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Application of Fourier Synthesis Technique to Low-resolution Fibre Diffraction Data: Preliminary Study of Deoxyribonucleic Acid

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Three-dimensional Fourier syntheses for the orthorhombic *B* form of the crystalline lithium salt of deoxyribonucleic acid (DNA) have been calculated. Phases were calculated with the use of the DNA model derived earlier by molecular model-building combined with Fourier transform methods. The syntheses confirm the correctness of the model and show peaks in the region between DNA molecules. Some of these peaks may correspond to positions of water molecules.

Introduction

X-ray diffraction studies of deoxyribonucleic acid (DNA) (Wilkins, Gosling & Seeds, 1951; Wilkins, Stokes & Wilson, 1953; Franklin & Gosling, 1953*a*) indicated that the DNA molecule was helical and gave the main dimensions of the helix. Watson & Crick (1953; Crick & Watson, 1954) built a molecular model consisting of two helical polynucleotide chains joined together by hydrogen bonds between pairs of bases. Subsequent X-ray studies fairly firmly established the double-helical nature of DNA and the correctness of the Watson–Crick base-pairing. The chief obstacles in studying DNA by means of X-ray diffraction have been lack of single crystals and the restricted nature of the diffraction data available from fibre patterns. The amount of data has, however, been gradually increased as fibres of DNA, consisting of oriented microcrystals, with an increasing degree of crystalline perfection have become available (Wilkins, 1961*a*, *b*).

In the most extensive study so far made (Langridge, Wilson, Hooper, Wilkins & Hamilton, 1960; Langridge, Marvin, Seeds, Wilson, Hooper, Wilkins & Hamilton, 1960) a molecular model was built and the Fourier transform of the model compared with the X-ray intensities; the model was then adjusted until its transform correlated with the X-ray data cylindrically averaged about the fibre axis.‡ The patterns provided many three-dimensional data, and a preliminary three-dimensional study was then made by establishing that the correlation between calculated and observed intensities was also present when the distributions of intensities on layer planes were examined. Even so, in view of the great biological importance of DNA, it was desirable to extend this work, to obtain better X-ray data and to analyse the data more thoroughly (Wilkins 1961*a*, *b*). The need for this was apparent from recent suggestions (*e.g.* Donohue & Trueblood, 1960) that the arrangement of hydrogen bonds in base-pairs in DNA – the basis of molecular template formation by nucleic acids – might be different from that proposed by Watson & Crick. Fortunately we have been able to obtain improved X-ray diffraction photographs from microcrystalline fibres of the lithium salt of DNA (LiDNA). In these photographs the X-ray reflexions are sufficiently sharp to enable a considerable proportion of the reflexions to be separated and indexed on a three-dimensional lattice, and their intensities measured. As a result, a more thorough three-dimensional analysis of the X-ray data can be made, and the technique of three-dimensional Fourier synthesis, which is not normally applied to data from fibre diagrams, can be used to some advantage. The present paper describes preliminary studies of this kind. The work led to a Fourier-synthesis study of various base-pairing schemes for DNA (Arnott, Wilkins, Hamilton & Langridge, 1965).

The initial phases used in the Fourier-synthesis calculations are calculated using the molecular model we have previously derived (the amplitudes are given by the X-ray data). The Fourier syntheses so derived may provide two types of information – about refinement of the model itself and about those parts of the structure not included in the model. Because the data used do not resolve spacings less than 2·5 Å, atoms covalently linked cannot be seen separately. However, the shape and position of groups of atoms can be fairly accurately defined; *e.g.* the possibility exists of checking the correctness of the proposed arrangement of atoms in a base-pair and of eliminating alternatives (*e.g.* Hoogsteen, 1959) that are appreciably different. Also the Fourier-synthesis technique enables a search to be made for water molecules and ions in fixed positions between the DNA molecules.

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‡ For a similar study of the sodium salt of DNA see Fuller, Wilkins, Wilson & Hamilton (1965).

Techniques for analysing the X-ray data from DNA fibres

The lithium salt of deoxyribonucleic acid (LiDNA) crystallizes in an orthorhombic form at 66% relative humidity. X-ray diffraction data (Langridge, Wilson, Hooper, Wilkins & Hamilton, 1960) from this crystalline form have been used to derive a molecular structure for DNA by building molecular models and comparing the Fourier transform of the models with the X-ray intensities (Langridge, Marvin *et al.*, 1960). This Fourier transform method of structure analysis is useful in the initial stages of refining a trial structure but becomes increasingly difficult to apply as refinement progresses. It is therefore desirable to systematize the trial-and-error fitting of calculated data to that observed. A least-squares method of refining helical structures was considered by Langridge (1957),* and a method of Fourier synthesis applicable to helical structures was described by Klug, Crick & Wyckoff (1958). Either of these methods would probably be more efficient than the Fourier-transform method once a reasonably accurate model was obtained. But both these methods, in the form described, involve the restriction that all the diffracting material is considered as a regular helix. This is an advantage in so far as it is only necessary to consider a single residue of the helix during the refinement. However, it was decided not to use these methods of refinement, for some of the diffraction data indicate that the crystal structure is not entirely composed of tenfold helical material. For instance, the fourth and sixth layer lines show faint meridional reflexions: these could not appear if a tenfold helix were the only diffraction material present. Certain pairs of reflexions have intensity ratios that appear inconsistent with an entirely helical structure (Langridge, Marvin *et al.*, 1960). These effects are probably due to water molecules or salt ions being in non-helical positions in the unit cell. To try to find the positions of such non-DNA atoms it was desirable to use three-dimensional Fourier synthesis.

Nature of the X-ray data

DNA fibres consist of microcrystals oriented with one axis approximately parallel to the fibre axis but disoriented about the fibre axis. Reflexions from reciprocal lattice points with the same ξ value (distance from the fibre axis direction) and on the same layer plane overlap on the fibre pattern. The Lorentz factor causes the minimum observable intensity of reflexion on a layer line to increase in proportion to ξ. Factors causing this minimum intensity to increase with ϱ (distance from the origin in reciprocal space) are the spread of reflexions into arcs, due to lack of parallelism of the crystals in the fibre, and imperfection of the microcrystals themselves. As a result, most of the measurable DNA diffraction corresponds to spacings greater than 2·5 Å. New data extending beyond this range are now becoming available but have not been used in the present work (Wilkins, 1961*a*).

The diffraction data used in the present work include all spacings larger than 2·5 Å. Within this region of reciprocal space there are about 900 reciprocal lattice points. Intensities could be measured for 302 of these lattice points. Of these, 179 are observed as single reflexions or are partly resolved; the other 124 occur in groups of lattice points, seventy per cent of the groups consisting of two points only.

Intensity correction

Intensities were measured by taking a radial densitometer trace across the peak of each reflexion and measuring the areas under the traces (Langridge, Wilson *et al.*, 1960). This technique automatically corrected for oblique intersection of the incident beam with the film (Cox & Shaw, 1933) and for increase in specimen-to-film distance with diffraction angle. Corrections were applied to these measurements (Langridge, Wilson *et al.*, 1960). These corrections could not be applied to the observed meridional reflexions 004, 006, 0,0,10; for these reflexions a nominal ξ value equal to the half-width of the reflexion (measured in $Å^{-1}$ along the layer line) was used. The polarization factor correction was applied to the measured intensities.

Intensities of reflexions 004 and 006 were obtained by tilting the specimen at the Bragg angle for these reflexions. All other data were taken from specimens tilted at the Bragg angle for 0,0,10 as described before (Langridge, Wilson *et al.*, 1960).

The unit cell and space group

Lattice parameters were measured as described by Langridge, Wilson *et al.* (1960). The three axes were at right angles, the average unit-cell dimensions being $a=30·98$, $b=22·51$ and $c=33·76$ Å, the errors of measurement being about $\pm 0·1\%$. These dimensions, combined with density measurements, indicated that two DNA molecules pass through the unit cell (Langridge, Wilson *et al.*, 1960). The fact that the axes are mutually perpendicular suggests that the lattice may be orthorhombic, and the systematic absences $h00$, $0k0$, $00l$, when h, k, or $l=2n+1$ suggest that the space group is $P2_12_12_1$. Because the number of absences was insufficient to establish the space group with certainty, an attempt was made to check the assignment by studying Harker sections, but the results did not appear conclusive. Consideration of the symmetry of the DNA molecule confirms that the space group is $P2_12_12_1$: the

* Attempts to refine the *B* structure of DNA by a least-squares analysis (Arnott & Coulter, 1963), in which the base, sugar and phosphate parts of a nucleotide were treated as rigid groups with fixed stereochemistry, have shown that it is necessary to include stereochemical constraints corresponding to linking of the groups. This can be achieved by using Lagrange multipliers (Arnott & Wonacott, 1966).

fibre pattern of DNA (Langridge, Wilson *et al.*, 1960) strongly indicates that DNA molecules are tenfold helices, and, if they are helical, the only possible orthorhombic space group is $P2_12_12_1$.* Since the general position in $P2_12_12_1$ is fourfold, the helix axes of the DNA molecules coincide with screw axes of the unit cell. There are ten nucleotides in the asymmetric unit (one helix turn of one polynucleotide chain) the positions of the molecules being at $\frac{1}{4}, 0, z$; $\frac{3}{4}, \frac{1}{2}, \frac{1}{2}-z$, following the conventions of *International Tables for X-ray Crystallography* (1952).

In addition to the absences mentioned, there are absences for h, k, l, when $l=3n$ and $h+k=2n+1$. This means that the two molecules in the unit cell are identical except for a relative translation along the x, y and z directions of $a/2$, $b/2$ and $c/3$. Since the two molecules are related by screw diads, this is possible only if the helical molecule has a diad axis perpendicular to the helix axis [as suggested by Crick & Watson (1954)] and relating the two polynucleotide chains in the DNA molecule. This diad axis must be parallel to either the x or the y direction. Intensity data on various layer planes show that the diad is parallel to the b axis (Langridge, Marvin *et al.*, 1960). As we have said, consideration of absent reflexions alone indicates that the two molecules in the unit cell have a relative displacement of about $c/3$ in the z direction. An approximate treatment of observed intensities (Langridge, Wilson *et al.*, 1960) gave a value of $0{\cdot}328c$. A more precise determination was made using a Patterson method related to that of Giglio, Liquori & Ripamonti (1958). If two molecules are present in the unit cell in the same orientation, the Patterson map will show a high peak due to the intermolecular vectors; the position of this peak will be displaced owing to the effect of intramolecular vectors. However, if the Fourier transform and orientation of the molecules is known, the contribution of the intramolecular vectors to the map can be removed. Patterson coefficients have the form $F_0^2(hkl)/T^2(hkl)$ where $T(hkl)$ is the value of the Fourier transform of a single molecule. The value so determined for the relative translation was $0{\cdot}325c$.

A least-square analysis using 125 perfectly resolved reflexions (Arnott & Coulter, 1963) gave the value $(0{\cdot}328 \pm 0{\cdot}002)c$.

Preparation of data

A major problem is to decide how to make use of the measured intensities of diffraction arcs consisting of overlapping reflexions. In this work the total measured intensity of an arc was divided in the ratio of the squares of the calculated structure amplitudes of the model unit cell used for phasing. This method has the disadvantage that the data are weighted so that the synthesis tends to correspond to the model. Since the majority of the reflexions are at least partly resolved, these effects are probably not important. Moreover, the procedure is justifiable if one assumes that the model is substantially correct and one is interested in refining it: during successive cycles of refinement the ratio of unresolved intensities should converge to the true value. In contrast, if one wishes to confirm that the basic form of the model is correct, the observed data should not be weighted in a way depending on that form. To avoid such weighting the simplest method is to divide the total measured intensity of a reflexion equally between the reciprocal lattice points involved, allowance being made for interference between scattering from the two molecules in the unit cell. With the use of data in this form, Fourier F_o syntheses have been obtained and the correctness of the model confirmed.

When reflexions were not observed, their intensities were assumed to be half the value of the threshold for observation, when the calculated intensity was greater than the threshold. Intensities of unobserved reflexions were taken as zero when the calculated intensity was less than the threshold. Although this procedure is open to criticism, it has the advantage that a large number of terms for below-threshold intensities for reflexions at large ξ or ϱ were omitted from the calculations. It was found that omission of all below-threshold intensities had little effect on the resulting synthesis. Reflexions were put on an absolute scale by a method related to those of Wilson (1942) and Harker (1948).

Determination of phases

Phosphorus atoms are the heaviest atoms in the DNA structure; there are ten in the asymmetric unit. The simplicity of the helical arrangement simplifies the problem of locating the atoms by Patterson methods (Franklin & Gosling, 1953*b*, *c*). It might be supposed that a direct method for determining the structure of DNA without constructing molecular models could be developed as follows.

First, assume that the molecule is helical and find the position of the phosphate groups by two-dimensional Patterson analysis. Because the data have low resolution it will be legitimate to treat the phosphate group as a large atom at the phosphorus position. Second, calculate phases from the phosphate groups. Since these groups contain 20% of the electrons in the crystal, one might expect that a Fourier synthesis involving these phases would indicate the position of some of the non-phosphate parts of the structure. [In the study of vitamin B_{12} phases were obtained from the cobalt atoms which contained 14% of the electrons (Hodgkin, Kamper, Lindsey & MacKay, 1957)]. Third, include in the phase calculations the non-phosphate parts that appear in the synthesis, recalculate the synthesis with the new phases and repeat until the whole structure is derived.

We have found that a synthesis calculated with phases derived from the phosphate groups alone (the coordinates were taken from the model and not from a Patterson map) does show electron density in the

* For study of intensity statistics see Arnott (1965).

regions where one expects the bases to be. The difficulty is that the low resolution data do not give the positions of individual atoms; to proceed further and include non-phosphate atoms in the phase calculations, one needs to build large parts of the model, *e.g.* the base-pair, and place these in the positions indicated by the synthesis in order to obtain new atomic coordinates. The method is, therefore, dependent on molecular model building: having placed the base pair and phosphate group in the structure it is only a small step to connect the base and phosphate together by the deoxyribose ring and thereby complete the molecular model. Since construction of a model cannot be avoided we thought it best to rely on the straightforward procedure of building molecular models, adjusting them until they correlated with the X-ray data, and using the whole of the DNA model in our calculations of phases. The syntheses so obtained could give information of two kinds; they might indicate how the model requires to be refined, and they might show how the non-DNA parts of the structure are arranged.

When the whole contents of the unit cell were assumed to be helical, phases were undefined for 00*l* reflexions for $l \neq 10$, and these reflexions (of low intensity) were omitted from the calculations.

Refinement of the DNA model

Examples of F_o synthesis sections are shown in Fig. 1. Calculations were made with phases derived from the DNA model (no allowance being made for scattering from water) and atomic scattering factors according to Vand, Eiland & Pepinsky (1957). The maps give no clear indication that the model should be altered. Because covalently linked atoms were not resolved, and separate atomic peaks were not visible, it was difficult to make precise comparison between the model and the synthesis. Hence there is reason more than usual to expect $(F_o - F_c)$ syntheses (Fig. 2) to give clearer indication of errors in the model. In calculating these $(F_o - F_c)$ syntheses the scattering from the water in the structure was taken into account in the phase calculations by using special scattering factors for the atoms of the DNA. These scattering factors were derived on the assumption that the atoms of DNA are partly immersed in water which fills the regions between the DNA molecules and has uniform electron density (Langridge, Marvin *et al.*, 1960). The electron density in the $(F_o - F_c)$ syntheses is not as small as one would wish, but, provided the structure of DNA is a regular helix, no clear indication is given that the structure should be modified. There are some indications that the helical structure should be made irregular, but these indications are of doubtful significance. There are some quite large peaks on the syntheses; most of these peaks are close to positions of strongly scattering groups, *e.g.* phosphate groups, and may have been produced by use of incorrect scattering factors for the groups. These scattering factors might be in error as a result of parts of the molecule being in thermal motion or structurally disordered to a greater extent than other parts, or because the allowance for effects due to the aqueous environment of DNA was in error. There was a similar lack of indication that the DNA model required refining when an $(F_o - F_c)$ synthesis was calculated assuming that the space between DNA molecules was filled with water molecules in fixed positions (see next section).

Because the data have low resolution, the tetrahedral phosphate group appears roughly spherical and it is difficult to determine its orientation. The bases are planar and the sugar rings roughly so; as a result it is possible to confirm their orientations as well as positions.

The value of the Fourier transform of a single DNA molecule is low for spacings < 3 Å; hence diffraction effects in the F_o synthesis, due to the cut-off of terms, should not be large.

It should be noted that evidence for the correctness of the DNA model is, in the main, derived from the direct comparison of the F_o and F_c values. Use of Fourier syntheses has so far not led to refinement of the model and has given only slight improvement in agreement between F_o and F_c values – this being obtained as a result of the study, described below, of the arrangement of water molecules in the structure. The lack of obvious need for refinement of the model is the result of careful adjustment of the model, using the Fourier transform method, to give optimum agreement between F_o and F_c values before the Fourier synthesis method was used. In fact, the limit of refinement of the model possible with the data was probably attained. Consequently the correctness of the model and the validity of the Fourier procedure using phases derived from the model has not been established, as is usual in structure analysis, by refinement of the model and, during successive cycles of Fourier syntheses, convergence of the F_c values towards the F_o values.

Structure in the non-DNA regions

A search was made for structure in the region, containing water and ions, between DNA molecules. Since the data should resolve spacings of 2·5 Å, which is less than the average length of the hydrogen bonds in water, it might be possible to see oxygen atoms of water molecules placed at specific sites in the unit cell.

The $(F_o - F_c)$ synthesis illustrated in Fig. 2 showed many positive peaks in the region between DNA molecules. Most of these peaks were also visible in $(F_o - F_c)$ maps calculated with phases derived from DNA atoms alone (without assuming that water of uniform electron density filled the space between DNA molecules) and also in maps calculated with earlier and less accurate intensity data. There are a number of reasons for supposing that these peaks may represent actual positions of water molecules. All the main positive peaks are in the non-DNA part of the structure. The peaks tend to

be roughly spherical. The heights of peaks are often more than half the height obtained when an oxygen atom at the peak position is included in the phase calculation [For an acentric space group, a single atom omitted from phasing should appear with peak height of half its correct value (Luzzati, 1953).] Several of the peak heights were 2–3 times the value of the root mean square electron density of the $(F_o - F_c)$ synthesis and are therefore not very likely to be due to random error. However, the possibility cannot be excluded that the peaks might be due to errors in the intensity measurements or might arise from some undetermined source.

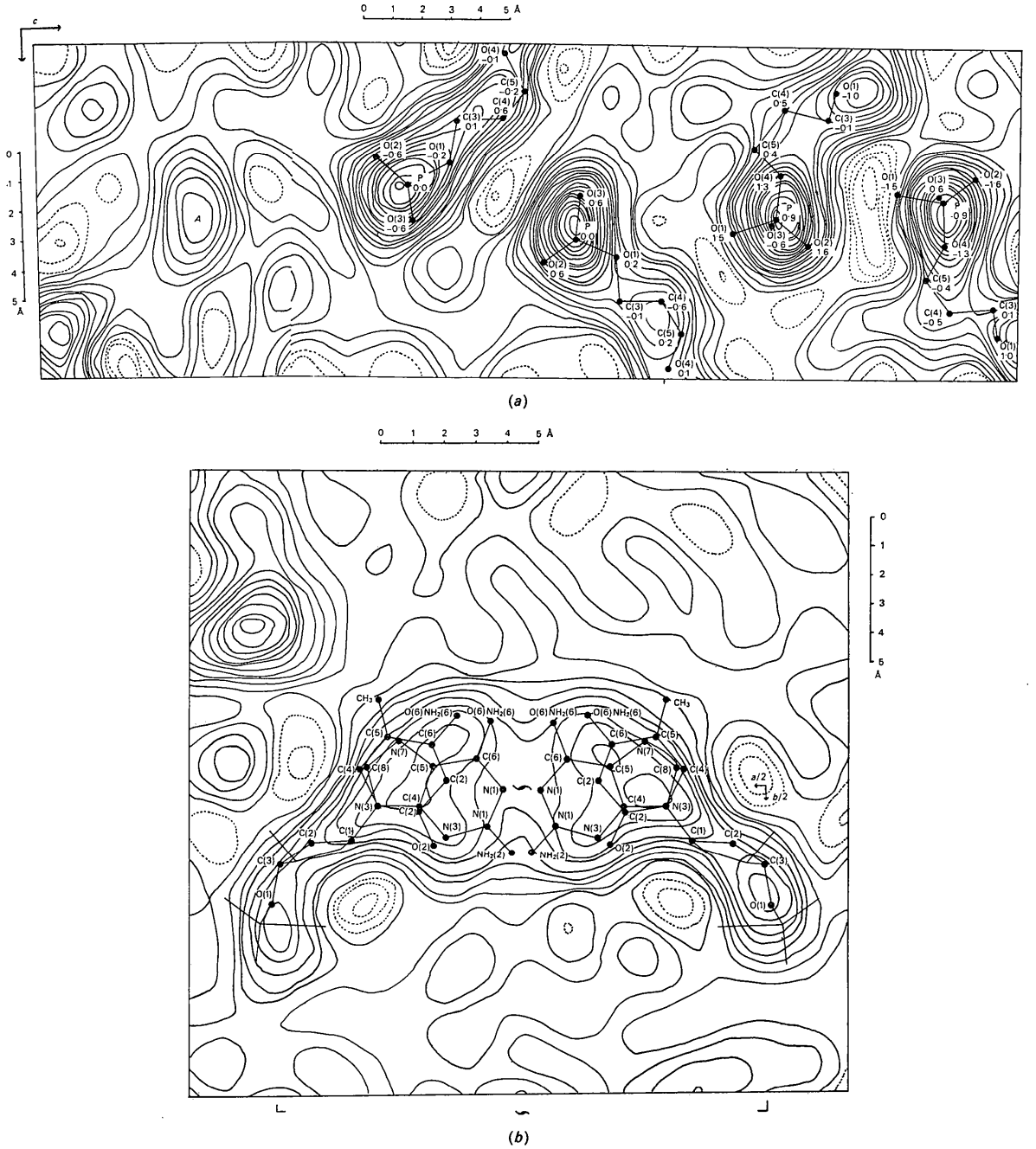

Fig. 1. Sections of F_o synthesis (phases were derived from DNA atoms only; reflexions below threshold were ignored). Positions of atoms in the DNA molecular model (numbered as in Langridge, Marwin *et al.*, 1960) that are close to the plane of the section are shown. (*a*) Section in the *bc* plane for $x=0$. The section passes through phosphate groups of two neighbouring DNA molecules. *A* is a particularly well defined peak in the region between DNA molecules. Contours are at intervals of 0·13 e.Å^{-3}. Dotted contours are negative. Distances of atoms from the plane are shown. (*b*) Section parallel to the *ab* plane for $z=1/60$. The section is very nearly in the plane of the hydrogen-bonded base-pair. The positions of atoms in the DNA model are shown. Contours are at intervals of 0·2 e.Å^{-3}.

Although we did not believe that all the peaks corresponded to positions of water molecules, we used the peaks as a guide in filling the space, between DNA molecules, with water molecules in stereochemically reasonable positions. We then used these positions in calculating phases from all atoms in the unit cell. We considered that Fourier syntheses calculated with these phases would be useful in studying the refinement of the DNA model and would complement the syntheses obtained assuming that the water in the unit cell formed regions of uniform electron density. It was found that both types of synthesis gave rather similar results regarding refinement of the model.

Positions for the water molecules were derived as follows. A three-dimensional (F_o-F_c) synthesis was calculated with the use of the DNA model alone for obtaining phases. Oxygen atoms of water molecules were inserted at positions of peaks with electron den-

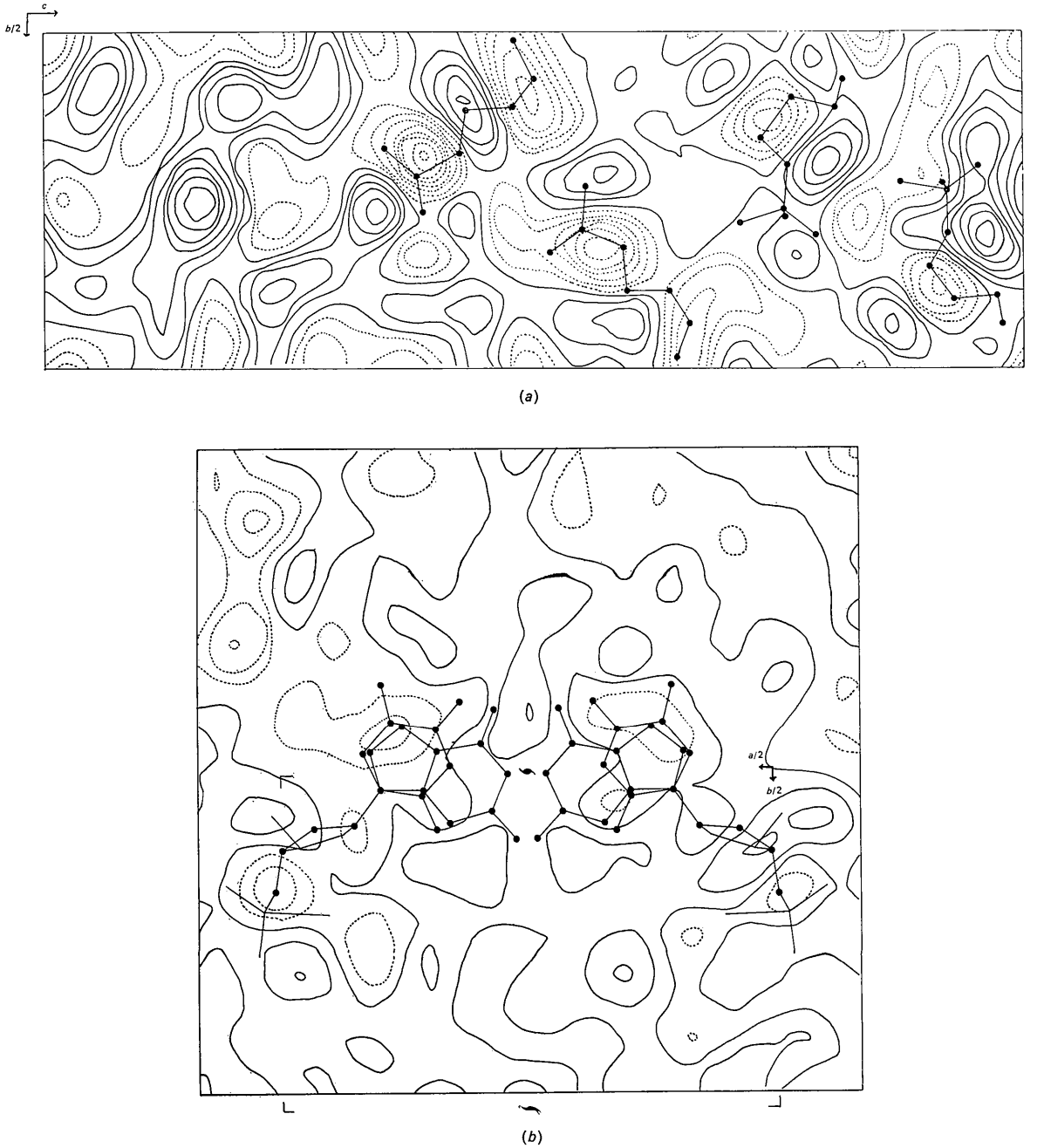

Fig. 2. (F_o-F_c) synthesis calculated assuming that water of uniform electron density fills the space between DNA molecules. Contour intervals correspond to 0·2 e.Å^{-3}; the average electron density in the non-DNA regions was set at approximately zero, dotted contours being negative. (*a*) Section in the same plane as in Fig. 1(*a*). (*b*) Section in the same plane as in Fig. 1(*b*).

sity greater than 0·5 e.Å^{-3}. (Structure factor calculations for atoms with a temperature factor of $B=4$ Å^2, with reflexions extending to 2·5 Å, gave peak heights as follows:

Carbon 1·0 e.Å^{-3}
Oxygen 1·6
Nitrogen 1·4
Phosphorus 2·8.)

Five cycles of (F_o-F_c) syntheses were then calculated. In each cycle, stereochemistry of the water positions was checked, so that chosen positions were not much closer than 2·5 Å to each other or to DNA atoms; the positions of water oxygen atoms were, where indicated, moved in the direction of increasing contour height on the (F_o-F_c) map; oxygen atoms were inserted where new peaks occurred, and atoms were removed from old positions if they were at the bottom of deep hollows on the (F_o-F_c) map. It was found desirable to apply a temperature factor of $B=8$ Å^2 to the scattering from oxygen atoms; this corresponds to a mean displacement of 0·3 Å in atomic position. In this way 75 water molecules were placed in the asymmetric unit; this is the number indicated by density and water content measurements.

When the structure factors were calculated by the approximate method, which allows for a uniform density of water between the DNA molecules by modifying the scattering factors of the DNA atoms, the R index was 0·29. With the 75 water molecules placed in fixed positions and normal scattering factors used for the DNA atoms, the value of R fell to 0·24. Because atoms had been placed in positions such that peaks in the (F_o-F_c) maps would be reduced, some reduction in R was inevitable, and therefore the reduction, in itself, may have little significance; it was hoped, however, that more adequate treatment of the water in the structure would enable one to see more clearly how to refine the DNA model. How to refine did not become much clearer, however. Presumably this meant that the accuracy of the DNA model was nearing the limit set by the low resolution and limited accuracy of the X-ray data; it also indicated that the approximate method of allowing for water in the structure was in the present case reasonably satisfactory.

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