordinate system is not used for indexing the reflections in the two derivatives, say the coordinate system used for the second derivative has been reversed, as compared with the first one, then $(\Delta|F|_{\rm ano})_2$ would change sign. Consequently, equation (11) reduces to

$$(\Delta|F|_{\rm iso}+i\Delta|F|_{\rm ano})_1\times(\Delta|F|_{\rm iso}+i\Delta|F|_{\rm ano})_2=F_{H1}^*F_{H2}^*\exp\{i(\alpha_{PH1}+\alpha_{PH2})\}\,. \tag{13}$$

Thus, the right hand side in equation (13) is similar to one of the background terms appearing in equations (4) or (7) and does not lead to any strong correlation peaks. Thus, the appearance of strong peaks in the iso-ano correlation function is also a good check of consistency in the indexing procedures.

In computing the iso-ano correlation maps combining $\Delta|F|_{\rm iso}$ and $\Delta|F|_{\rm ano}$ as described above, it should be remembered that the symmetry of these maps is not the usual diffraction symmetry involving the center of inversion, but the actual intensity symmetry taking into account the Bijvoet inequalities (Ramachandran & Parthasarathy, 1963 *a,b*). In other words, whereas the correlation function of Rossmann (1960) or Kartha (1962) for a given space group (say $P2_1$) wuold have diffraction symmetry corresponding to the Laue group (namely $P2/m$), the iso-ano correlation function would have intensity symmetry ($P2$), because it includes the effects of anomalous dispersion.

Origin correlation function

If the relative configuration of the heavy atoms in either of the two derivatives is known, then the heavy atom positions in the other can be obtained by deconvolution of the correlation map, obtained by using the left hand side of equation (11) as coefficients. In cases where both the configurations are completely established and the only unknown parameter is the vector $\mathbf{R}_{12}$ relating the origin of derivative 2 with respect to that of 1, then this single parameter can be obtained more directly by the following procedure. Referring all coordinates to the origin of derivative 1, we have

$$\mathbf{r}_{H2}=\mathbf{R}_{12}+\mathbf{r}_{H'2}$$
$$F_{H1}^*=|F_{H1}|\exp(-i\alpha_{H1})\,,$$
$$F_{H2}=|F_{H2}|\exp(i\alpha_{H'2})\times\exp(i\,\mathbf{R}_{12}\,.\,\mathbf{S})$$

where the primes over H in $\alpha_{H'2}$ and $\mathbf{r}_{H'2}$ indicate that these are referred to the origin of 2,

$$\exp(i\,\mathbf{R}_{12}\,.\,\mathbf{S})=\frac{(\Delta|F|_{\rm iso}+i\Delta|F|_{\rm ano})_1\times(\Delta|F|_{\rm iso}-i\Delta|F|_{\rm ano})_2}{|F_{H1}|\exp(-i\alpha_{H1})\times|F_{H2}|\exp(-i\alpha_{H'2})}\,. \tag{14}$$

Now, the numerator of the right hand side contains only quantities that can be measured and all the terms in the denominator can be computed from the known heavy atom configurations $\mathbf{r}_{H1}$ and $\mathbf{r}_{H'2}$. It is easily seen that a Fourier map computed with the right hand side of equation (14) as coefficients would give rise to a single positive peak at the end of the vector $\mathbf{R}_{12}$ relating the origins. However, to reduce the effect of large uncertain terms introduced when the heavy atom contribution of either one or the other of the configurations becomes too small, suitable weighting of the coefficients is necessary.

Comparison of the different correlation functions

Let us denote by $H1$ and $H2$ the number of heavy atoms in derivatives 1 and 2, respectively. The results of the various correlation functions are summarized in Table 1. It is seen from the Table that the combination of isomorphous derivative and anomalous scattering data tend to give a correlation map which has in general less unwanted background than one gets when either of them is used alone.

We have outlined, in the previous sections and in part I, methods for determining and correlating the heavy atom sites in the protein derivatives. The first stage in the study of proteins by the X-ray diffraction method, where various heavy atom derivatives are examined for selecting suitable derivatives for complete data collection, is likely to be a slow and time-consuming process. We have shown that, even though the information regarding the positions of the heavy atom is contained in either the isomorphous or anomalous differences alone, proper combination of these leads to more unambiguous results. This is particularly so because the undesirable features in the map obtained with the use of either of the differences alone are 'anticomplementary' and proper combination of the isomorphous and anomalous differences cancels out these undesirable features and results in cleaner maps.

The methods developed above have been applied in the study of the structure of ribonuclease in this laboratory, and the details will be published shortly. It is hoped that these methods will prove useful in similar studies.

The authors are grateful to Prof. David Harker for the many stimulating discussions they had with him and his keen interest in this study. We are thankful to Drs D. R. Harris, H. H. Mills and Miss Elaine DeJarnette for help in collecting and processing the data which were used in testing some of the above methods. The investigation was supported in part by the Public Health Service Research Career Development Program Award GM-K3-16737 from the National Institutes of Health to one of us (G. K.) and research grants NIH-A-3942, NSF-GB-429 and the Dean Langmuir Foundation.

Table 1. *Comparison of the correlation functions*

The subscripts $H1$ and $H2$ refer to the heavy atom positions in protein, and i and j are dummy indices.

Coefficient	Origin peak	Correlation vectors: Positions $(\mathbf{r}_{H2}-\mathbf{r}_{H1})$ Number $H1\ H2$	Centrosymmetric mate vectors: Positions $(\mathbf{r}_{H1}-\mathbf{r}_{H2})$ Number $H1\ H2$	Self Patterson of the heavy atoms: Positions $\pm(\mathbf{r}_{H1i}-\mathbf{r}_{H1j})$ and $\pm(\mathbf{r}_{H2i}-\mathbf{r}_{H2j})$ Number $H1\,(H1-1)$ and $H2\,(H2-1)$	Background	Symmetry
$(\lvert F_{H1}\rvert-\lvert F_{H2}\rvert)^2$	Present	Present (As negative peaks)	Present (As negative peaks)	Present	Present	Patterson
$(\Delta\lvert F\rvert_{\rm iso})_1\,.\,(\Delta\lvert F\rvert_{\rm iso})_2$	Absent	Present	Present	Absent	Present	Patterson
$(\Delta\lvert F\rvert_{\rm ano})_1\,.\,(\Delta\lvert F\rvert_{\rm ano})_2$	Absent	Present	Present	Absent	Present	Patterson
$(\Delta\lvert F\rvert_{\rm iso})_1\,.\,(\Delta\lvert F\rvert_{\rm iso})_2$ $+(\Delta\lvert F\rvert_{\rm ano})_1\,.\,(\Delta\lvert F\rvert_{\rm ano})_2$	Absent	Present	Present	Absent	Absent	Patterson
$(\Delta\lvert F\rvert_{\rm iso}+i\Delta\lvert F\rvert_{\rm ano})_1$ $\times(\Delta\lvert F\rvert_{\rm iso}-i\Delta\lvert F\rvert_{\rm ano})_2$	Absent	Present	Absent	Absent	Absent	Intensity symmetry including anomalous dispersion
Origin correlation function	Only a single positive peak at $\mathbf{R}_{12}$					

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Localisation des Atomes d'Hydrogène dans l'Acide Subérique $COOH(CH_2)_6COOH$

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The crystal structure of suberic acid has been determined, by three-dimensional X-ray crystallographic methods, to determine the positions of hydrogen atoms. Bond lengths and angles have been calculated and are consistent with the currently accepted values for aliphatic compounds. Suberic acid is monoclinic with space group $P2_1/c$ and cell dimensions $a=8\cdot98$, $b=5\cdot06$, $c=10\cdot12$ Å; $\beta=97°\ 50'$.

Introduction

Nous avons déjà déterminé la structure de l'acide subérique à l'aide de deux projections sur les plans (001) et (010) (Housty & Hospital, 1964). Il nous a paru souhaitable de reprendre ce travail, dans tout l'espace, pour en améliorer la précision et déterminer la position des atomes d'hydrogène.

Les paramètres de la maille sont: $a=8{,}98$, $b=5{,}06$, $c=10{,}12$ Å, $\beta=97°\ 50'$. Le groupe spatial est $P2_1/c$ avec $Z=2$.

Affinement de la structure

Nous avons commencé cet affinement en partant des positions atomiques déjà déterminées (Housty & Hospital, 1964).

Les premiers cycles d'affinement portant sur 435 reflexions ont permis de préciser les positions des atomes de carbone et d'oxygène, sans tenir compte des atomes d'hydrogène. On peut remarquer que les positions atomiques varient peu par rapport à celles trouvées à deux dimensions. Nous avons terminé cette première partie du calcul en appliquant à chaque atome un facteur d'agitation thermique isotrope; le facteur de reliabilité en fin d'affinement est $R=0{,}16$.

Localisation des atomes d'hydrogène

A partir de ce stade de l'affinement nous avons introduit dans le calcul les contributions des atomes d'hydrogène. Les positions de départ ont été déterminées en respectant les angles de valences tétraédriques du carbone.

Après quelques cycles d'affinement les positions des atomes d'hydrogène se stabilisent, nous obtenons alors $R=0{,}13$ (Tableau 1).

Tableau 1. *Paramètres des atomes*

	x/a	y/b	z/c
C(1)	0,0622	0,0917	0,0282
C(2)	0,1487	0,0035	0,1612
C(3)	0,2760	0,1879	0,2122
C(4)	0,3701	0,1009	0,3384
O(1)	0,3414	−0,0953	0,4016
O(2)	0,4840	0,2550	0,3801

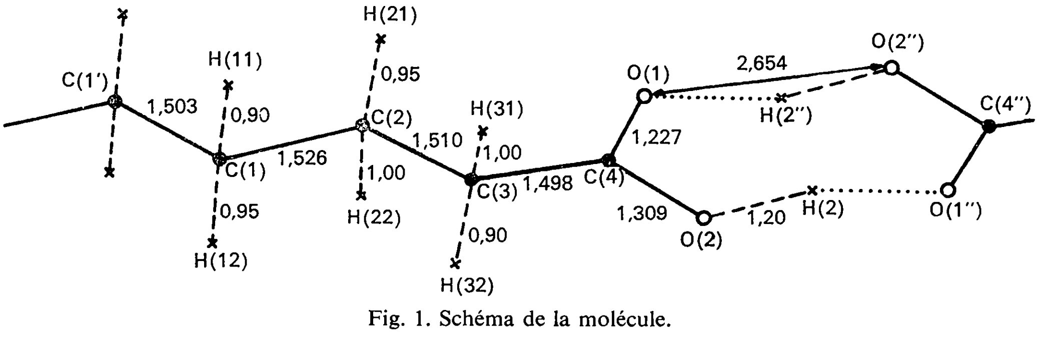

Fig. 1. Schéma de la molécule.