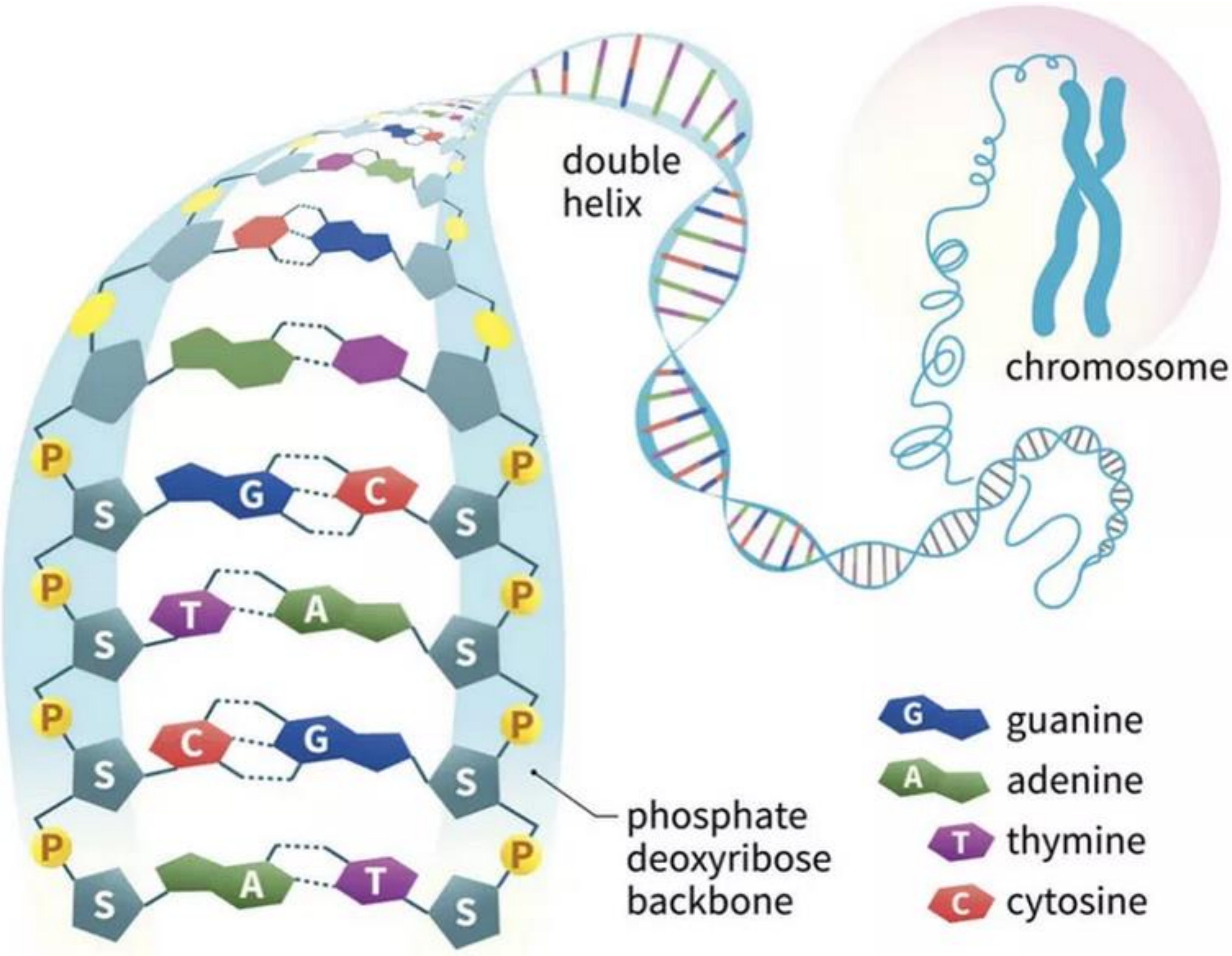
Nucleic acids and Protein Synthesis



Dr. Kinkar Biswas

Introduction

- Each cell of our bodies contains thousands of different proteins.
- How do cells know which proteins to synthesize out of the extremely large number of possible amino acid sequences?
- the transmission of hereditary information took place in the nucleus, more specifically in structures called chromosomes.
- The hereditary information was thought to reside in genes within the chromosomes.
- Chemical analysis of nuclei showed chromosomes are made up largely of proteins called histones and nucleic acids.

Nucleic acids

Backbones of chromosomes

Nucleic acids
- Ribonucleic acids (RNA)
- Deoxyribonucleic acids (DNA)

The Central Dogma (F. Crick):

DNA (genome) → mRNA (transcriptome) → Protein (proteome)

The monomeric units for nucleic acids are nucleotides
Nucleotides are made up of three structural subunits

1. Sugar: ribose in RNA, 2-deoxyribose in DNA
2. Heterocyclic base
3. Phosphate

Nucleic acids

DNA stores the genetic information of an organism and transmits that information from one generation to another.

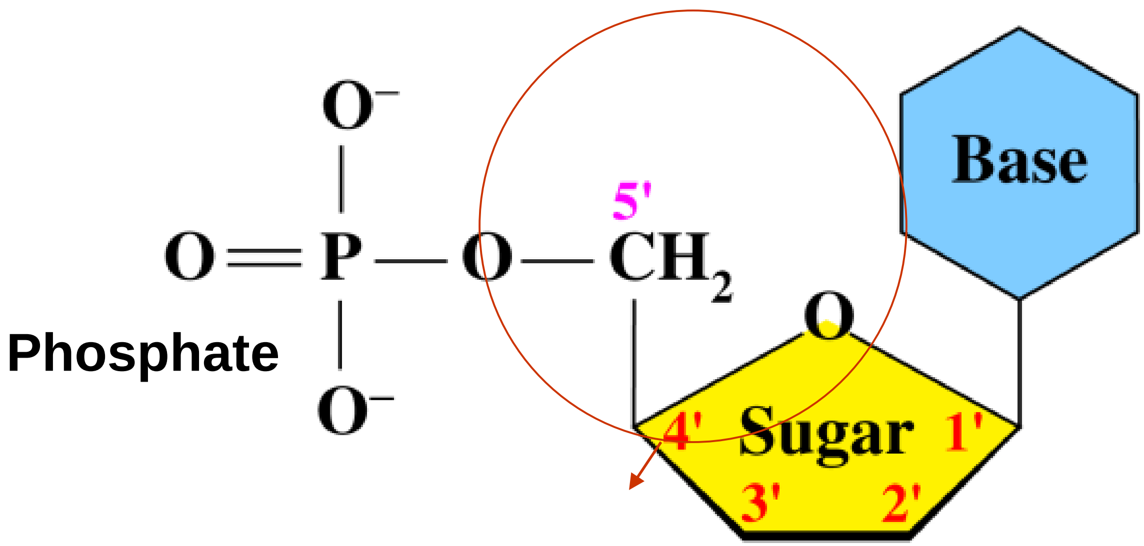
RNA translates the genetic information contained in DNA into proteins needed for all cellular function.

RNA and DNA are unbranched polymers (monomers: nucleotides).

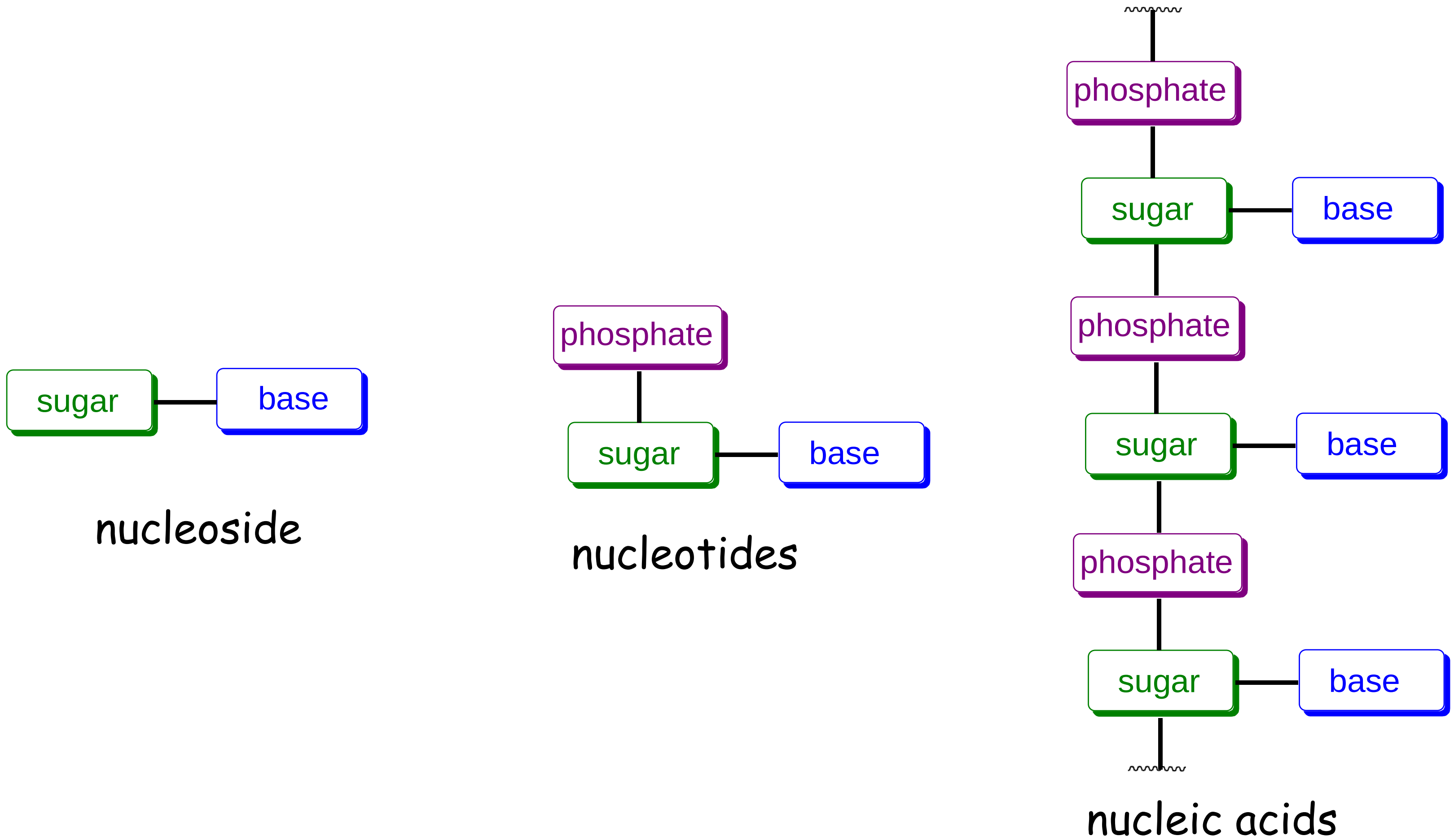
Nucleotide

Nucleotides

- Sugar (Ribose and 2-deoxyribose)
- Heterocyclic base
- Phosphate

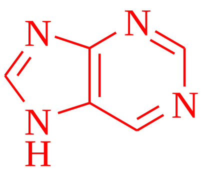


Nucleoside, nucleotides and nucleic acids

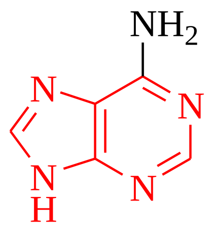


The chemical linkage between monomer units in nucleic acids is a phosphodiester

Heterocyclic Bases

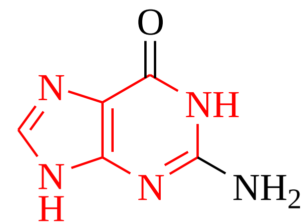


Purine



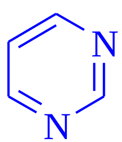
Adenine(A)
9*H*-purin-6-amine

(DNA or RNA)

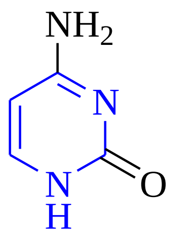


Guanine(G)
2-amino-1*H*-purin-6(9*H*)-one

(DNA or RNA)

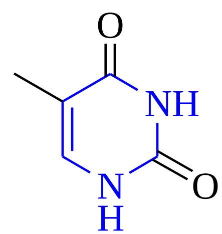


Pyrimidine

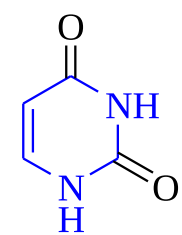


Cytosine (C)
4-aminopyrimidin-2(1*H*)-one

(DNA or RNA)



Thymine (T)
5-methylpyrimidine
-2,4(1*H*,3*H*)-dione
(DNA)



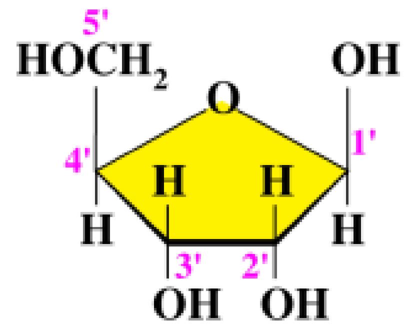
Uracil (U)
pyrimidine-2,4(1*H*,3*H*)-dione

(RNA)

Sugars (monosaccharide)

RNA contains:

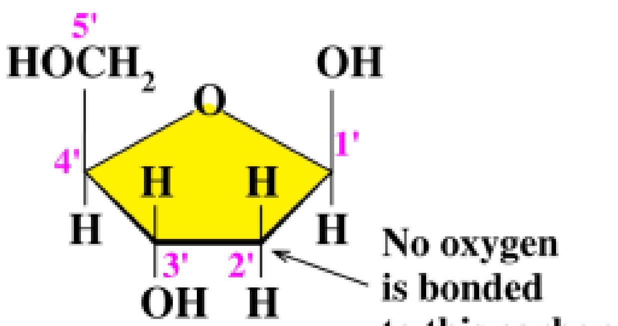
- D-Ribose sugar



Ribose in RNA

DNA contains:

- 2-Deoxy-D-Ribose sugar (without O on carbon 2)

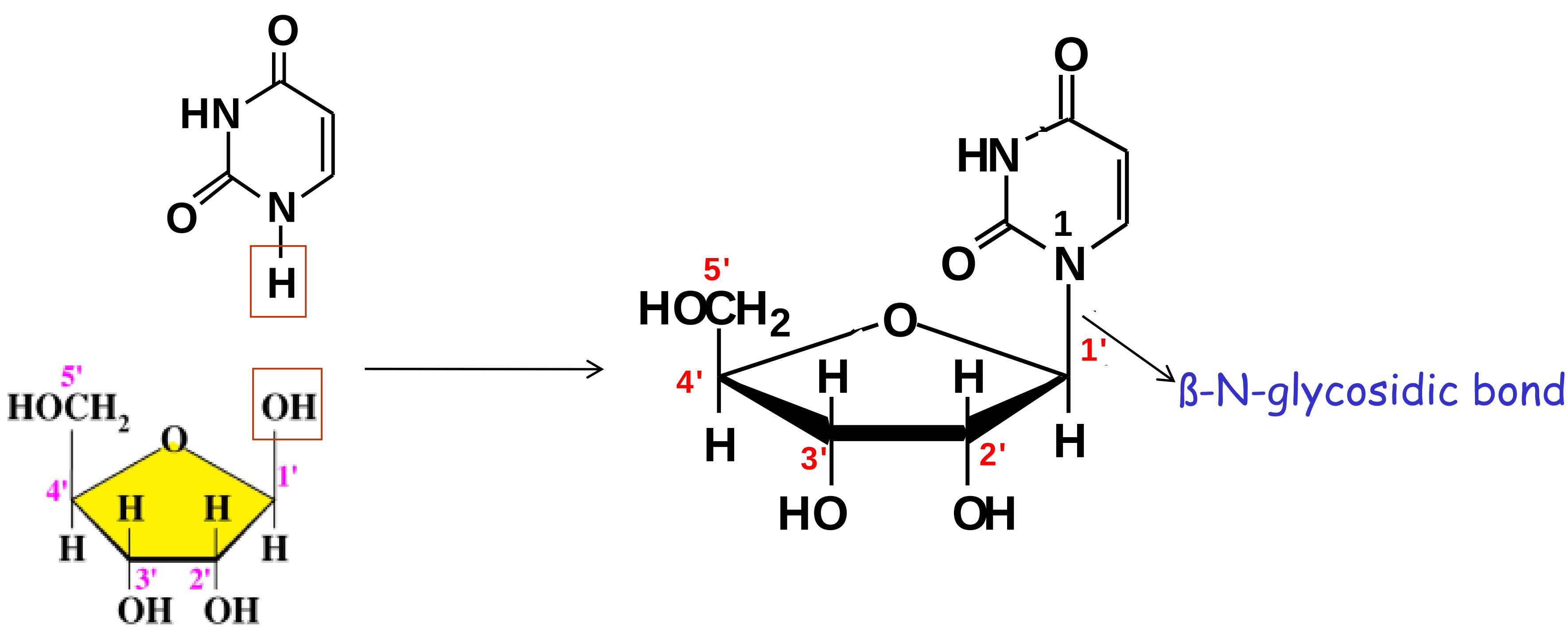


Deoxyribose in DNA

Nucleoside

When a N atom of the base forms a glycosidic bond to C_1' (anomeric C) of a sugar.

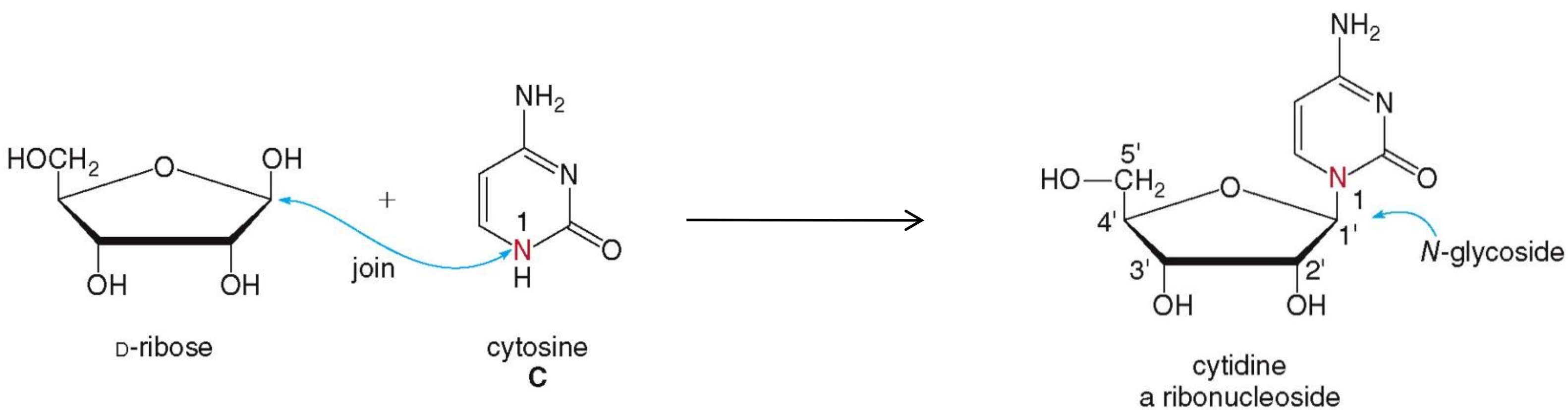
Base + Sugar ⟶ Nucleoside

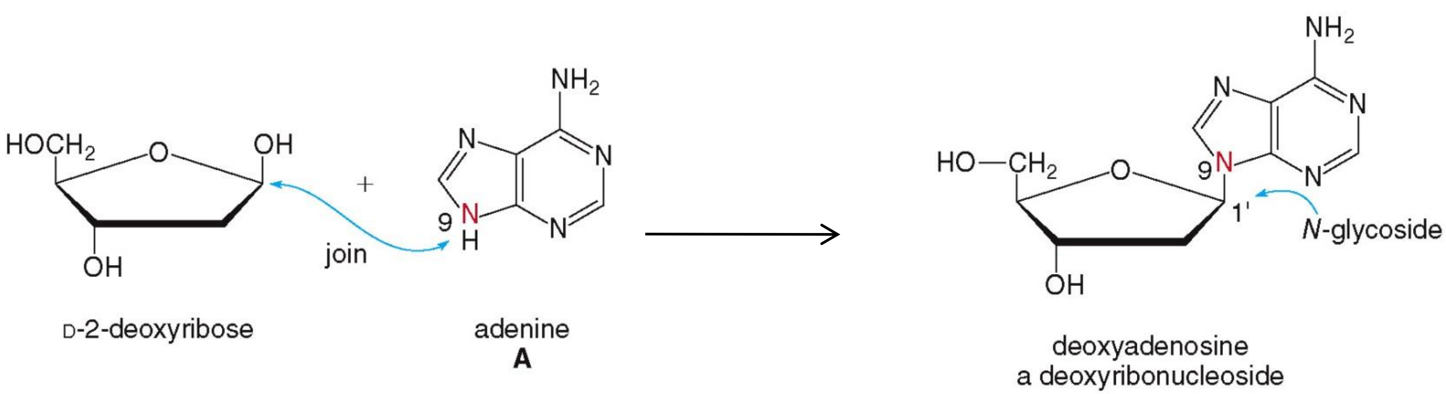


Nucleoside

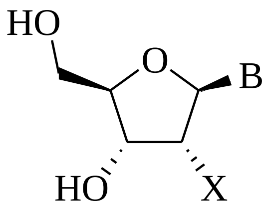
To name a nucleoside derived from a pyrimidine base, use the suffix "-idine".
To name a nucleoside derived from a purine base, use the suffix "-osine".

For deoxyribonucleosides, add the prefix "deoxy-".



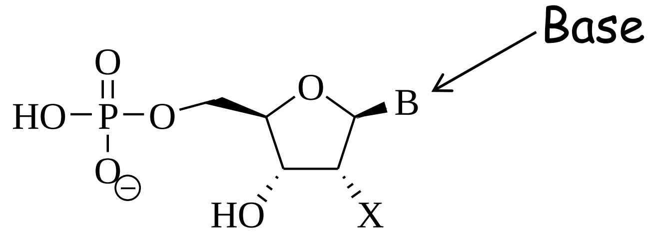


Nucleotide



Ribonucleoside X=OH

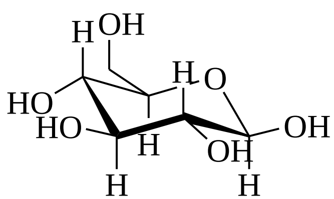
Deoxyribonucleoside X=H



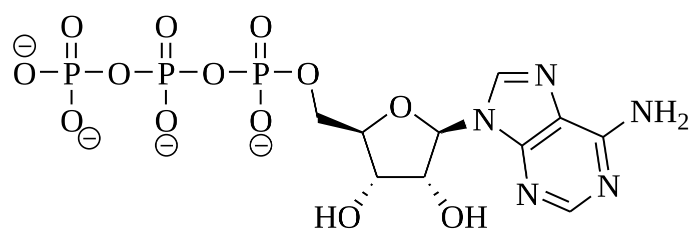
Ribonucleoside 5'-monophosphate X=OH, NMP

Deoxyribonucleoside 5'-monophosphate X=H, dNMP

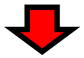
Kinase-Enzymes that catalyze the phosphoryl transfer reaction from ATP to an acceptor substrate.

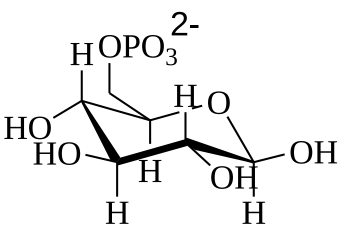


Glucose



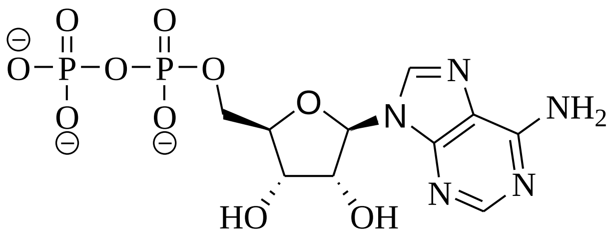
Adenosine tri phosphatae, ATP





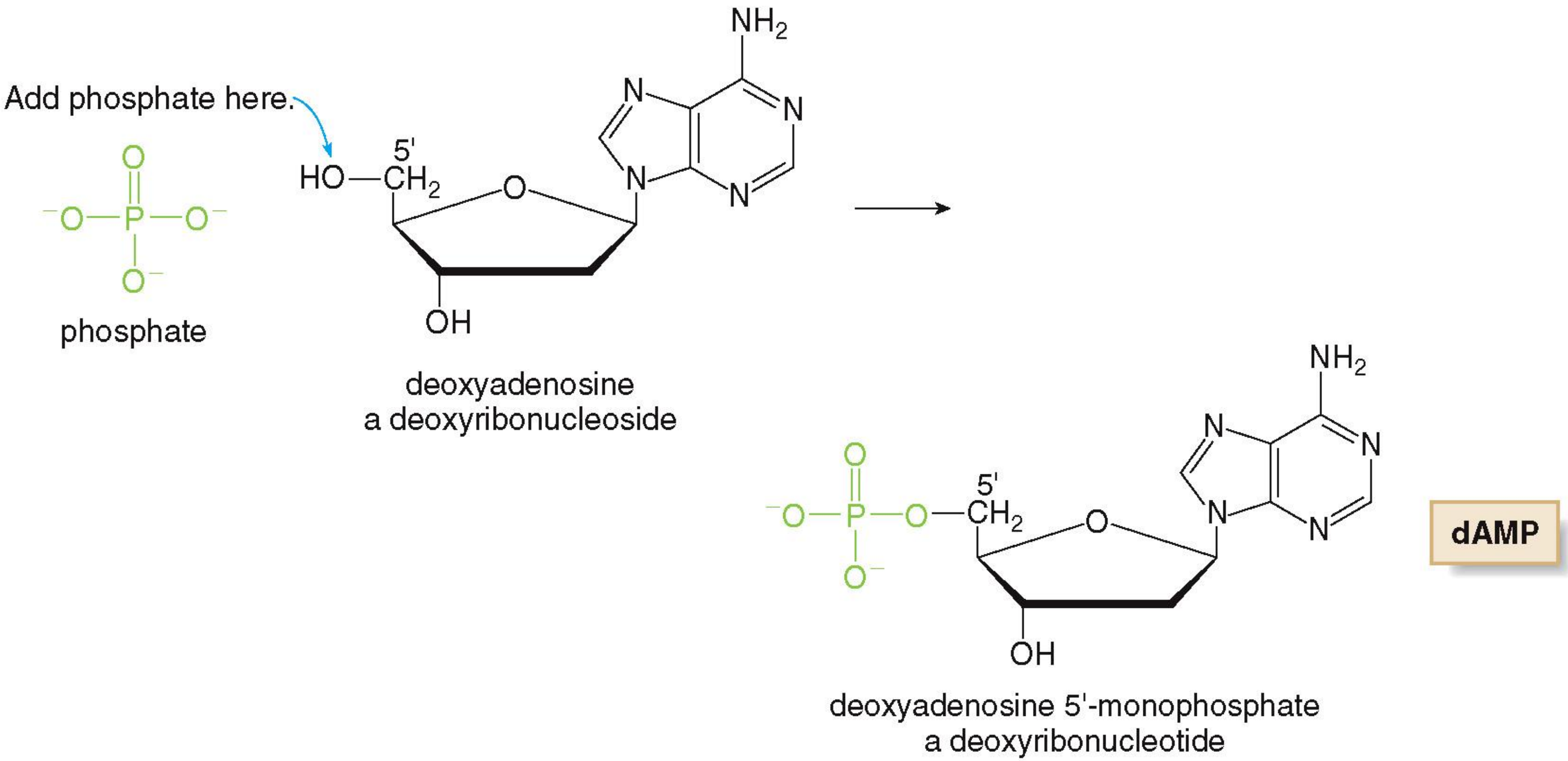
Glucose

+



Adenosine di-phosphatae, ADP

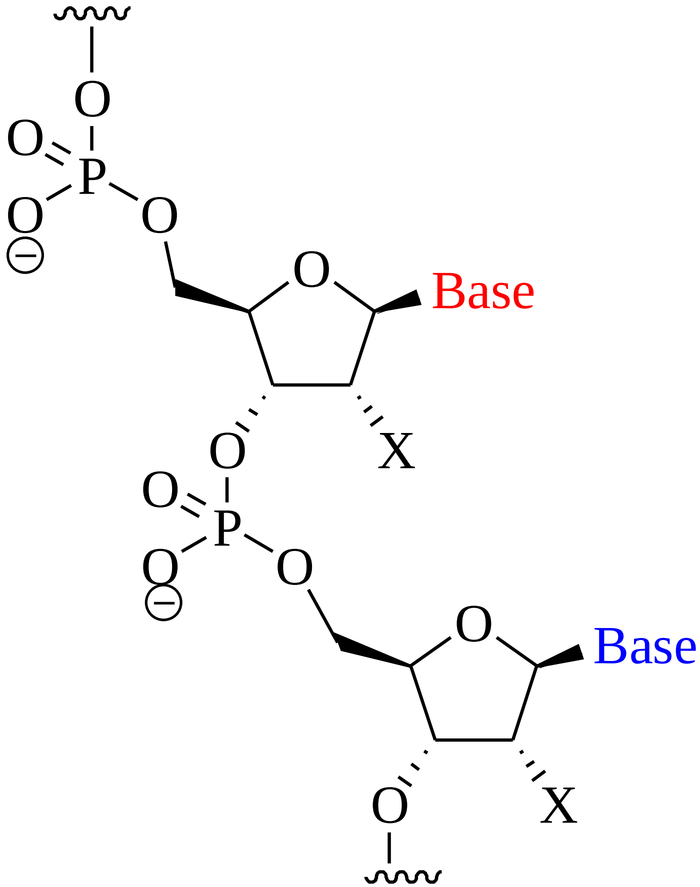
Nucleotide



The name deoxyadenosine 5′-monophosphate is abbreviated as dAMP.

Phosphodiester

The chemical linkage between nucleotide units in nucleic acids is a phosphodiester

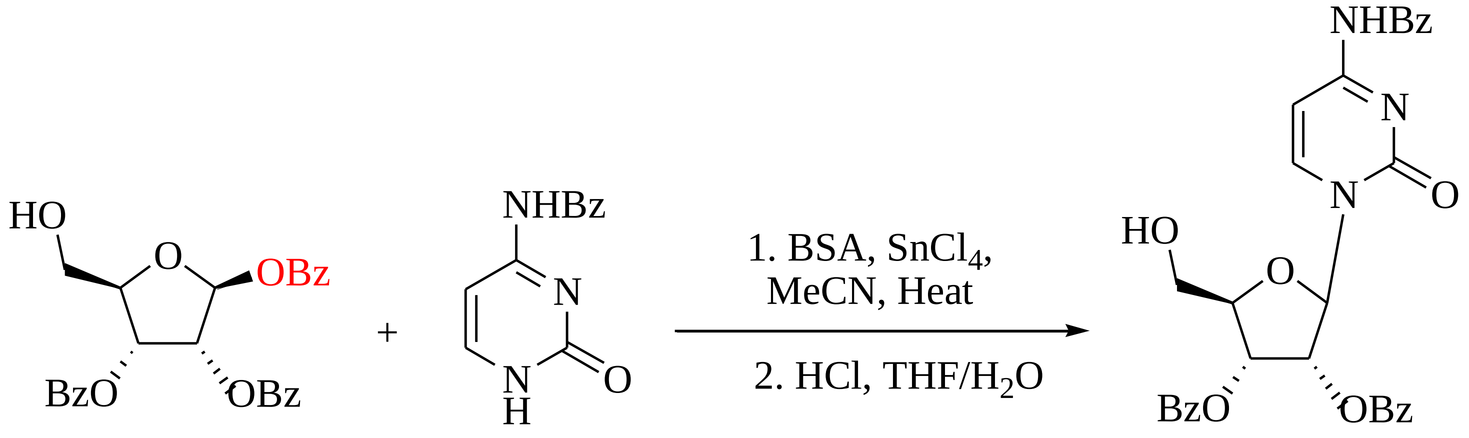


Deoxyribonucleoside X=H
Ribonucleoside X=OH

3' — 5' Connection

Laboratory synthesis of Nucleosides

1. Silyl-Hilbert-Johnson nucleosidation



D-Ribose
[Bz protected]

N^4-Benzoylcytosine

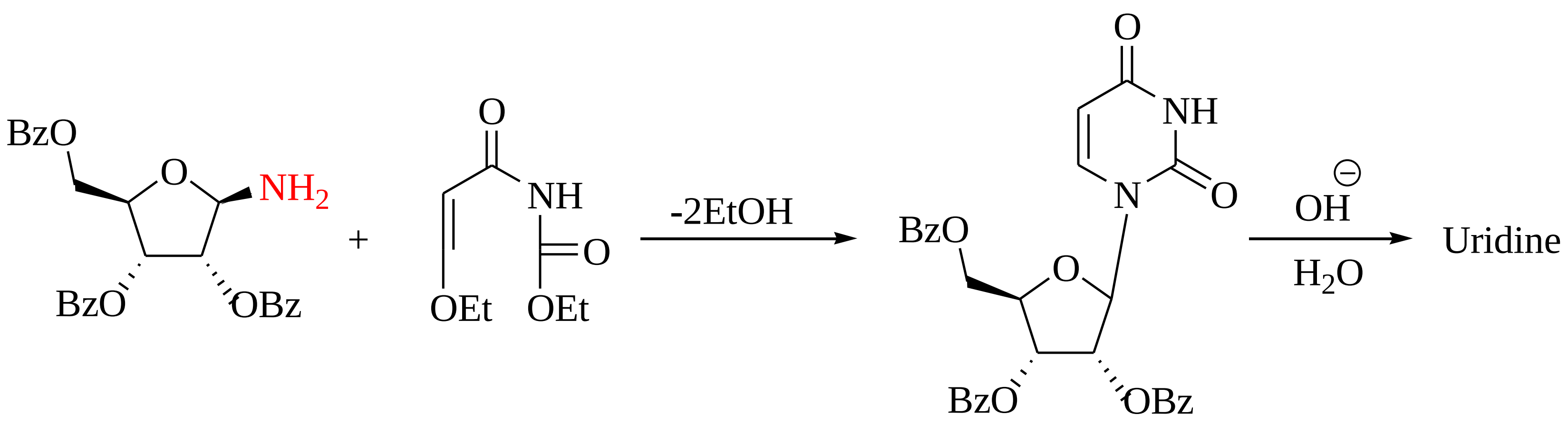
Cytidine
[Bz protected]

BSA = $CH_3C[=NSi(CH_3)]OSi(CH_3)_3$

N,O-bis(trimethylsilyl)acetamide

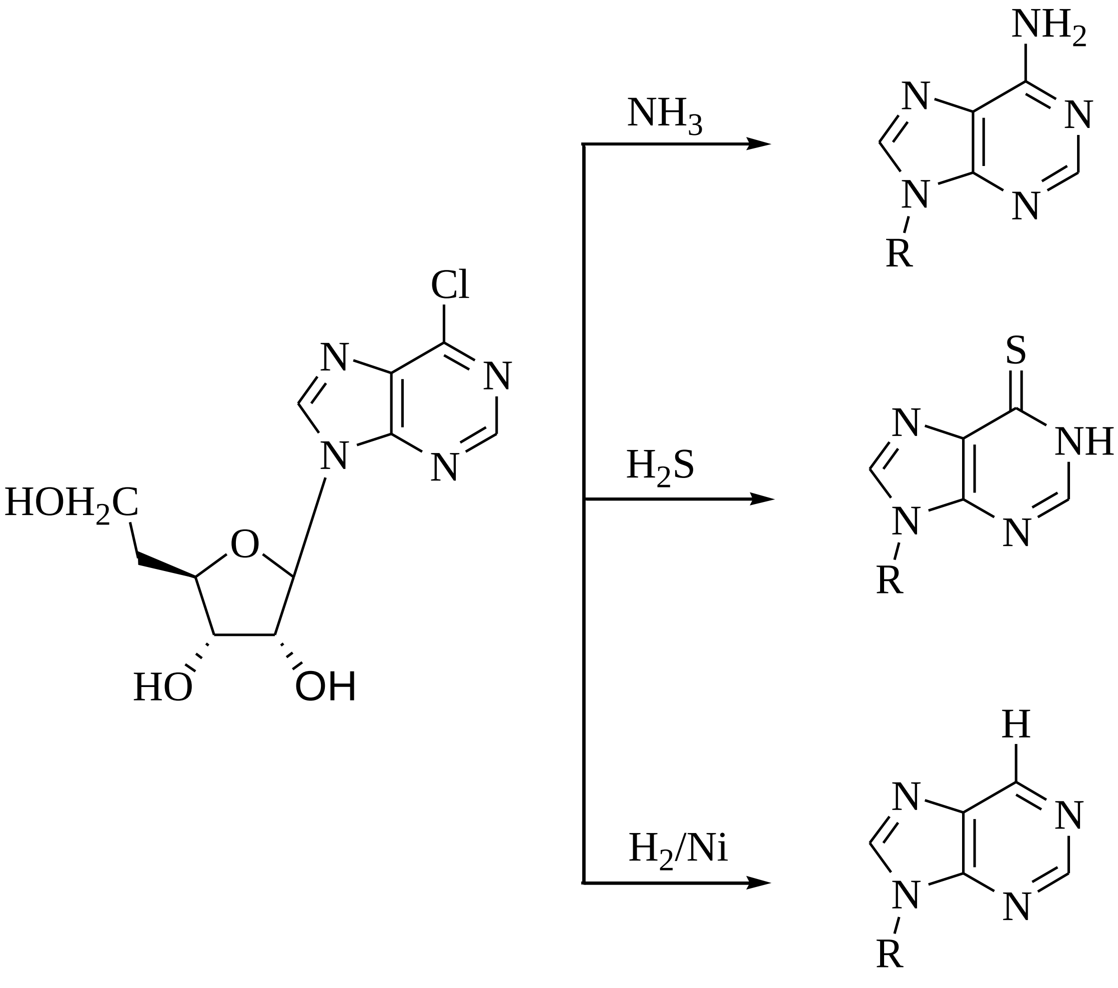
Laboratory synthesis of Nucleosides

2. Another technique for the synthesis of nucleosides



Laboratory synthesis of Nucleosides

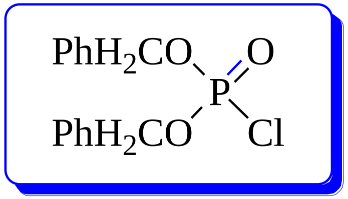
3. Using 6-chloropurine derivatives



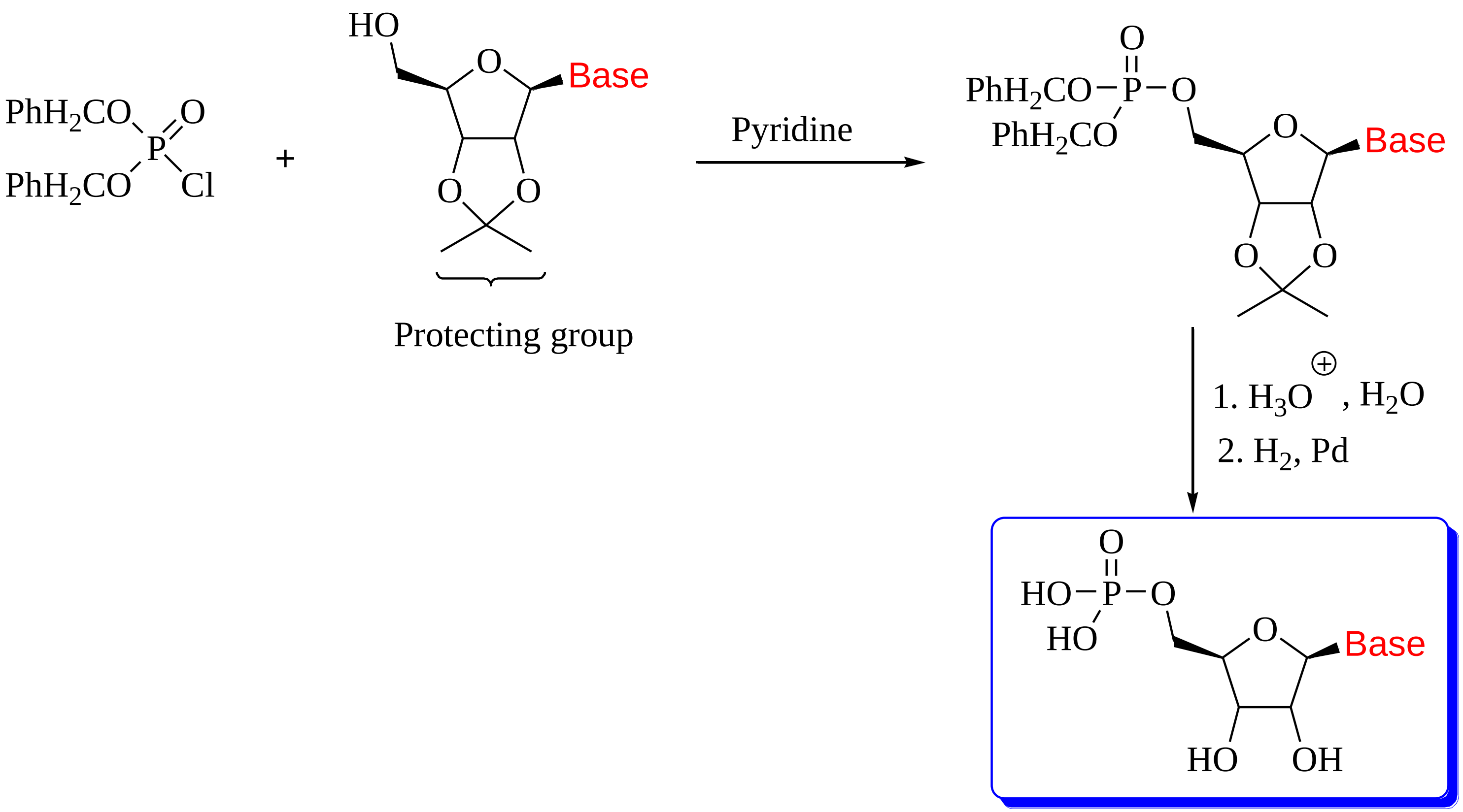
R = β–D-Ribosyl

Laboratory synthesis of Nucleotides

Phosphorylating agents

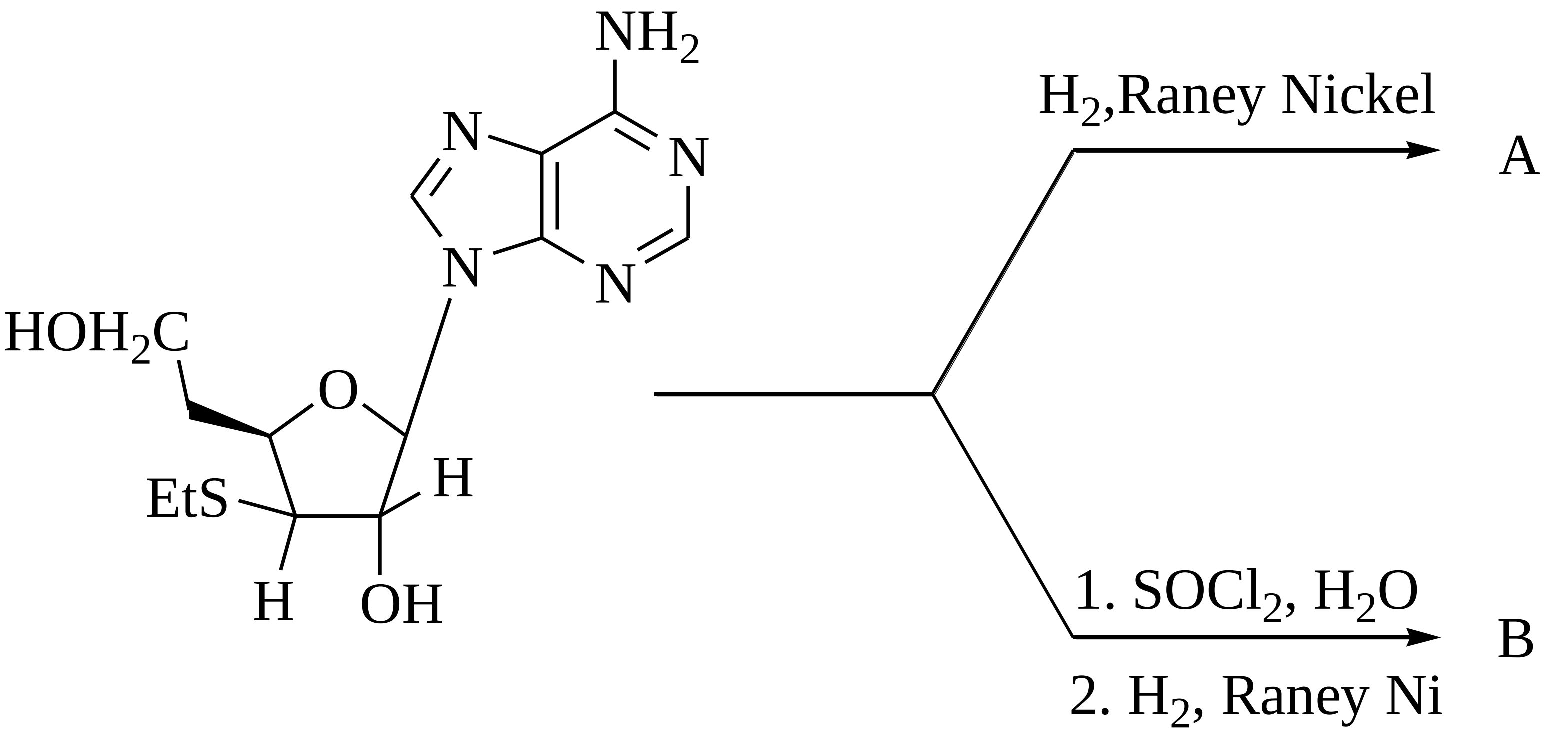


Dibenzyl phosphochloridate



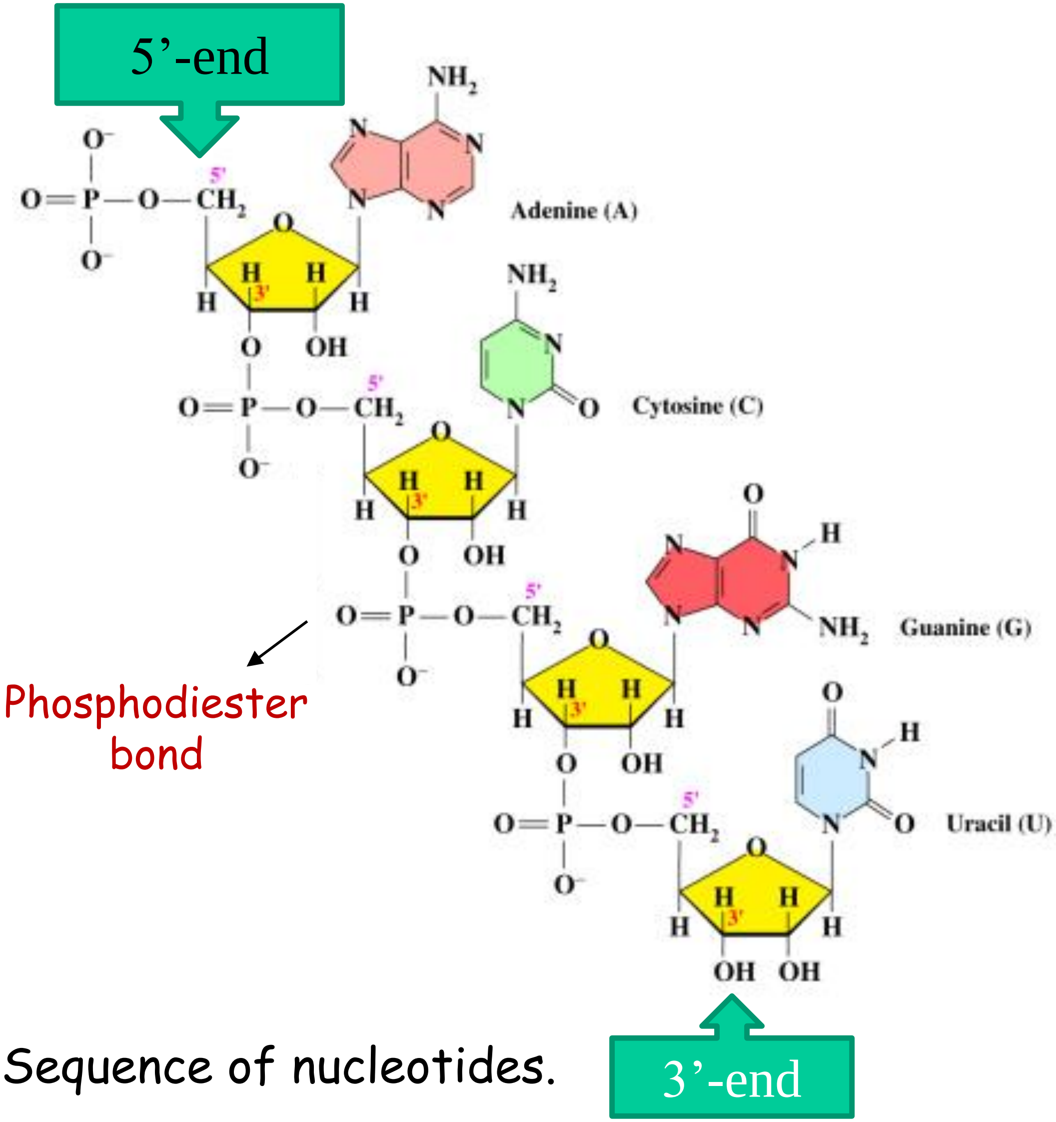
Nucleotide

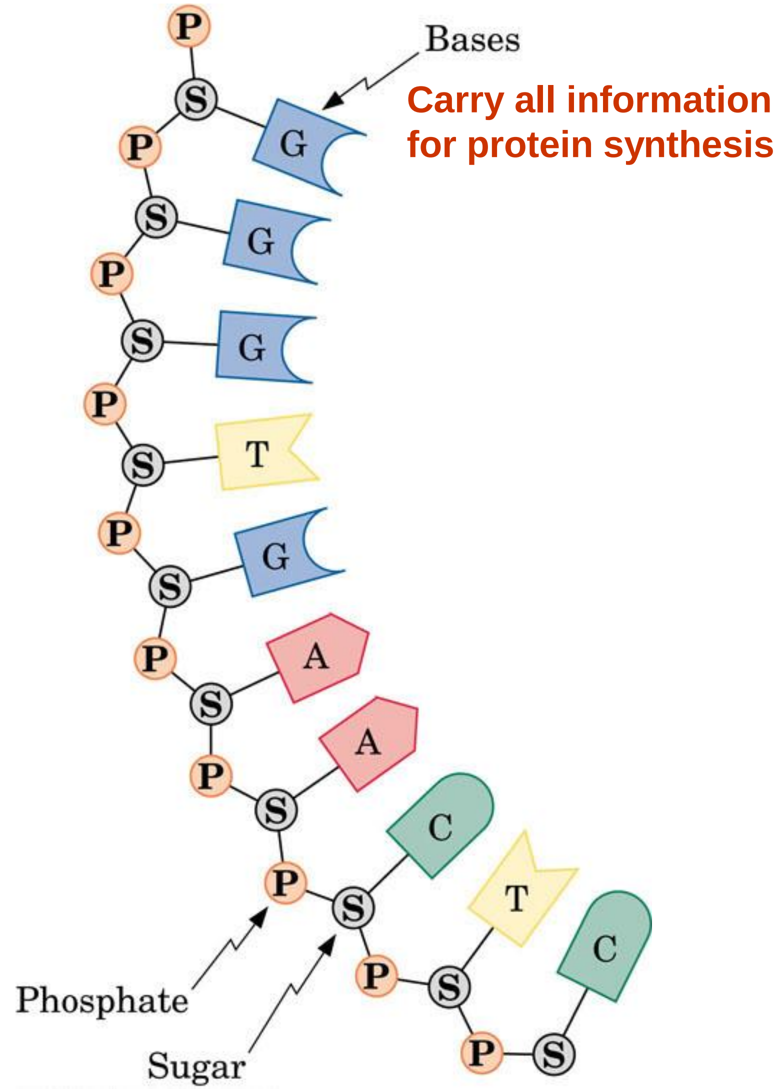
Problems


NH2
N
N
N
N
HOH2C
O
EtS
H
H
OH
H2,Raney Nickel
A
1. SOCl2, H2O
2. H2, Raney Ni
B

Polynucleotide

Primary structure of DNA and RNA





Sequence of nucleotides.

Each phosphate is linked to C3′ and C5′ of two sugars.

Primary structure of DNA and RNA

A nucleoside = Base + Sugar

A nucleotide = Base + Sugar + Phosphate

A nucleic acid = A chain of nucleotides

Like amino acids (C-terminal and N-terminal):

Base sequence is read from the C5′ (free phosphate) end to the C3′ (free hydroxyl) end.

-ACGU-

Secondary Structure of DNA: The Double Helix

It was the now-classic proposal of James Watson and Francis Crick (made in 1953 and verified shortly thereafter through the X-ray analysis by Maurice Wilkins) that gave a model for the secondary structure of DNA. This work earned Crick, Watson, and Wilkins the 1962 Nobel Prize in Physiology or Medicine. Many believe that Rosalind Franklin, whose X-ray data was also key to solving the structure of DNA, should have shared the Nobel prize, but her death from cancer in 1958 precluded it.

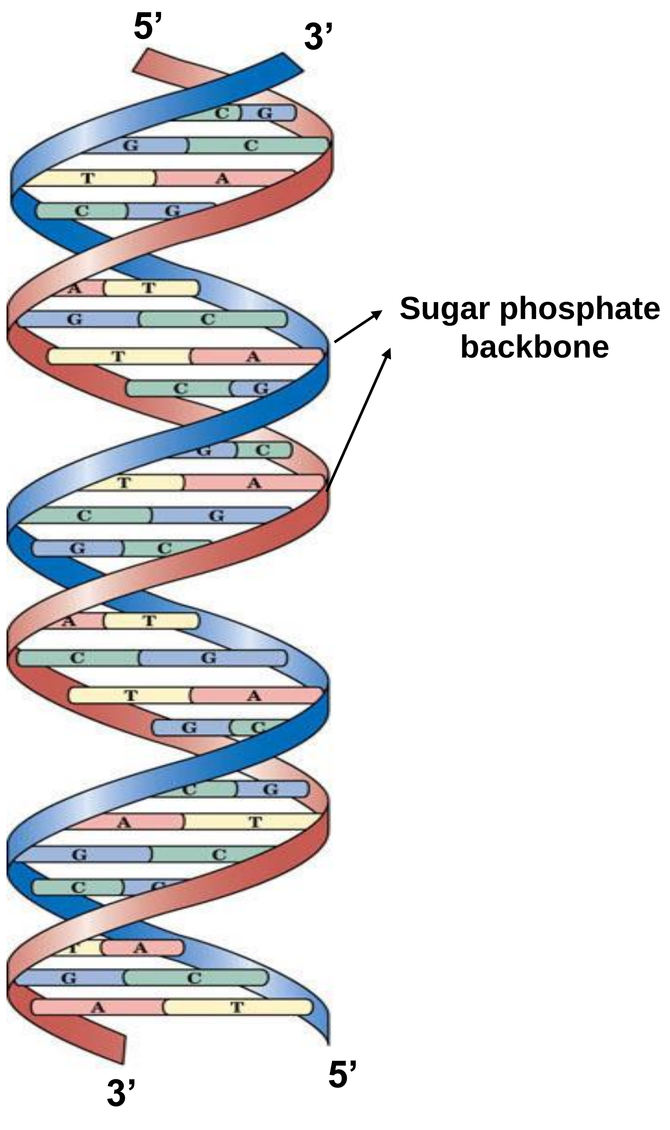
Secondary structure of DNA

- Hydrogen bonds link paired bases:

  Adenine-Thymine (A–T)
  Guanine-Cytosine (G-C)

3D structure

- Sugar-Phosphate backbone is hydrophilic and stays on the outside (bases are hydrophobic).



DNA Composition of Various Species

	Base Proportions (mol %)							
Species	G	A	C	T	$\frac{G+A}{C+T}$	$\frac{A+T}{G+C}$	$\frac{A}{T}$	$\frac{G}{C}$
Sarcina lutea	37.1	13.4	37.1	12.4	1.02	0.35	1.08	1.00
Escherichia coli K12	24.9	26.0	25.2	23.9	1.08	1.00	1.09	0.99
Wheat germ	22.7	27.3	22.8[a]	27.1	1.00	1.19	1.01	1.00
Bovine thymus	21.5	28.2	22.5[a]	27.8	0.96	1.27	1.01	0.96
Staphylococcus aureus	21.0	30.8	19.0	29.2	1.11	1.50	1.05	1.11
Human thymus	19.9	30.9	19.8	29.4	1.01	1.52	1.05	1.01
Human liver	19.5	30.3	19.9	30.3	0.98	1.54	1.00	0.98

[a]Cytosine + methylcytosine.

Source: Smith, E. L.; Hill, R. L.; Lehman, I. R.; Lefkowitz, R. J.; Handler, P.; and White, A. *Principles of Biochemistry: General Aspects*, 7th ed. McGraw-Hill: New York, 1983; p. 132.

Chargaff's rule

1. (%G + %A)/(%C + %T) ≈ 1.
2. Mol % of adenine = Mol % of thymine i.e. %A/ %T ≈ 1 and

   Mol % of guanine = Mol % of cytosine i.e. %G/ %C ≈ 1.
3. Watson and Crick Model

   Two nucleic acid chains are held together by hydrogen bonds between base pair on opposite strands.

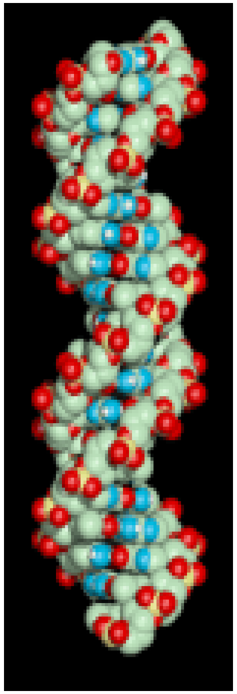
   The base-pairs are on the inside of the helix and the sugar-phosphate backbone is on the outside.

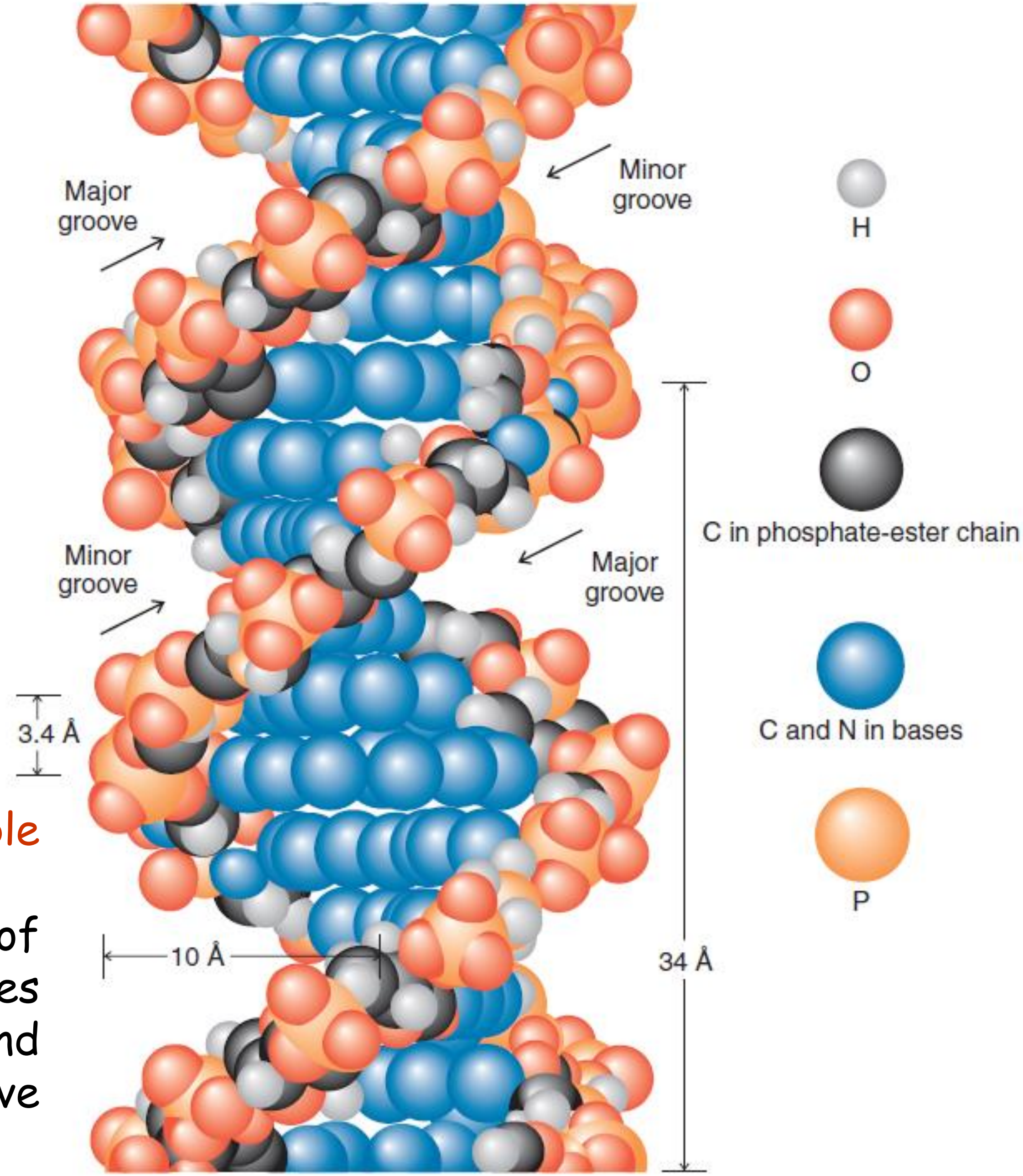
   The pitch of the helix- 10 successive nucleotide pairs gives rise to one complete turn in 34 Å (the repeat distance)

   Double helix: Purine-pyrimidine hydrogen bonding between base-pairs.

   Purine-purine : ✖ because they would be too large to fit

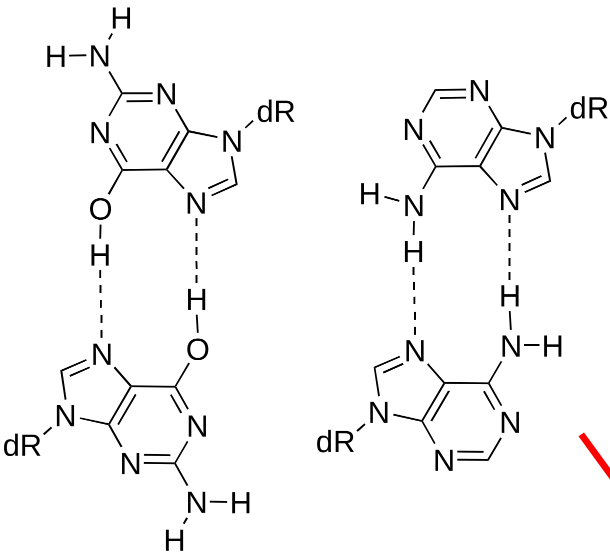
   Pyrimidine-pyrimidine : ✖ because they would be too far apart to form effective hydrogen bonds



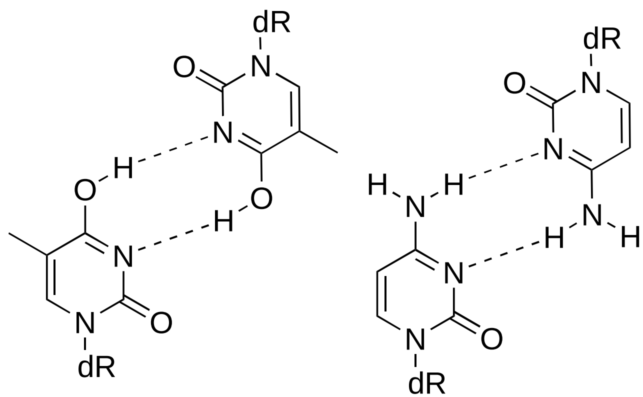


A molecular model of a portion of the DNA double helix.
(Reprinted with permission of The McGraw-Hill Companies from Neal, L., Chemistry and Biochemistry: A Comprehensive Introduction, © 1971.)

Initial “like-with-like”, parallel helix:

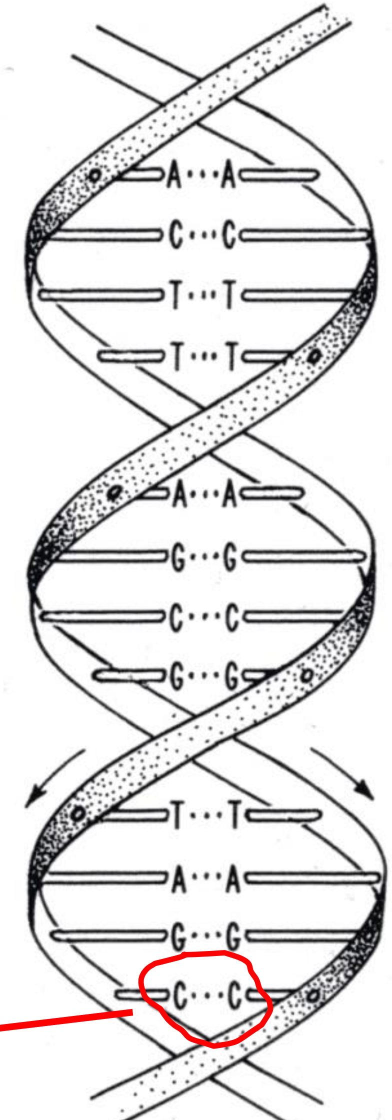


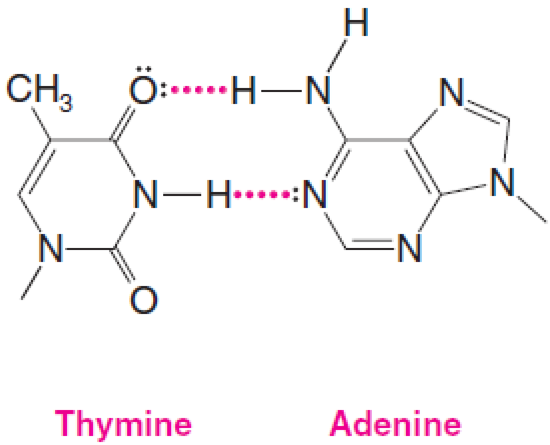
purine - purine



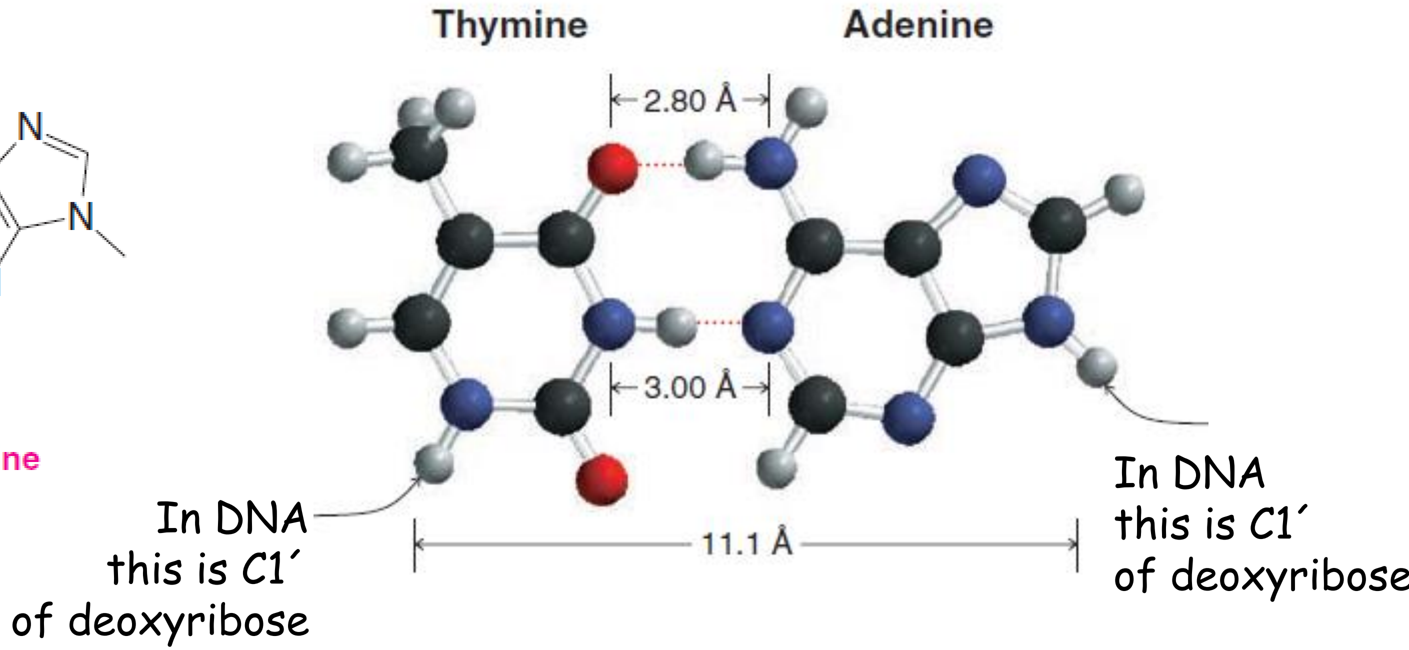
pyrimidine - pyrimidine

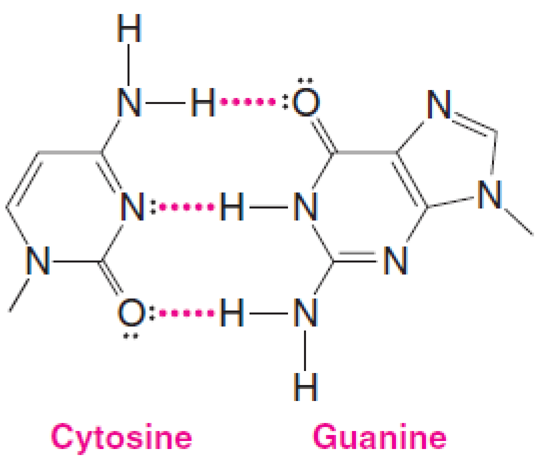
Wrong tautomers



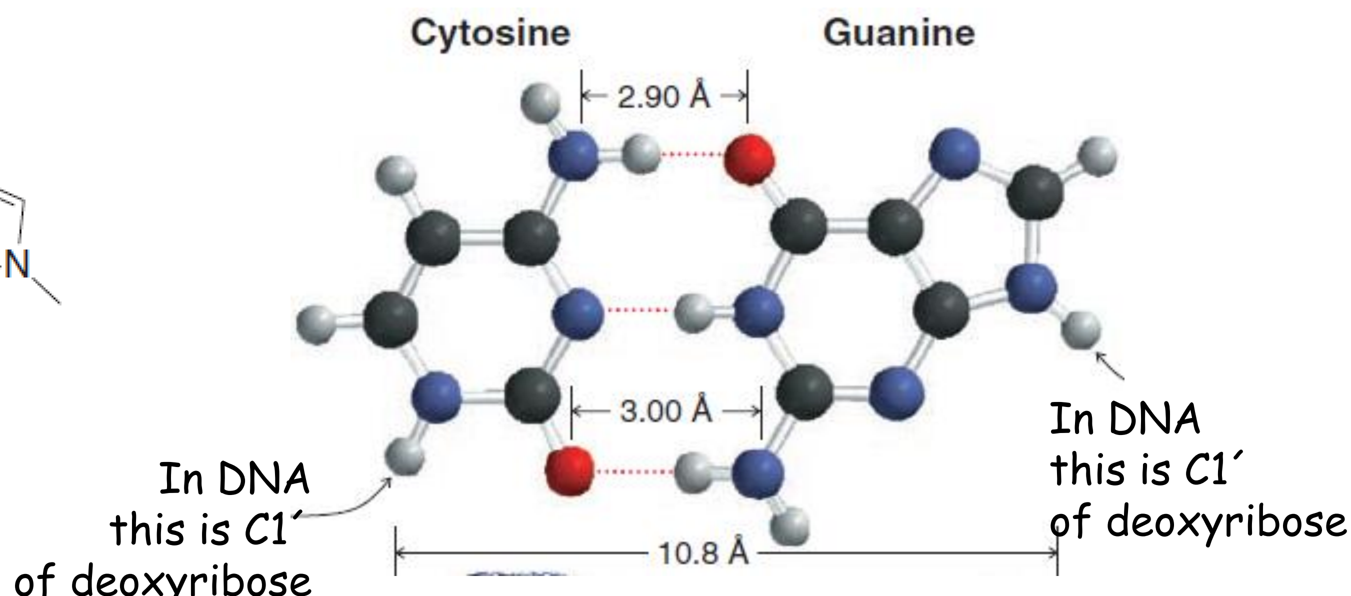


2H Bonds





3H Bonds



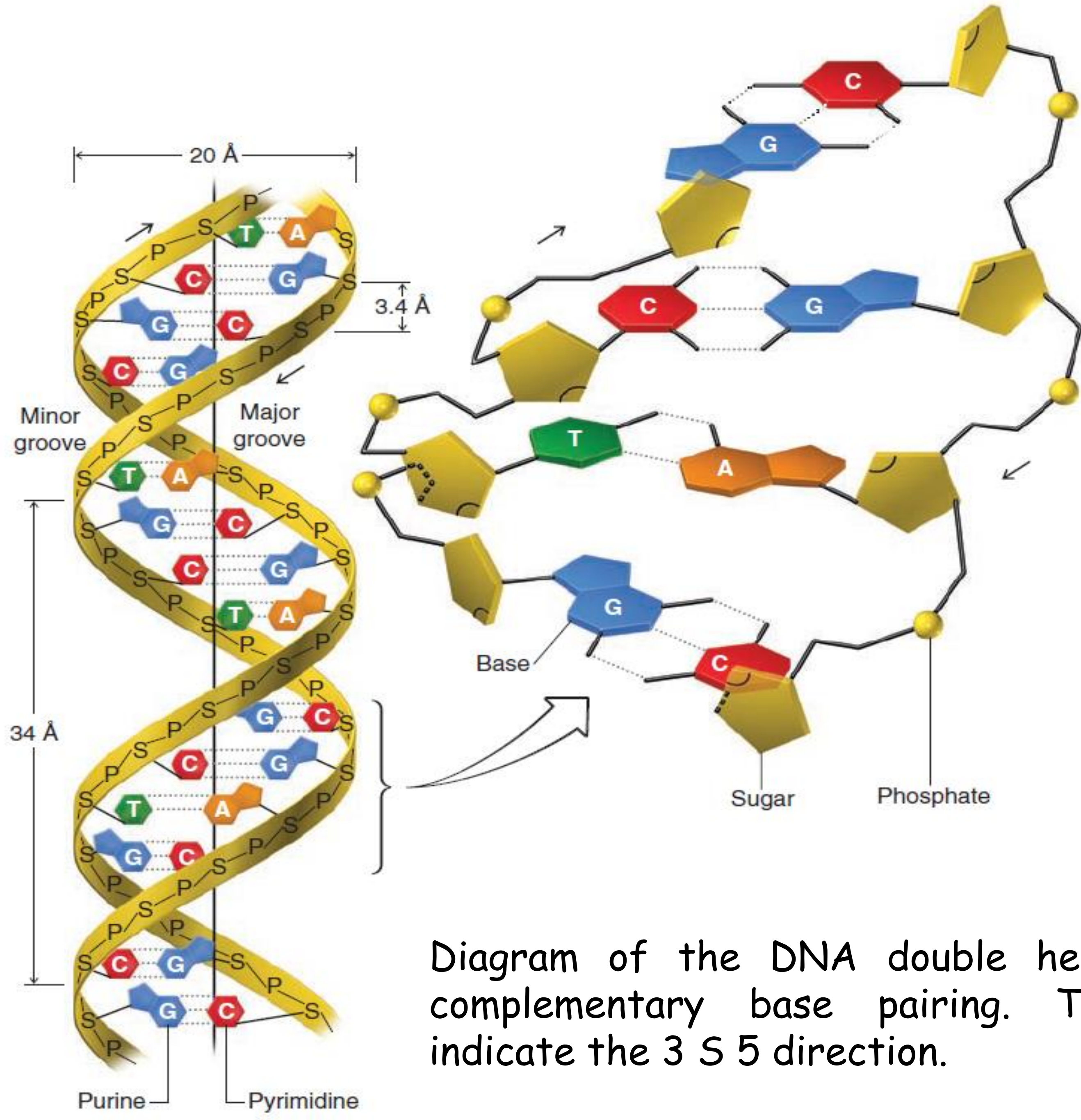


Diagram of the DNA double helix showing complementary base pairing. The arrows indicate the 3 S 5 direction.