NUCLEOTIDES CHEMISTRY

BIOCHEMISTRY

“The whole art of teaching is only the art of awakening the natural curiosity of young minds for the purpose of satisfying it afterwards”

NUCLEOPROTEINS

- One of the conjugated proteins, characterized by the presence of a prosthetic group (nucleic acid),
- Attached to a simple protein- Histone or Protamine.

Biomedical Importance

- Building blocks of nucleic acids
- Energy currency
- Carriers of activated intermediates
- Allosteric regulators of metabolism
- Control oxidative phosphorylation
- Second messengers
- Synthetic analogues used in chemotherapy

NUCLEIC ACIDS

- Genetic material of all known organisms
- DNA: deoxyribonucleic acid
- RNA: ribonucleic acid (e.g., some viruses)
- Consist of chemically linked sequences of nucleotides
  - Nitrogenous base
  - Pentose- 5-carbon sugar (ribose or deoxyribose)
  - Phosphate group
- The sequence of bases provides the genetic information

- There are two classes of nitrogen bases called **purines** (double-ringed structures) and **pyrimidines** (single-ringed structures). The four bases in DNA's alphabet are:
- **adenine (A)** - a purine
- **cytosine(C)** - a pyrimidine
- **guanine (G)** - a purine
- **thymine (T)** - a pyrimidine

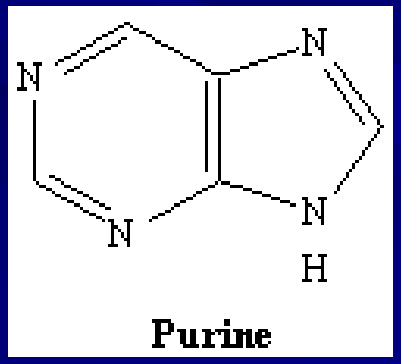
BASES

- Two types of bases:

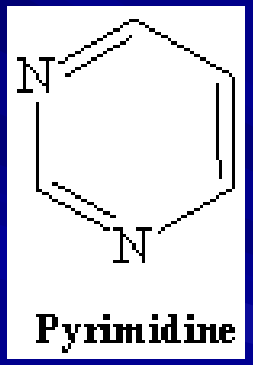
1. Purines are fused five- and six-membered rings
   - Adenine A DNA RNA
   - Guanine G DNA RNA
2. Pyrimidines are six-membered rings
   - Cytosine C DNA RNA
   - Thymine T DNA
   - Uracil U RNA

Nitrogenous Bases

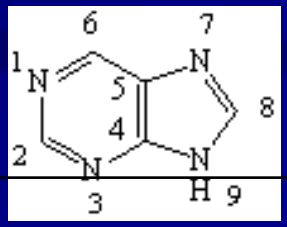
- Planar, aromatic, and heterocyclic
- Derived from purine or pyrimidine
- Numbering of bases is “unprimed”

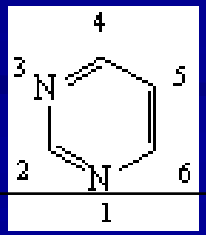


Purine



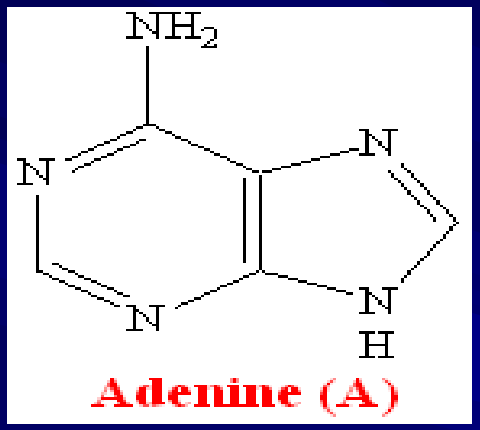
Pyrimidine



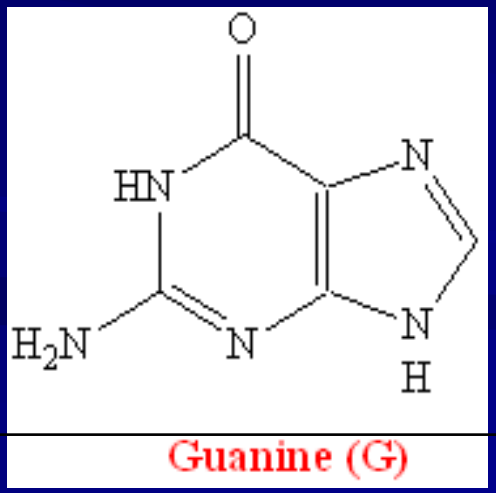


Nucleic Acid Bases

Purines

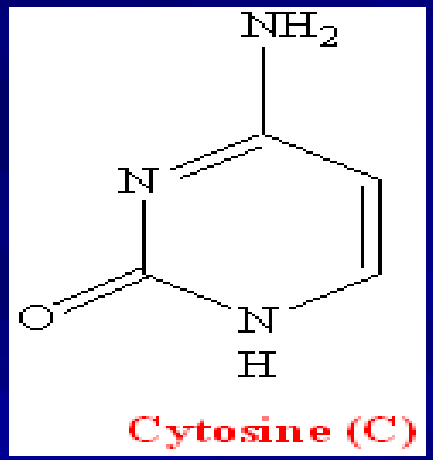


Adenine (A)

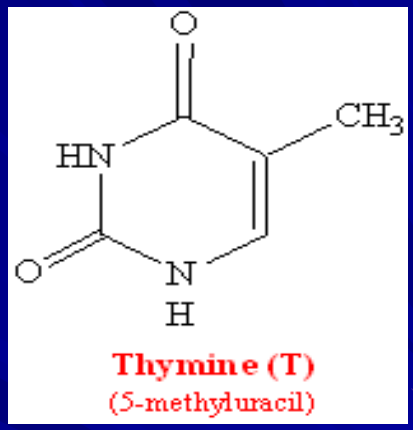


Guanine (G)

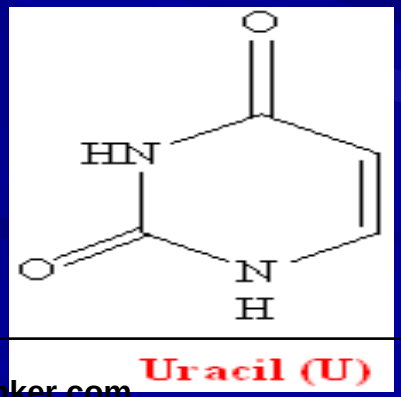
Pyrimidines



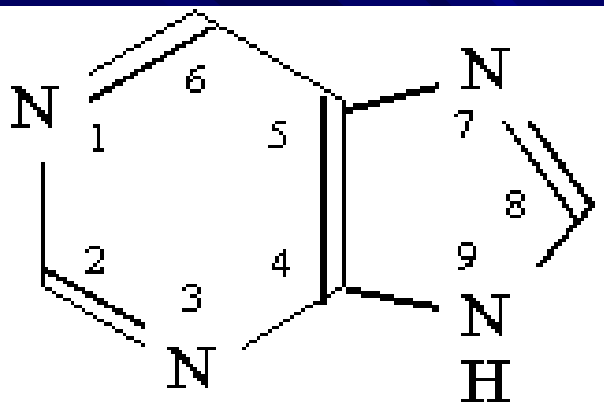
Cytosine (C)



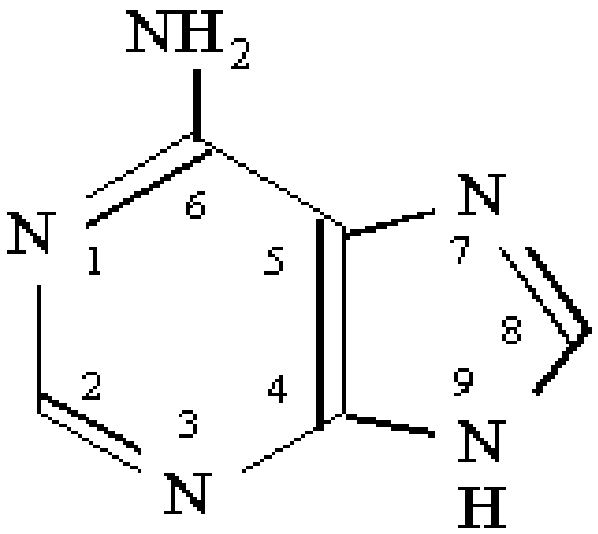
Thymine (T)
(5-methyluracil)



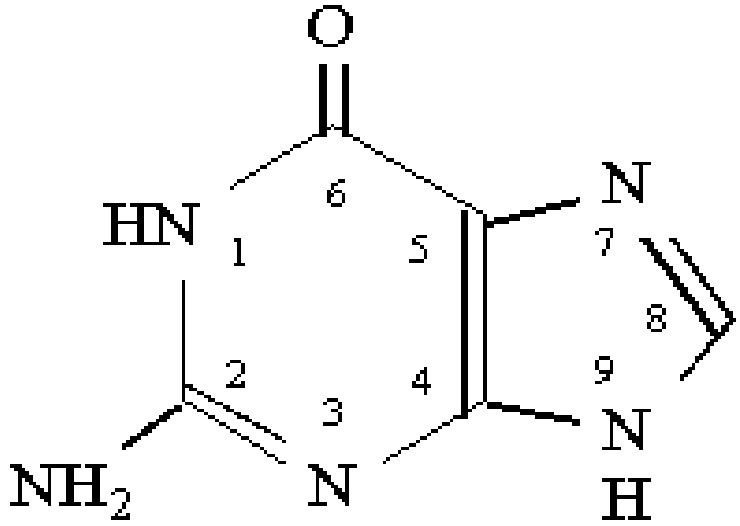
Uracil (U)



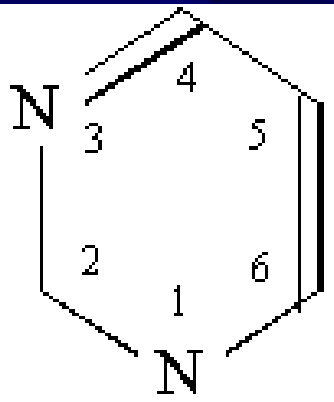
Purine



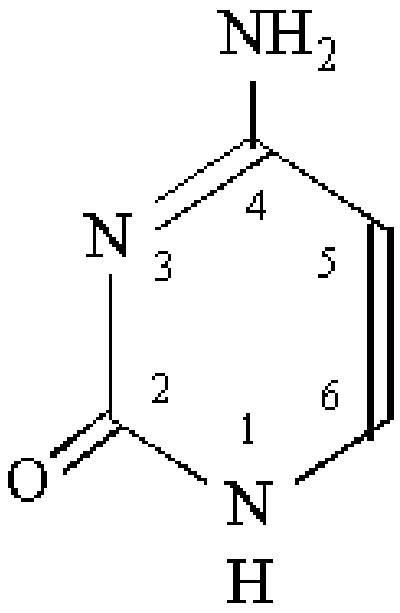
Adenine
135.1 gm/mol



Guanine
151.1 gm/mol

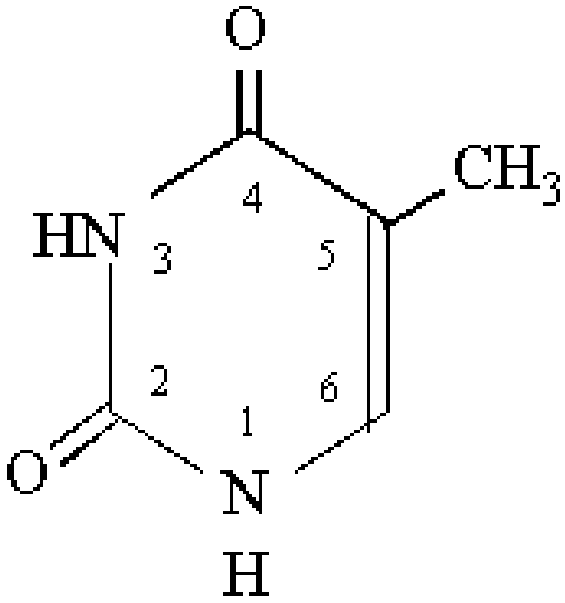


Pyrimidine



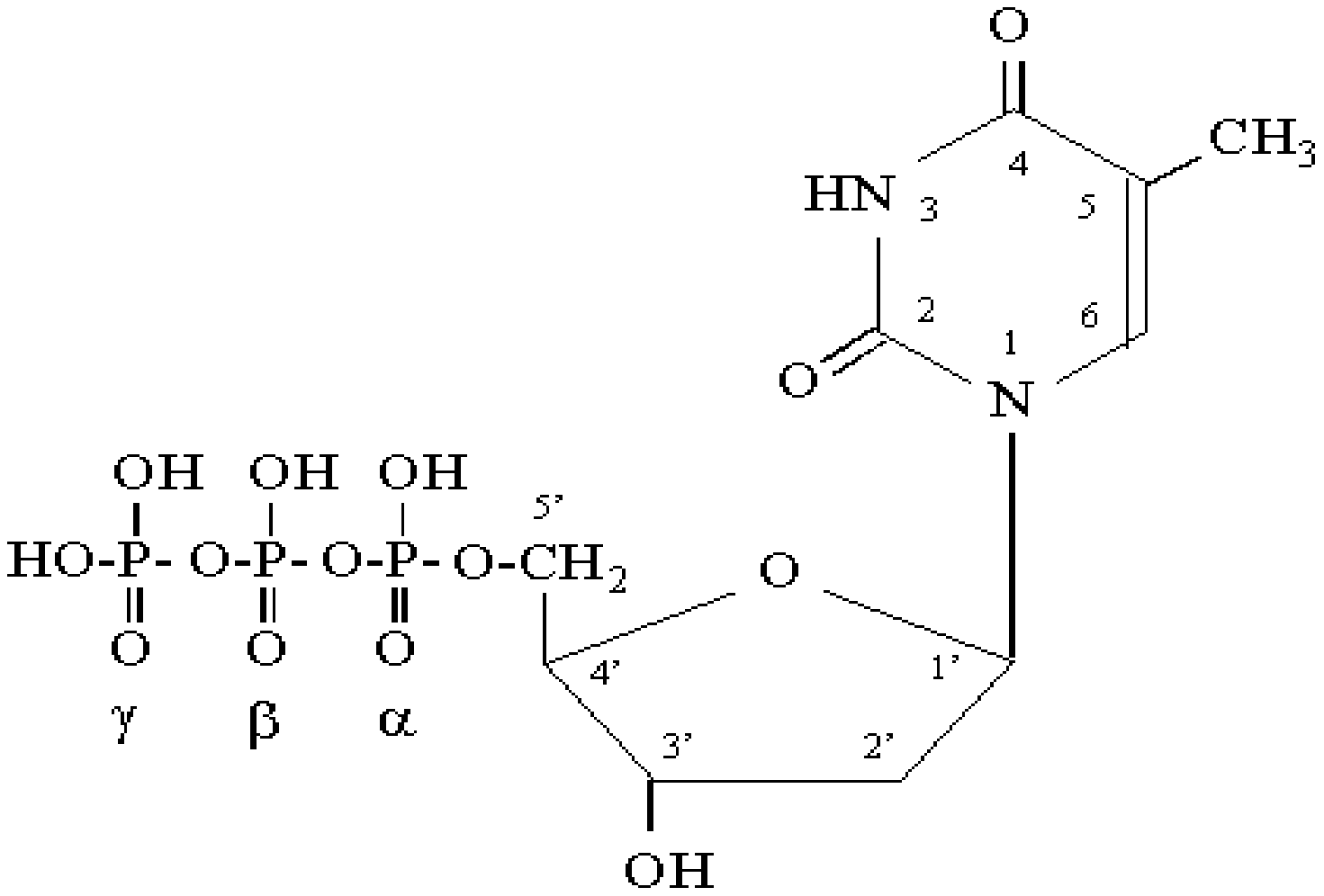
Cytosine

111.1 gm/mol



Thymine

126.1 gm/mol



2'-deoxy Thymidine triphosphate
(nucleotide)

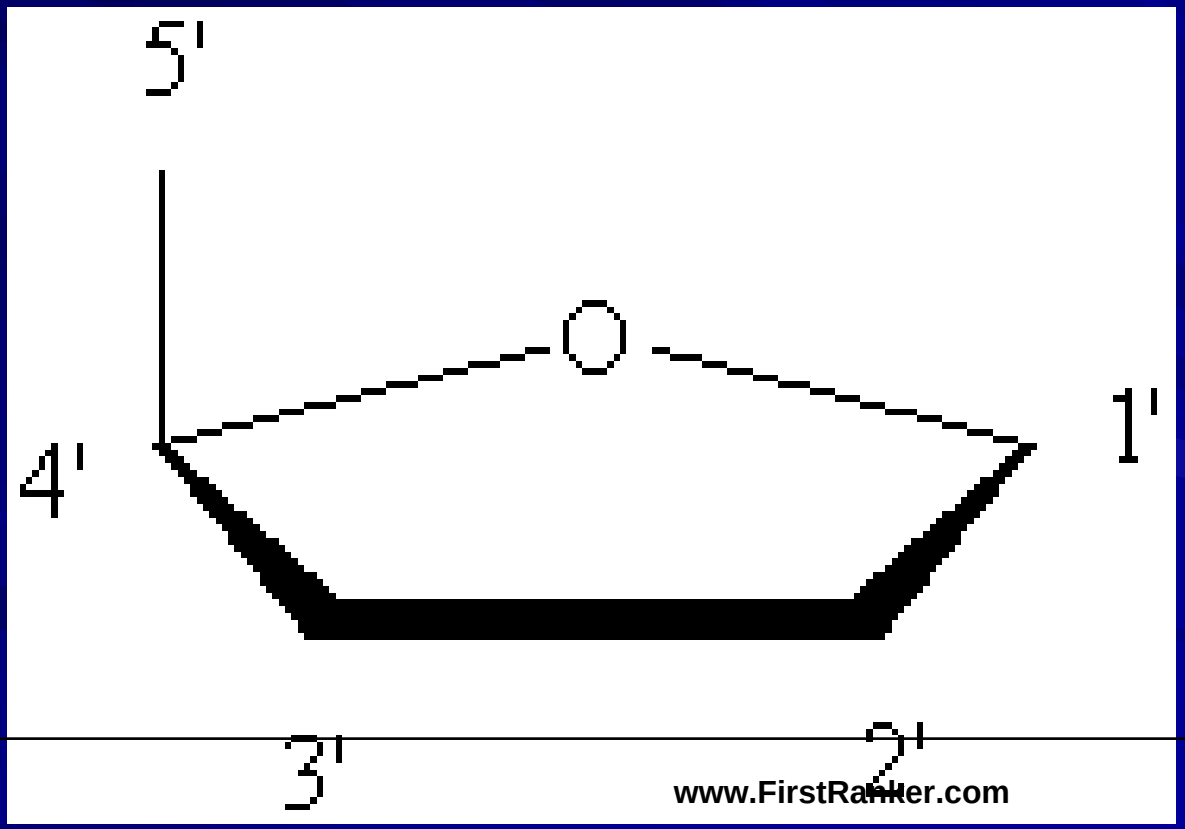
SUGARS

- There are two different kinds of sugars in a nucleotide, deoxyribose and ribose.

- If the polynucleotide chain forms DNA then the sugars in its nucleotides are deoxyribose while nucleotides containing ribose as its sugar form RNA.

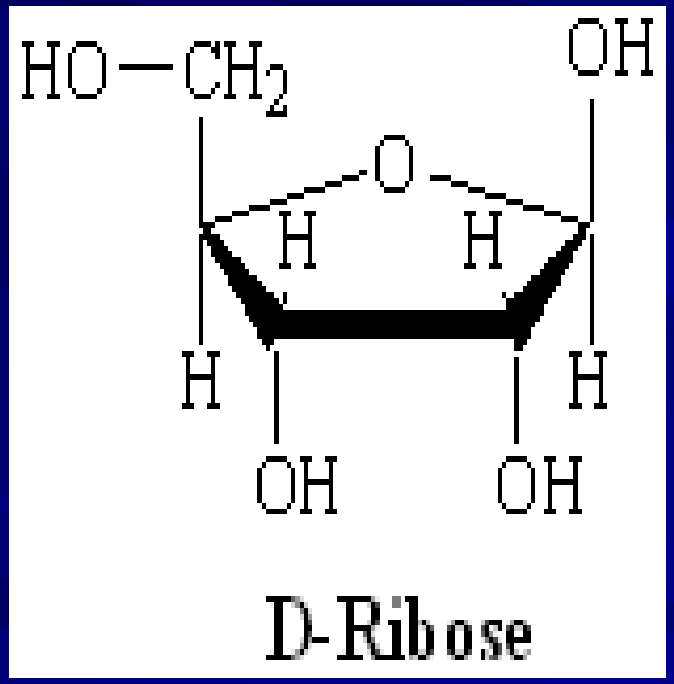
Sugars

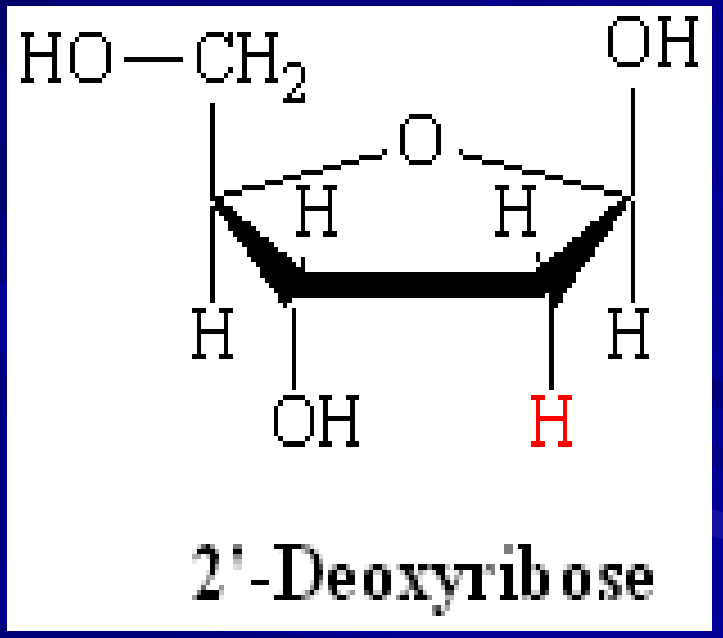
- Pentoses (5-C sugars)
- Numbering of sugars is “primed”



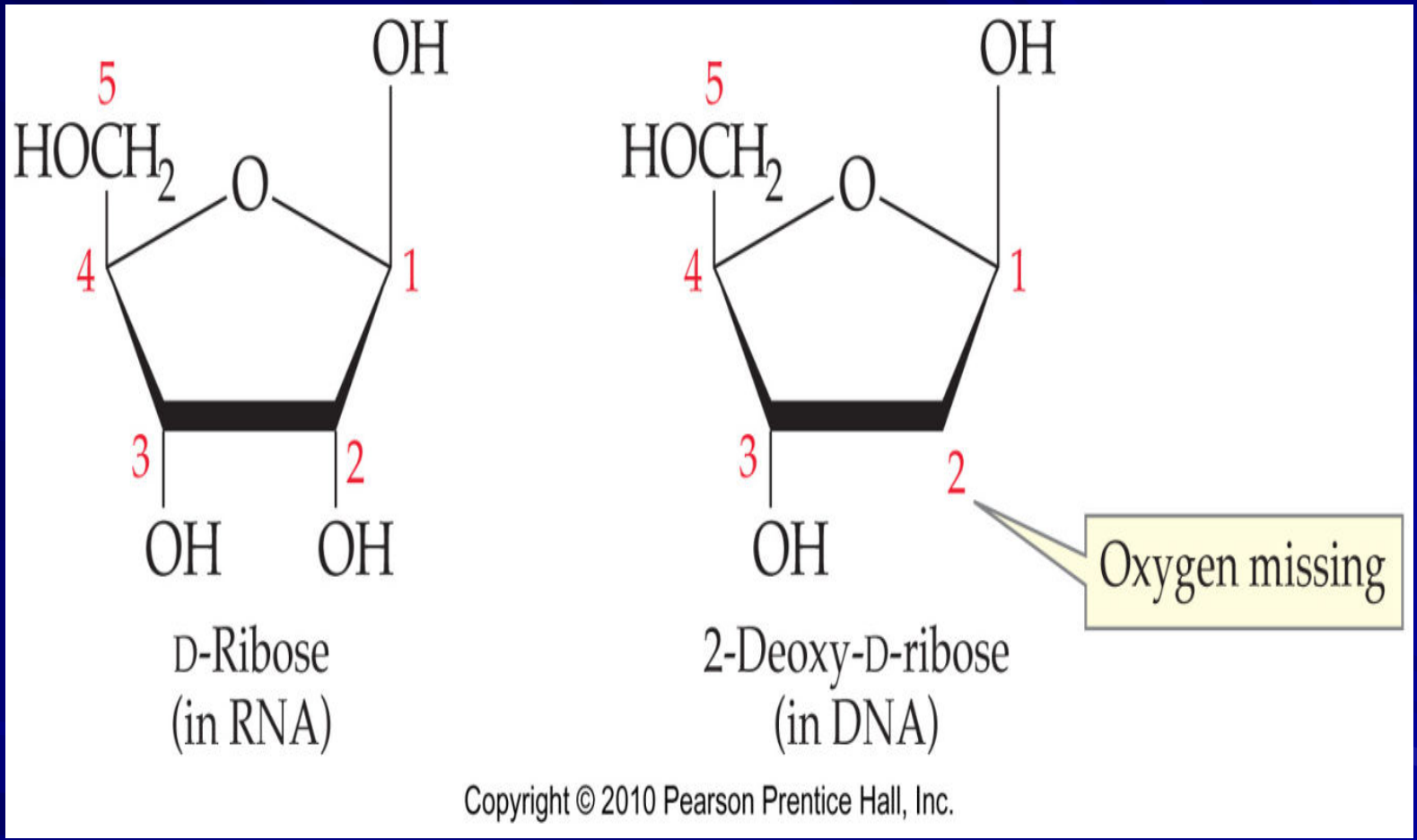
Sugars

D-Ribose and 2’-Deoxyribose

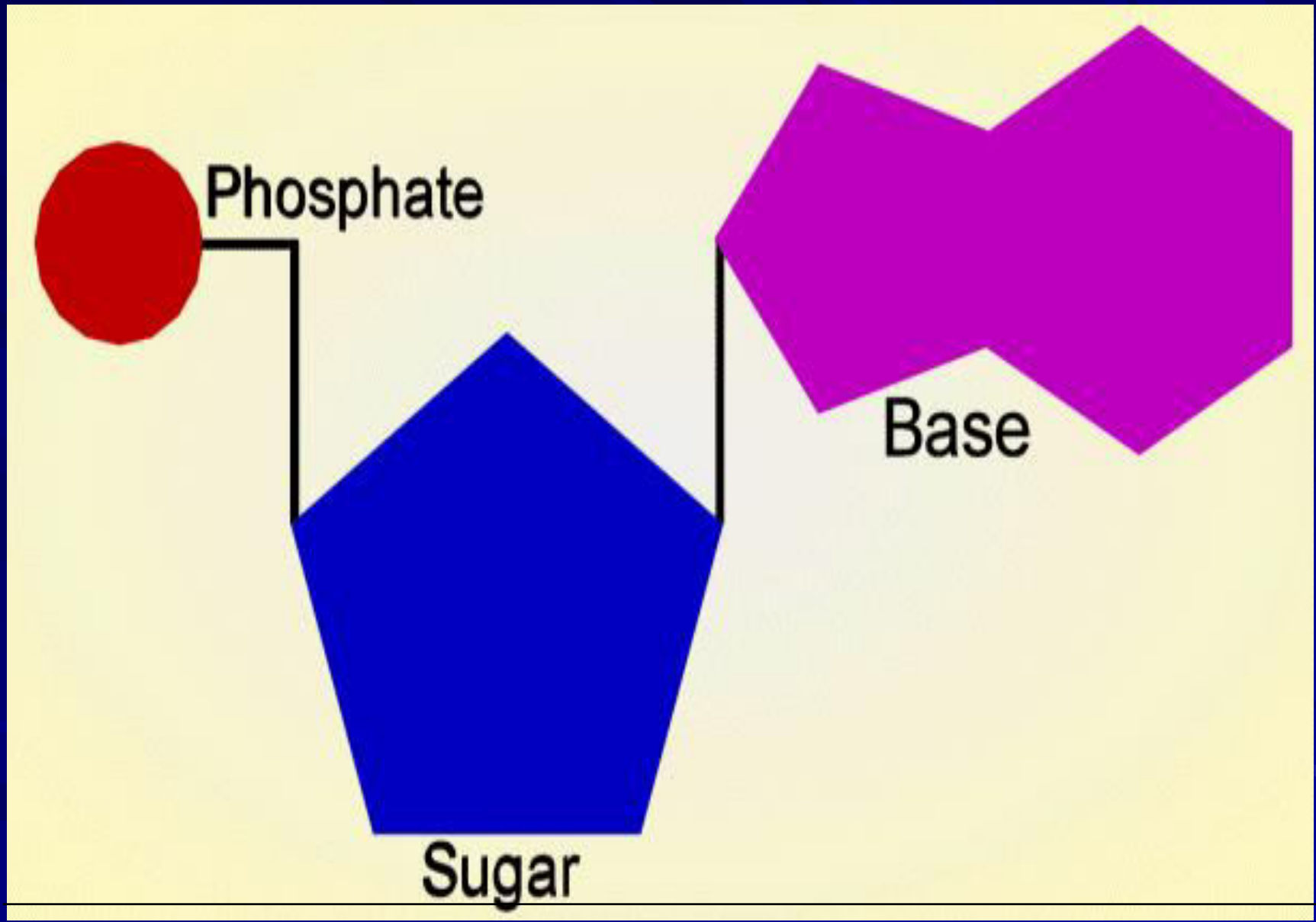


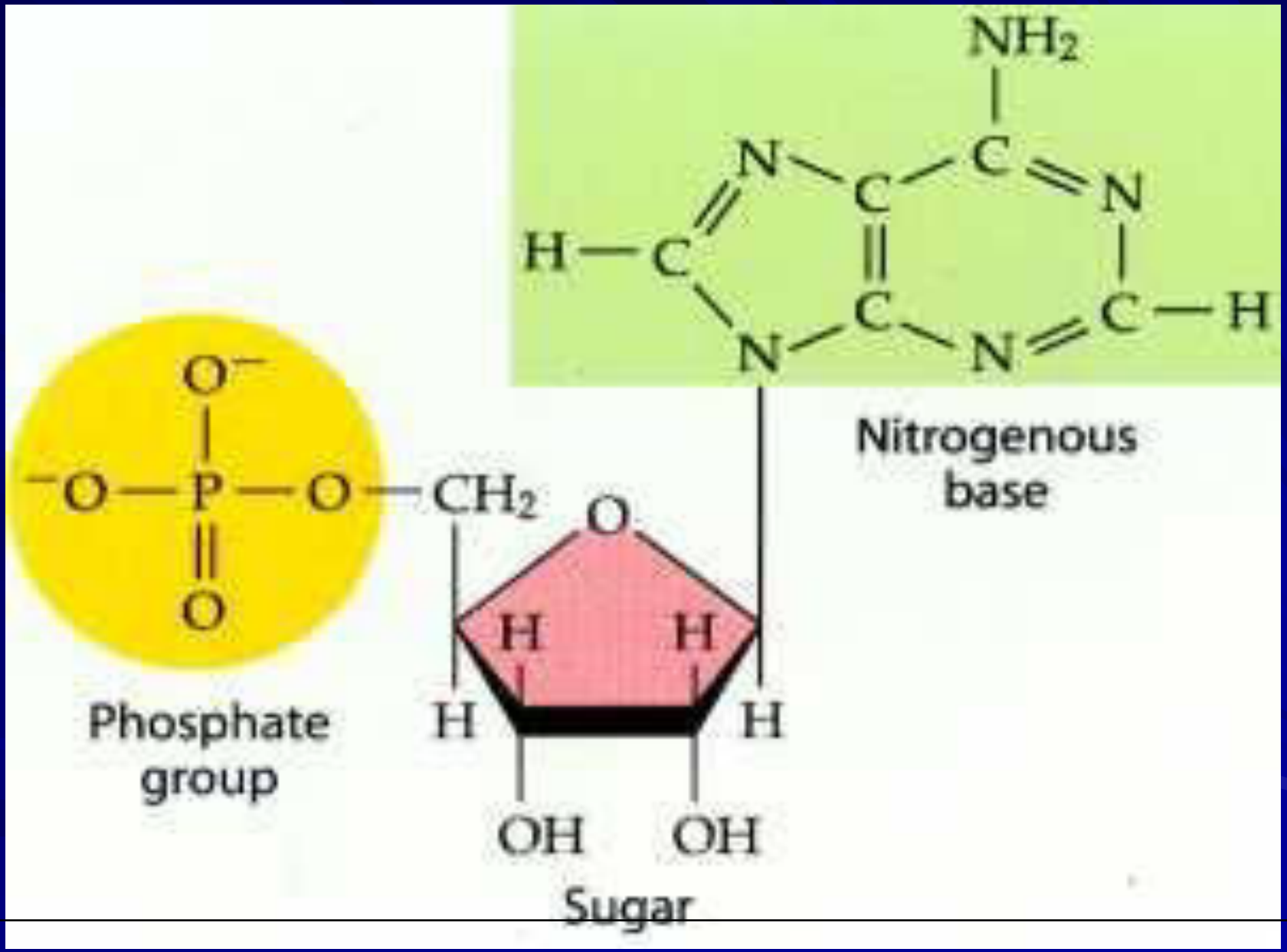


*Lacks a 2’-OH group



- Each nucleotide consists of a sugar (**deoxyribose**) bound on one side to a **phosphate group** and bound on the other side to a **nitrogenous base**.

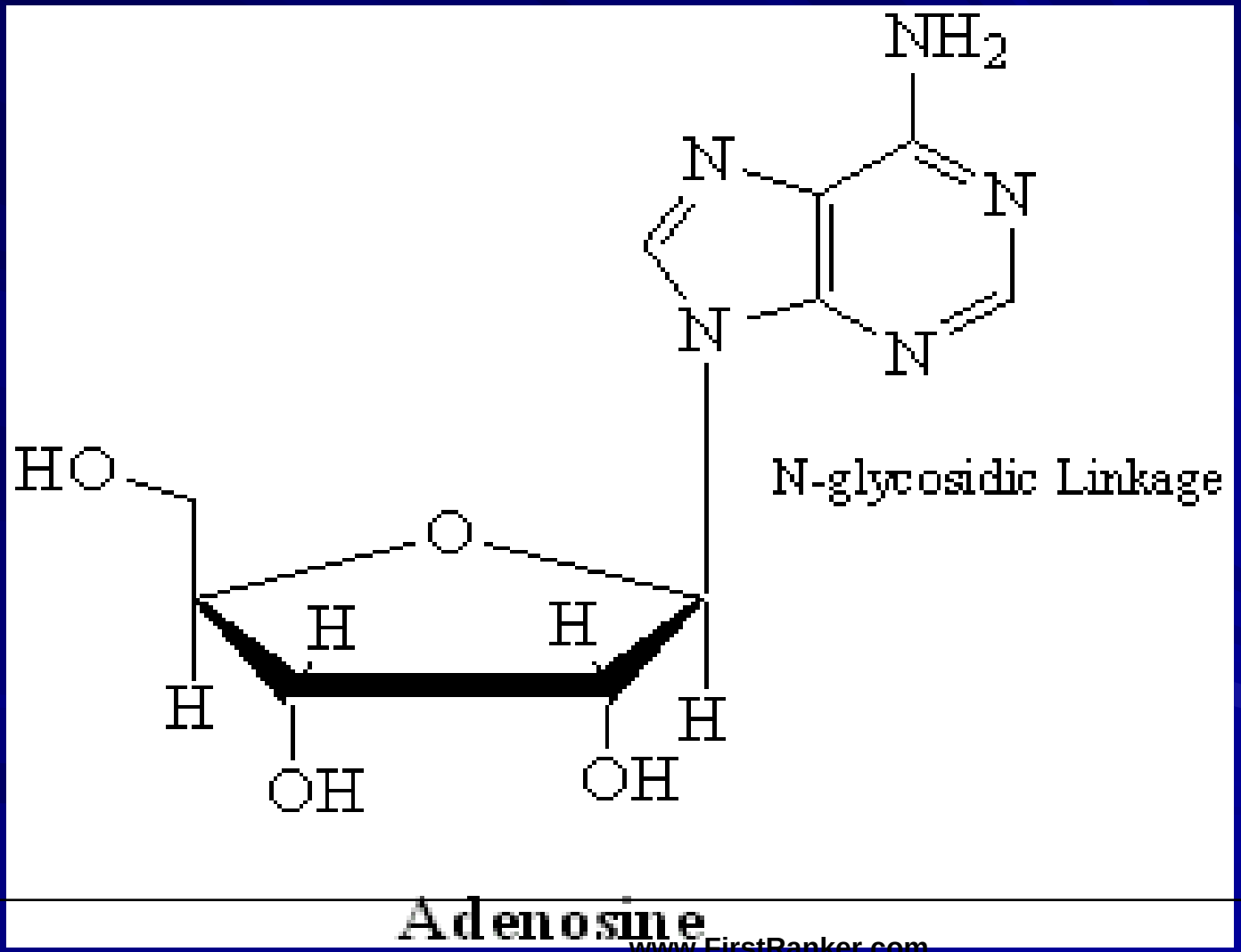




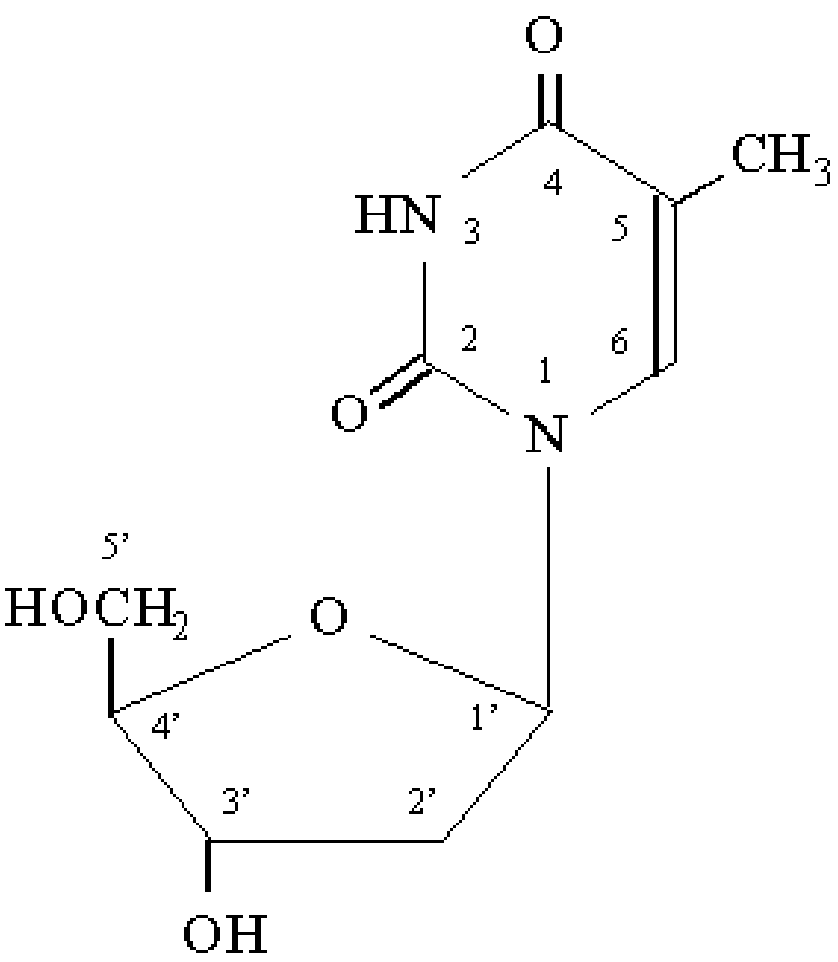
Nucleosides

- Result from linking one of the sugars with a purine or pyrimidine base through an **N-glycosidic linkage**
  - Purines bond to the C1’ carbon of the sugar at their N9 atoms
  - Pyrimidines bond to the C1’ carbon of the sugar at their N1 atoms

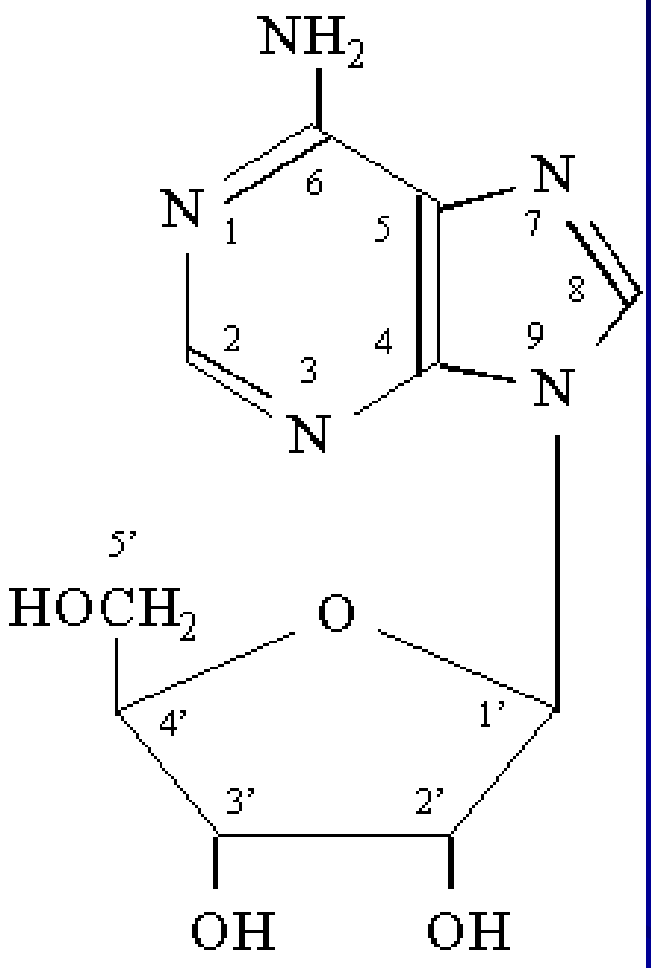
Nucleosides



Adenosine



2'-deoxy Thymidine
(2'-deoxy ribose sugar
DNA precursor)



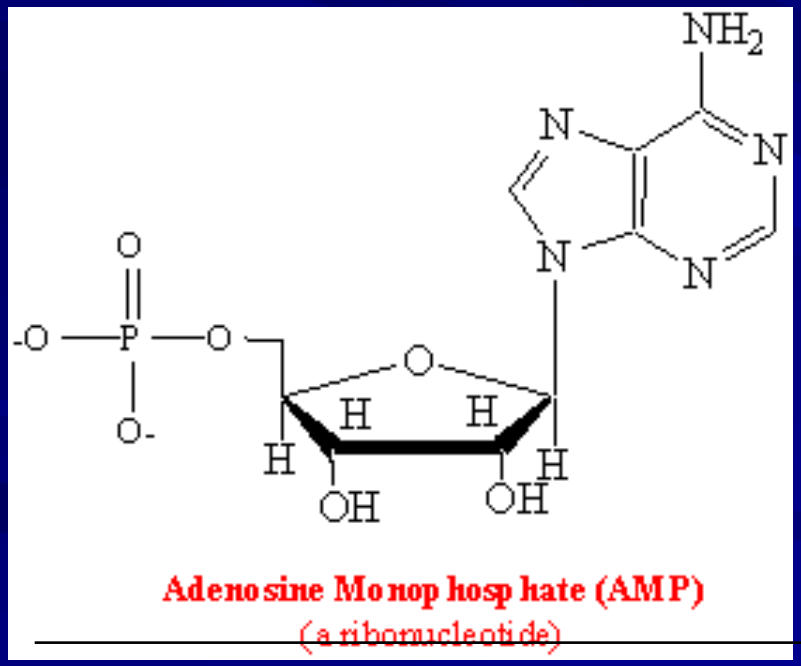
Adenosine
(ribose sugar
RNA precursor)

Phosphate Groups

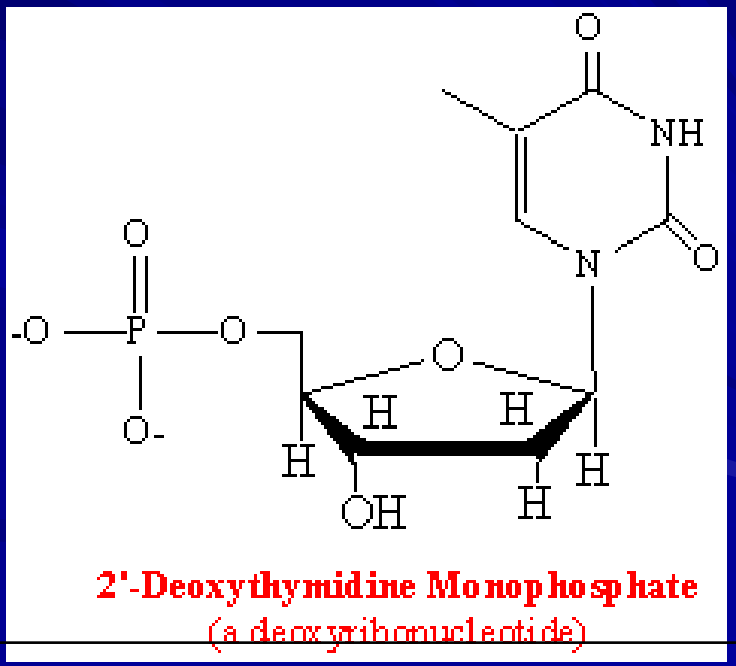
- Mono-, di- or triphosphates
- Phosphates can be bonded to either C3 or C5 atoms of the sugar

Nucleotides

- Result from linking one or more phosphates with a nucleoside onto the 5’ end of the molecule through esterification



Adenosine Monophosphate (AMP)
(a ribonucleotide)



2'-Deoxythymidine Monophosphate
(a deoxyribonucleotide)

Naming Conventions

- Nucleosides:
  - Purine nucleosides end in “-sine”
    - Adenosine, Guanosine
  - Pyrimidine nucleosides end in “-dine”
    - Thymidine, Cytidine, Uridine
- Nucleotides:
  - Start with the nucleoside name from above and add “mono-”, “di-”, or “triphosphate”
    - Adenosine Monophosphate, Cytidine Triphosphate, Deoxythymidine Diphosphate

Nucleotides

- RNA (ribonucleic acid) is a polymer of ribonucleotides
- DNA (deoxyribonucleic acid) is a polymer of deoxyribonucleotides
- Both deoxy- and ribonucleotides contain Adenine, Guanine and Cytosine
  - Ribonucleotides contain Uracil
  - Deoxyribonucleotides contain Thymine

Nucleotides

- Monomers for nucleic acid polymers
- Nucleoside Triphosphates are important energy carriers (ATP, GTP)
- Important components of coenzymes
  - FAD, NAD^+ and Coenzyme A

- There are two main cellular functions for purines and pyrimidines:
- 1. the purines adenine and guanine and the pyrimidines cytosine, thymine and uracil are all utilized for the production of DNA and RNA.

- These nitrogenous bases are synthesized linked to a phosphorylated ribose sugar residue, and these nucleoside monophosphates are incorporated into growing strands of new DNA or RNA during replication or transcription.

- 2. The second function of pyrimidines and purines is short-term energy storage.

- 3. Guanine triphosphate and guanine diphosphate are utilized by certain enzymes and receptors as an on/off switch.
- 4. while cytosine triphosphate and uridine triphosphate are both used in the production of biomolecules

Adenosine Derivatives

- The most common adenosine derivative is the cyclic form, 3'-5'-cyclic adenosine monophosphate, **cAMP.**
- This compound is a very powerful second messenger involved in passing signal transduction events from the cell surface to internal proteins.

- Regulate glycogen breakdown, lipids breakdown, stop cholesterol synthesis
- Regulate transcription and translation.
- Regulate permeability of cell membrane

- Regulate insulin secretion
- Catecholamines biosynthesis

- cAMP is rapidly degraded by phosphodiesterases.
- Phosphodiesterases when activated will promote the degradation of cAMP.
- Phosphodiesterases when inhibited will prevent the degradation of cAMP

- Inhibitors are methylxanthines- caffeine, theophylline, theobromine.

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- The most common form of energy in all cells is adenosine triphosphate, or **ATP**.

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- Release of the third phosphate to produce adenosine diphosphate, or **ADP**, is an extremely favorable reaction and can drive reactions requiring energy input.

- **S-adenosylmethionine (SAM)** is a form of activated methionine which serves as a methyl donor in methylation reactions

- Active sulphate- **Adenosine -3- PO_4 5 Phosphosulphate.**
- It incorporates sulfate groups.

Guanosine Derivatives

- **GTP-** Protein synthesis, Purine Synthesis, ATP formation, gluconeogenesis.

- A cyclic form of GMP **(cGMP)** is found in cells involved as a second messenger molecule. In many cases its' role is to antagonize the effects of c-AMP.

- **(cGMP)** is formed from GTP by guanylyl cyclase, regulated by effectors.

- The most important cGMP coupled signal transduction cascade is that of:
  1. Photoreception.
  2. for Atrial Natriuretic Peptide &
  3. Nitric oxide.

All these are potent vasodilators and cause smooth muscle relaxation.

Uracil Derivatives

- **UDP- glucose---** glucose donor in glycogen synthesis.

- **UDP-sugar derivatives** participate in sugar epimerization e.g.------ interconversion of glucose-1- PO4 to galactose 1-PO4 (UDP-glucose & UDP-galactose) (glycoproteins, glycolipids,GAGS).

- **UDP-galactose, UDPglucoronate, UDP-N-acetylgalactosamine** act as sugar donors for biosynthesis of glycoproteins & proteoglycans

- **UDP glucoronate** ---- glucuronic acid donor.

Cytidine Derivatives

- **CMP-N acetylneuraminic acid** required for the biosynthesis of **glycoproteins.**
- **CDP-choline**- required for the biosynthesis of **sphingomyelin.**
- **CTP**- required for the biosynthesis of **phosphoglycerides.**

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Coenzymes

- Many coenzymes are nucleotide derivatives e.g. **NAD, NADP, FAD, coenzyme- A.**

Unusual Bases

- Present in nucleic acids of bacteria and viruses
- Also found in DNA and tRNA of both prokaryotes and eukaryotes.

- 1-methyl adenosine is a modified adenosine base found on tRNA:
- N2,N2-dimethylguanosine is a modified guanosine
- Dihydro uridine is a modified Uridine
- Pseudo uridine is a modified Uridine

- Methylcytosine is a modified cytosine
- Hydroxymethylcytosine is a modified cytosine
- Free nucleotides are:

1. Xanthine
2. Hypoxanthine
3. Uric acid

- Methylated bases present in plants- they are xanthine derivatives:

1. Caffeine of coffee
2. Theobromine of tea
3. Theophyline of cocoa

Synthetic Analogues of Nucleotides

- These are also called antimetabolites- -- therapeutic application
- Prepared by altering the ring or sugar moiety.
- Used in chemotherapy.

- Example: removal of the hydroxyl group from 3’ carbon of the deoxyribose ring as in 2’ 3’ dideoxy inosine.

- Conversion of deoxyribose to another sugar as in arabinose (antiviral, anticancer)

- 5-fluorouracil
- 6- mercaptopurine
- Cytarabine etc.