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A PROPOSED STRUCTURE FOR THE NUCLEIC ACIDS

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The nucleic acids, as constituents of living organisms, are comparable in importance to the proteins. There is evidence that they are involved in the processes of cell division and growth, that they participate in the transmission of hereditary characters, and that they are important constituents of viruses. An understanding of the molecular structure of the nucleic acids should be of value in the effort to understand the fundamental phenomena of life.

We have now formulated a promising structure for the nucleic acids, by making use of the general principles of molecular structure and the available information about the nucleic acids themselves. The structure is not a vague one, but is precisely predicted; atomic coordinates for the principal atoms are given in table 1. This is the first precisely described structure for the nucleic acids that has been suggested by any investigator. The structure accounts for some of the features of the x-ray photographs; but detailed intensity calculations have not yet been made, and the structure cannot be considered to have been proved to be correct.

The Formulation of the Structure.—Only recently has reasonably complete information been gathered about the chemical nature of the nucleic acids. The nucleic acids are giant molecules, composed of complex units. Each unit consists of a phosphate ion, HPO_4^{--}, a sugar (ribose in the ribonucleic

acids, deoxyribose in the deoxyribonucleic acids), and a purine or pyrimidine side chain (adenine, guanine, thymine, cytosine, uracil, 5-methylcytosine). The purine or pyrimidine group is attached to carbon atom 1′ of the sugar, through the ring nitrogen atom 3 in the case of the pyrimidine nucleotides,[1] and the ring nitrogen atom 9 in the case of the purine nucleotides.[2] Good evidence has recently been obtained as to the nature of the linkage between the sugar and the phosphate, through the investigations of Todd and his collaborators;[3] it seems likely that the phosphate ester links involve carbon atoms 3′ and 5′ of the ribose or deoxyribose. New chemical evidence that the natural ribonucleosides have the β-D-ribofuranose configuration has also been reported by Todd and his collaborators,[4] and spectroscopic evidence indicating that the deoxyribonucleosides have the same configuration as the ribonucleosides has been obtained.[5] The β-D-ribofuranose configuration has been verified for cytidine by the determination of the structure of

TABLE 1

ATOMIC COORDINATES FOR NUCLEIC ACID

ATOM	ρ	φ	z	ATOM	ρ	φ	z
P	2.65 Å	0.0°	0.00 Å	O_1'	4.4 Å	45.4°	2.65 Å
O_I	2.00	28.3°	−0.67	O_2'	6.1	81.0°	2.1
O_{II}	2.00	−28.3°	0.67	N_3	6.7	52.8°	2.8
$O_{III} = O_5'$	3.72	13.5°	0.93	C_4	7.85	59.3°	2.8
$O_{IV} = O_3'$	3.72	−13.5°	−0.93	C_5	9.1	55.2°	2.8
C_5'	3.4	35.3°	0.7	C_6	9.35	46.9°	2.8
C_4'	3.2	51.6°	1.9	N_6	10.7	44.9°	2.8
C_3'	3.8	74.6°	1.55	N_1	8.45	39.9°	2.8
C_2'	5.3	70.3°	1.75	C_2	7.05	41.5°	2.8
C_1'	5.3	58.2°	2.8	O_2	6.35	32.4°	2.8

Identity distance along z axis = 27.2 Å.

Twenty-four atoms of each kind, with cylindrical coordinates (right-handed axes).

$\rho, \phi + n \cdot 105.0°, n \cdot 3.40 + z$; $\rho, \phi + n \cdot 105.0° + 120°, n \cdot 3.40 + z$; $\rho, \phi + n \cdot 105.0° + 240°, n \cdot 3.40 + z$; $n = 0, 1, 2, 3, 4, 5, 6, 7$.

the crystal by x-ray diffraction; cytidine is the only nucleoside for which a complete x-ray structure determination has been reported.[6]

X-ray photographs have been made of sodium thymonucleate and other preparations of the nucleic acids by Astbury and Bell.[7, 8] It has recently been reported by Wilkins, Gosling, and Seeds[9] that highly oriented fibers of sodium thymonucleate have been prepared, which give sharper x-ray photographs than those of Astbury and Bell. Our own preparations have given photographs somewhat inferior to those of Astbury and Bell. In the present work we have made use of data from our own photographs and from reproductions of the photographs of Astbury and Bell, especially those published by Astbury.[10] Astbury has pointed out that some information about the nature of the nucleic acid structure can be obtained from the x-ray photographs, but it has not been found possible to derive the structure from x-ray data alone.

A configuration of polypeptide chains in many proteins is the α helix.[11] In this structure the amino-acid residues are equivalent (except for differences in the side chains); there is only one type of relation between a residue and neighboring residues, one operation which converts a residue into a following residue. Through the continued application of this operation, a rotation-translation, the α helix is built up. It seems not unlikely that a single general operation is also involved in the construction of nucleic acids, polynucleotides, from their asymmetric fundamental units, the nucleotide residues. The general operation involved would be a rotation-reflection, and its application would lead to a helical structure. We assume, accordingly, that the structure to be formulated is a helix. The giant molecule would thus be cylindrical, with approximately circular cross section.

Some evidence in support of this assumption is provided by the electron micrographs of preparations of sodium thymonucleate described by Williams.[12] The preparation seen in the shadowed electron micrograph is clearly fibrous in nature. The small fibrils or molecules seem to be circular in cross-section, and their diameter is apparently constant; there is no evidence that the molecules are ribbon-like. The diameter as estimated from the length of the shadow is 15 or 20 Å. Similar electron micrographs, leading to the estimated molecular diameter 15 ± 5 Å, have been obtained by Kahler and Lloyd.[13] Also, estimates of the diameter of the molecules of native thymonucleic acid in the range 18 to 20 Å have been made[14, 15] on the basis of sedimentation velocity in the ultracentrifuge and other physicochemical data. The molecular weights reported are in the range 1 million to 4 million.

The x-ray photographs of sodium thymonucleate show a series of equatorial reflections compatible with a hexagonal lattice. The principal equatorial reflection, corresponding to the form 10·0, has spacing 16.2 Å or larger, the larger values corresponding to a higher degree of hydration of the substance. The minimum value,[7] 16.2 Å, corresponds to the molecular diameter 18.7 Å. From the average residue weight of sodium thymonucleate, about 330, and the density, about 1.62 g. cm.$^{-3}$, we calculate that the volume per residue is 338 Å.^{3} The cross-sectional area per residue is 303 Å^2; hence the length per residue along the fiber axis is about 1.12 Å.

The x-ray photographs show a very strong meridional reflection, with spacing about 3.40 Å. This reflection corresponds to a distance along the fiber axis equal to three times the distance per residue. Accordingly, the reflection is to be attributed to a unit consisting of three residues.

If the molecule of nucleic acid were a single helix, the reflection at 3.4 Å. would have to be attributed to a regularity in the purine-pyrimidine sequence, or to some other structural feature causing the three nucleotides in the structural unit to be different from one another. It seems unlikely

that there is a structural unit composed of three non-equivalent nucleotides.

The alternative explanation of the x-ray data is that the cylindrical molecule is formed of three chains, which are coiled about one another. The structure that we propose is a three-chain structure, each chain being a helix with fundamental translation equal to 3.4 Å, and the three chains being related to one another (except for differences in the nitrogen bases) by the operations of a threefold axis.

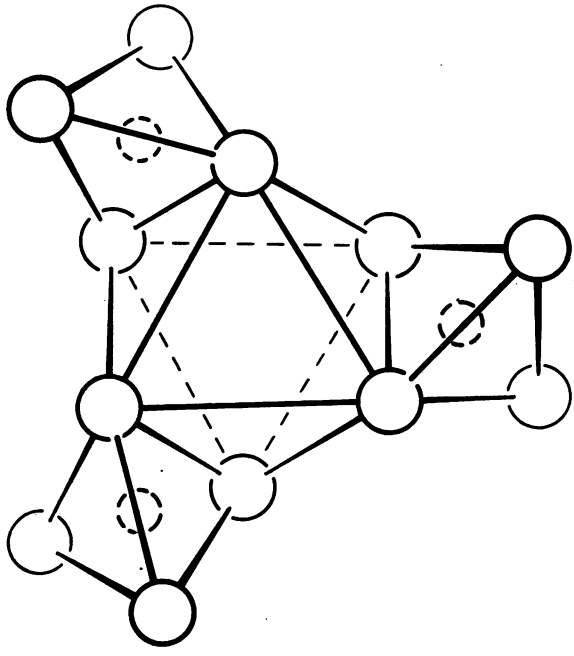
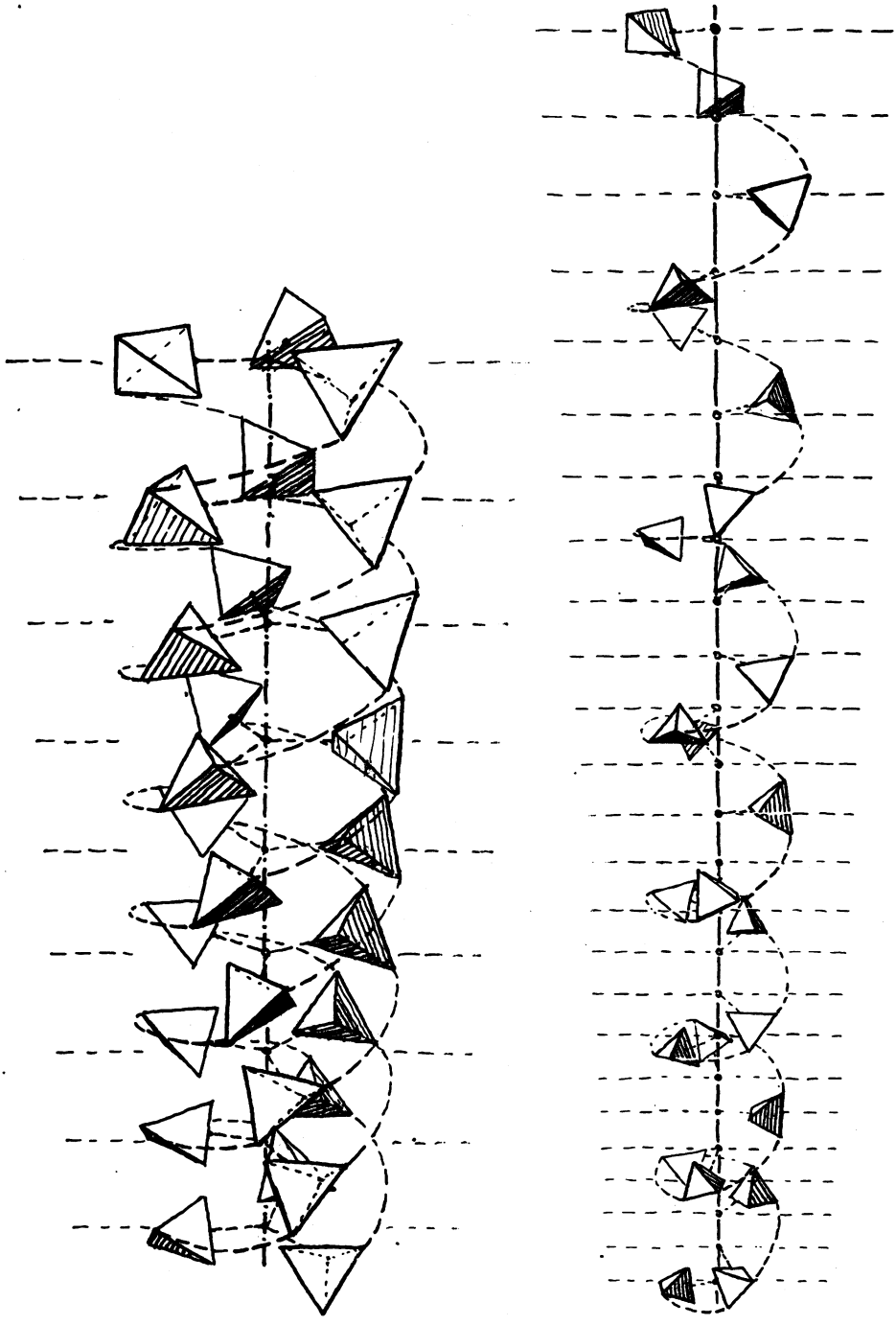


FIGURE 1

A group of three phosphate tetrahedra near the axis of the nucleic acid molecule. Oxygen atoms are indicated by full circles and phosphorus atoms by dashed circles.

The first question to be answered is that as to the nature of the core of the three-chain helical molecule—the part of the molecule closest to the axis. It is important for stability of the molecule that atoms be well packed together, and the problem of packing atoms together is a more difficult one to solve in the neighborhood of the axis than at a distance away from the axis, where there is a larger distance between an atom and the equivalent atom in the next unit. (An example of a helical structure which seems to satisfy all of the structural requirements except that of close packing of atoms in the region near the helical axis is the 5.2-residue helix of polypeptide chains. This structure seems not to be represented in proteins, whereas



the similar α helix, in which the atoms are packed in a satisfactorily close manner about the axis, is an important protein structure.) There are three possibilities as to the composition of the core: it may consist of the purine-pyrimidine groups, the sugar residues, or the phosphate groups. It is found by trial that, because of their varied nature, the purine-pyrimidine groups cannot be packed along the axis of the helix in such a way that suitable bonds can be formed between the sugar residues and the phosphate groups; this choice is accordingly eliminated. It is also unlikely that the sugar groups constitute the core of the molecule; the shape of the ribofuranose group and the deoxyribofuranose group is such that close packing of these groups along a helical axis is difficult, and no satisfactory way of packing them has been found. An example that shows the difficulty of achieving close packing is provided by the polysaccharide starch, which forms helixes with a hole along the axis, into which iodine molecules can fit. We conclude that the core of the molecule is probably formed of the phosphate groups.

A close-packed core of phosphoric acid residues, HPO_4^{--}, can easily be constructed. At each level along the fiber axis there are three phosphate groups. These are packed together in the way shown in figure 1. Six oxygen atoms, two from each tetrahedral phosphate group, form an octahedron, the trigonal axis of which is the axis of the three-chain helical molecule. A similar complex of three phosphate tetrahedra can be superimposed on this one, with translation by 3.4 Å along the fiber axis, and only a small change in azimuth. The neighborhood of the axis of the molecule is then filled with oxygen atoms, arranged in groups of three, which change their azimuthal orientation by about 60° from layer to layer, in such a way as to produce approximate closest packing of these atoms.

The height (between two opposite edges) of a phosphate tetrahedron is about 1.7 Å. If the same distance were preserved between the next oxygen layers, the basal-plane distance along the fiber axis would be 3.4 Å. This value is the spacing observed for the principal meridional reflection.

It is to be expected that the outer oxygen atoms of the complex of three phosphate groups would be attached to the ribofuranose or deoxyribofuranose residues, and that the hydrogen atom of the HPO_4^{--} residues

FIGURE 2

Figure 2 (*left*). A 24-residue 7-turn helix representing a single polynucleotide chain in the proposed structure for nucleic acid. The phosphate groups are represented by tetrahedra, and the ribofuranose groups by dashed arcs connecting them.

FIGURE 3

Figure 3 (*right*). One unit of the 3-chain nucleic acid structure. Eight nucleotide residues of each of the three chains are included within this unit. Each chain executes $3^1/_3$ turns in this unit.

would be attached to one of the two inner oxygen atoms, and presumably would be involved in hydrogen-bond formation with another of the inner oxygen atoms, of an adjoining phosphate group. The length of the O–H $\cdots$O bond should be close to that observed in potassium dihydrogen phosphate, 2.55 Å. The angle P—O—H should be approximately the tetrahedral angle. It is found that the spacing 3.4 Å is not compatible with this bond angle, if the hydrogen bonds are formed between one phosphate group

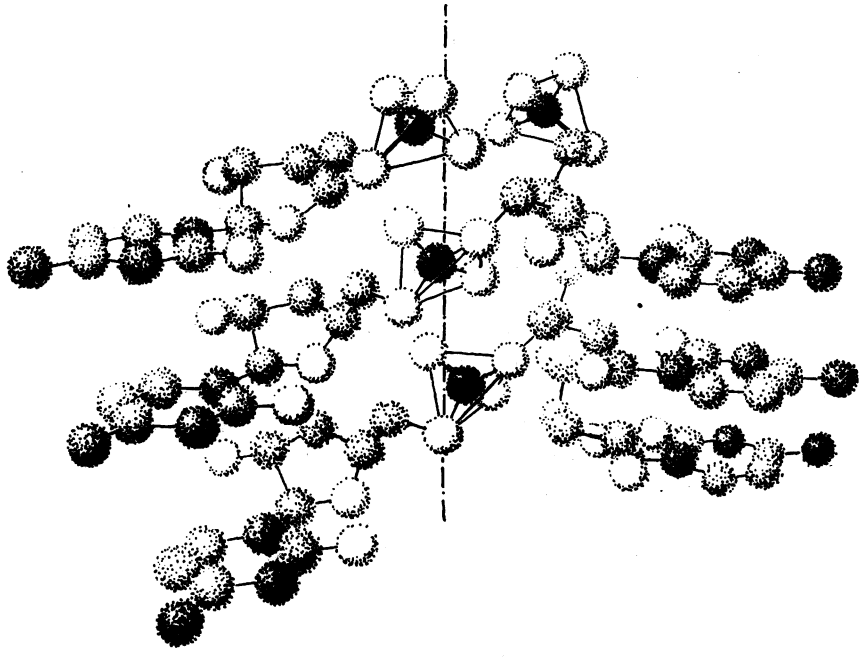


FIGURE 4

Perspective drawing of a portion of the nucleic acid structure, showing the phosphate tetrahedra near the axis of the molecule, the β-D-ribofuranose rings connecting the tetrahedra into chains, and the attached purine and pyrimidine rings (represented as purine rings in this drawing). The molecule is inverted with respect to the coordinates given in table 1.

and a group in the layer above or below it. Accordingly we assume that hydrogen bonds are formed between the oxygen atoms of the phosphate groups in the same basal plane, along outer edges of the octahedron in figure 1.

The maximum distance between the oxygen atoms 3′ and 5′ of a ribofuranose or deoxyribofuranose residue permitted by the accepted structural parameters (C—C = 1.54 Å, C—O = 2.43 Å, bond angles tetrahedral, with the minimum distortion required by the five-membered ring, one atom of

the five-membered ring 0.5 Å from the plane of the other four, as reported by Furberg[6] for cytidine) is 4.95 Å. It is found that it is very difficult to assign atomic positions in such a way that the residues can form a bridge between an outer oxygen atom of one phosphate group and an outer oxygen atom of a phosphate group in the layer above, without bringing some atoms into closer contact than is normal. The atomic parameters given in Table

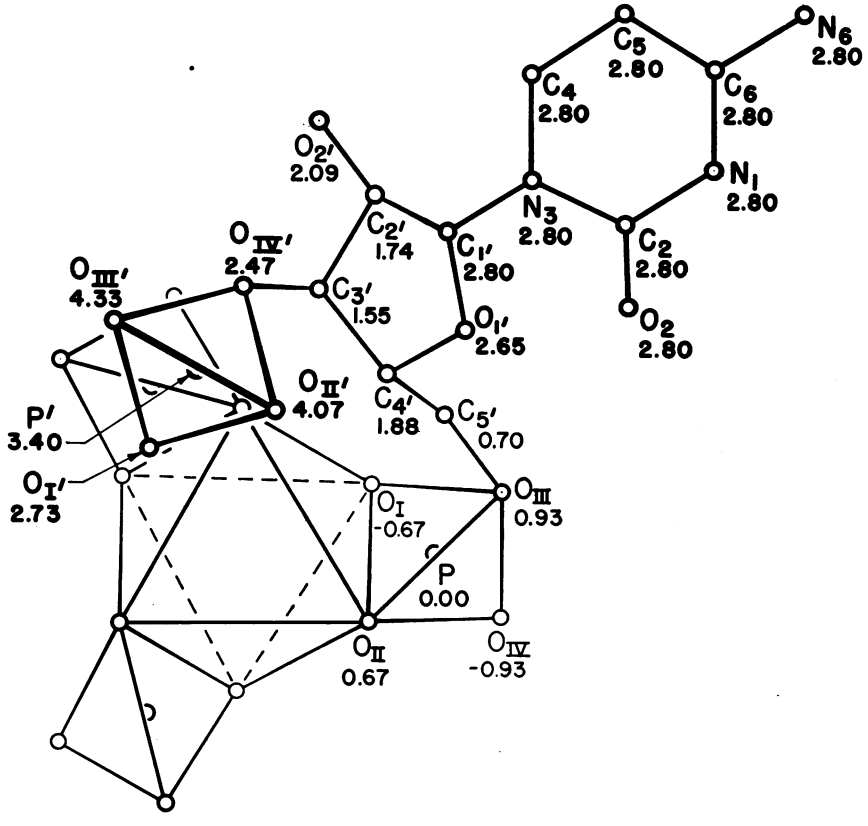


FIGURE 5

A plan of the nucleic acid structure, showing four of the phosphate groups, one ribofuranose group, and one pyrimidine group.

1 represent the best solution of this problem that we have found; these parameters, however, probably are capable of further refinement. The structure is an extraordinarily tight one, with little opportunity for change in position of the atoms.

The phosphate groups are unsymmetrical: the P—O distance is 1.45 Å for the two inner oxygen atoms, and 1.60 Å for the two outer oxygen atoms,

which are involved in ester linkages. This distortion of the phosphate group from the regular tetrahedral configuration is not supported by direct experimental evidence; unfortunately no precise structure determinations have been made of any phosphate di-esters. The distortion, which corresponds to a larger amount of double bond character for the inner oxygen atoms than for the oxygen atoms involved in the ester linkages, is a reason-

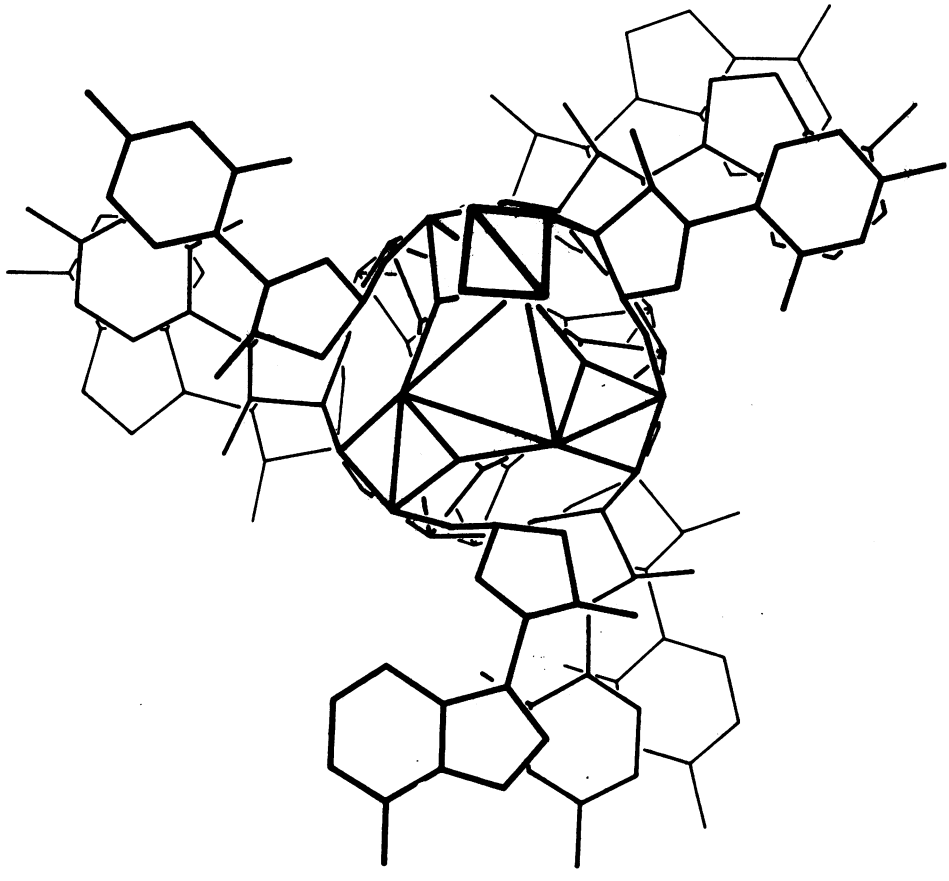


FIGURE 6

Plan of the nucleic acid structure, showing several nucleotide residues.

able one, and the assumed distances are those indicated by the observed values for somewhat similar substances, especially the ring compound S_3O_9, in which each sulfur atom is surrounded by a tetrahedron of four oxygen atoms, two of which are shared with adjacent tetrahedra, and two unshared. The O—O distances within the phosphate tetrahedron are 2.32 Å (between the two inner oxygen atoms), 2.46 Å, 2.55 Å, and 2.60 Å. The

hydrogen-bond distance is 2.50 Å, and each phosphate tetrahedron has two O—O contacts at 2.50 Å, with tetrahedra in the layer above. The group of three phosphate tetrahedra in each layer is obtained from that in the layer below by translation upward by 3.40 Å, and rotation in the direction corresponding to a left-handed screw by the azimuthal angle 15°. Thus there are strings of phosphate tetrahedra that are nearly superimposed, and execute a slow twist to the left. These strings are not connected together into a single polynucleotide chain, however. The sugar residues connect each phosphate group with the phosphate group in the layer above that is obtained from it by the translation by 3.40 Å and rotation through the azimuthal angle 105°, in the direction corresponding to a right-handed screw, as shown in figure 2. This gives rise to a helical chain, with pitch 11.65 Å, and with 3.43 residues per turn of the helix. The chain has an identity distance or approximate identity distance of 81.5 Å, corresponding to 24 nucleotide residues in seven turns, as shown in figure 3. The three chains of the molecule interpenetrate in such a way that the pitch of the triple helix is 3.88 Å, and the identity distance or approximate identity distance is 27.2 Å, corresponding to eight layers (see also Figs. 4, 5, and 6).

The structure requires that the sugar residues have the β-furanose configuration; steric hindrance would prevent the introduction of purine or pyrimidine groups in the positions corresponding to the α configuration. The planes of the purine and pyrimidine residues may be perpendicular or nearly perpendicular to the axis of the molecule. This causes these groups to be superimposed in layers that execute a slow left-handed turn about the molecule, the distance between the planes of successive groups being 3.4 Å. The orientation of the groups is accordingly that required by the observed strong negative birefringence of the nucleic acid fibers. The assignment of the sense of the helical molecules corresponding to the right-handed screw is required by the nature of the structure (the packing of the atoms near the axis, and the absolute configuration of the sugar, as given by the recent experimental determination[16] that absolute configurations are correctly given by the Fischer convention).

The structure bears some resemblance to the structures that have been suggested earlier, and described in a general way, without atomic coordinates. Astbury and Bell[7] suggested that the nucleic acid molecule consists of a column of nucleotide residues, with the purine and pyrimidine groups arranged directly above one another, in planes 3.4 Å apart. Astbury[10] considered the possibility that the nucleotides are arranged in a spiral around the long axis of the molecule, and rejected it, on the grounds that it does not lead to a sufficiently close packing of the groups, as is required by the high density of the substance. He pointed out that it is unlikely that adjacent molecules could interleave their purine and pyrimidine residues in such a way as to lead to the high density. Our structure solves this problem by

the device of intertwining three helical polynucleotide chains, in such a way that there are three nearly vertical purine-pyrimidine columns, consisting of purine and pyrimidine residues from the three chains in alternation. Furberg[17] suggested two single helical configurations, each resembling in a general way one of our helical polynucleotide chains, but his structures involve orientations of phosphate tetrahedra and the ribofuranose rings that are quite different from ours, and it is doubtful that three chains with either of the configurations indicated in his drawing could be intertwined.

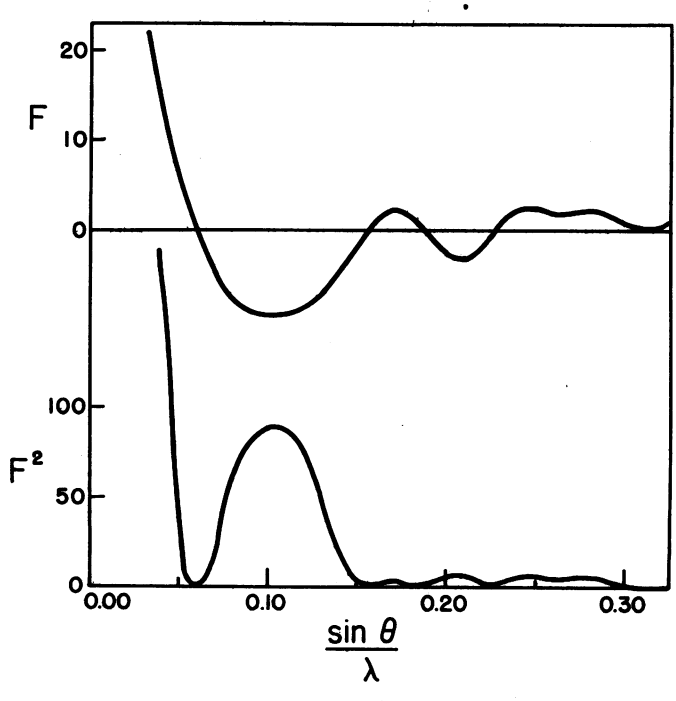


FIGURE 7

The calculated x-ray form factor F and its square F^2 for equatorial reflections of nucleic acid.

The proposed structure accounts moderately well for the principal features of the x-ray patterns of sodium thymonucleate and other nucleic acid derivatives. The spacing 3.40 Å between successive layers of three nucleotides along the molecular axis is required to within about 0.10 Å by the structural parameters of the nucleotides. The prediction that the helixes have 24 nucleotide residues per turn, corresponding to identity distance 8×3.4 Å in the direction of the fiber axis, is in good agreement with the fact that the x-ray diagrams can be reasonably well indexed by placing the 3.4 Å meridional reflection on the eighth layer line. The formula of Cochran,

Crick, and Vand[18] for the form factor for helical structures requires that the orders of Bessel functions for the successive layer lines from 0 to 8 be 0, 3, 6, 9, 12, 9, 6, 3, and 0. The layer-line intensities agree satisfactorily with this prediction, in the region from layer line 4 to layer line 8. There is an unexplained blackening near the meridian for layer lines 2 to 4, which, however, differs in nature for sodium thymonucleate and clupein thymonucleate, and which probably is to be attributed to material between the polynucleotide chains.

The distribution of intensity along the equator can be accounted for satisfactorily. In figure 7 there are shown the calculated form factor in the

TABLE 2

CALCULATED AND OBSERVED EQUATORIAL X-RAY REFLECTIONS FOR SODIUM THYMONUCLEATE. HEXAGONAL UNIT WITH $a_0 = 22.1$ Å

hkl	$d_{calc.}$	F_1	F_2	pF_2^2	$I_{obs.}$[a]	$d_{obs.}$[a]
10.0	19.1 Å	55	47	6600	m	18.1 Å
11.0	11.0	9.6	21	1350	m	11.2
20.0	9.5	4.7	−1.0	3		
21.0	7.22	−3.4	−8.9	480	w	7.16
30.0	6.37	−7.7	3.1	29		
22.0	5.52	−9.2	1.3	5		
31.0	5.30	−9.4	−14.6	1280	m	5.30
40.0	4.78	−9.3	−14.4	620		
32.0	4.38	−9.1	−14.1	1200	m	19[b]
41.0	4.17	−8.8	1.0	6		
50.0	3.83	−6.1	−10.8	350		
33.0	3.68	−5.1	4.2	53		
42.0	3.61	−4.3	−8.9	480	vw	3.57
51.0	3.43	−2.6	−7.1	300		

The symbol p in column 5 is the frequency factor for the form.

[a] The observed intensity values and interplanar distances are those reported by Astbury and Bell.

[b] The reflection covers the angular range corresponding to interplanar distances 4.0 to 4.4 Å, and may arise in part from overlapping from the adjacent layer lines.

equatorial direction, and the square of the form factor. It is seen that the form factor vanishes at a spacing of about 8 Å, and has a maximum in the region near 5 Å. Calculated intensities, given in table 2, are obtained by making a correction for interstitial material, at the coordinates 1/3 2/3 and 2/3 1/3, the amount of this material being taken as corresponding in scattering power to 1.5 oxygen atoms per nucleotide residue. There is reasonably satisfactory agreement with the experimental values; on the other hand, similar agreement might be given by any cylindrical molecule with approximately the same diameter. A comparison of observed and calculated radial distribution functions would provide a more reliable test of the structure; this comparison has not yet been carried out.

It is interesting to note that the purine and pyrimidine groups, on the periphery of the molecule, occupy positions such that their hydrogen-bond forming groups are directed radially. This would permit the nucleic acid molecule to interact vigorously with other molecules. Moreover, there is enough room in the region of each nitrogen base to permit the arbitrary choice of any one of the alternative groups; steric hindrance would not interfere with the arbitrary ordering of the residues. The proposed structure accordingly permits the maximum number of nucleic acids to be constructed, providing the possibility of high specificity. As Astbury has pointed out, the 3.4-Å x-ray reflection, indicating a similar distance along the axis of the molecule, is approximately the length per residue in a nearly extended polypeptide chain, and accordingly the nucleic acids are, with respect to this dimension, well suited to the ordering of amino-acid residues in a protein. The positions of the amino-acid residues might well be at the centers of the parallelograms of which the corners are occupied by four nitrogen bases. The 256 different kinds of parallelograms (neglecting the possibility of two different orientations of each nitrogen base) would permit considerable power of selection for each position.

(Added in proof.) Support of the assumed phosphorus-oxygen distances in the phosphate di-ester group is provided by the results of the determination of the structure of ammonium tetrametaphosphate.[19, 20] In this crystal there are P_4O_{12} complexes, consisting of four tetrahedra each of which shares two oxygen atoms with other tetrahedra. The phosphorus-oxygen distance is 1.46 Å for the oxygen atoms that are not shared, and 1.62 Å for those that are shared. These values are to be compared with the values that we have assumed, 1.45 Å for the inner oxygen atoms (which are not shared), and 1.60 Å for the outer ones, which have bonds to carbon atoms.

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*INDUCED DOMINANT LETHALITY IN LILIUM**

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In 1927, H. J. Muller[1] noticed a marked decrease in the fertility of female *Drosophila melanogaster* mated to irradiated males, and attributed this decrease to dominant lethals induced by the x-ray treatment.

As pointed out by Stancati,[2] in 1932, the primary choice under such circumstances is between the induction of dominant lethals and the inactivation of sperm. Either effect of x-rays would give the observed decrease in fertility. Although Muller and Settles[3] had proved in 1927 that sperm could function normally even though carrying chromosome sets which would be lethal in combination with the normal chromosome complement, Stancati's work with *Habrobracon* was the first to demonstrate conclusively that dominant lethality was the result, not the lack, of fertilization by irradiated sperm. After treatment, the frequency of the biparental females (arising from fertilized eggs) decreased while the frequency of the matroclinous, uniparental males (arising from unfertilized eggs) was neither diminished nor increased. The missing biparental females were those which would have appeared if dominant lethals had not been induced in the sperm.

Later Demerec and Kaufmann[4] examined cytologically Drosophila eggs presumably fertilized by sperm treated with 5000 r. Failure of fertilization was apparent in only one case out of the 99 studied. Therefore the high degree of sterility at this dose was assignable to dominant lethality rather than sperm inactivation. On the other hand, any studies of dominant lethality at yet higher doses would again require that the sperm be shown to act in fertilizing.

Work with *Habrobracon* also gave information on the dosage necessary to achieve sperm inactivation. At the relatively low doses generally used, the