

⁸ C. C. Stock, "Experimental Cancer Chemotherapy," in *Advances in Cancer Research*, ed. J. P. Greenstein and A. Haddow, 2 (New York: Academic Press, Inc., 1954), 425-492.

⁹ D. M. Shapiro and A. Gellhorn, "Combinations of Chemical Compounds in Experimental Cancer Therapy," *Cancer Research*, 11, 35-41, 1951; D. M. Shapiro, "Combination Chemotherapy with 8-Azaguanine and Sex Hormones on a Mouse Mammary Carcinoma," *Cancer Research*, 12, 713-715, 1952; G. L. Woodside and D. E. Kelton, "Combination Chemotherapy of Mouse Tumors with 8-Azaguanine and Flavotin," *Cancer Research*, 15, 390-393, 1955.

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HYDROGEN-BONDED HELICAL CONFIGURATIONS OF POLYNUCLEOTIDES*

BY JERRY DONOHUE

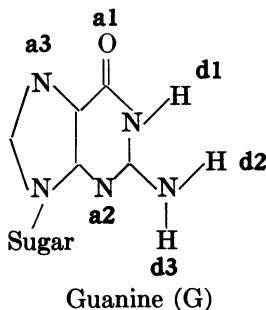
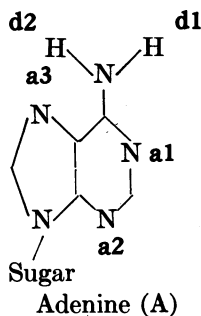
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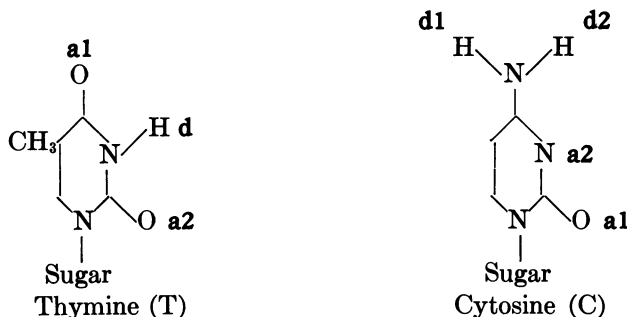
Communicated by L. Pauling, November 23, 1955

The structure for the sodium salt of deoxyribonucleic acid (DNA) proposed by Watson and Crick¹ requires, in agreement with the more recent analytical data, the occurrence in the molecule of equimolar amounts of adenine and thymine, on the one hand, and of guanine and cytosine, on the other. Since it is by no means certain that all nucleic acids, whether DNA or ribonucleic acid, whatever the source, will conform to this composition, it becomes of interest to inquire into the possibility of other structures which satisfy the chemical evidence concerning the bonding in a single nucleotide chain and which also conform to our knowledge of molecular structures. The basic feature of the Watson-Crick structure is the arrangement of the four bases: these come in the pairs, above, connected by hydrogen bonds which link two polynucleotide chains together, and lie perpendicular to the helical axis of the molecule, 3.4 Å apart.

A systematic study of structures which also have the bases perpendicular to a helical axis is described below. Although it may be possible to construct a polynucleotide molecule consisting of a single chain internally linked with hydrogen bonds, it seems reasonable to retain the planar separation of the basis, necessitating two or more nucleotide chains winding about a common helical axis.

We first consider base-base pairs, and, in order to facilitate their description, we number the hydrogen-bonding donor and acceptor sites as follows:





Precise X-ray crystallographic information on these and related compounds is meager. The models used had rings with regular pentagons and hexagons with sides equal to 1.36 Å, and external C—NH₂ and C=O bonds of 1.36 and 1.21 Å, respectively. The hydrogen-bond distances N—H...O and N—H...N were taken as 2.85 and 3.00 Å, respectively, and a maximum deviation of N—H...X from linearity of about 15° was allowed. The dimensions given above are within the limits of error for the published data on cytidine² and uracil³ and the hydrochlorides of adenine,⁴ guanine,⁵ and histidine,⁶ and conform to the hydrogen-bond characteristics of numerous compounds,⁷ but it should be pointed out that hydrogen-bond-length variations of as large as ±0.20 Å have been observed to occur and that deviations from the regularity of the rings will affect only qualitatively the conclusions reached below.

The base pairs resulting from the above considerations are listed in Table 1. The hydrogen bonds across each pair are indicated by identifying the donor and acceptor sites in each base. Deferring, for the moment, the question of the sugar-phosphate-sugar "backbone" chain between successive bases, each of the twenty-four pairs in Table 1 is a possible pairing scheme in a polynucleotide of that particular composition; but it is doubtful, of course, that all these are of significance in

TABLE 1
GEOMETRICALLY ACCEPTABLE BASE PAIRS IN POLYNUCLEOTIDES

	BASE I	BASE II	HYDROGEN BONDING I-II		BASE I	BASE II	HYDROGEN BONDING I-II
1.	Adenine	Adenine	d2—a3, a3—d2	13.	Guanine	Thymine	d1—a1, a1—d
2.	Adenine	Adenine	d1—a1, a1—d1	14.	Guanine	Thymine	d1—a2, a1—d
3.	Adenine	Adenine	d2—a1, a3—d1	15.	Guanine	Cytosine	d1—a2, a1—d2
4.	Adenine	Thymine	d1—a2, a1—d	16.	Guanine	Cytosine	d1—a2, d2—a1
5.	Adenine	Thymine	d1—a1, a1—d	17.	Guanine	Cytosine	d1—a1, d2—a2
6.	Adenine	Cytosine	d1—a2, a1—d2	18.	Thymine	Thymine	d—a1, a1—d
7.	Adenine	Guanine	d1—a1, a1—d1	19.	Thymine	Thymine	d—a2, a1—d
8.	Adenine	Guanine	d1—a2, a1—d3	20.	Thymine	Thymine	d—a2, a2—d
9.	Guanine	Guanine	d1—a1, a1—d1	21.	Thymine	Cytosine	d—a2, a2—d2
10.	Guanine	Guanine	d1—a1, d2—a3	22.	Thymine	Cytosine	d—a2, a1—d2
11.	Guanine	Guanine	d1—a3, d2—a1	23.	Cytosine	Cytosine	d2—a2, a2—d2
12.	Guanine	Guanine	d3—a2, a2—d3	24.	Cytosine	Cytosine	d2—a1, a1—d2

nature. Pairing 1 occurs in crystals of adenine hydrochloride,⁴ pairing 12 is observed in guanine hydrochloride,⁵ pairing 18 is found in uracil,³ and pairings 13, 14, 18, 19, and 20 are like that found in diketopiperazine.⁸ Figure 1 shows pairing 1 and represents a possible basis for polyadenylic acid, the two chains being equivalent provided that they run in the same direction. Of interest are those pairs for which the base-nitrogen to sugar-carbon bonds are related, or nearly so, by a twofold axis,

since this then allows the one base to replace the other along one chain, provided that the complementary replacement occurs in the other chain; of more particular interest are pairs of pairs for which the $N_{\text{base}}-C_{\text{sugar}}$ bonds lie in the same positions relative to each other, allowing additional flexibility in the composition. The Watson-Crick structure combines pairings 5 and 15,⁹ which predicts the observed analytical data for DNA from several sources and allows the order of bases in either chain to be completely irregular, provided that the two chains have the biologically pleasing complementary relation to each other.

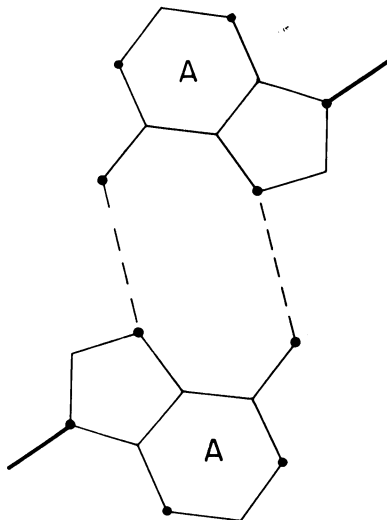


FIG. 1.—Base pairing 1 of Table 1, adenine with adenine. The nitrogen atoms are represented as filled circles and the oxygen atoms as open circles. The hydrogen bonds are the dashed lines, and the bond from the base nitrogen to the sugar is shown as the heavy line.

There is a second pair of pairs, 4 and 17, which has this feature in common with the above. In order to achieve complete equivalence of the $N_{\text{base}}-C_{\text{sugar}}$ bonds here, however, some distortion from the assumed regular dimensions is necessary. This base-pairing scheme is shown in Figure 2, where it is seen that $N_{\text{base}}-C_{\text{sugar}}$ bonds are related by a twofold axis parallel to the helical axis, as contrasted to the perpendicular twofold axis in the Watson-Crick formulation.

A third pairing, 6 and 13, shown in Figure 3, is interesting in that it also allows a completely irregular order of all four bases on one nucleotide chain, with the second chain complementary, but in the opposite sense, namely, adenine with cytosine and guanine with thymine. This pairing, like the second, requires some distortion from the regular structures assumed in order to create equivalence of the $N_{\text{base}}-C_{\text{sugar}}$ bonds.

As shown in Figure 4, a fourth pairing, 2 and 9, is the basis of a two-chain structure having only purine bases, while Figure 5 shows the pairing 18 and 23, which allows only pyrimidines.

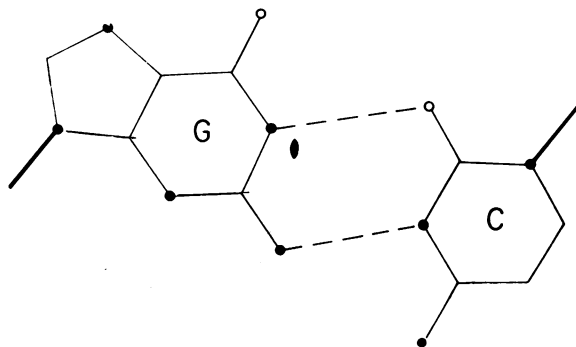
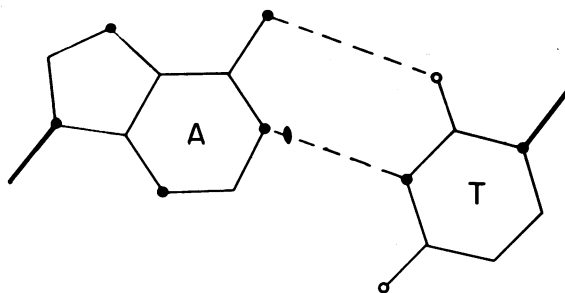


FIG. 2.—Base pairings 4 and 17, adenine with thymine and guanine with cytosine.

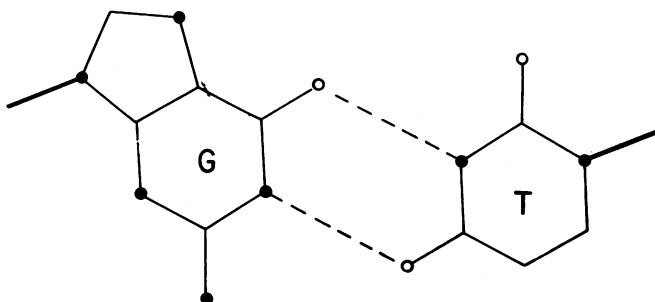
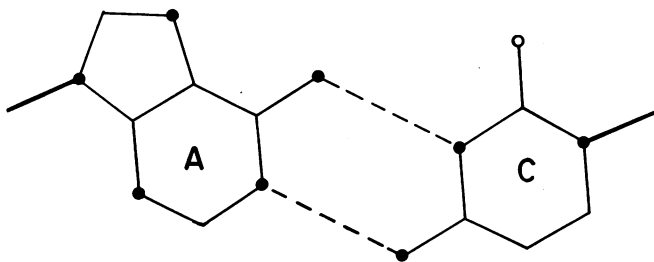


FIG. 3.—Base pairings 6 and 13, adenine with cytosine and guanine with thymine.

Investigation of the above-described pairs of pairs with molecular models shows that it is possible to construct satisfactory right-handed helical polynucleotide structures in which the planes in which the bases lie are 3.4 Å apart. For each of

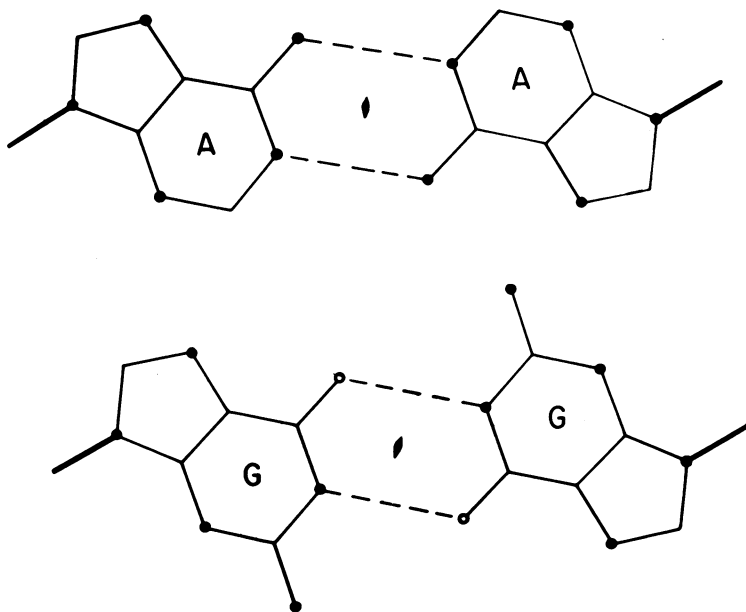


FIG. 4.—Base pairings 2 and 9, purines only.

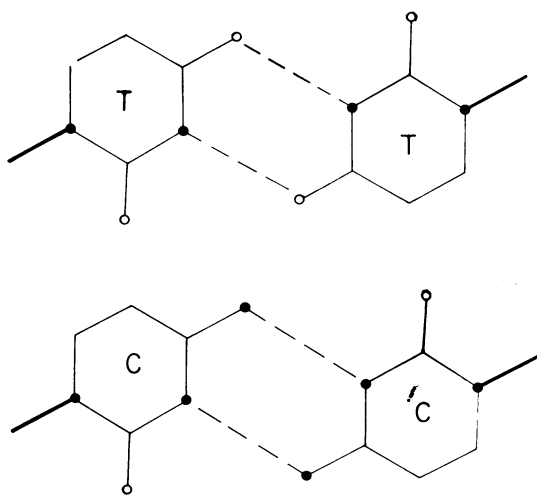


FIG. 5.—Base pairings 18 and 23, pyrimidines only.

them there are two structures: one in which the two chains run in the same direction and one in which they run in opposite directions. For those structures having the twofold axis coincident with the axis of the helix, the repeat along the helical

axis will be halved for the structures with the chain running in the same directions. The angular part of the screw operation of the helix was found to depend largely upon radial co-ordinates of the $N_{\text{base}}-C_{\text{sugar}}$ bond: for example, for the pairing 4 and 17, in which N_{base} has a radial co-ordinate of 4.5 Å, an angular co-ordinate of about 45° gives a satisfactory structure, as contrasted with the Watson-Crick pairing (5 and 15), which has 6.7 Å for the N_{base} radius and an angular co-ordinate of 36° , the larger radius requiring the shorter angular separation.

In the absence of more precise information on the bond lengths, bond angles, and particularly the favored orientations to be expected about the numerous single bonds in the polynucleotide chain, it does not seem appropriate to determine exact atomic co-ordinates, especially since there is latitude of $\pm 10^\circ$ or more in the angular separation of the bases.

We conclude from this study that polynucleotides may assume two-chain structures other than the one proposed by Watson and Crick.

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* Presented at a symposium on "Molecular Structure and Biological Specificity," October 28, 1955, Washington, D.C.

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⁹ It has been pointed out by Professor Pauling that it is possible with only small distortion for guanine and cytosine to pair by formation of three hydrogen bonds (d1—a2, a1—d2, d2—a1), combining pairings 15 and 16. The formation of this additional hydrogen bond may confer extra stability on the Watson-Crick Structure.

PHASE RELATIONS IN SYSTEMS COMPRISING BROMINE AND QUATERNARY AND TERNARY ALKYL AMMONIUM BROMIDES OR CHLORIDES

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The quaternary and ternary alkyl ammonium chlorides and bromides are highly soluble in bromine at 25° . Bowen and Barus¹ have shown that salts of this type complex with bromine molecules to form compounds melting below 60° . However, they did not investigate the phase relations in these systems in a systematic manner. In carrying out measurements of the conductance, viscosity, and vapor pressure of these systems, we found it desirable to determine the phase relations in some detail, in order to establish the nature of the compounds formed.