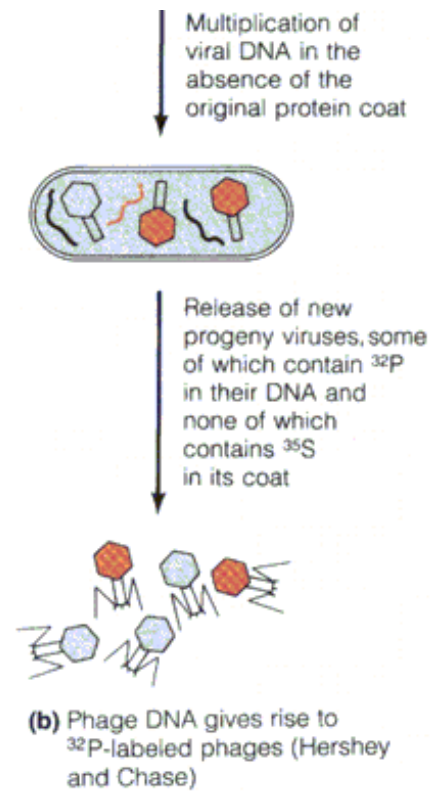
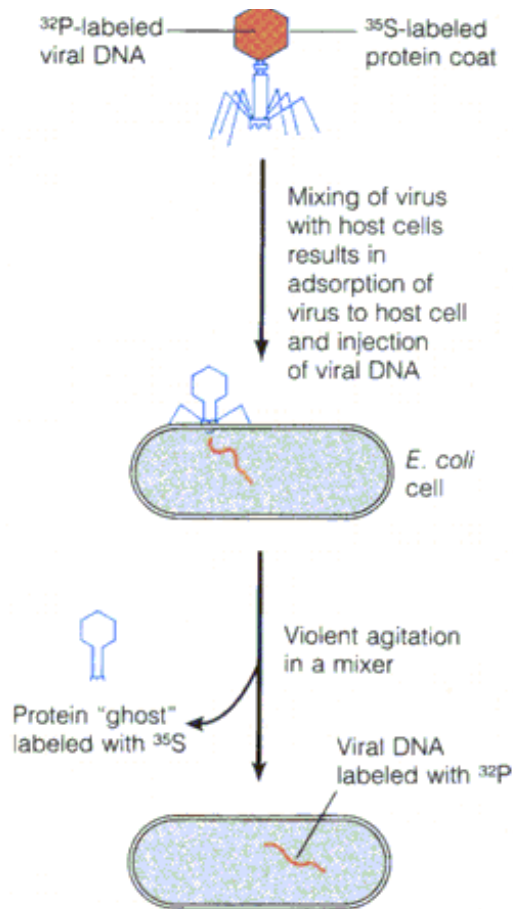


Hershey/Chase Experiment

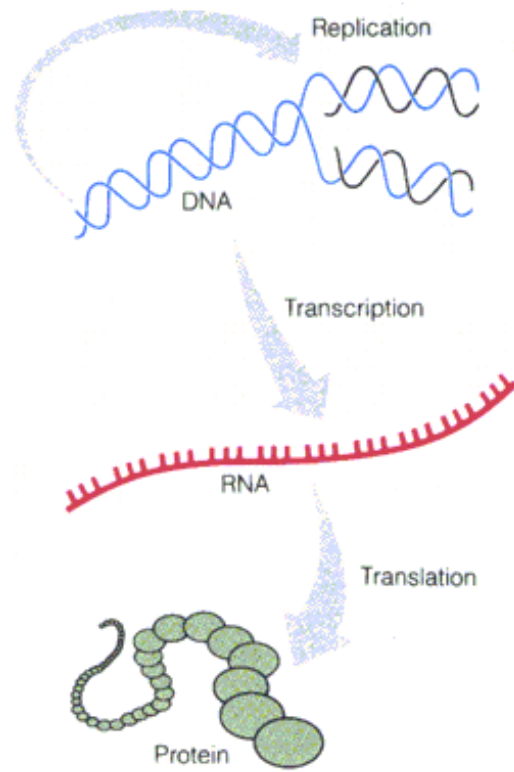


Central Dogma

DNA

RNA

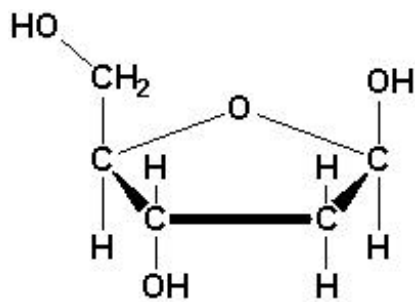
Protein



Nucleic Acids

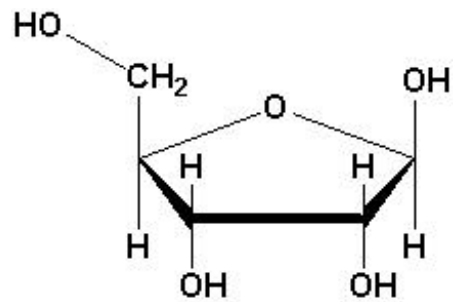
- Biology
- Monomer Building Blocks
- Primary Structure
 - Metastability and Energetics
- Secondary Structure
 - Watson and Crick

Furanose Sugars



Deoxyribose

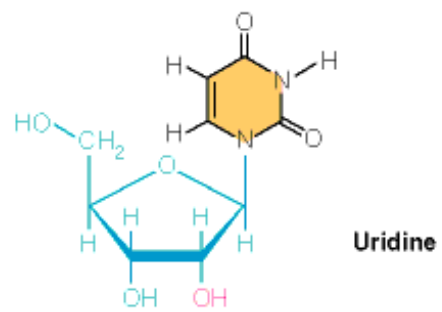
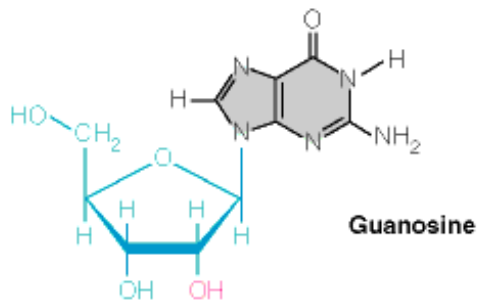
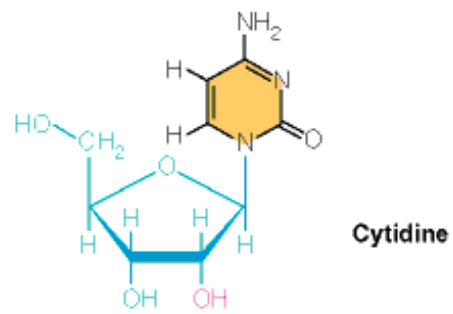
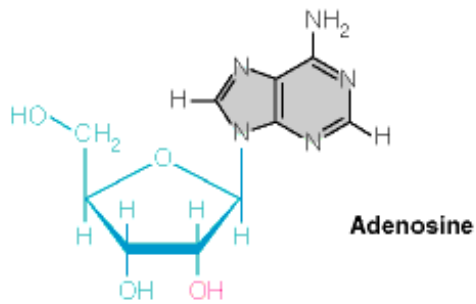
2' endo



D-Ribose

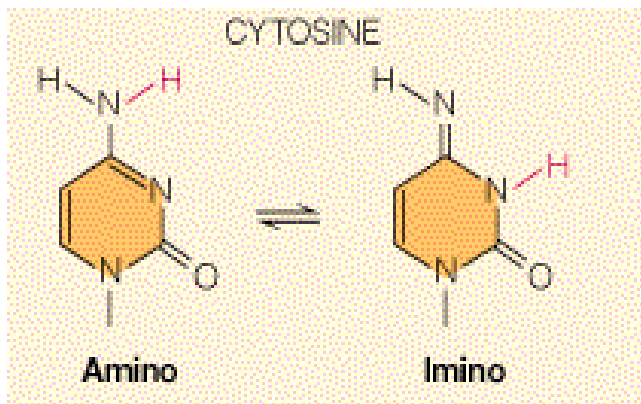
3' endo

NUCLEOSIDES

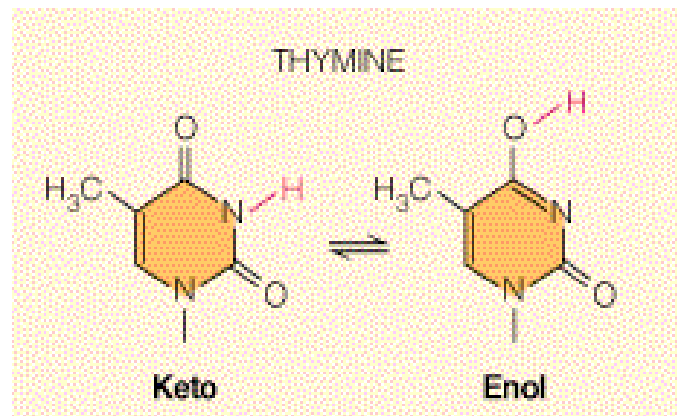


Purines--A and G

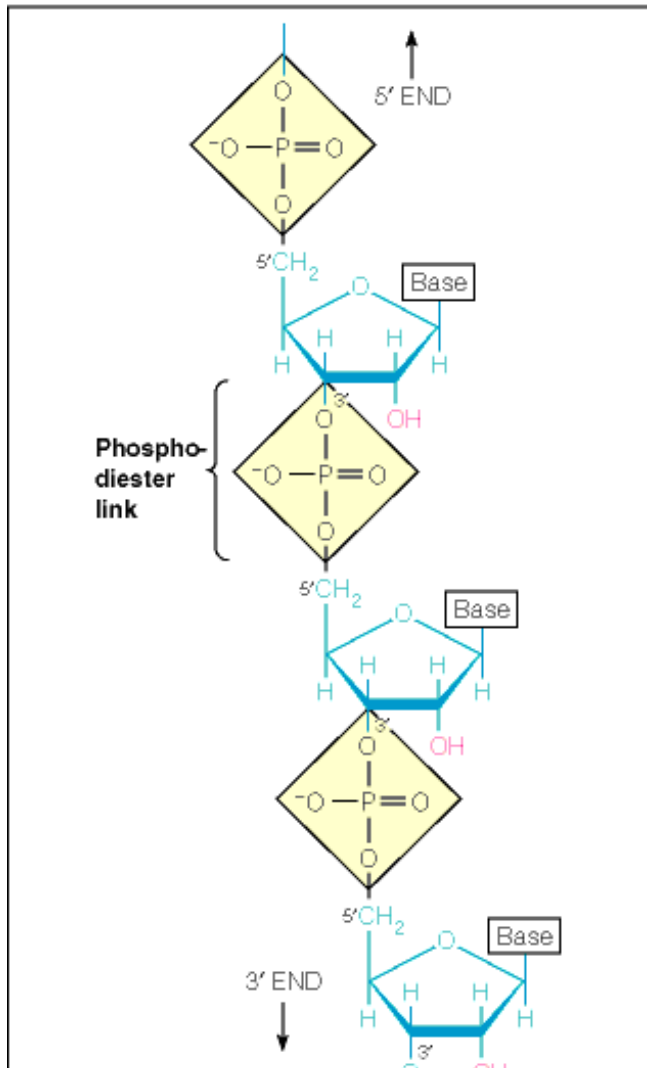
Pyrimidines--C, U, T



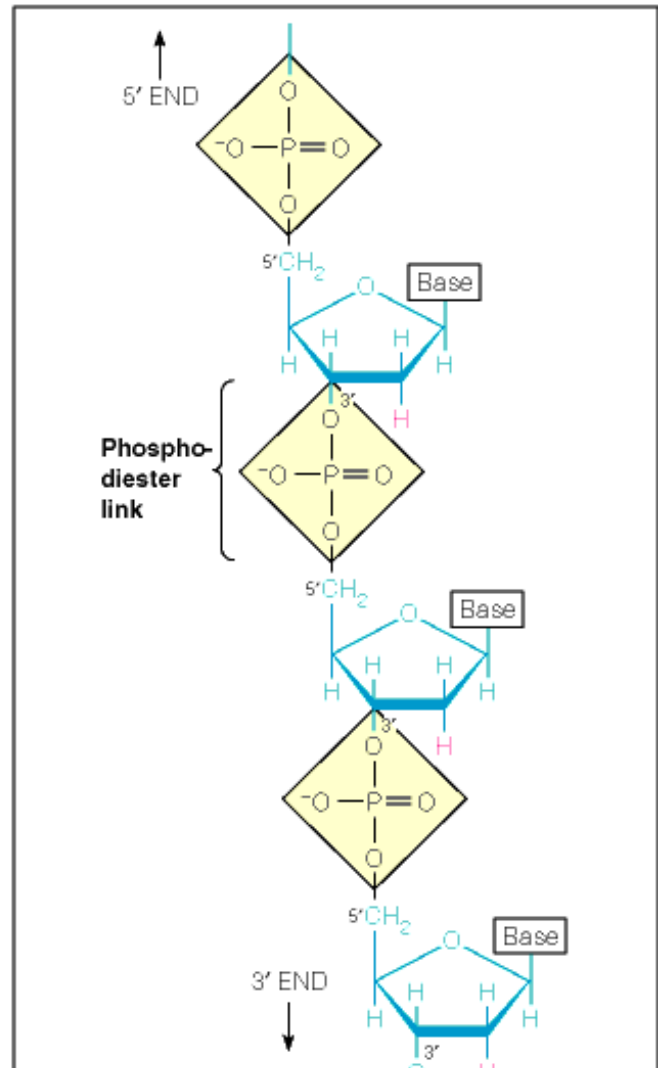
Keto-Enol
Amino-Imino
Tautomers

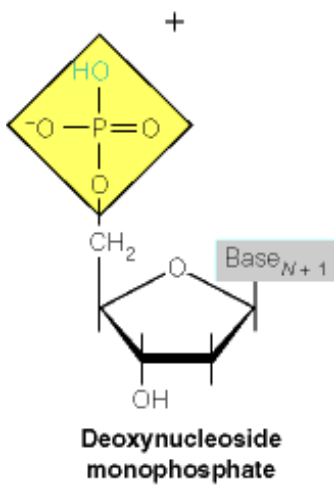
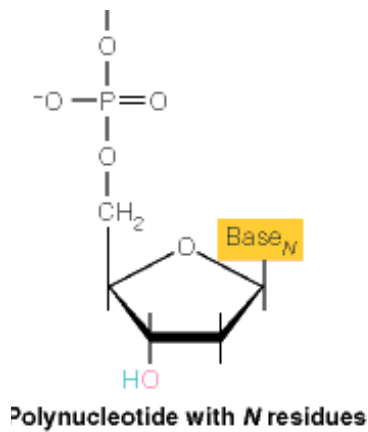


RNA



DNA

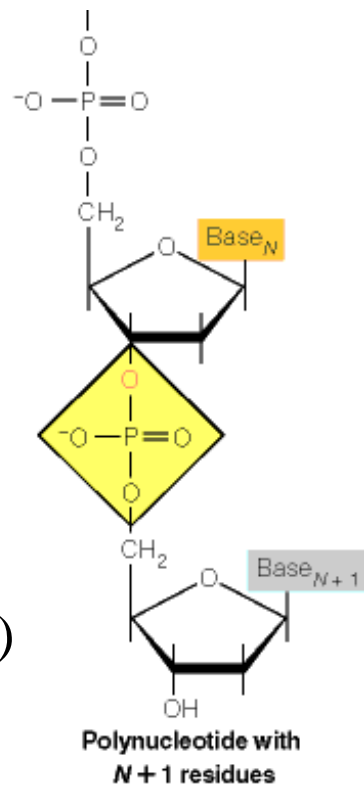




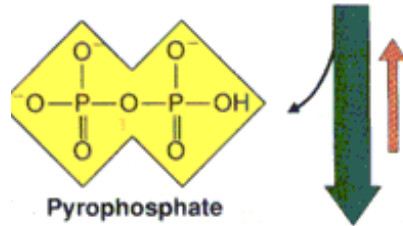
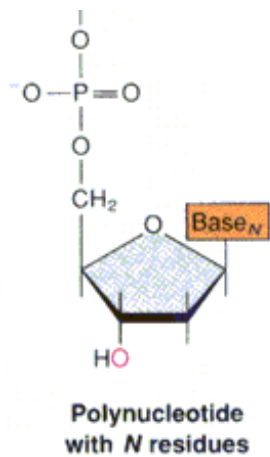
Dehydration
Is unfavorable
energetically



Degradation
(pH, nucleases)
Is favored.

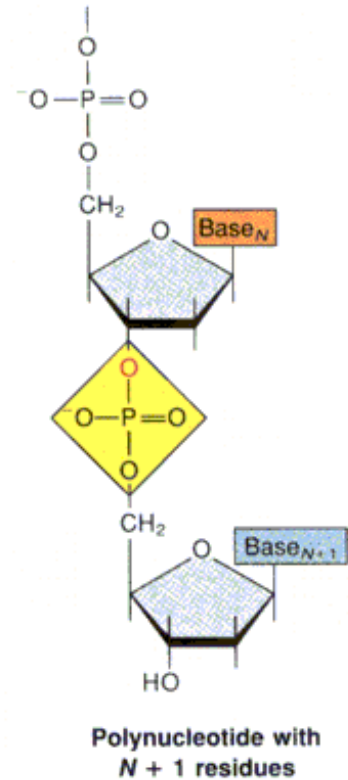
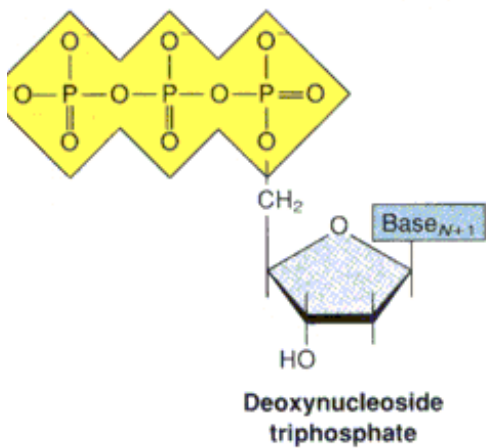


MetaStability



$\Delta G^{\circ} =$
-31 kJ/mole

+



What is ΔG° ' ????'

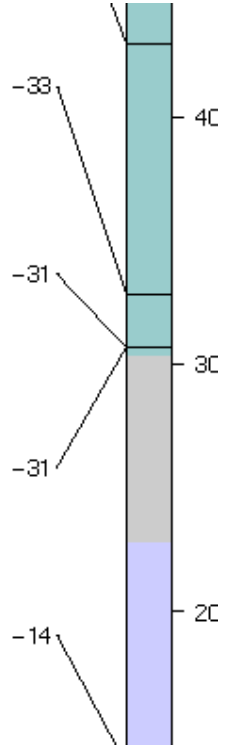
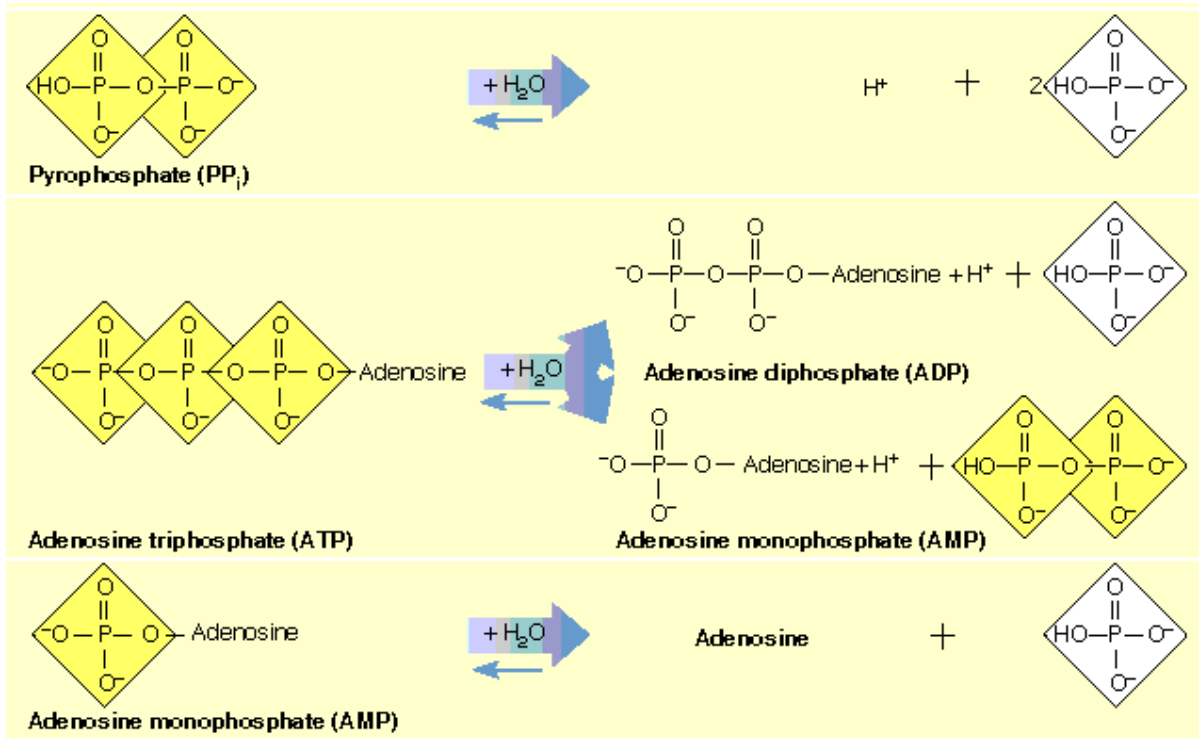
See page 78.

Biochemists assume H_2O and $pH = 7$

**Why is Triphosphate
hydrolysis so exergonic?**

Why is Triphosphate hydrolysis so exergonic?

- Adjacent negative charges
- Resonance stabilization of product
- Product easily solvated



Nucleic Acids

- Biology
- Monomer Building Blocks
- Primary Structure
 - Metastability and Energetics
- Secondary Structure
 - Watson and Crick

Nucleic Acids

- Tertiary Structure
 - A, B, Z
 - Grooves
 - Circular DNA and Supercoils

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β -D-deoxyribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's "standard configuration", the sugar being roughly perpendicular to the attached base. There



This figure is purely diagrammatic. The two ribbons symbolize the two phosphate-sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis.

repel the chains so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical *z*-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally^{2,3} that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data^{4,5} on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

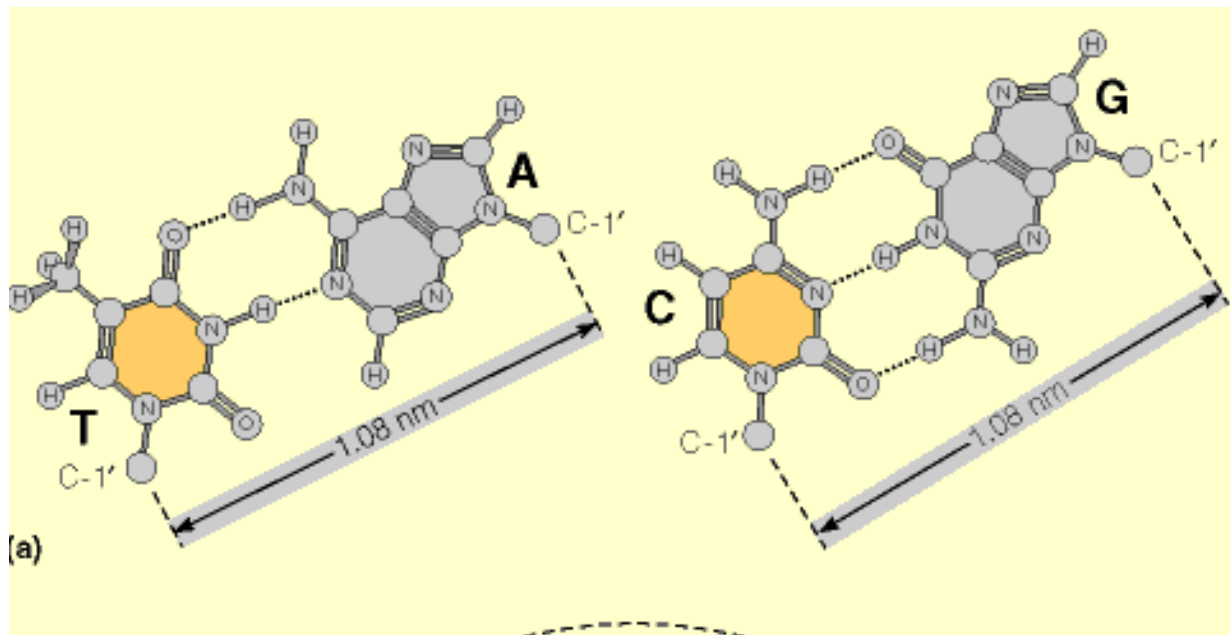
Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

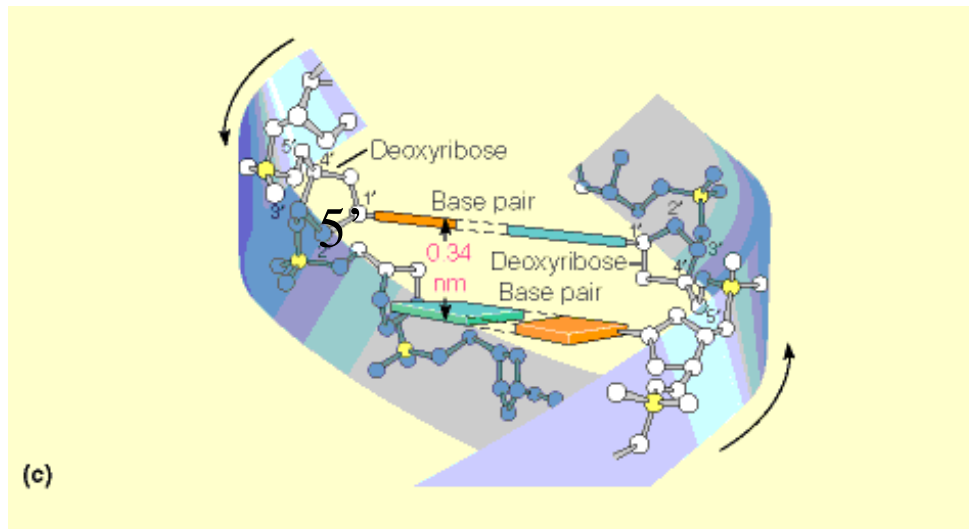
DNA Secondary Structure

- # G's = # C's
- # A's = # T's
- Keto and Amino forms important
- Phosphates on the outside
- Base Pairing--Hydrogen bonding
- Stacking--Aromatic

Isosteric Base Pairs

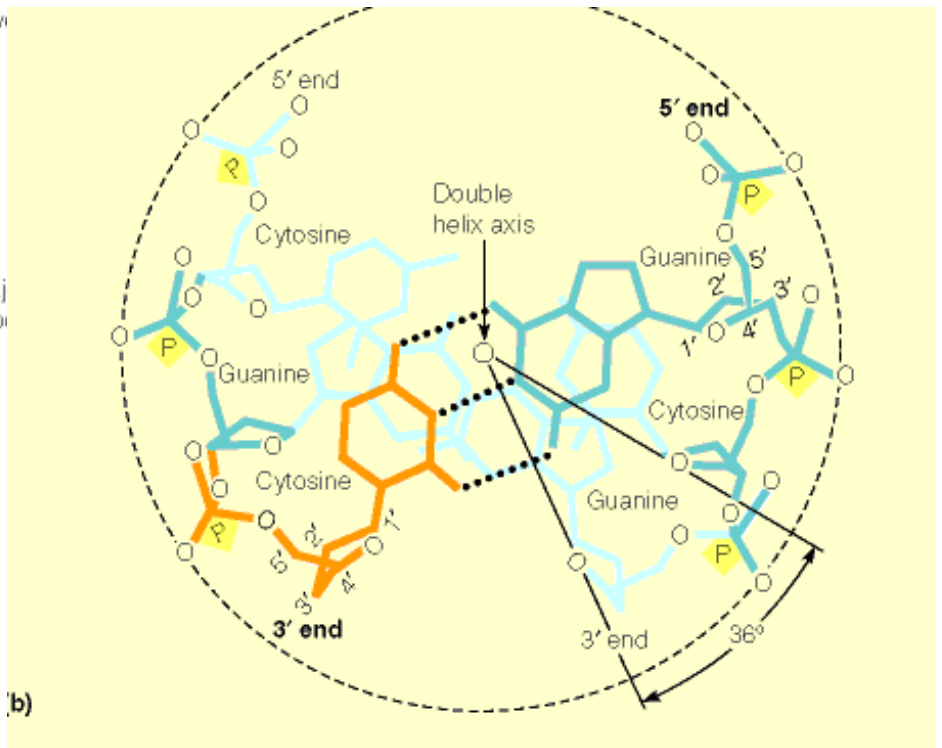
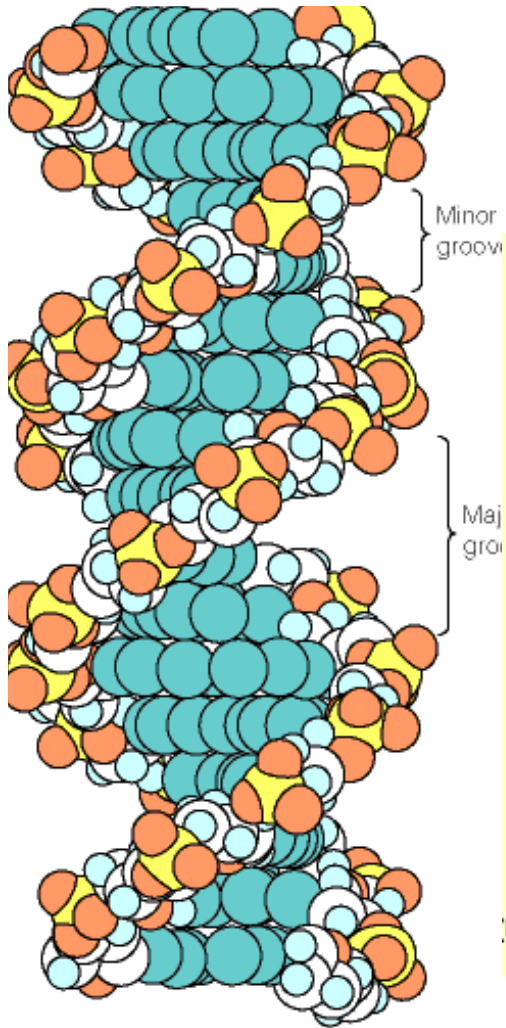


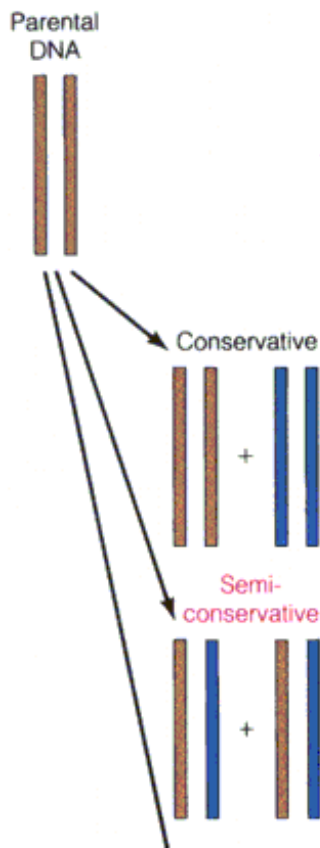
DNA Double Helix



5' \longleftrightarrow 2 antiparallel
5' DNA strands

DNA double helix (B form)

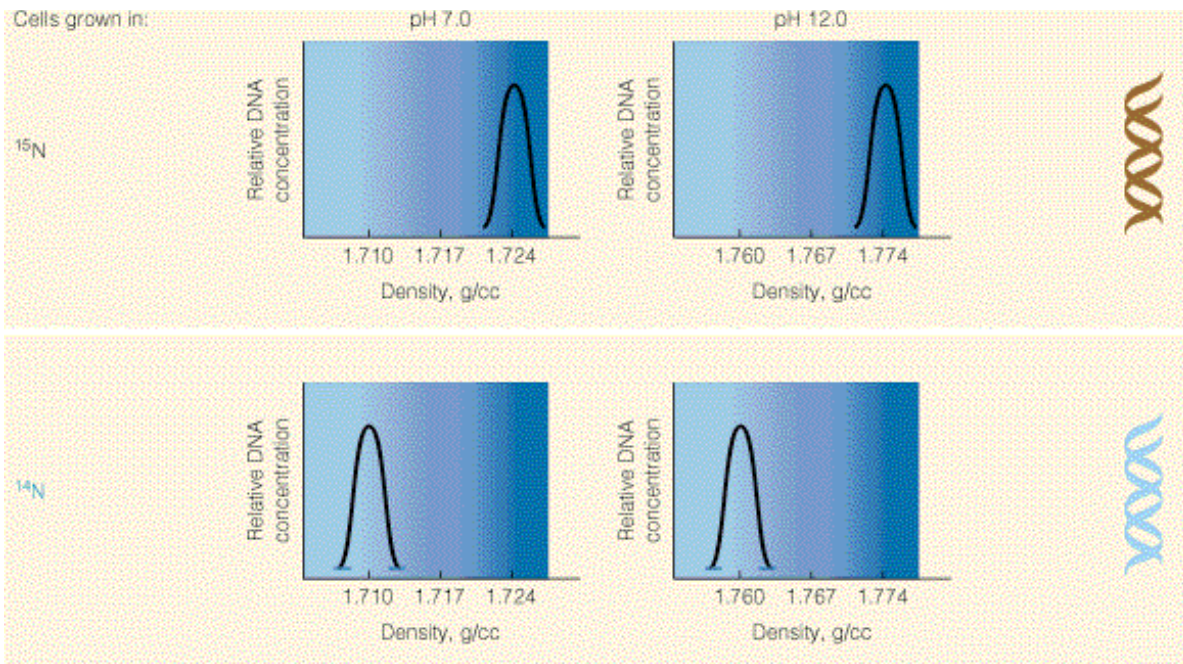


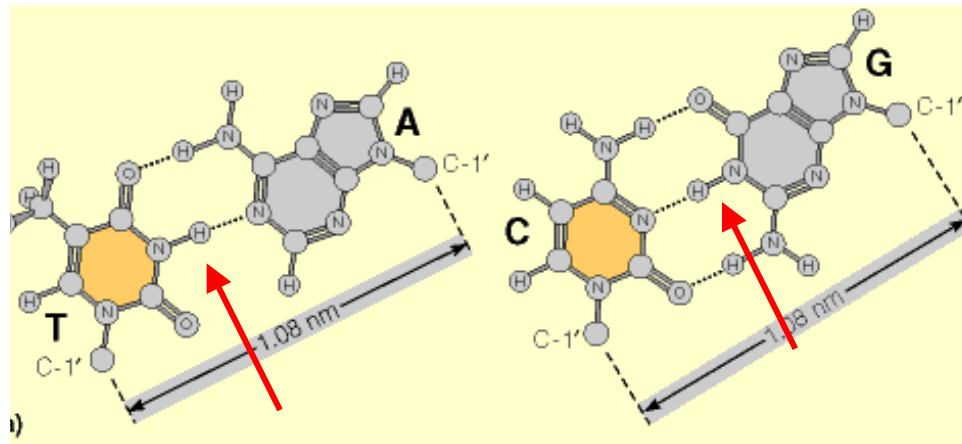


Two possible Replication Mechanisms

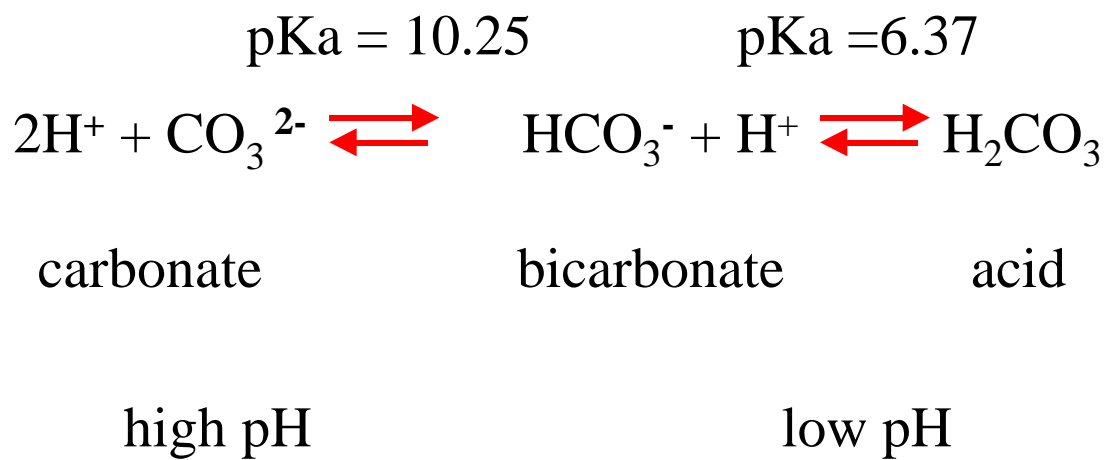
Double stranded

Single stranded





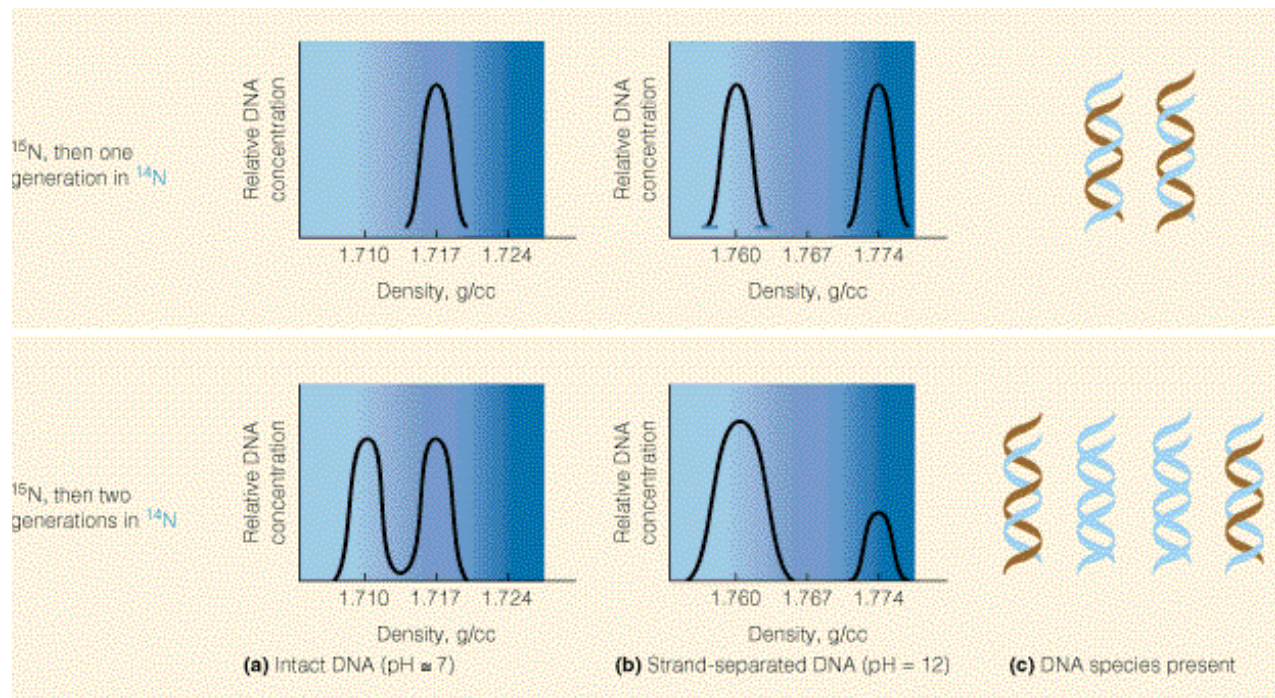
		Phosphate		Base	
		Primary Ionization	Secondary Ionization		
		$\text{HO}-\text{P}(\text{OH})_2-\text{R} \rightleftharpoons \text{HO}-\text{P}(\text{O})(\text{OH})-\text{R} + \text{H}^+$	$\text{HO}-\text{P}(\text{O})(\text{OH})-\text{R} \rightleftharpoons \text{O}^--\text{P}(\text{O})(\text{OH})-\text{R} + \text{H}^+$		
		pK_{a1}	pK_{a2}	pK_a	Reaction (as Loss of Proton from)
5' AMP	0.9	6.1	3.8		N-1
5' GMP	0.7	6.1	2.4		N-7
5' UMP	1.0	6.4	9.4	→	N-1
5' CMP	0.8	6.3	9.5	→	N-3
			4.5		N-3

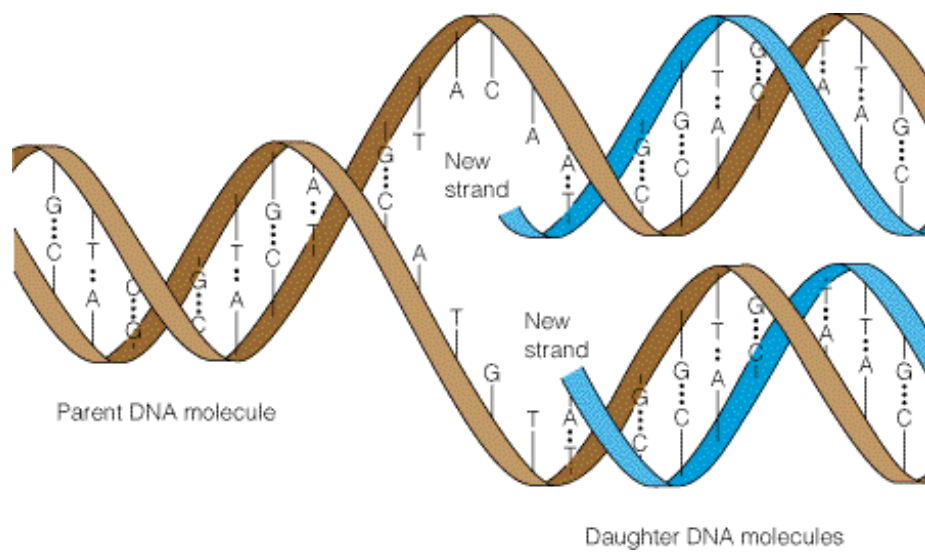


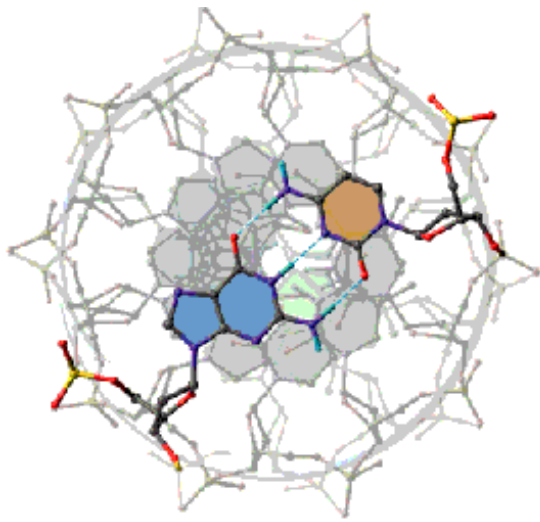
pH 7.4 ??

Double stranded

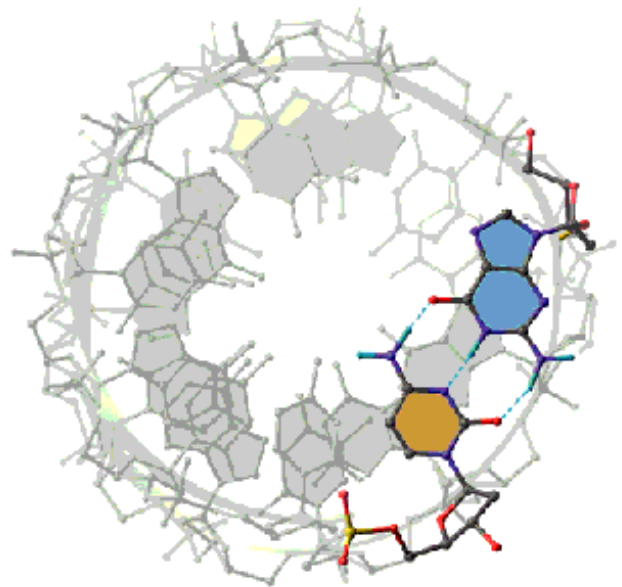
Single stranded



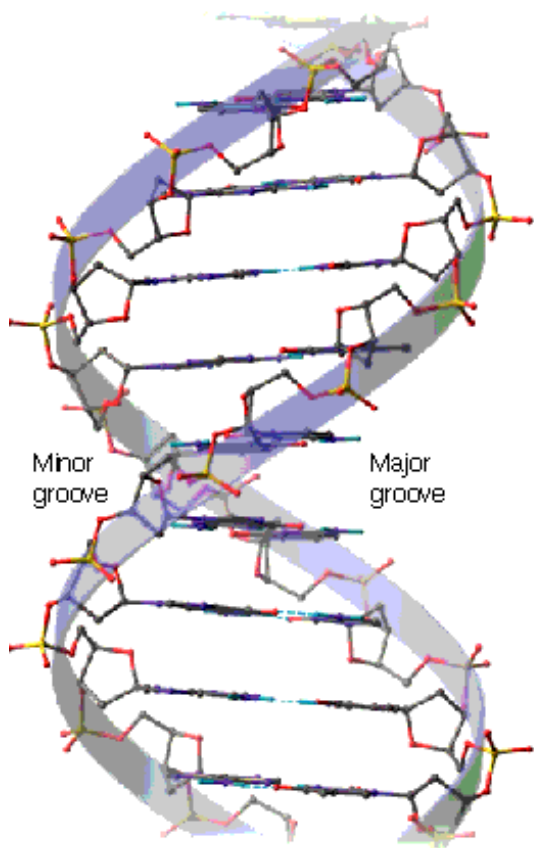




(a) B-DNA, end-on view

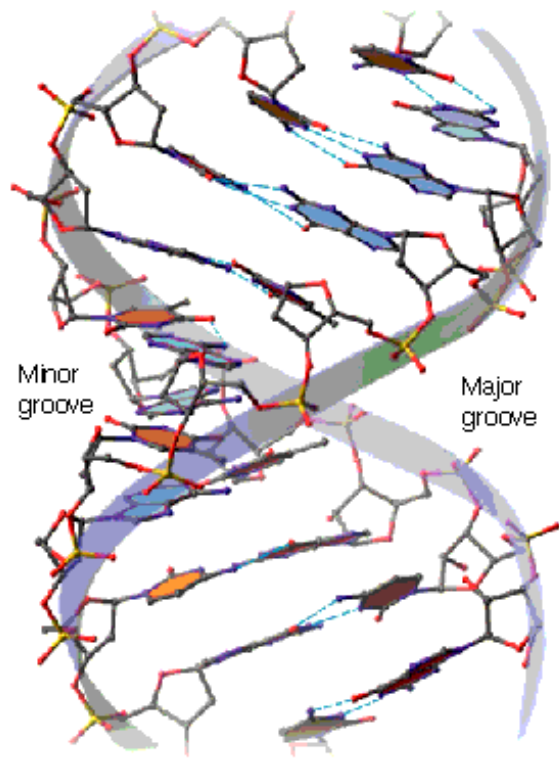


(c) A-DNA, end-on view

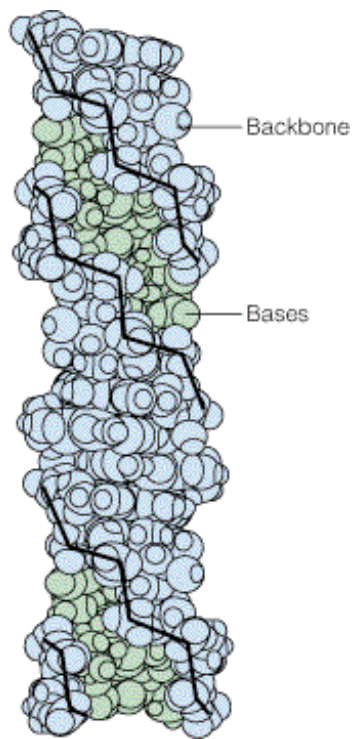


b) B-DNA, side view

very narrow and deep



(d) A-DNA, side view

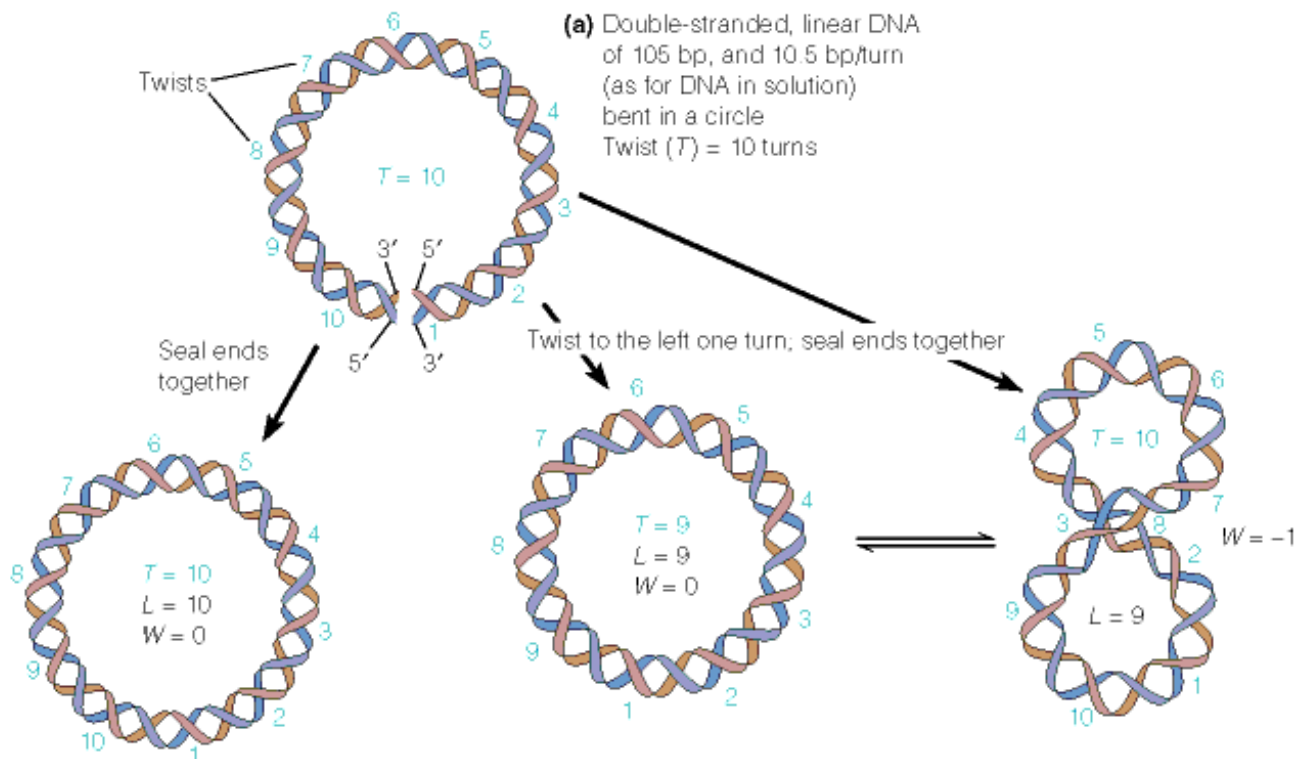


Z DNA is left-handed
But has no known
Biological function.

Actual DNA structure depends on
Primary sequence and varies slightly
From base pair to base pair along the
Helix.

This “microheterogeneity” is
important for proteins and drugs that
recognize particular sequences.

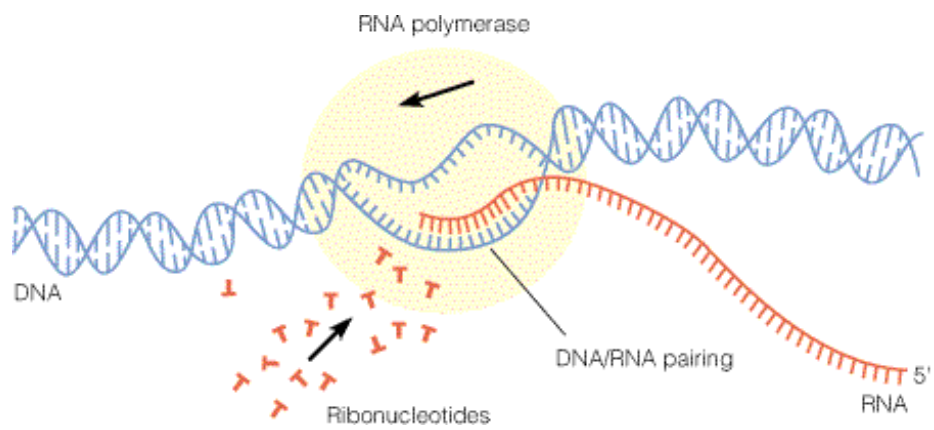
RNA must be A-form due to the
bulky 2' OH group. (see RRE RNA)



(b) Unstrained circle: Double-stranded circular DNA
 Linking number (L) = 10
 Twist (T) = 10 turns
 bp/turn = 10.5
 Writhe (W) = 0

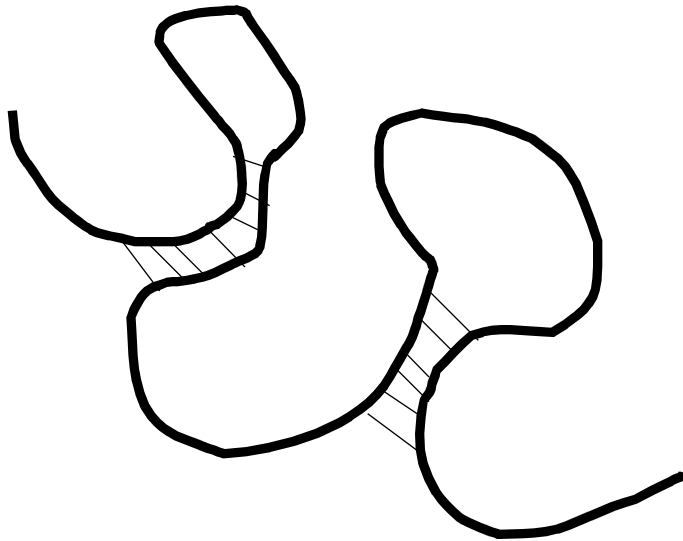
(c) Strained circle: Double-stranded circular DNA
 Linking number (L) = 9
 Twist (T) = 9 turns
 bp/turn = 11.67
 Writhe (W) = 0

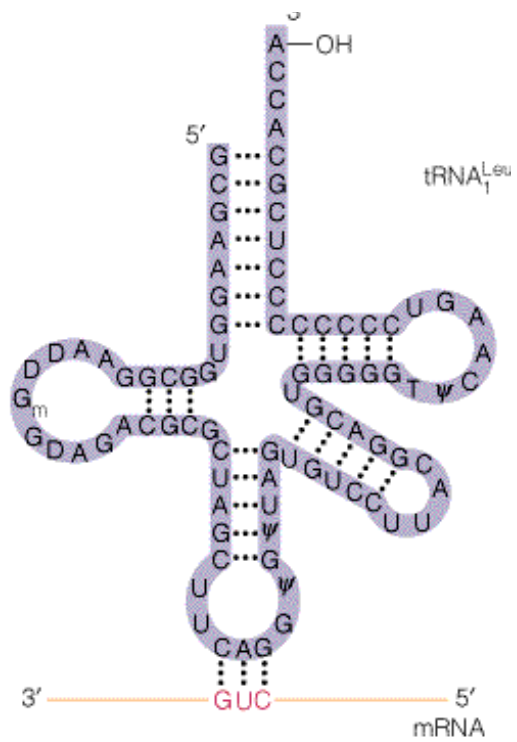
(d) Supercoil: Double-stranded DNA
 Linking number (L) = 9
 Twist (T) = 10 turns
 bp/turn = 10.5
 Writhe (W) = -1



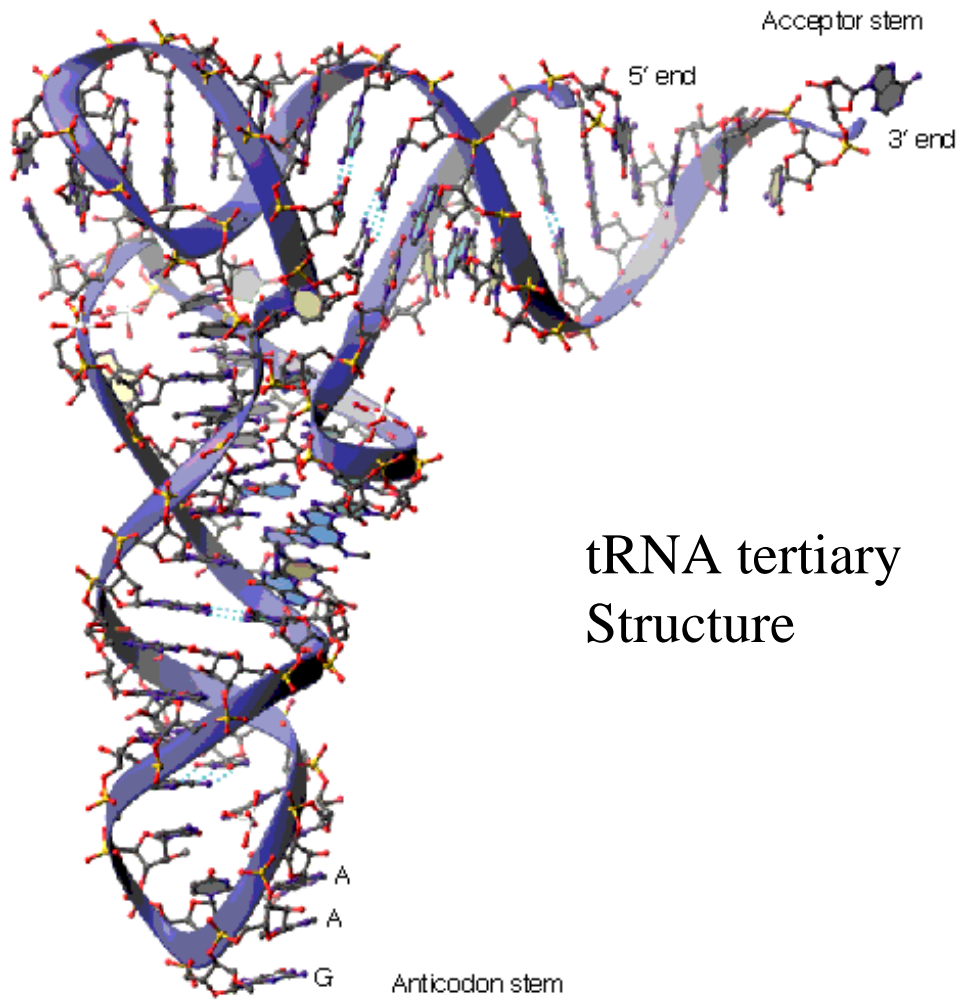
Creation of a transcription bubble reduces T
And introduces supercoiling.

**RNA is single stranded and forms as many
Base pairs as possible.**

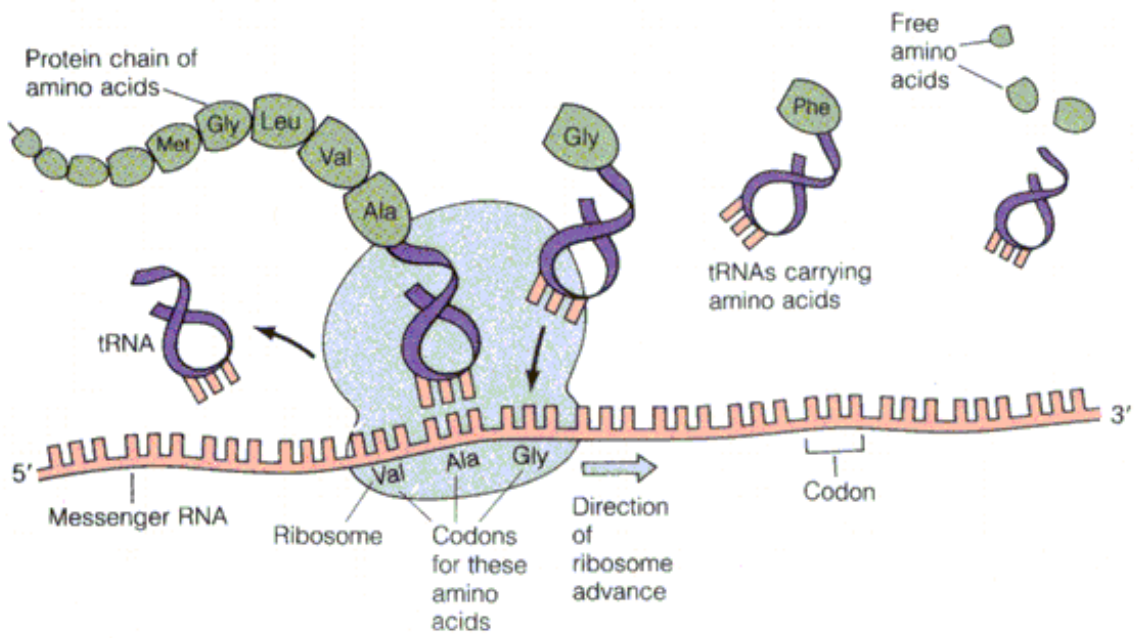




(b)



tRNA tertiary
Structure



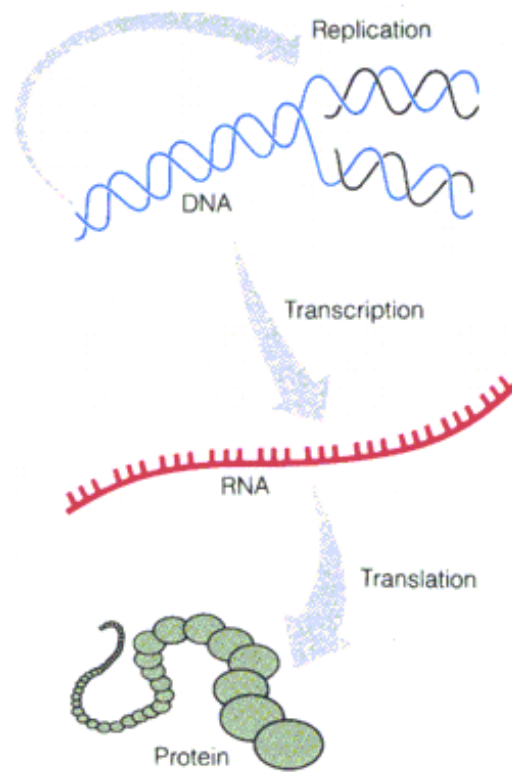
		Second position				
		U	C	A	G	
U	UUU } Phe	UCU } Ser	UAU } Tyr	UGU } Cys	U	
	UUC } Phe		UAC } Tyr	UGC } Cys	C	
	UUA } Leu		UCA } Ser	UAA Stop	UGA Stop	A
	UUG } Leu		UCG } Ser	UAG Stop	UGG Trp	G
C	CUU } Leu	CCU } Pro	CAU } His	CGU } Arg	U	
	CUC } Leu		CCC } Pro	CAC } His	CGC } Arg	C
	CUA } Leu		CCA } Pro	CAA } Gln	CGA } Arg	A
	CUG } Leu		CCG } Pro	CAG } Gln	CGG } Arg	G
A	AUU } Ile	ACU } Thr	AAU } Asn	AGU } Ser	U	
	AUC } Ile		ACC } Thr	AAC } Asn	AGC } Ser	C
	AUA } Ile		ACA } Thr	AAA } Lys	AGA } Arg	A
	AUG Met/start		ACG } Thr	AAG } Lys	AGG } Arg	G
G	GUU } Val	GCU } Ala	GAU } Asp	GGU } Gly	U	
	GUC } Val		GCC } Ala	GAC } Asp	GGC } Gly	C
	GUA } Val		GCA } Ala	GAA } Glu	GGA } Gly	A
	GUG } Val		GCG } Ala	GAG } Glu	GGG } Gly	G

Central Dogma

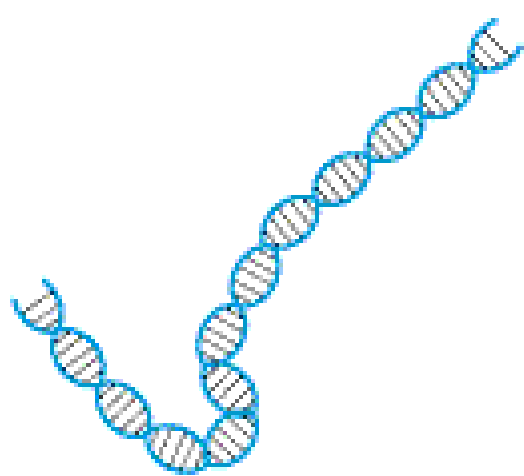
DNA

RNA

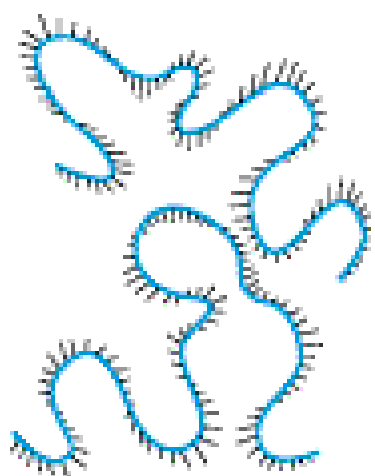
Protein



Base Pairing is important at each step



Native DNA



Denatured DNA

)