

## **Biochem-708 MOLECULAR BIOCHEMISTRY 3(3-0)**

Structural organization of genes and chromosomes in prokaryotes and eukaryotes, nucleosomes, properties of DNA and RNA in solution. Replication of DNA: Replication theory and semi-conservative replication, molecular mechanism of replication in prokaryotes and eukaryotes. Enzymes involved in replication. Molecular nature of mutations, DNA damage and repair. Modification and restriction. Transcription: synthesis and processing of RNA. Reverse transcription and RNA replication in viruses. Genetic code and Wobble hypothesis. Translation, essential factors, enzymes, initiation, elongation and termination of protein synthesis. Post-translational modifications and targeting of proteins. Control of transcription and translation. Regulation of gene expression in prokaryotes. Recent advances in biotechnology and genetic engineering.

## SUGGESTED READINGS

- Berg, J.M., J.L. Tymoczko and L. Stryer. 2007. Biochemistry, 6<sup>th</sup> ed. W.H. Freeman and Company. New York.
- Nelson, D.L and M.M. Cox. 2008. Lehninger Principles of Biochemistry. 5<sup>th</sup> ed. Worth Publishers, New York.**
- Old, R.W. and S.B. Primrose. 1995. 4<sup>th</sup> ed. Principles of Gene Manipulation: An Introduction to genetic Engineering. Blackwell Scientific Publications, London.
- Sambrook, J. F., Russell, D. W. and Irwin, N. 2000. Molecular cloning: A laboratory manual, 3<sup>rd</sup> ed. Cold Spring Harbor Laboratory press, Cold Spring Harbor, N.Y.
- Singer, M. and P. Berg. 1991. Genes and Genomes. University Science Books, Nill Valley, California.
- Voet, D. , J.G. Voet and C. W. Pratt. 2006 . Fundamentals of Biochemistry. 2nd ed. John Wiley and Sons. Inc. New York.
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# DNA as genetic material

Chromosomes are comprised of two types of macromolecules, proteins and DNA, but which one is the stuff of genes?

– the answer was 12.1 The Griffith Experiment discovered from a variety of different experiments, all of which shared the same basic design

- *if you separate the DNA in an individual's chromosomes from the protein, which of the two materials is able to change another individual's genes?*

Frederick Griffith in 1928 experimented with pathogenic (i.e., disease-causing) bacteria

– he experimented with two strains of *Streptococcus pneumoniae*

12.1 The Griffith Experiment

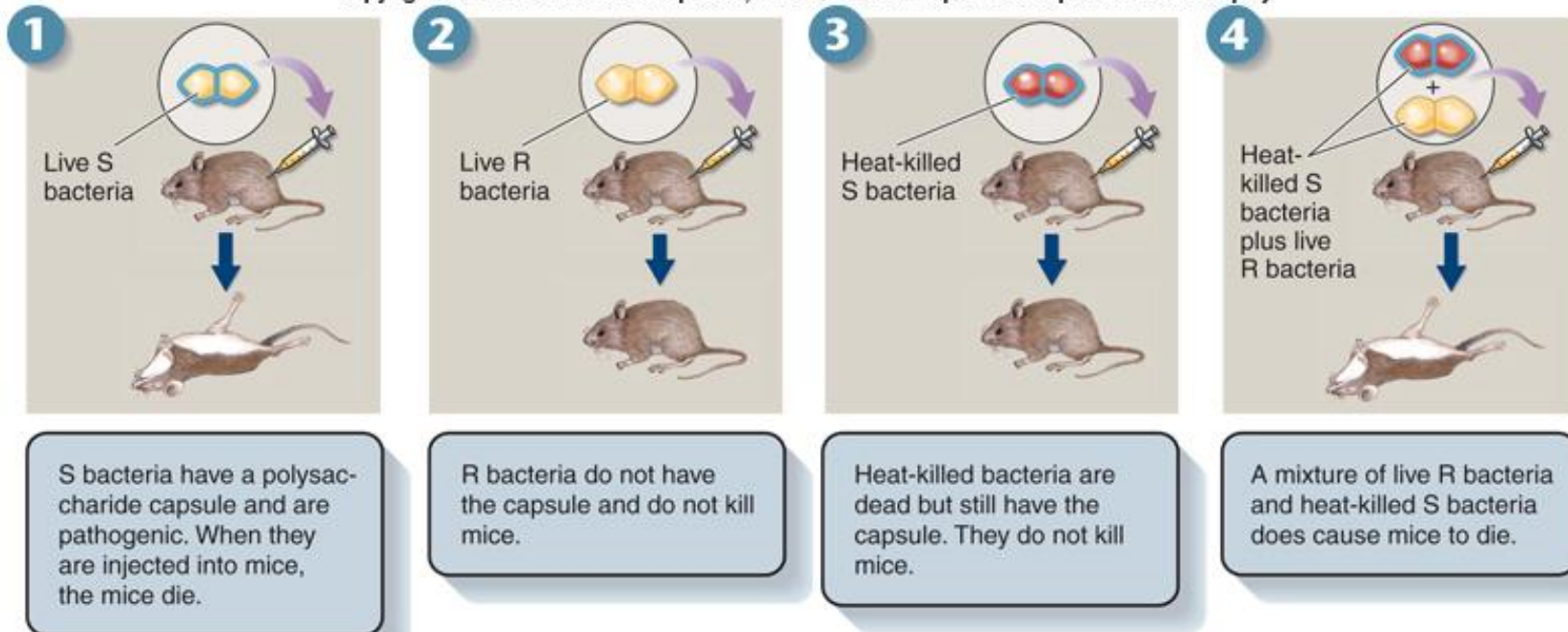
- the virulent strain, called the S form, was coated with a polysaccharide capsule and caused infected mice to die of blood poisoning
- a mutant form, called the R form, which lacked the capsule and was non-virulent

Griffith determined that when dead bacteria of the S form were injected into mice, the mice remained healthy

But, when Griffith injected mice with mixture of dead S bacteria and live bacteria of the R form, the mice unexpectedly died

- the R form bacteria now had transformed into the virulent S variety

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# Oswald Avery, Colin MacLeod and Maclyn McCarty

The agent responsible for transforming *Streptococcus* went undiscovered until a classic series of experiments by Oswald Avery and his coworkers Colin MacLeod and Maclyn McCarty

- they also worked with *Streptococcus* strains, both dead S and live R, but were able to remove first nearly 99.98% of the dead S
- they found that the transforming principle was not reduced by the removal of the protein

The Avery team discovered that the transforming principle resembled DNA in several ways

- same chemistry and behavior as DNA
- not affected by lipid and protein extraction
- not destroyed by protein- or RNA-digesting enzymes
- destroyed by DNA-digesting enzymes

Based on this overwhelming evidence, the Avery team concluded that the heredity material was DNA



# Alfred Hershey and Martha Chase experiment

Alfred Hershey and Martha Chase provided the final experimental evidence that pointed to DNA as the hereditary material

- the team studied viruses that infect bacteria
- the structure of these viruses is very simple: a core of DNA surrounded by a coat of protein
- the viruses attach themselves to the surface of bacteria cells and inject their genes into the interior
  - the infected bacterial cell is then forced to make hundreds of copies of new viruses, which then burst out of the cell to infect new cells

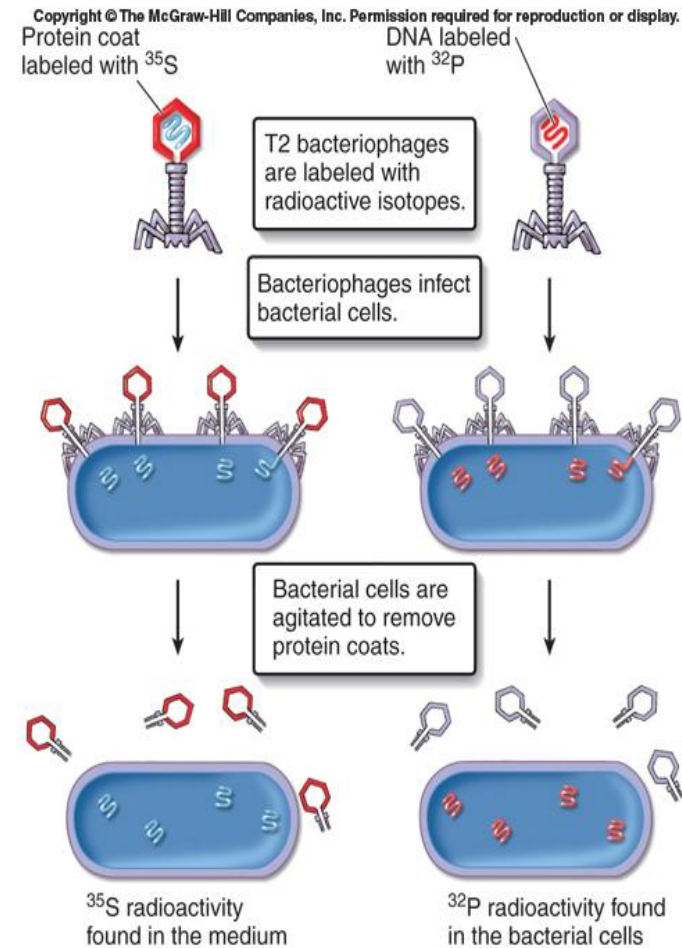
Hershey and Chase used radioactive isotopes to “label” or tag the DNA and the protein of the viruses

- some viruses were grown so that their DNA contained radioactive phosphorous ( $^{32}\text{P}$ )
- other viruses were grown so that their protein coats contained radioactive sulfur ( $^{35}\text{S}$ )

# The Experiment

After the labeled viruses were allowed to infect bacteria, only the viruses with  $^{32}\text{P}$  had labeled tracer in their interior

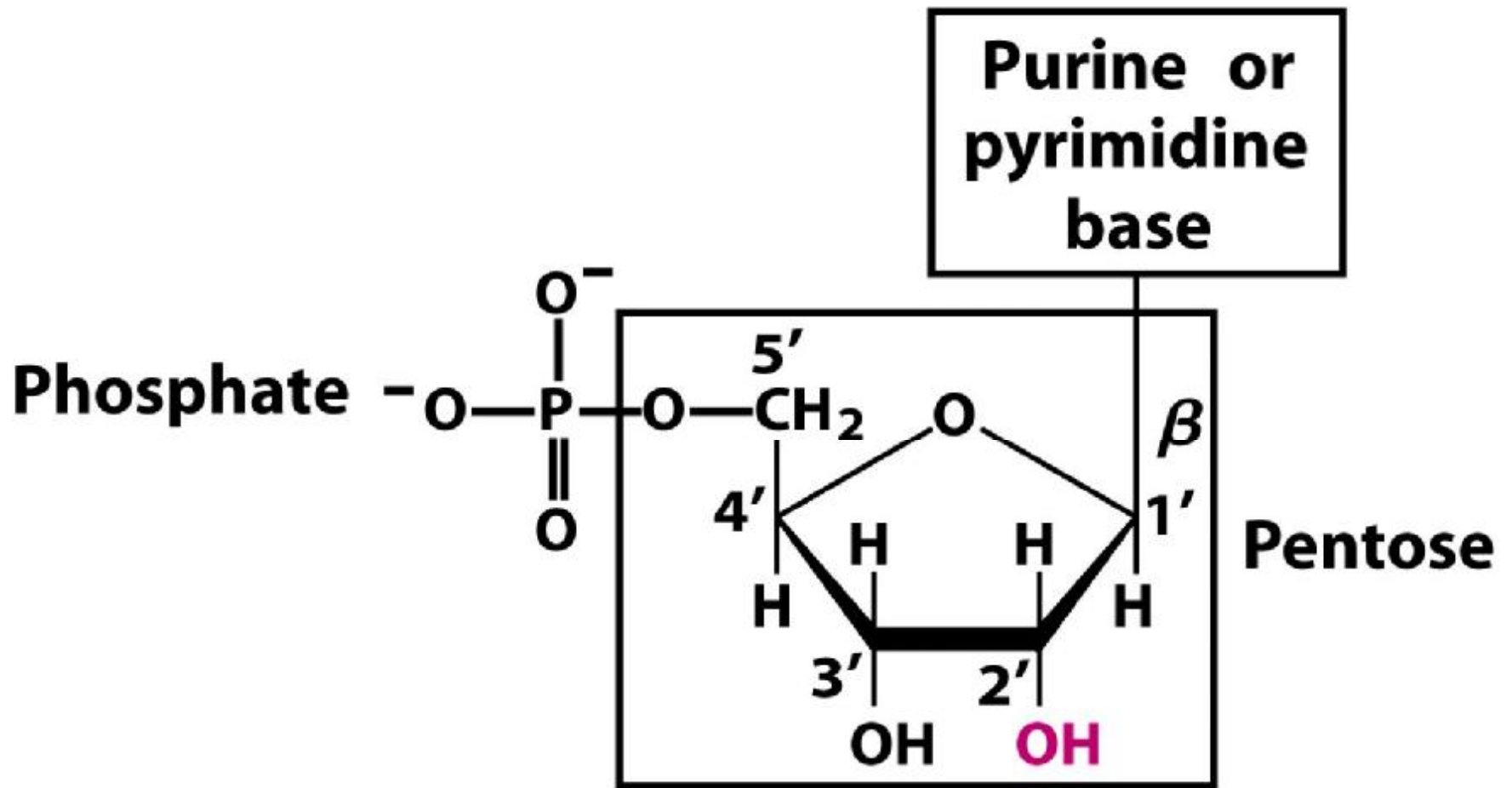
The conclusion was that the genes that viruses use to specify new viruses are made of DNA and not protein



# Components of Nucleic acids

In order to understand how DNA functioned as the molecules that stored heredity, researchers needed to understand the structure of DNA

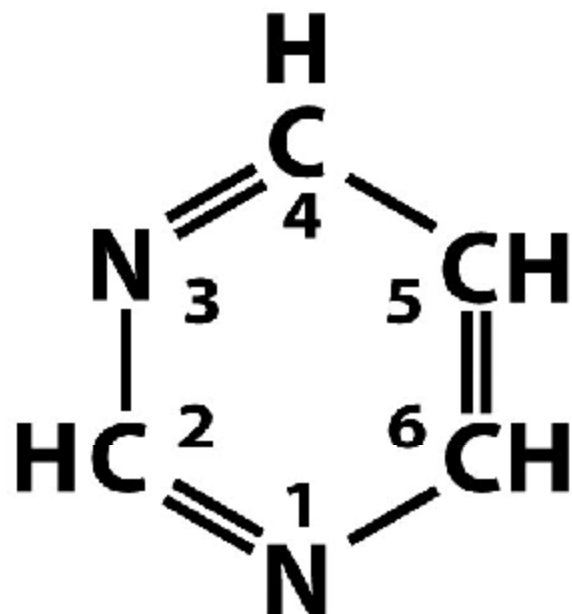
- DNA is comprised of subunits called nucleotides
- each DNA nucleotide has three parts
  - a central deoxyribose sugar
  - a phosphate group
  - an organic base



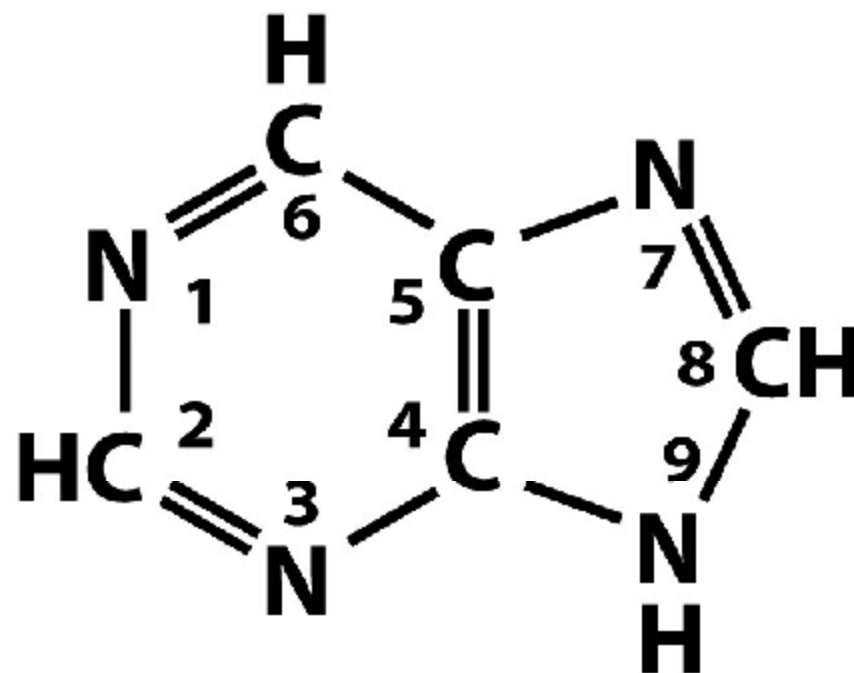
**Figure 8-1a**

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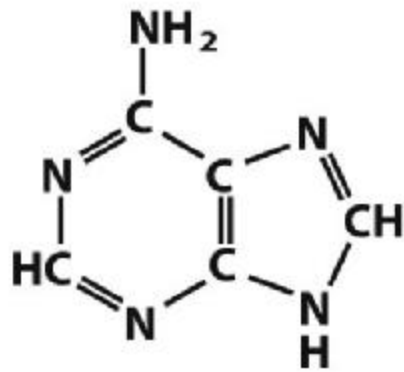
**Pyrimidine**



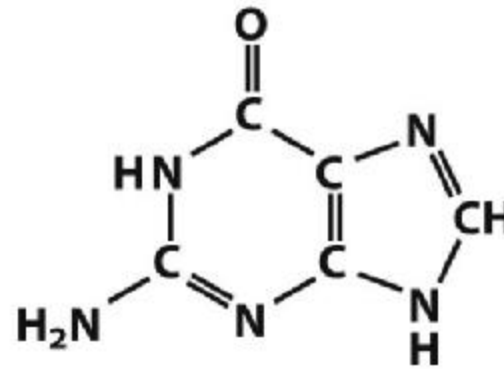
**Purine**

**Figure 8-1b**

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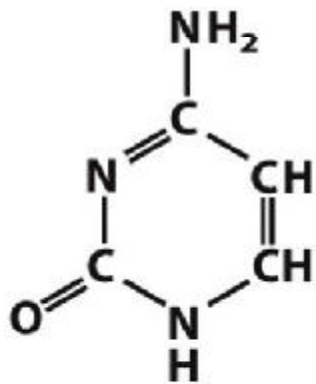


**Adenine**

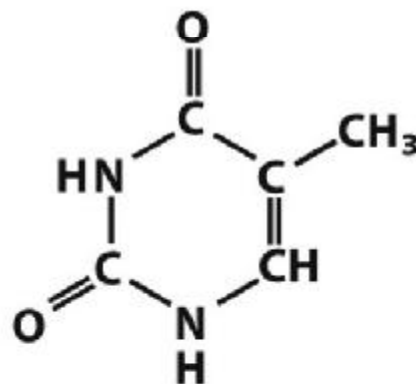


**Guanine**

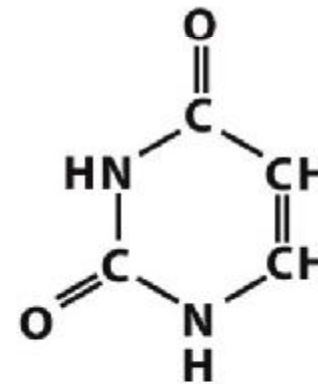
**Purines**



**Cytosine**



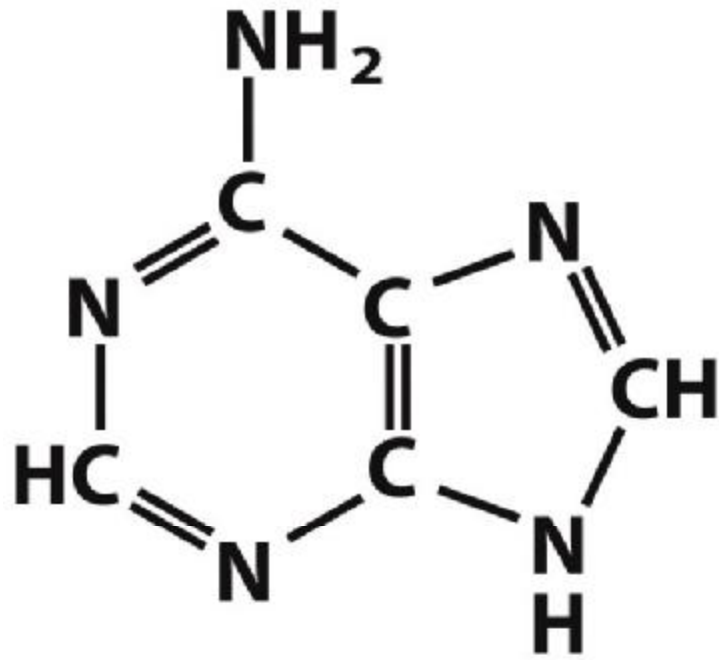
**Thymine  
(DNA)**



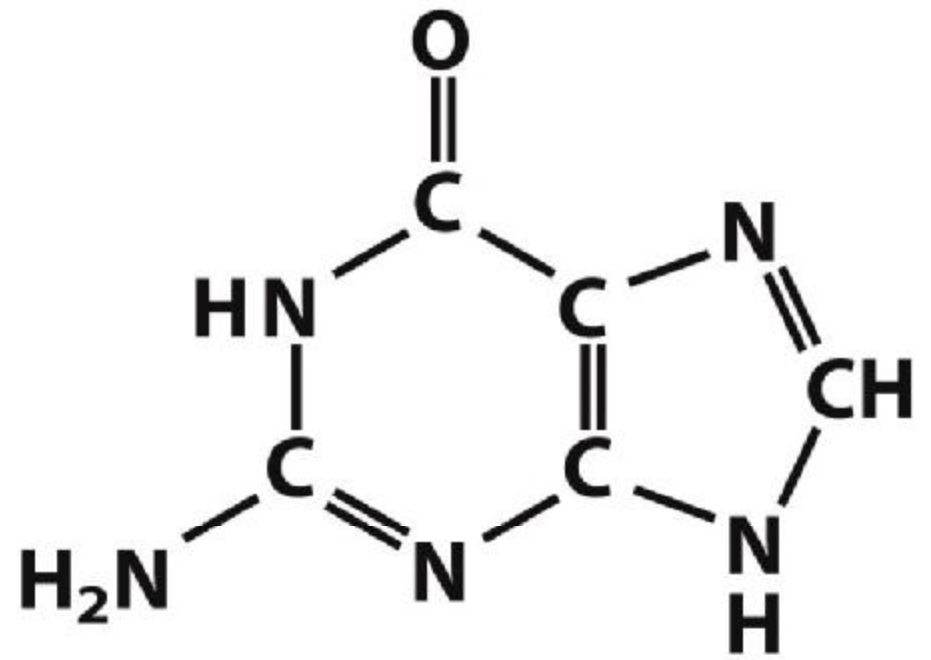
**Uracil  
(RNA)**

**Pyrimidines**

**Figure 8-2**  
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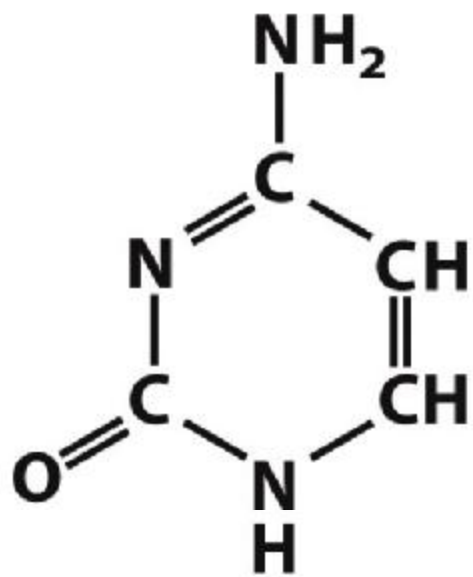
**Adenine**



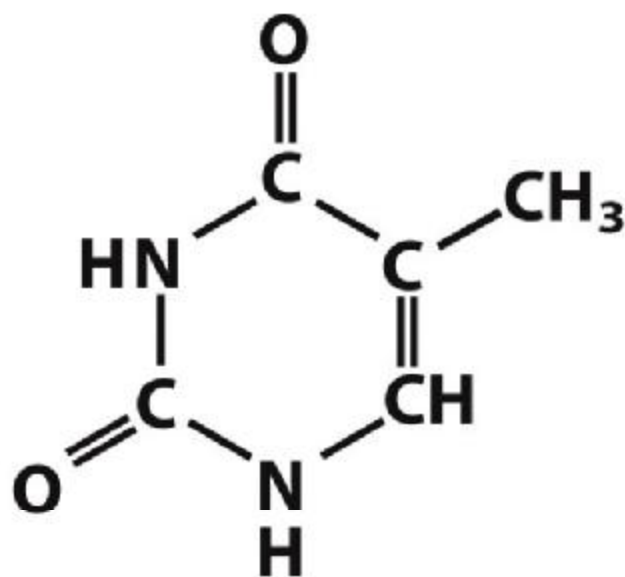
**Guanine**

**Purines**

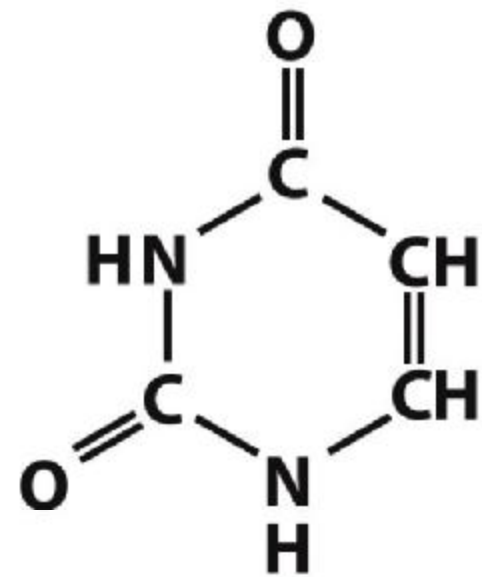




**Cytosine**



**Thymine  
(DNA)**



**Uracil  
(RNA)**

**Pyrimidines**

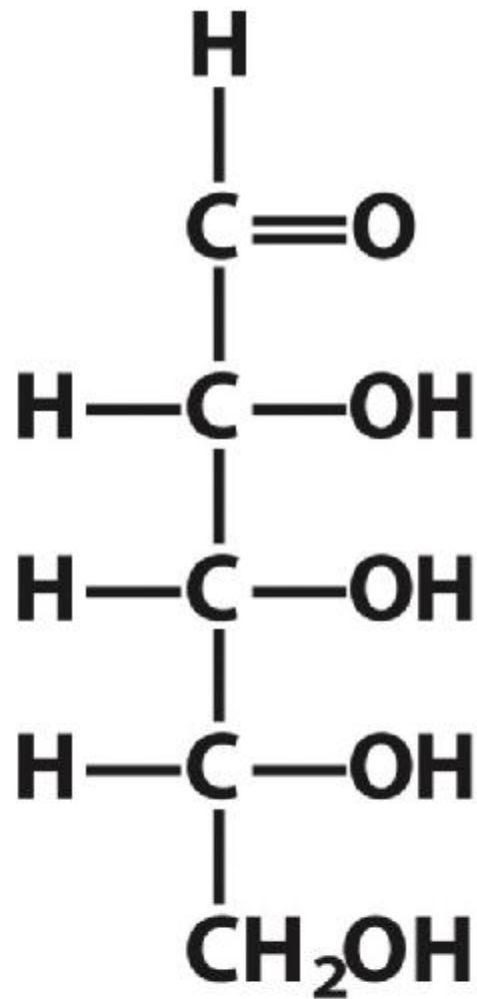
TABLE 8-1		Nucleotide and Nucleic Acid Nomenclature	
Base	Nucleoside	Nucleotide	Nucleic acid
<b>Purines</b>			
Adenine	Adenosine	Adenylate	RNA
	Deoxyadenosine	Deoxyadenylate	DNA
Guanine	Guanosine	Guanylate	RNA
	Deoxyguanosine	Deoxyguanylate	DNA
<b>Pyrimidines</b>			
Cytosine	Cytidine	Cytidylate	RNA
	Deoxycytidine	Deoxycytidylate	DNA
Thymine	Thymidine or deoxythymidine	Thymidylate or deoxythymidylate	DNA
Uracil	Uridine	Uridylate	RNA

**Note:** "Nucleoside" and "nucleotide" are generic terms that include both ribo- and deoxyribo- forms. Also, ribonucleosides and ribonucleotides are here designated simply as nucleosides and nucleotides (e.g., riboadenosine as adenosine), and deoxyribonucleosides and deoxyribonucleotides as deoxynucleosides and deoxynucleotides (e.g., deoxyriboadenosine as deoxyadenosine). Both forms of naming are acceptable, but the shortened names are more commonly used. Thymine is an exception; "ribothymidine" is used to describe its unusual occurrence in RNA.

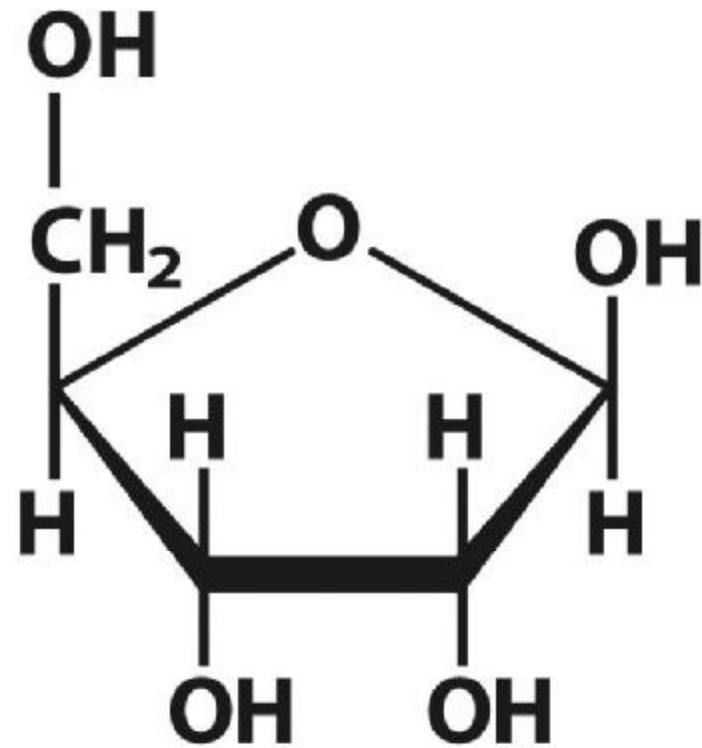
**Table 8-1**

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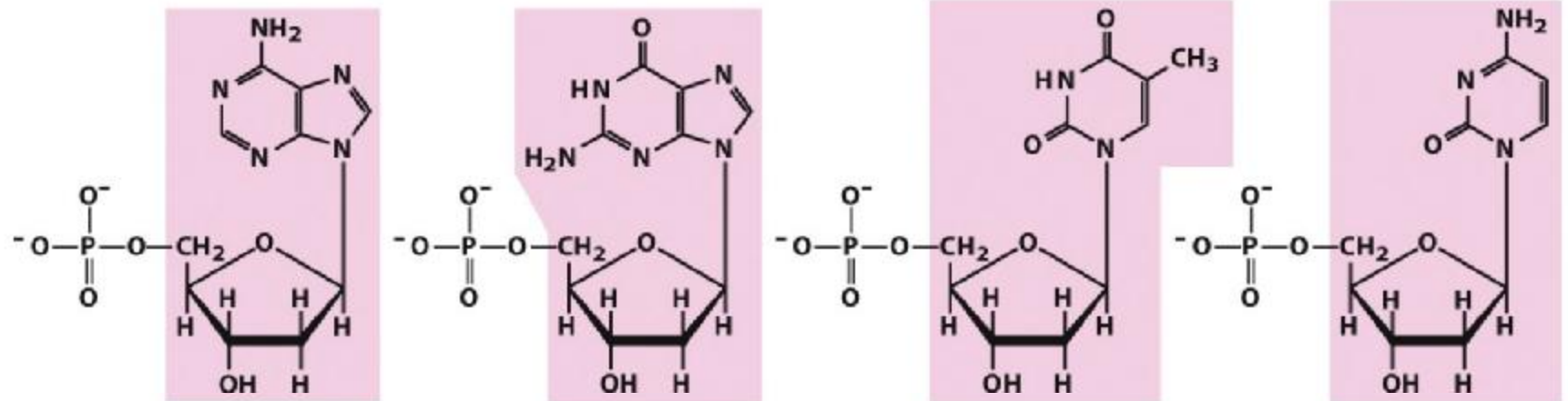


**Aldehyde**



**$\beta$ -Furanose**

**Figure 8-3a**  
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**Nucleotide:** Deoxyadenylate  
(deoxyadenosine  
5'-monophosphate)

**Symbols:** A, dA, dAMP

**Nucleoside:** Deoxyadenosine

**Nucleotide:** Deoxyguanylate  
(deoxyguanosine  
5'-monophosphate)

**Symbols:** G, dG, dGMP

**Nucleoside:** Deoxyguanosine

**Nucleotide:** Deoxythymidylate  
(deoxythymidine  
5'-monophosphate)

**Symbols:** T, dT, dTMP

**Nucleoside:** Deoxythymidine

**Nucleotide:** Deoxycytidylate  
(deoxycytidine  
5'-monophosphate)

**Symbols:** C, dC, dCMP

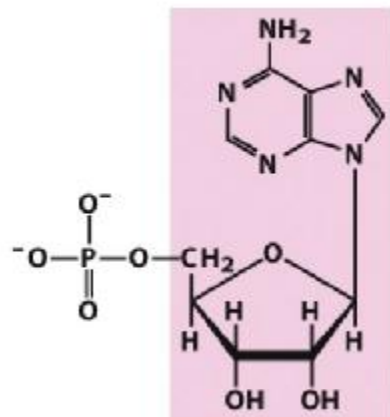
**Nucleoside:** Deoxycytidine

## Deoxyribonucleotides

**Figure 8-4a**

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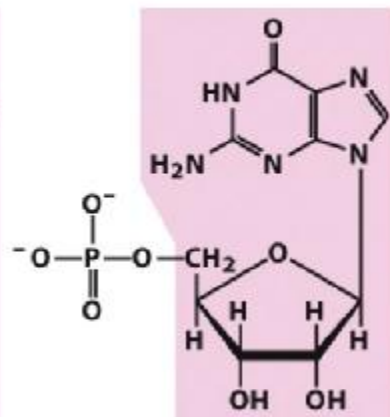
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**Nucleotide:** Adenylate (adenosine 5'-monophosphate)

**Symbols:** A, AMP

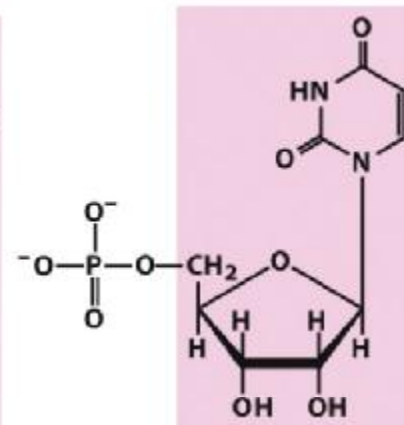
**Nucleoside:** Adenosine



**Nucleotide:** Guanylate (guanosine 5'-monophosphate)

**Symbols:** G, GMP

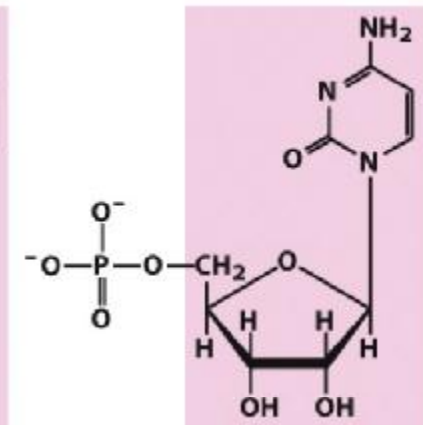
**Nucleoside:** Guanosine



**Nucleotide:** Uridylate (uridine 5'-monophosphate)

**Symbols:** U, UMP

**Nucleoside:** Uridine



**Nucleotide:** Cytidylate (cytidine 5'-monophosphate)

**Symbols:** C, CMP

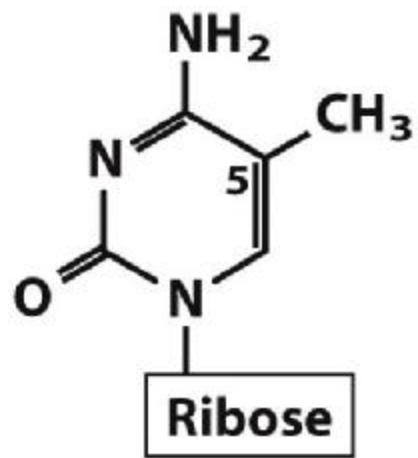
**Nucleoside:** Cytidine

### Ribonucleotides

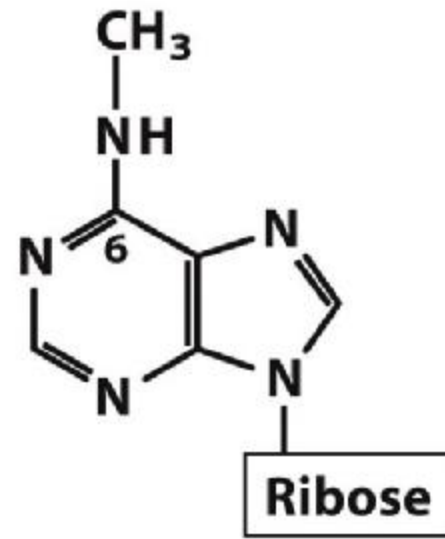
**Figure 8-4b**

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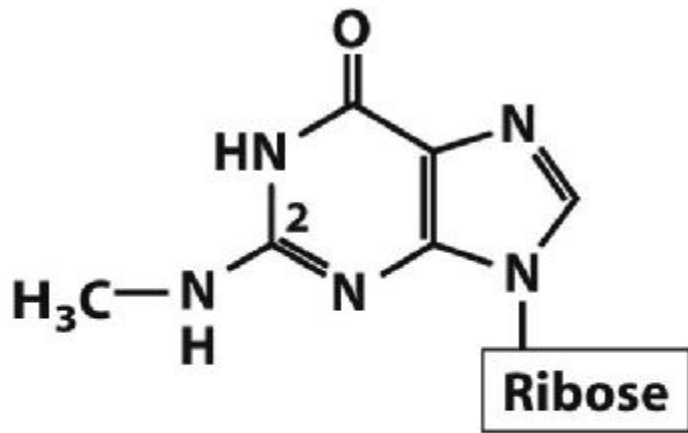
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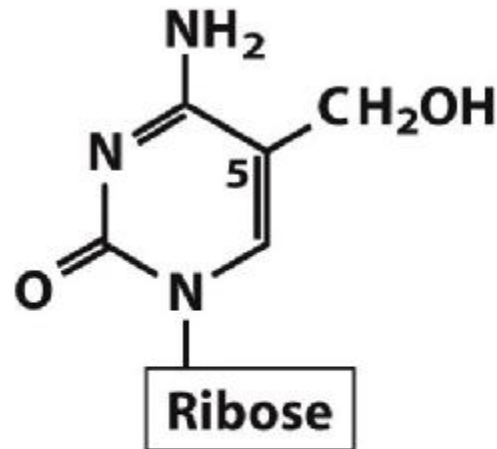
**5-Methylcytidine**



***N*<sup>6</sup>-Methyladenosine**

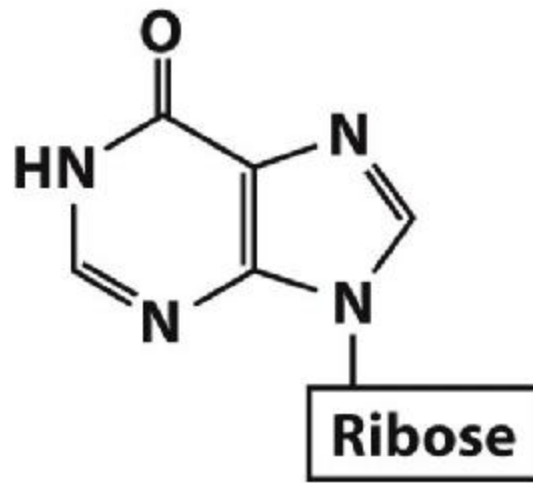


***N*<sup>2</sup>-Methylguanosine**

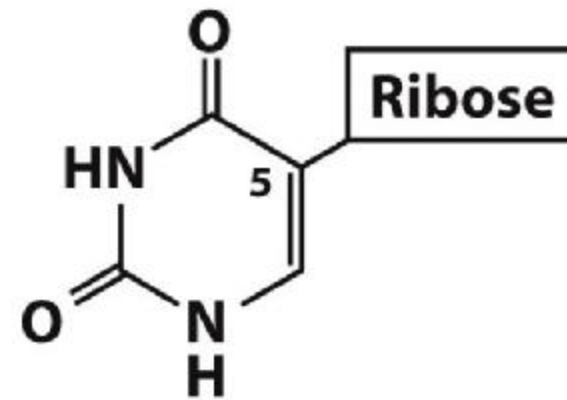


**5-Hydroxymethylcytidine**

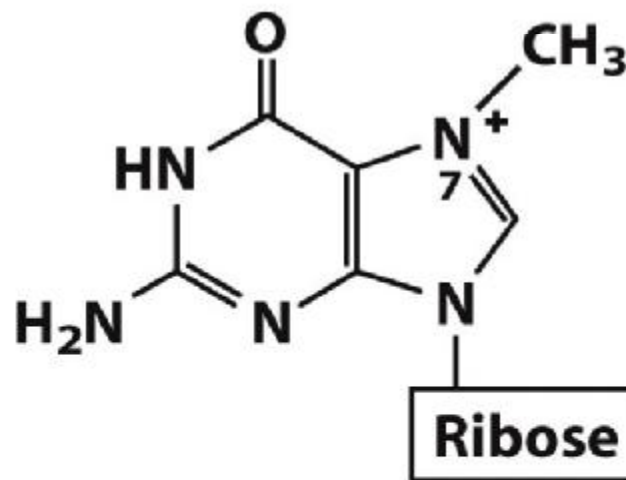
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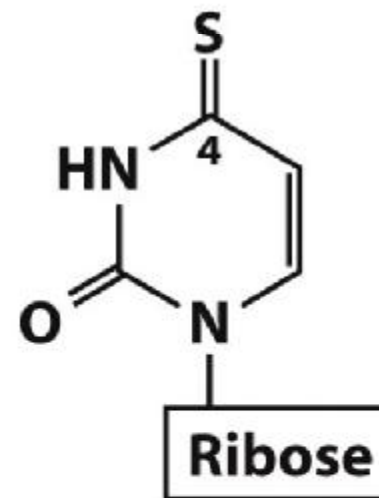
**Inosine**



**Pseudouridine**

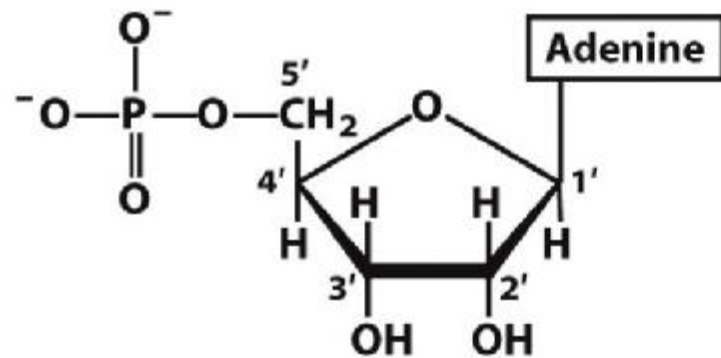


**7-Methylguanosine**

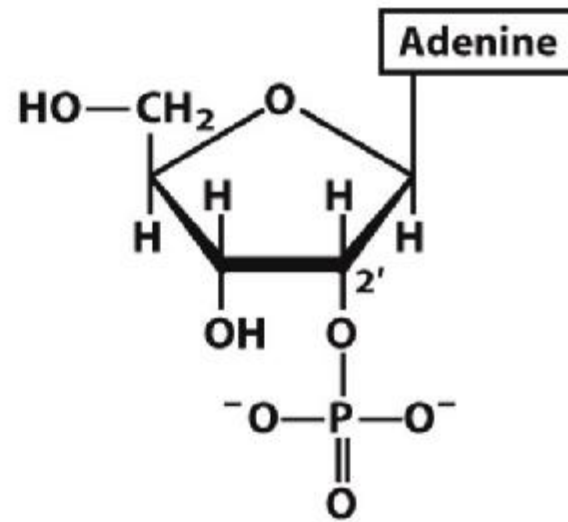


**4-Thiouridine**

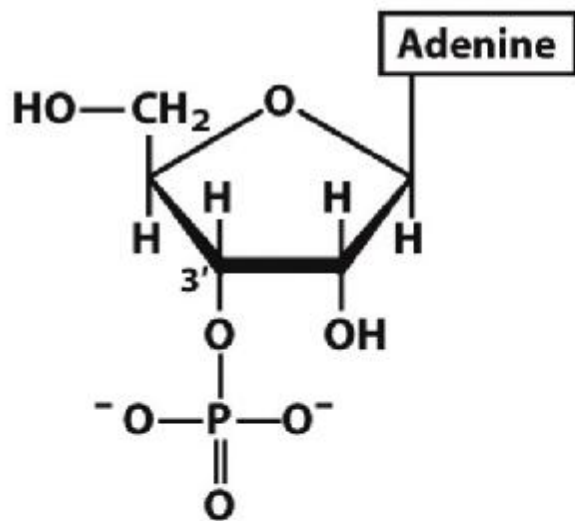
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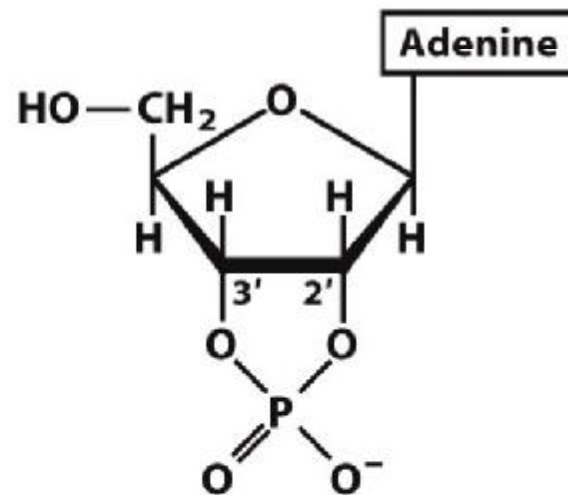
**Adenosine 5'-monophosphate**



**Adenosine 2'-monophosphate**



**Adenosine 3'-monophosphate**

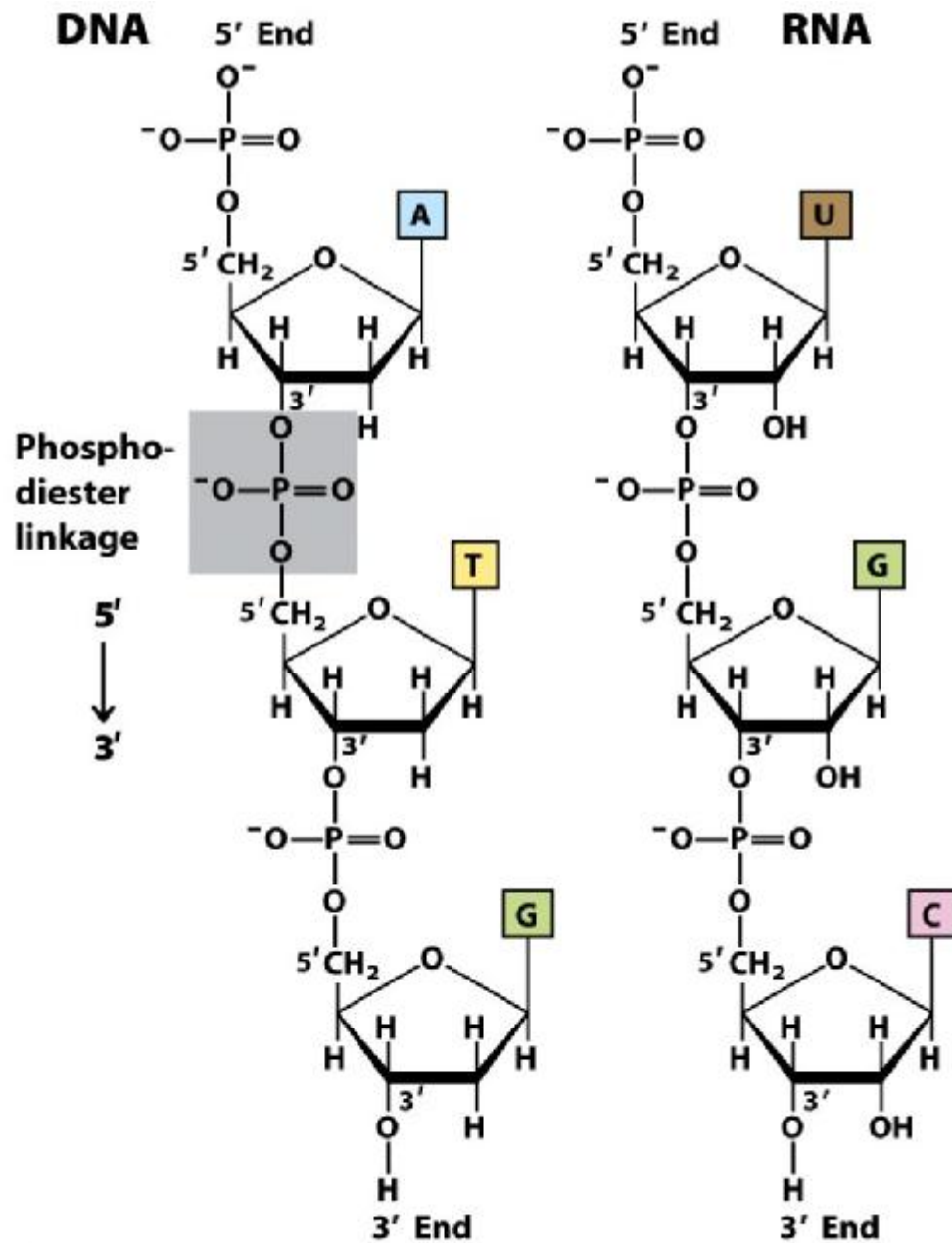


**Adenosine 2',3'-cyclic  
monophosphate**

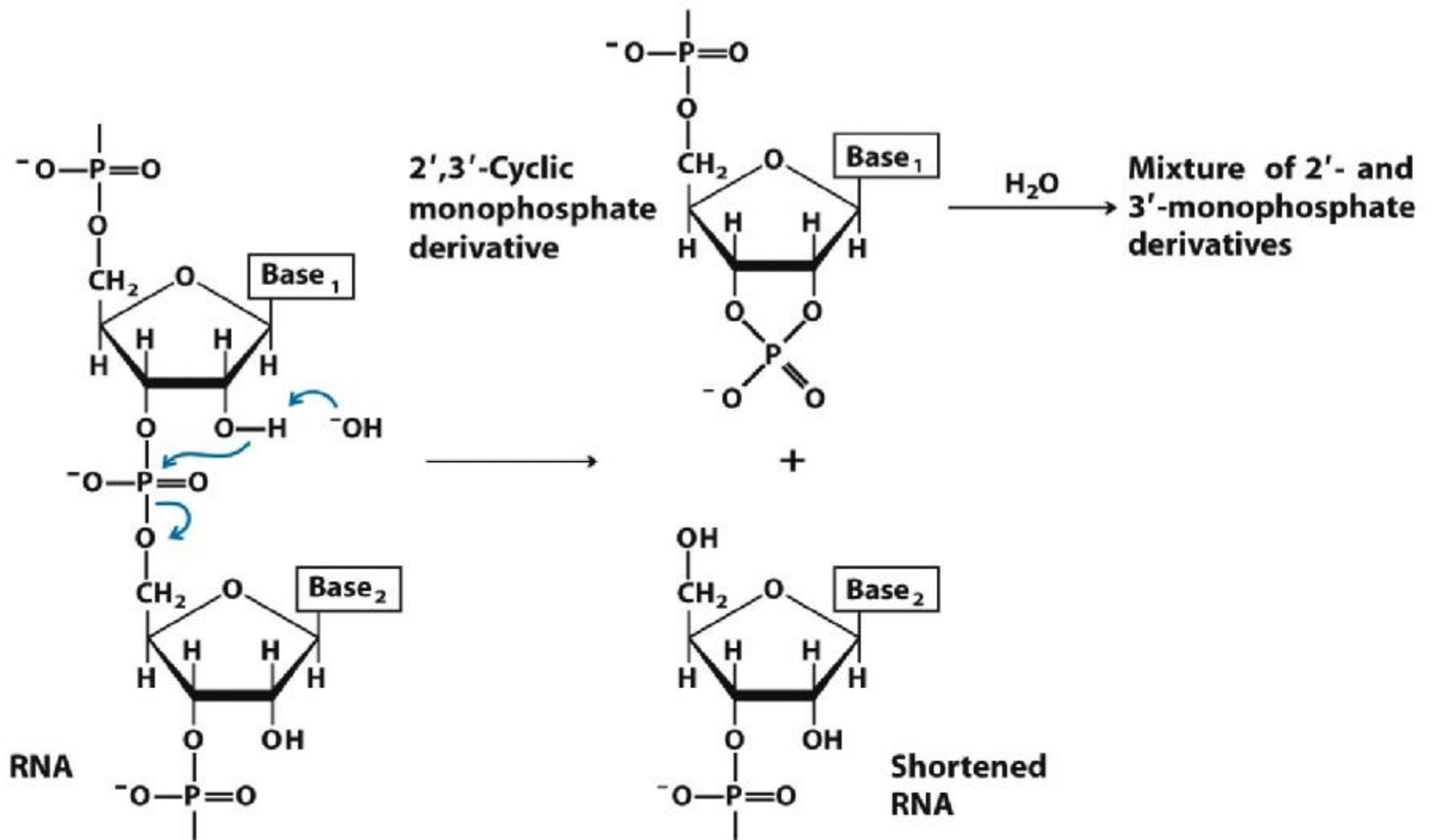
**Figure 8-6**

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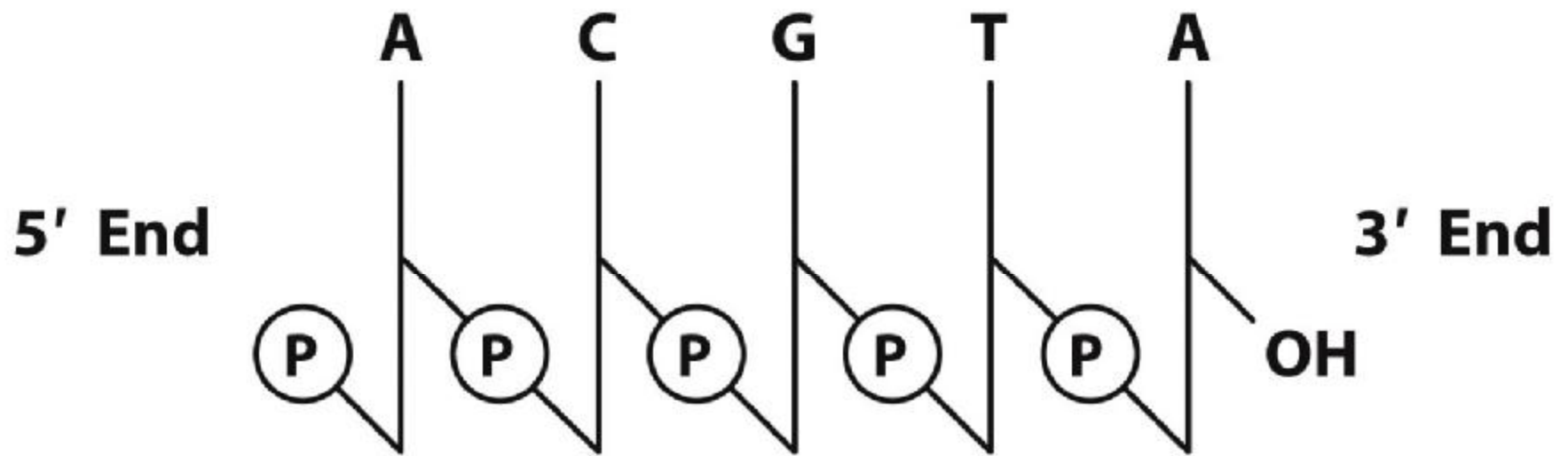




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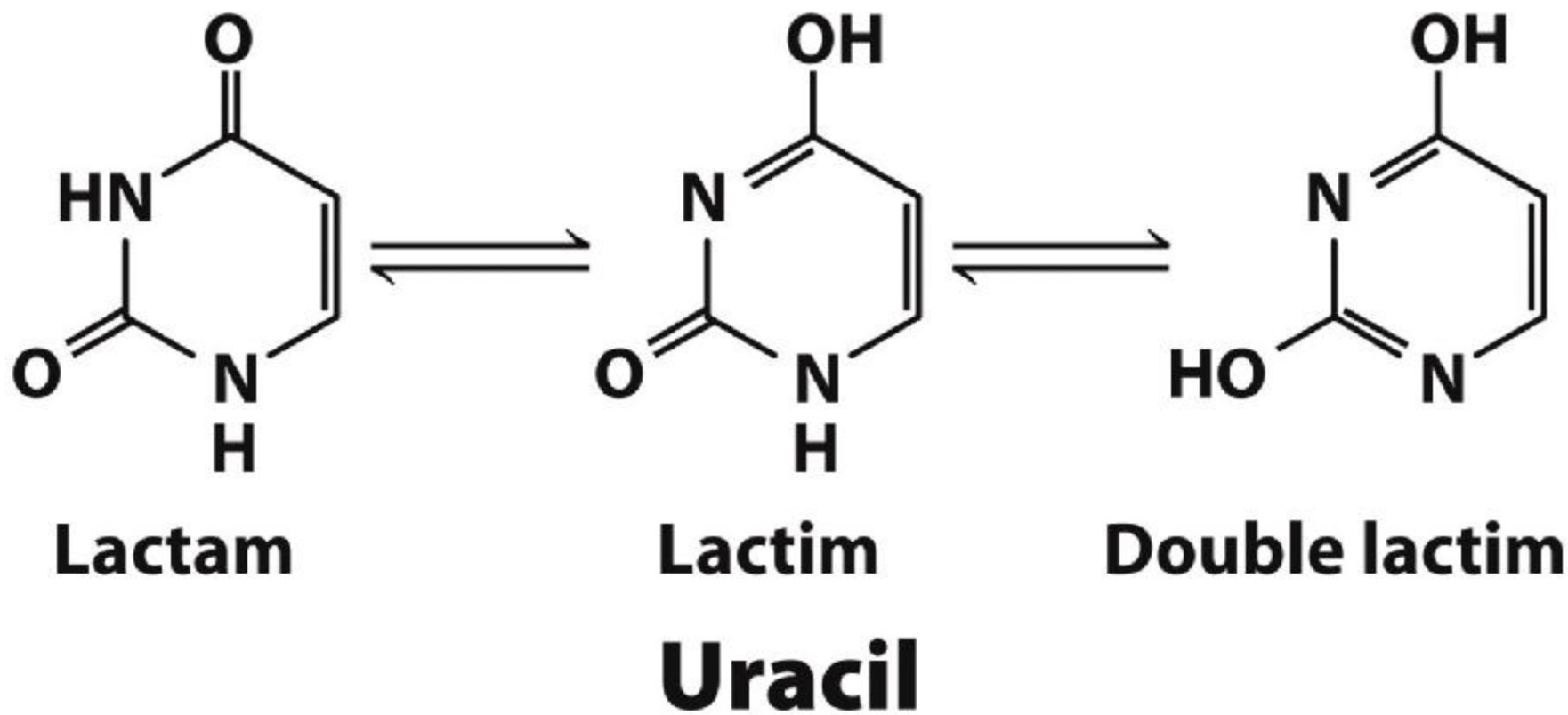
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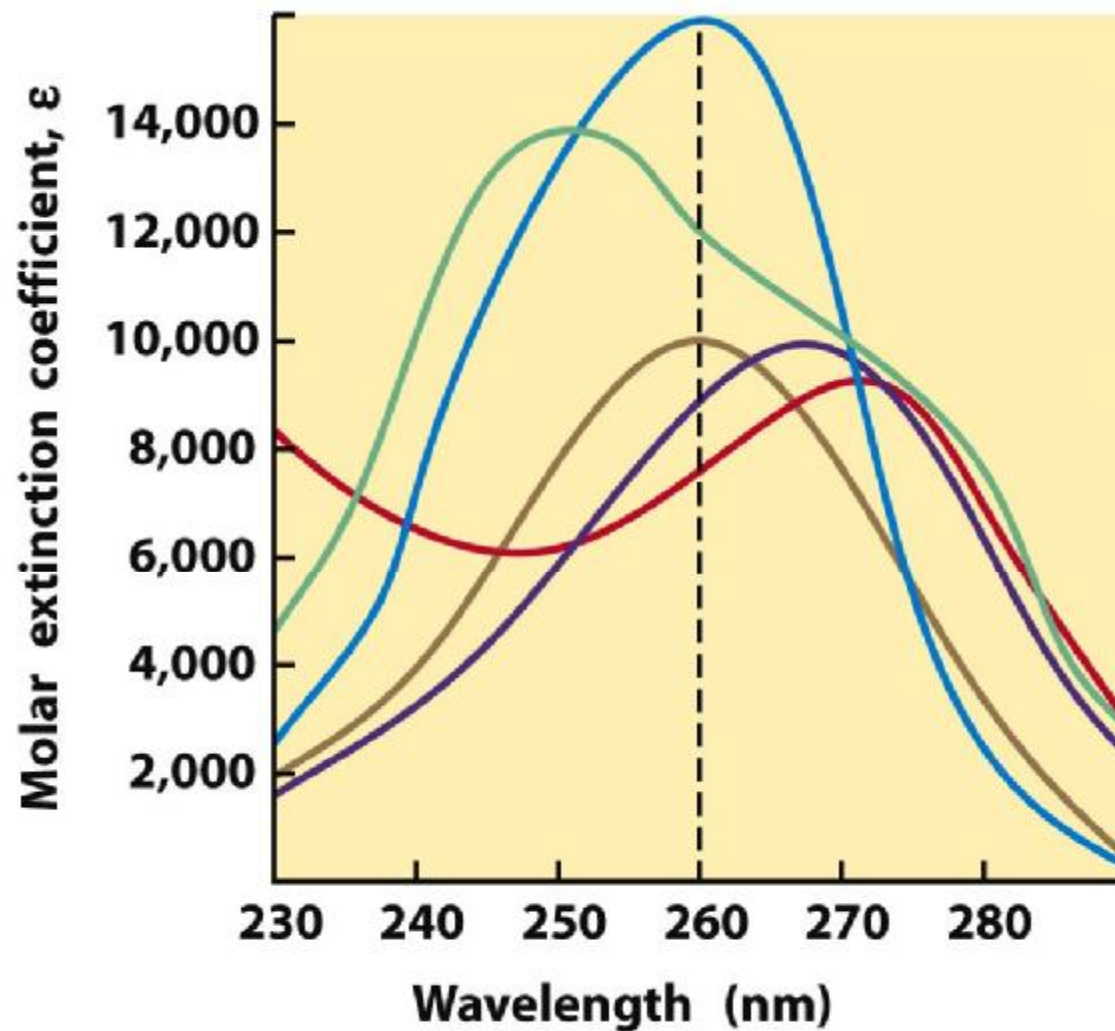
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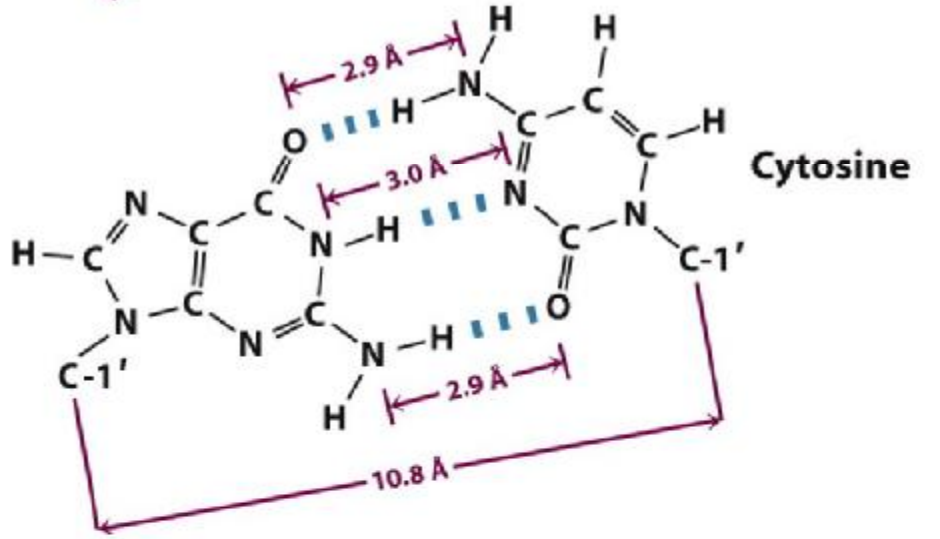
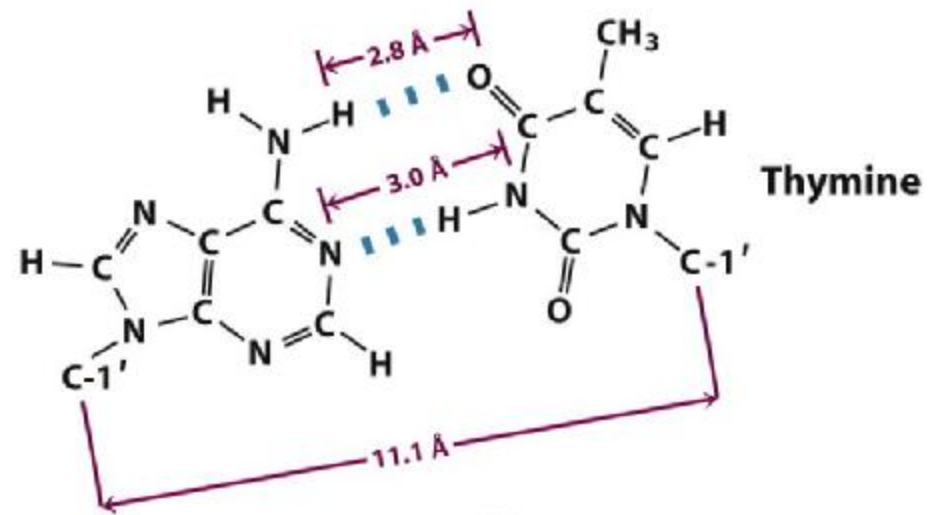
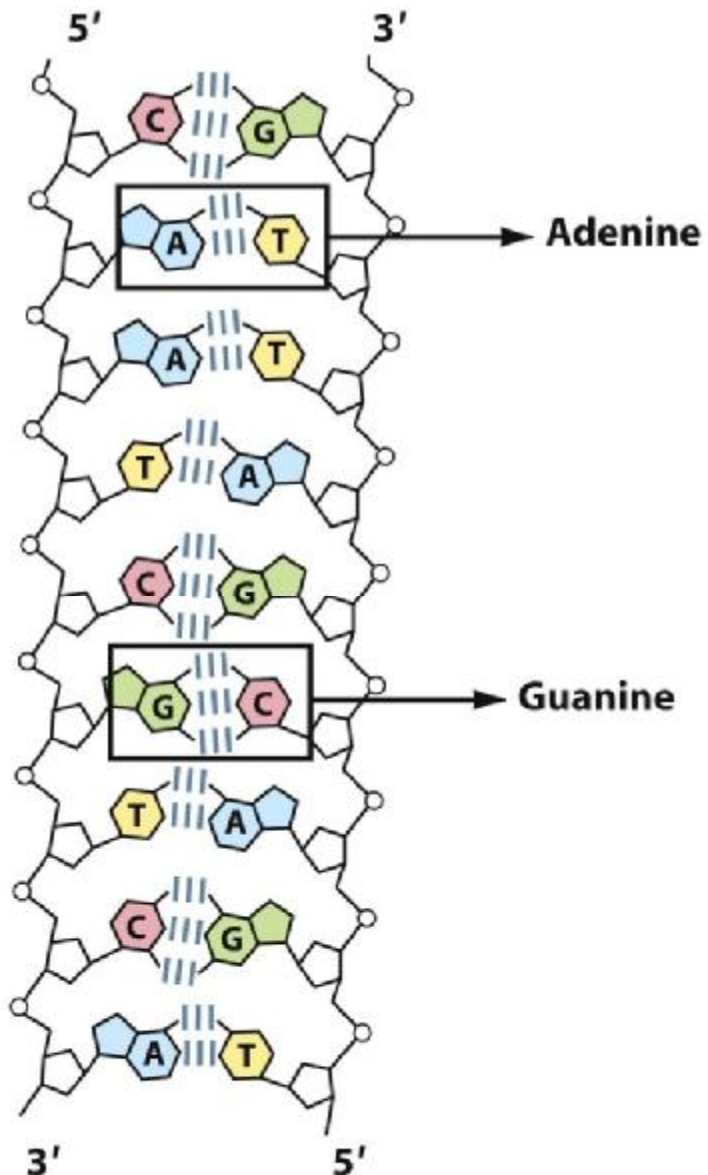
**Molar extinction coefficient at 260 nm,  $\epsilon_{260}$  ( $M^{-1}cm^{-1}$ )**

— AMP	15,400
— GMP	11,700
— UMP	9,900
— dTMP	9,200
— CMP	7,500

**Figure 8-10**

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**James D. Watson**

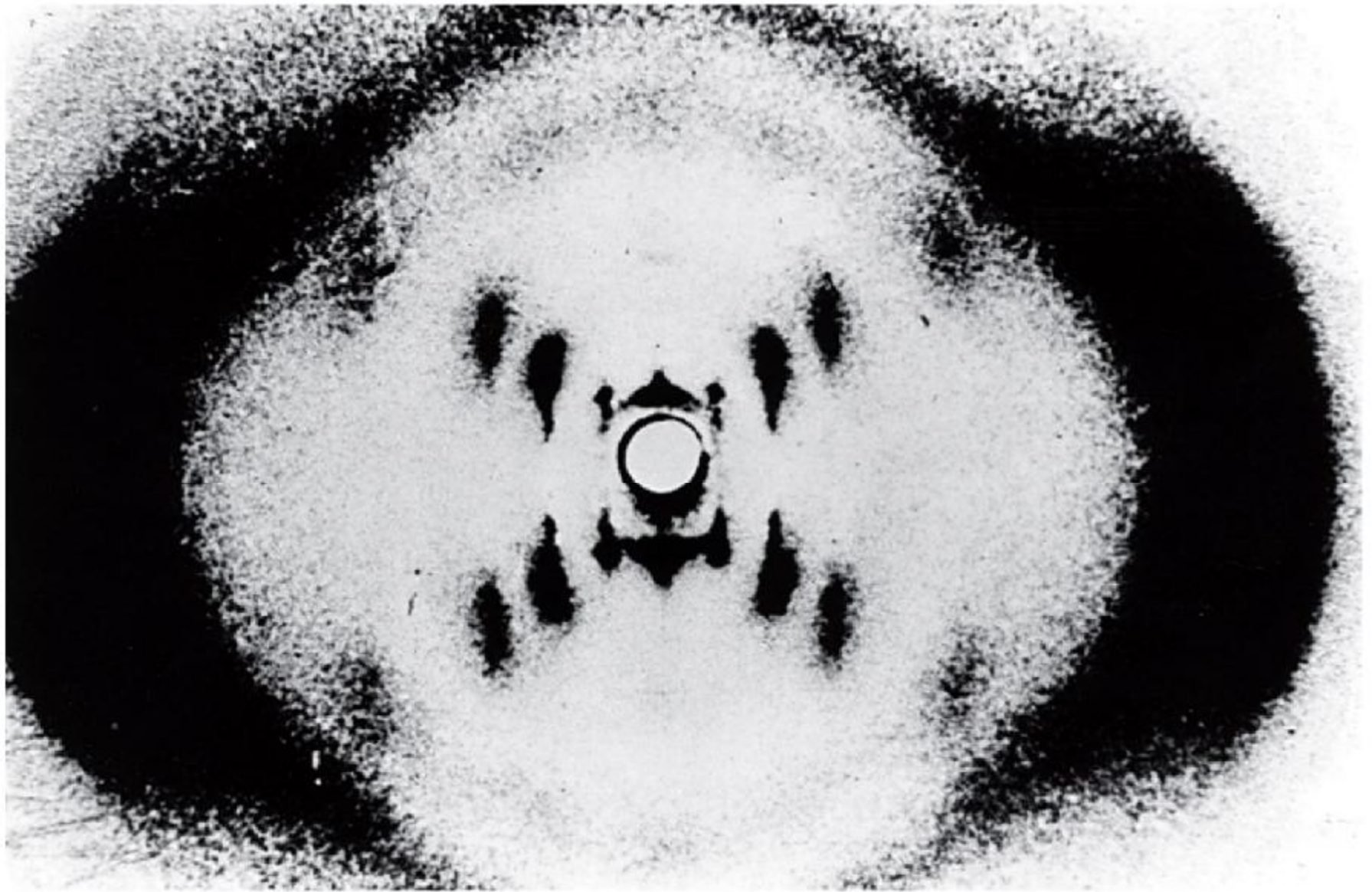


**Francis Crick,  
1916–2004**

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**Figure 8-12**

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**Rosalind Franklin,  
1920–1958**



**Maurice Wilkins,  
1916–2004**

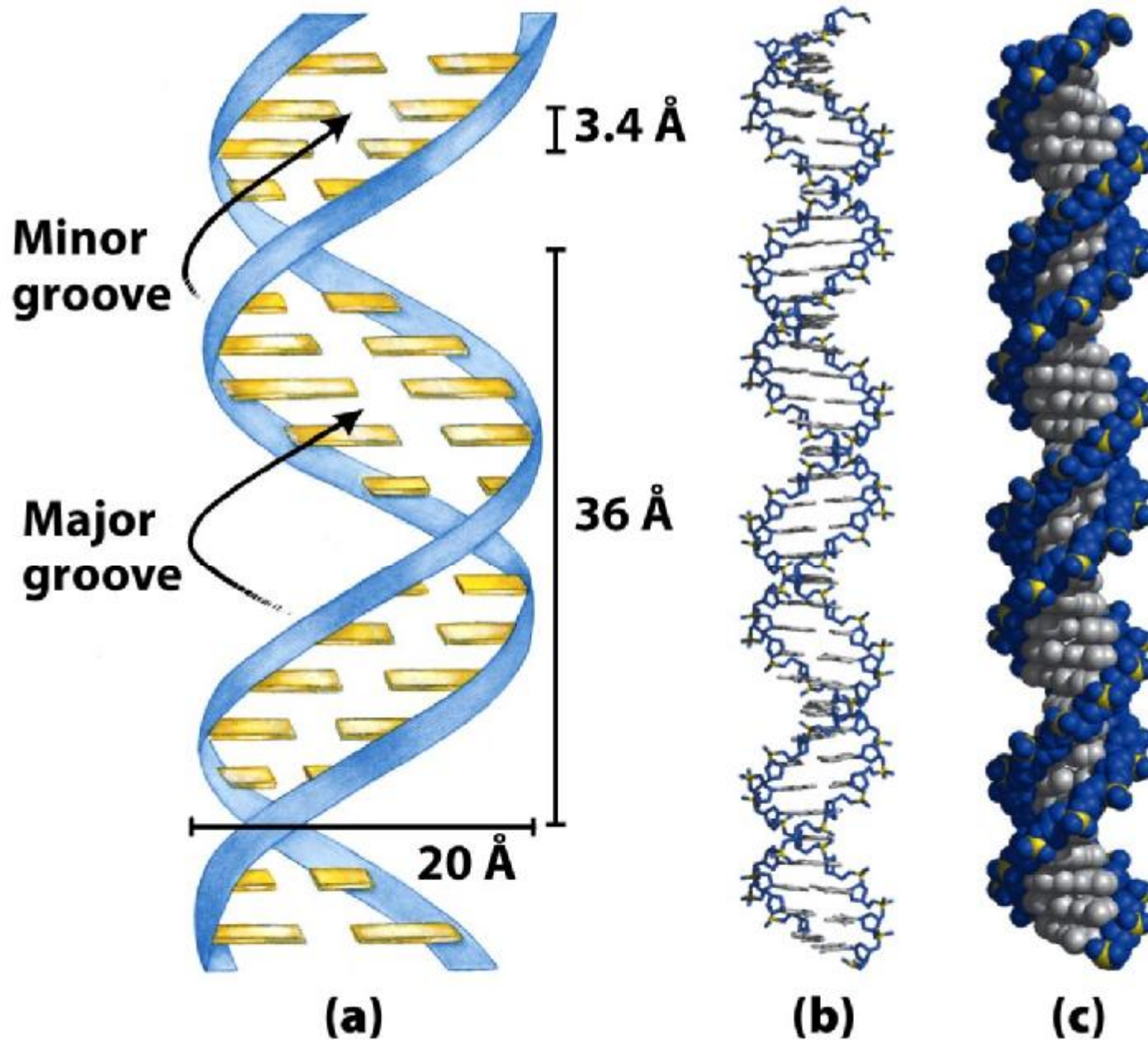
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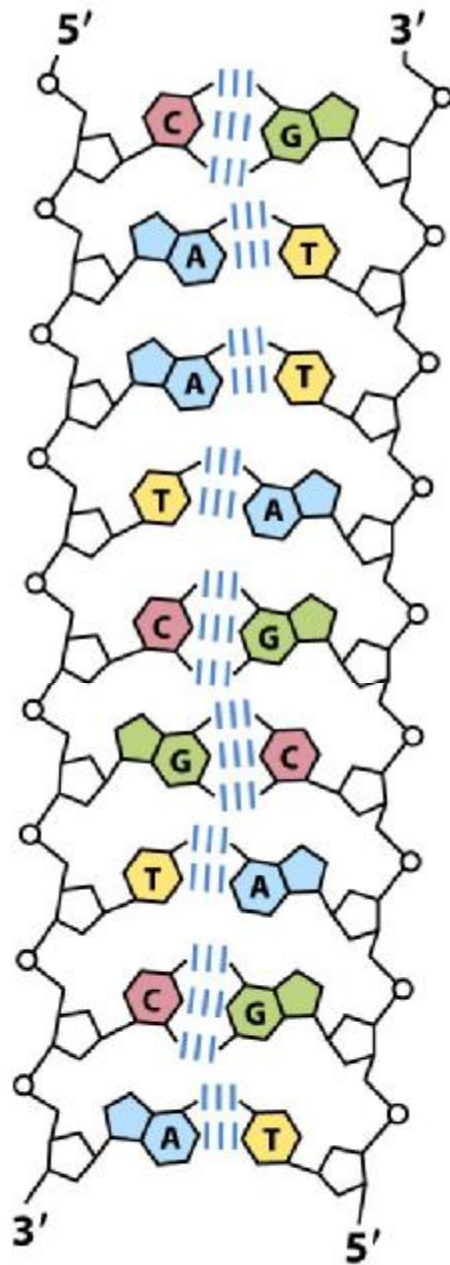
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# Erwin Chargaff and his colleagues in the late 1940s

- 1. The base composition of DNA generally varies from one species to another.**
  - 2. DNA specimens isolated from different tissues of the same species have the same base composition.**
  - 3. The base composition of DNA in a given species does not change with an organism's age, nutritional state, or changing environment.**
  - 4. In all cellular DNAs, regardless of the species the number of adenosine residues is equal to the number of the thymidine residues (that is, A : T), and the number of guanosine residues is equal to the number of cytidine residues (G : C)**
- Thus: the sum of the purine residues equals the sum of the pyrimidine residues; that is, A+G:T+C.**



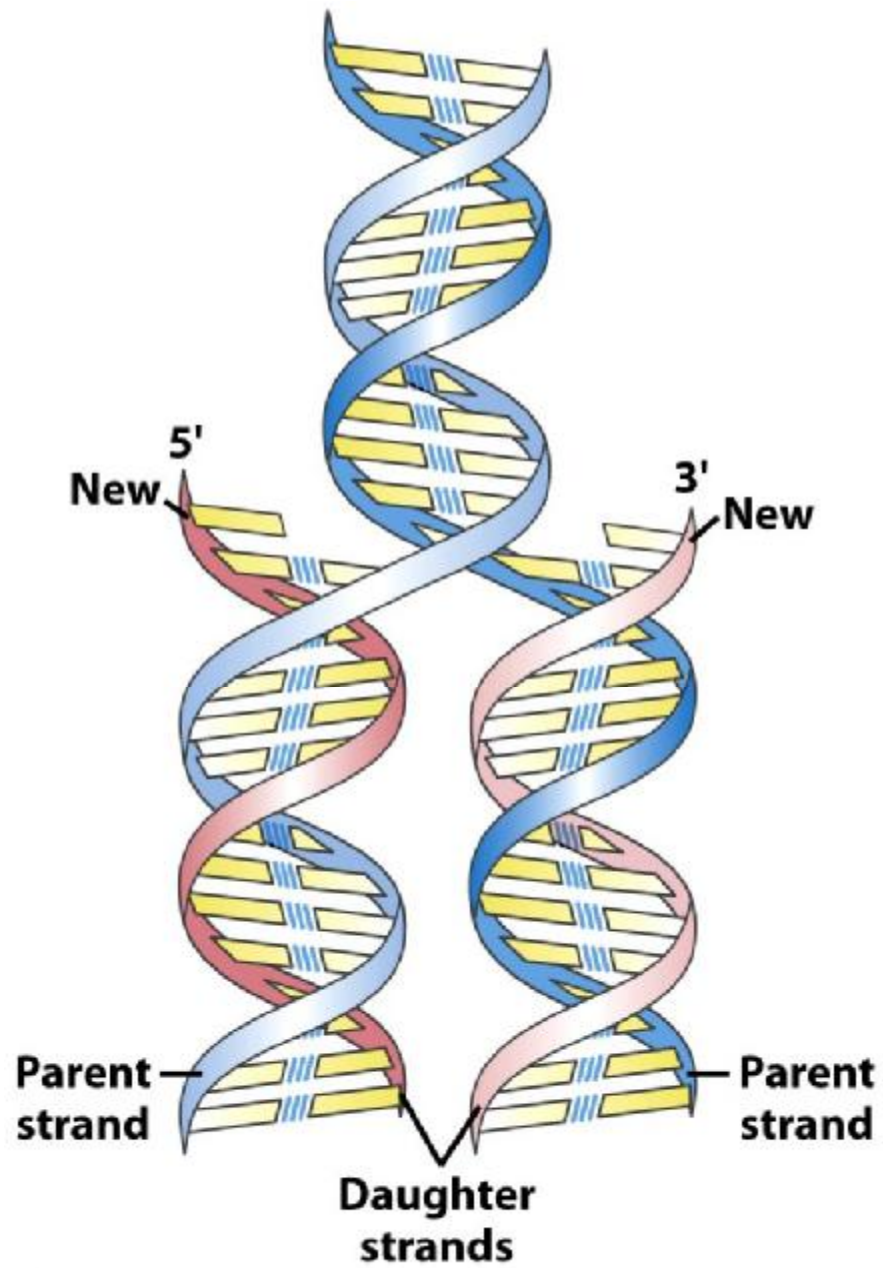
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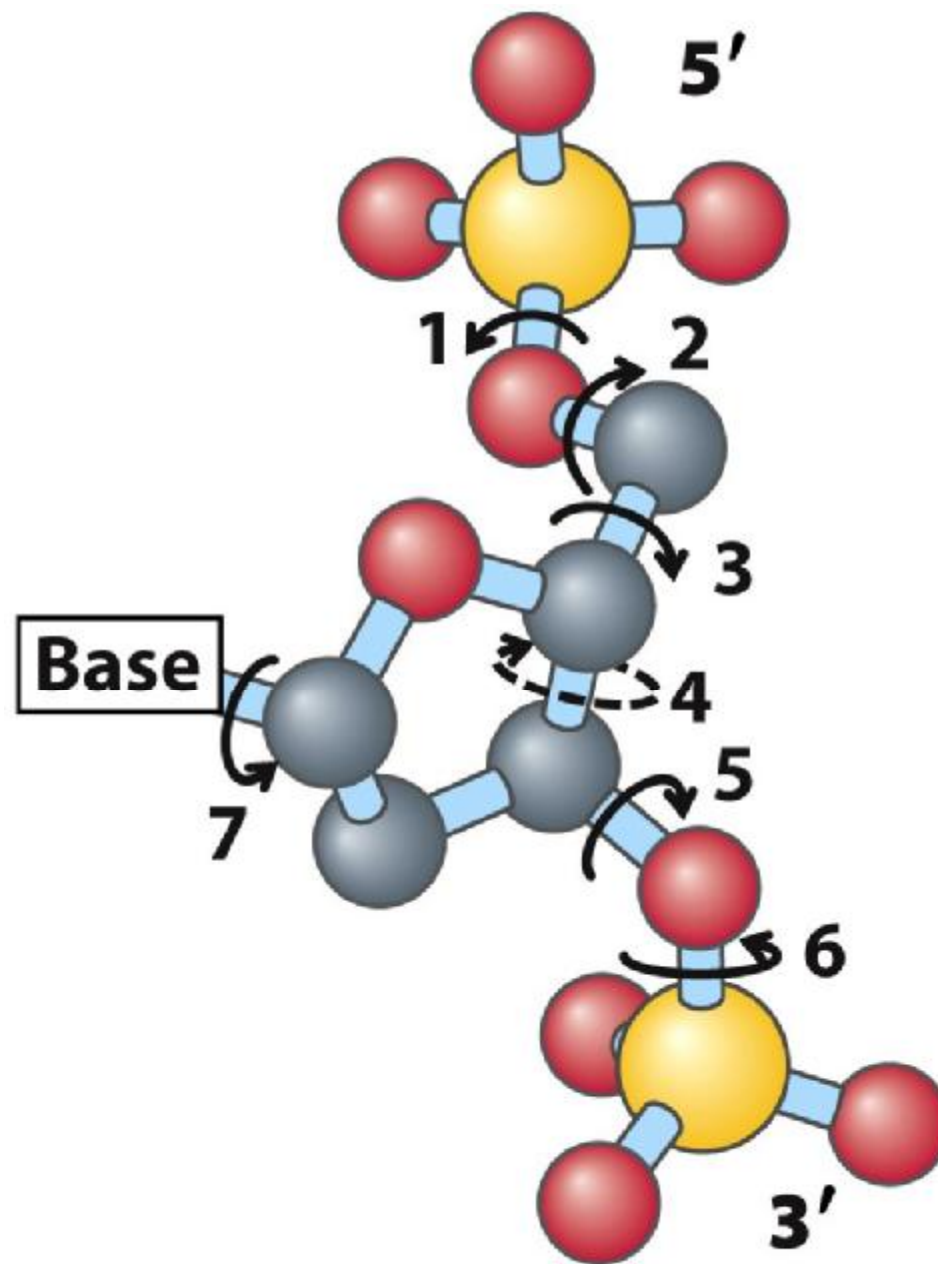
**Figure 8-14**

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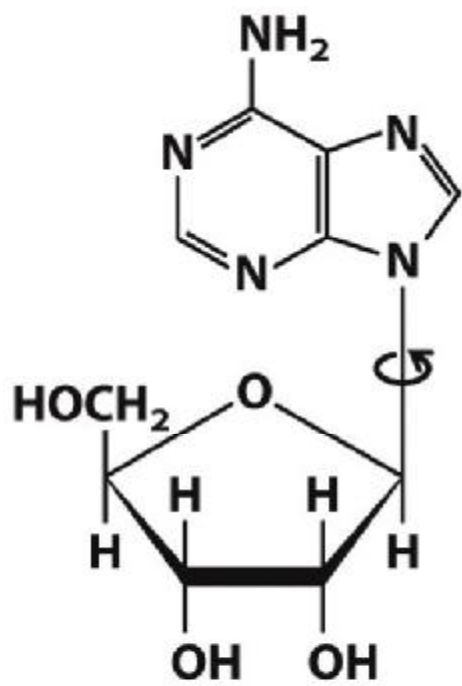
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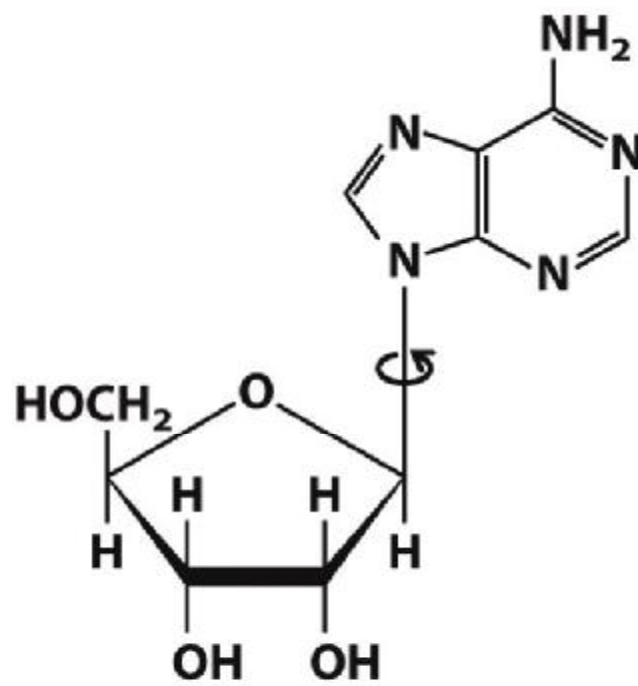
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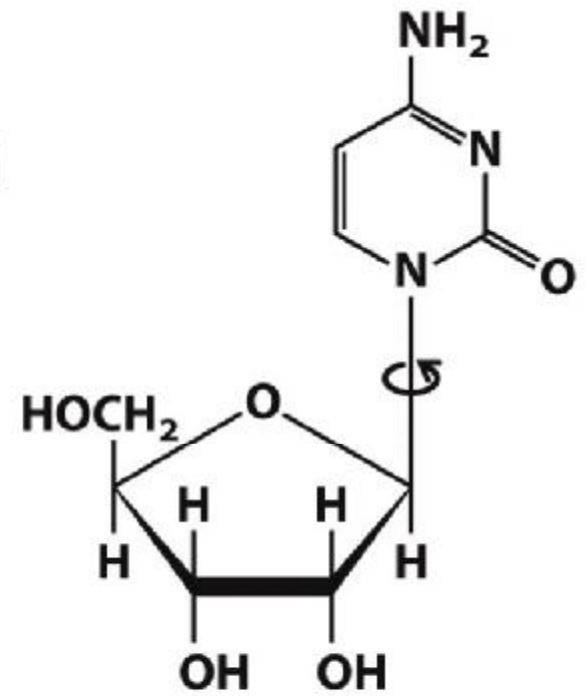
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***syn*-Adenosine**



***anti*-Adenosine**

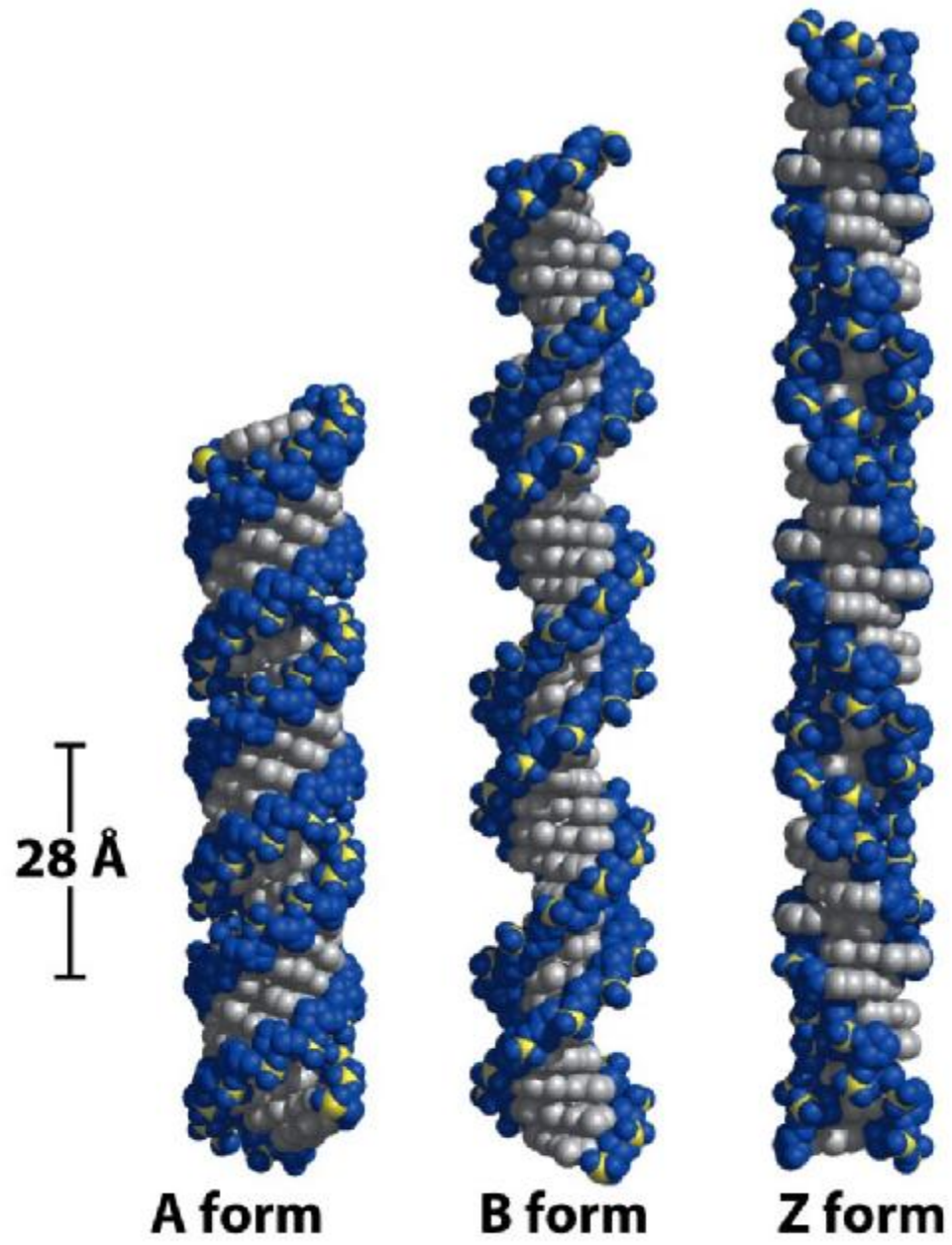


***anti*-Cytidine**

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**Figure 8-17 part 1**  
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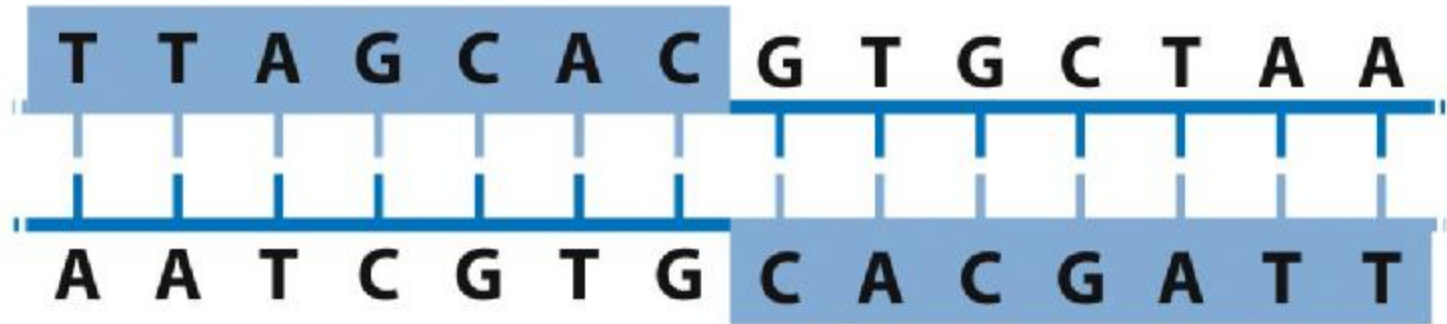
	<b>A form</b>	<b>B form</b>	<b>Z form</b>
<b>Helical sense</b>	Right handed	Right handed	Left handed
<b>Diameter</b>	~26 Å	~20 Å	~18 Å
<b>Base pairs per helical turn</b>	11	10.5	12
<b>Helix rise per base pair</b>	2.6 Å	3.4 Å	3.7 Å
<b>Base tilt normal to the helix axis</b>	20°	6°	7°
<b>Sugar pucker conformation</b>	C-3' endo	C-2' endo	C-2' endo for pyrimidines; C-3' endo for purines
<b>Glycosyl bond conformation</b>	Anti	Anti	Anti for pyrimidines; syn for purines

**Figure 8-17 part 2**

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# Palindrome



# Mirror repeat

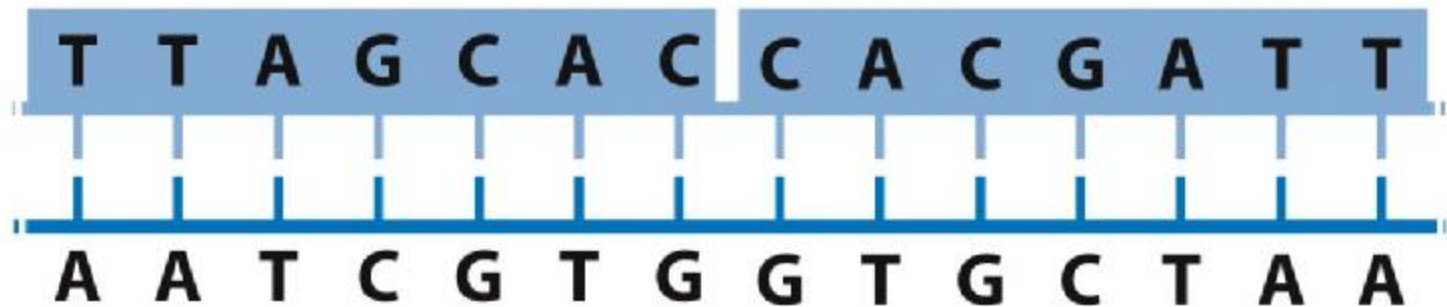
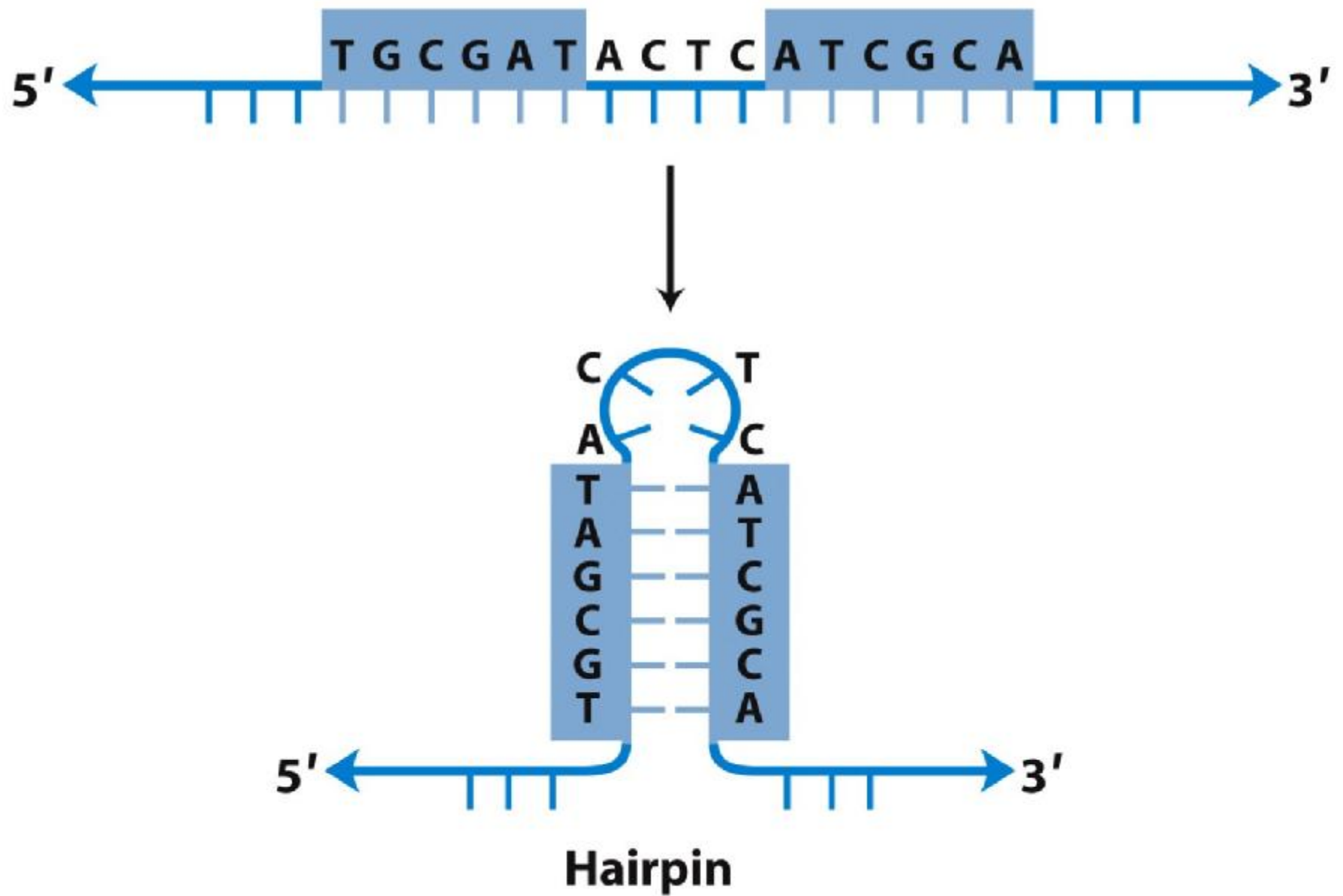
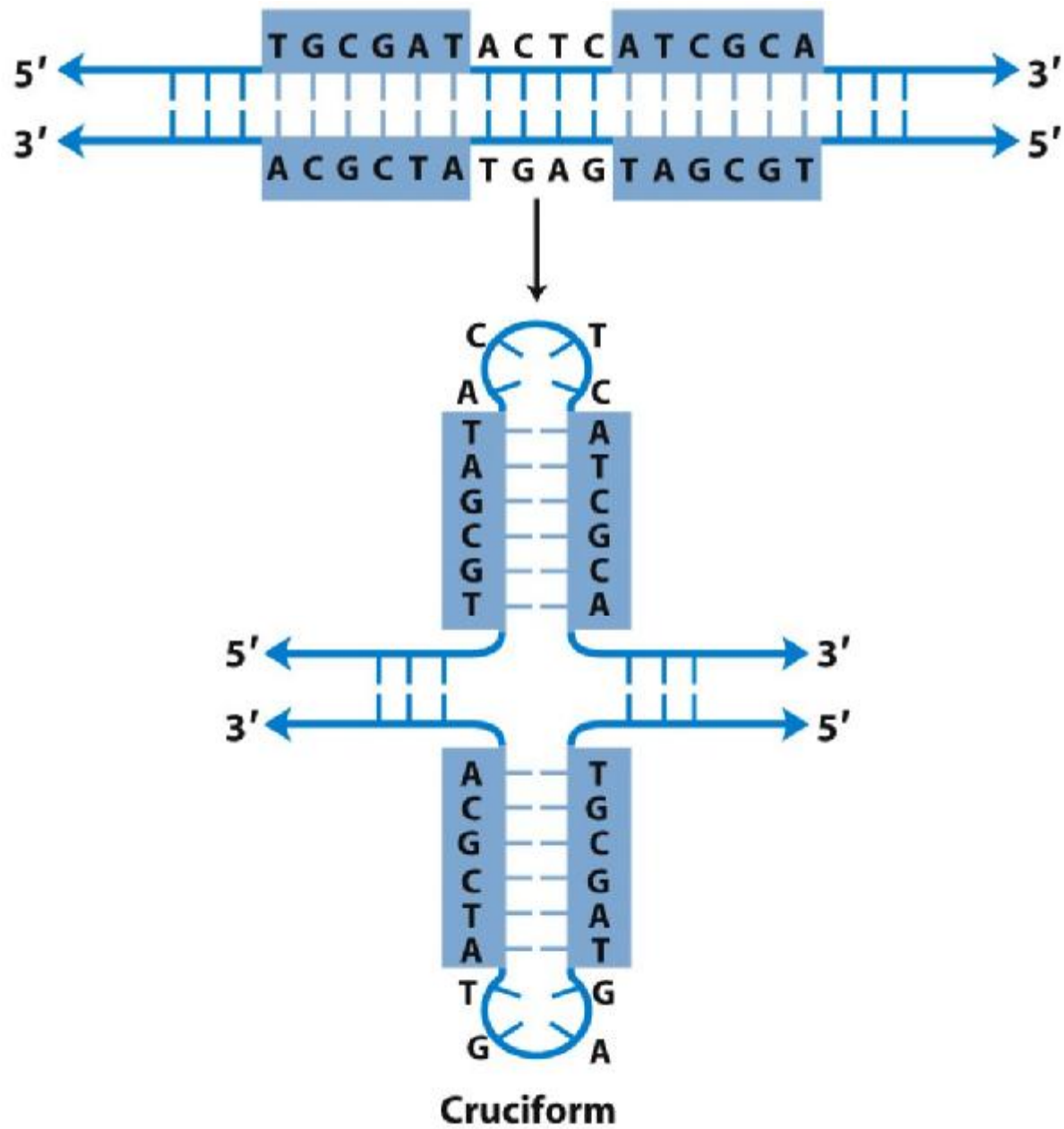


Figure 8-18

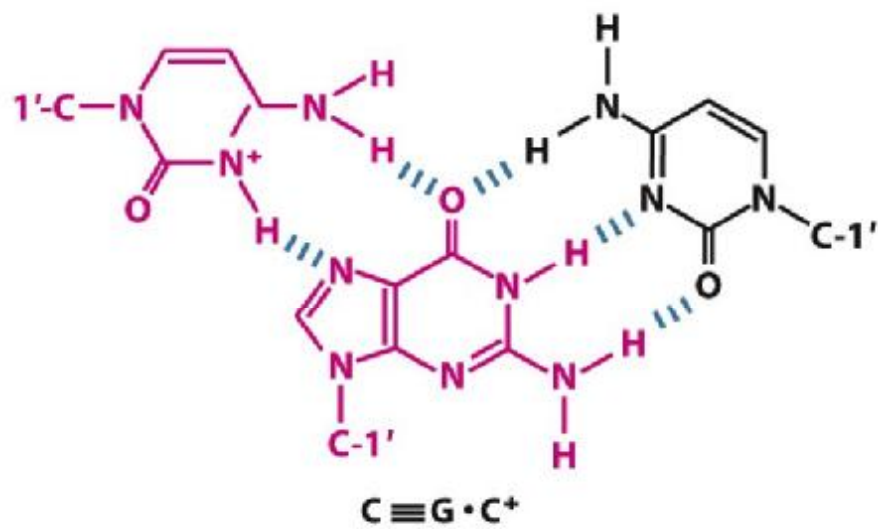
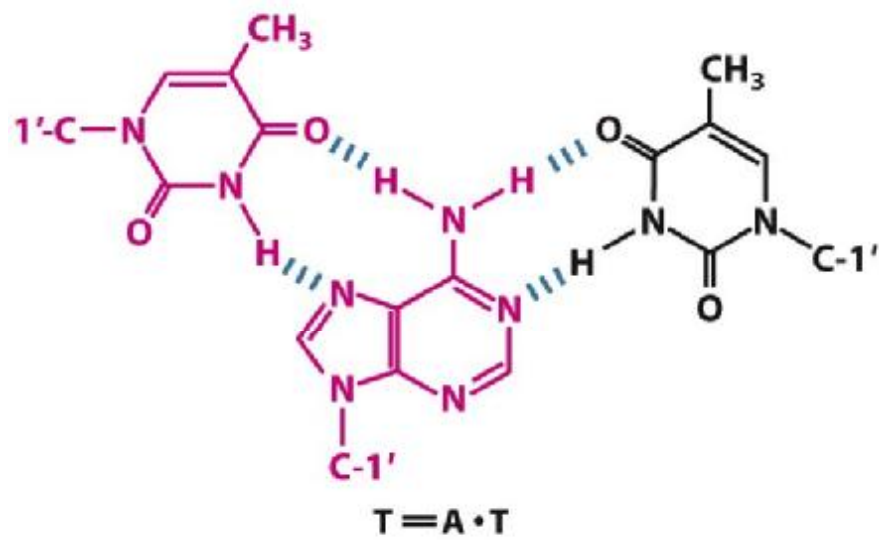
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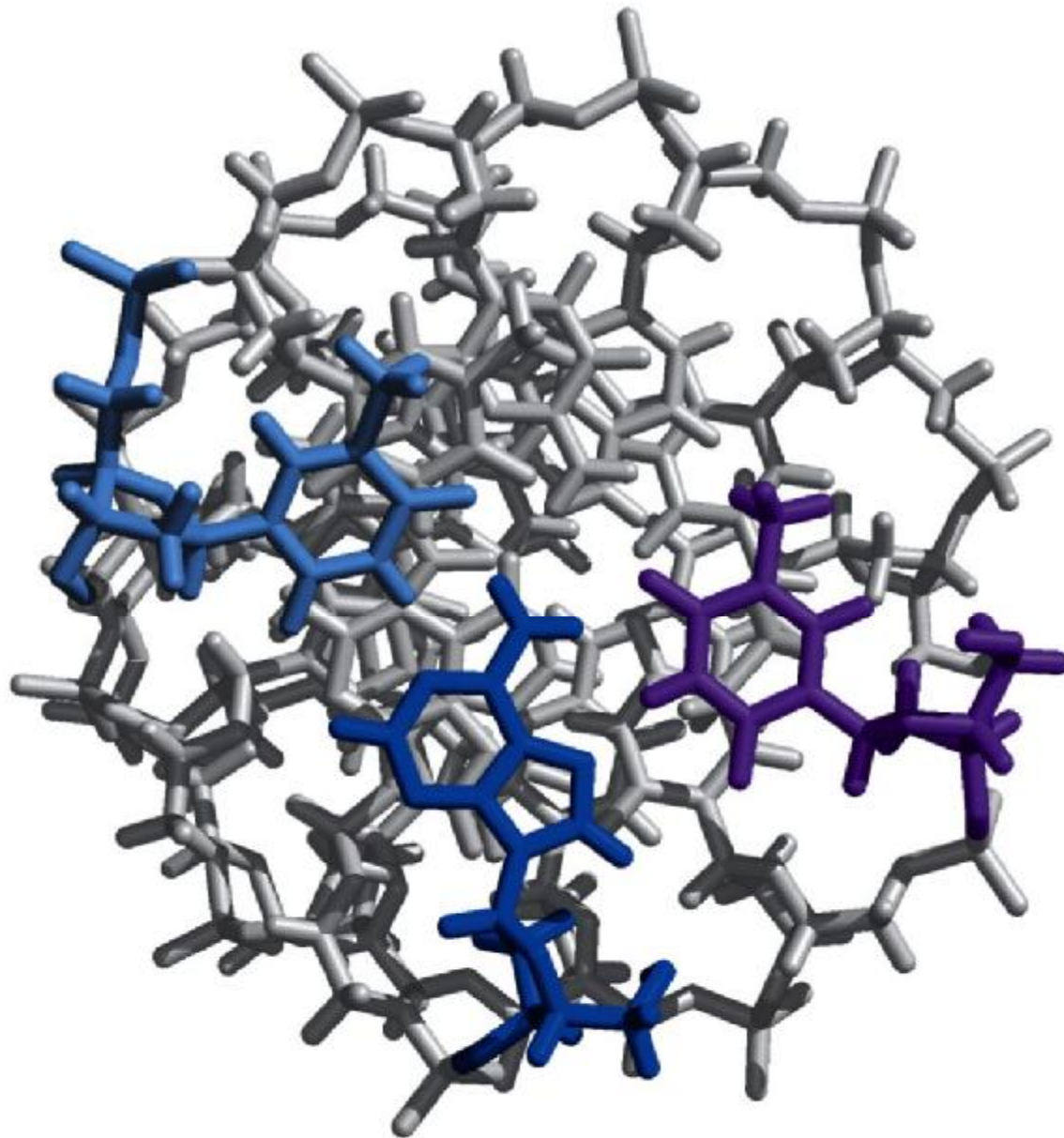
**Figure 8-19b**  
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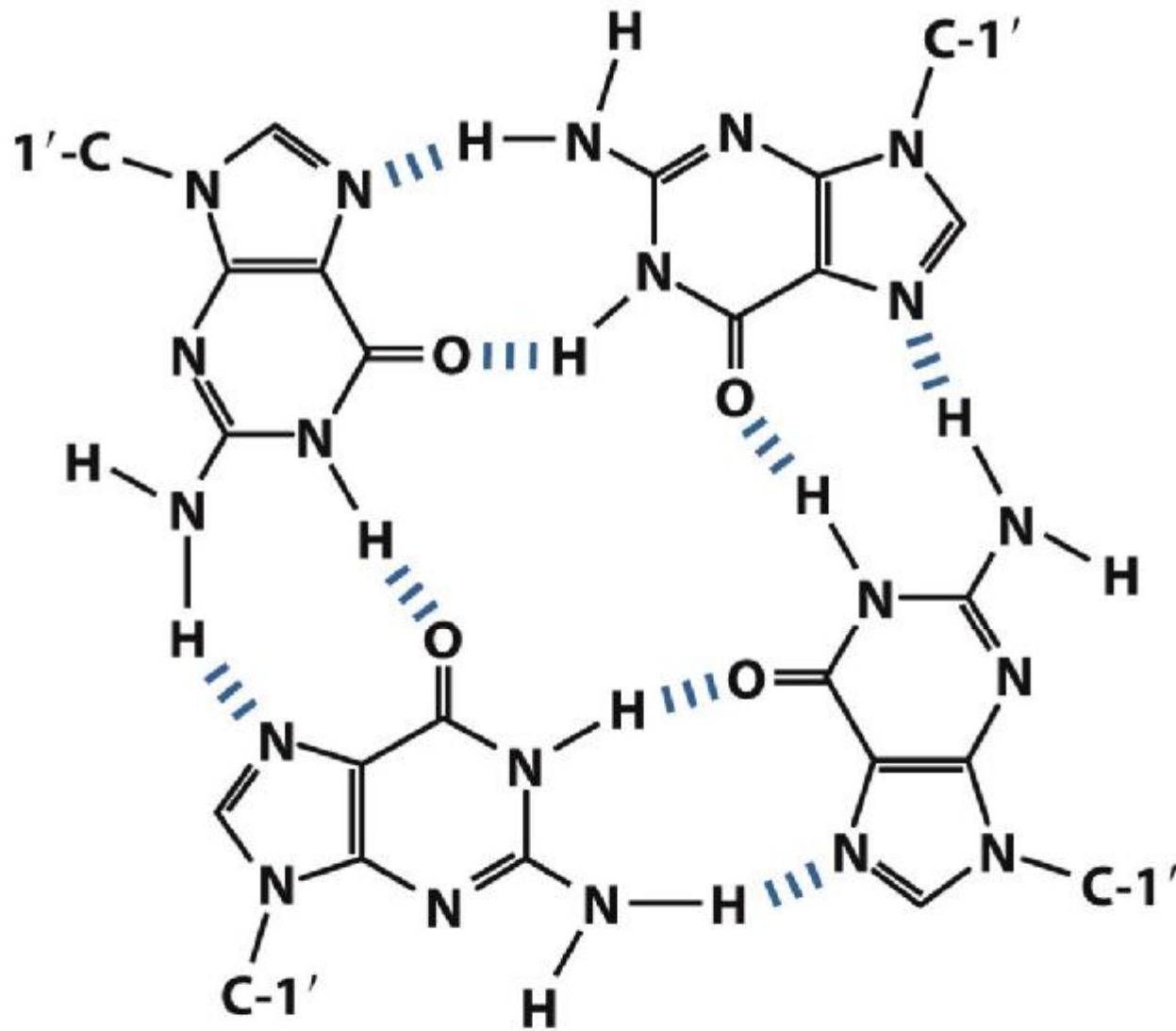
**Figure 8-20a**

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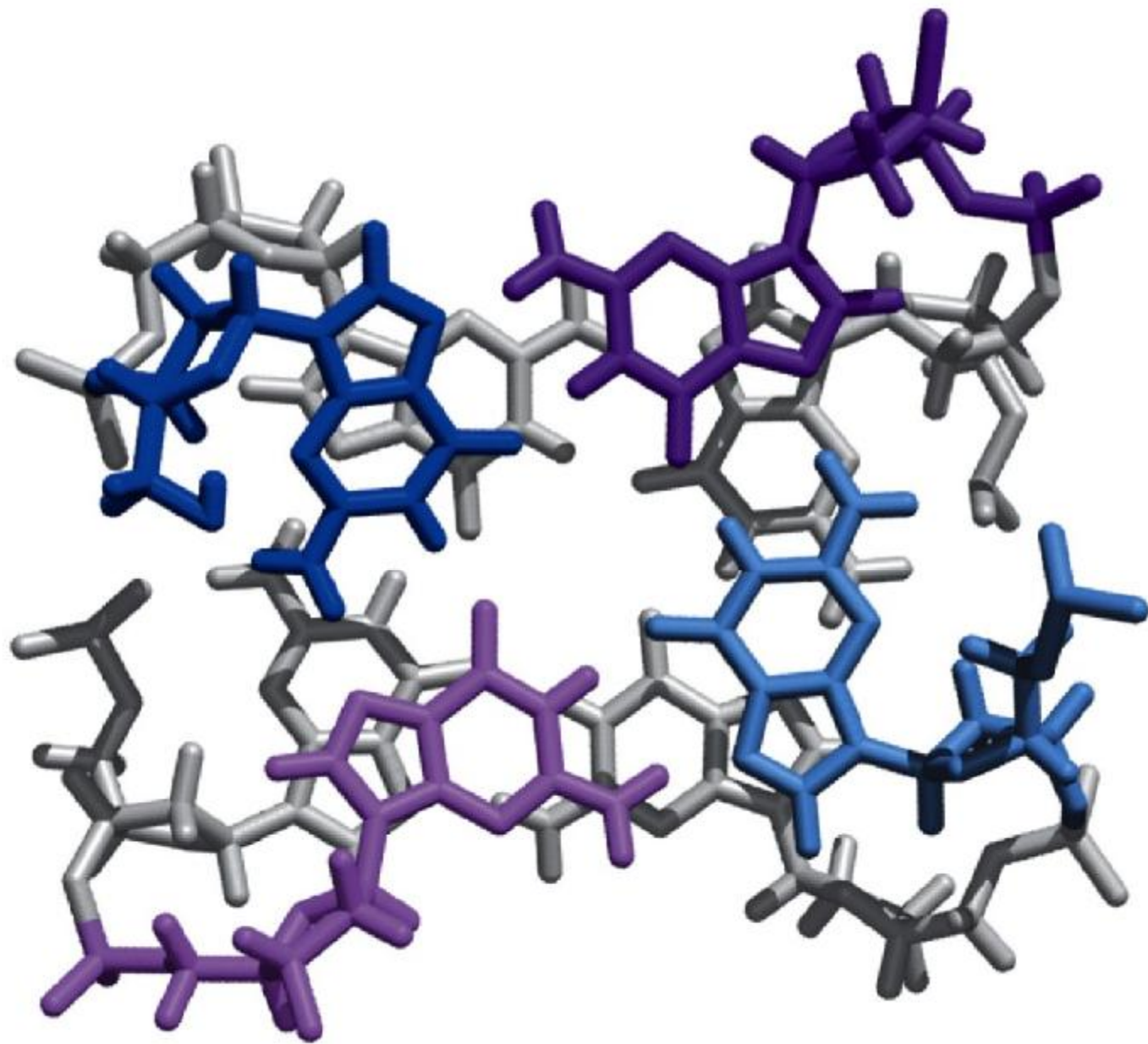


**Figure 8-20b**  
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## Guanosine tetraplex

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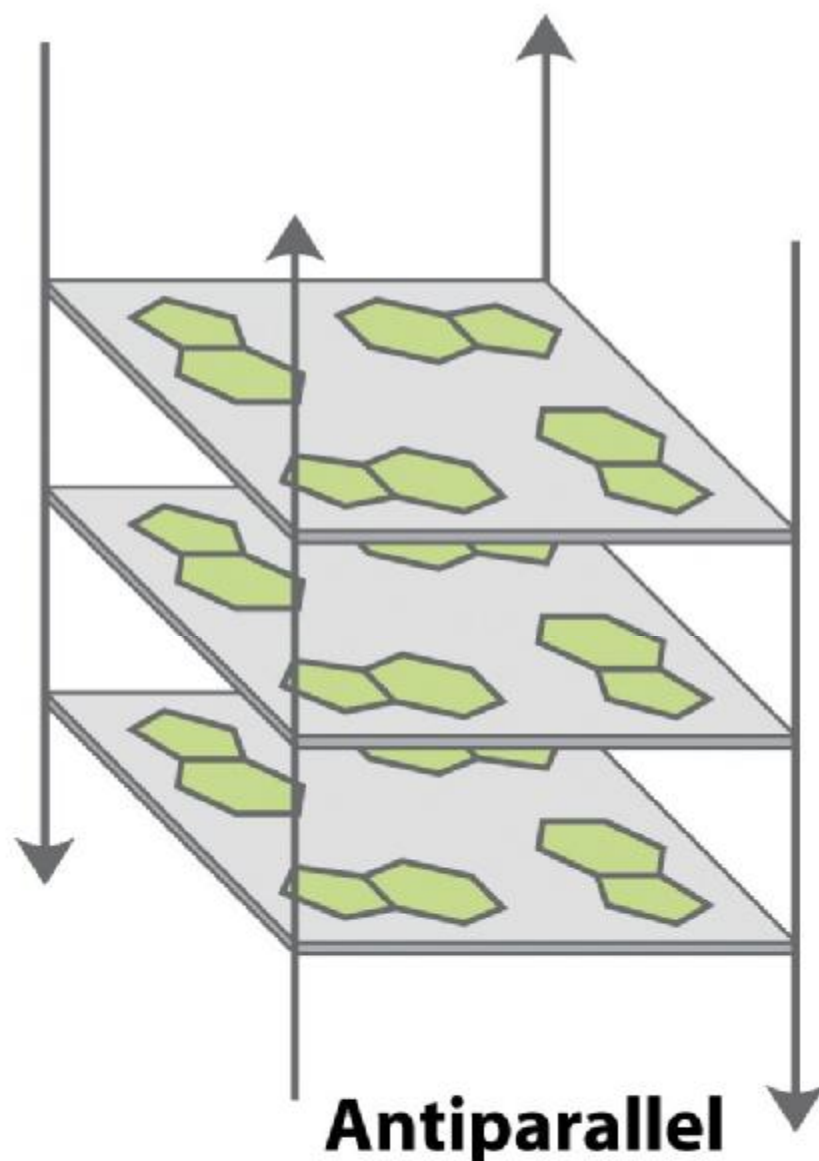
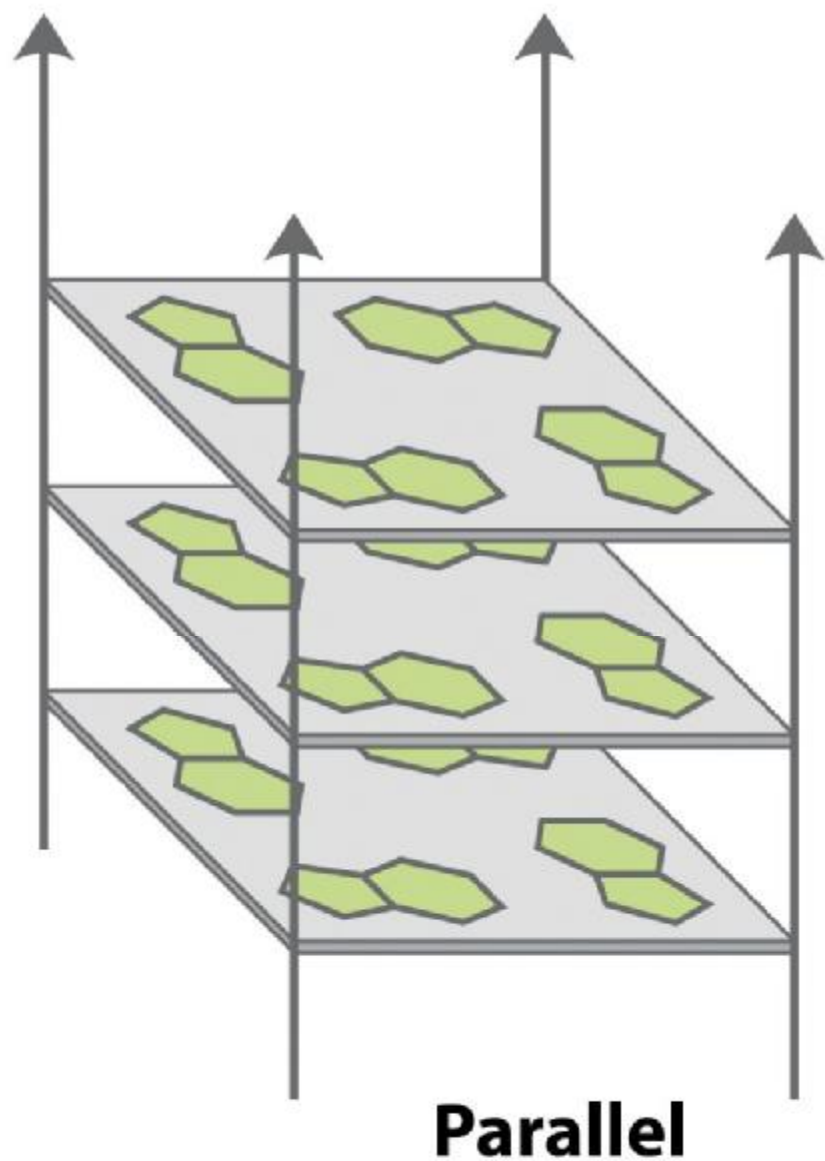


**Figure 8-20d**

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**Figure 8-20e**  
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**(a) Monocistronic**



**(b) Polycistronic**

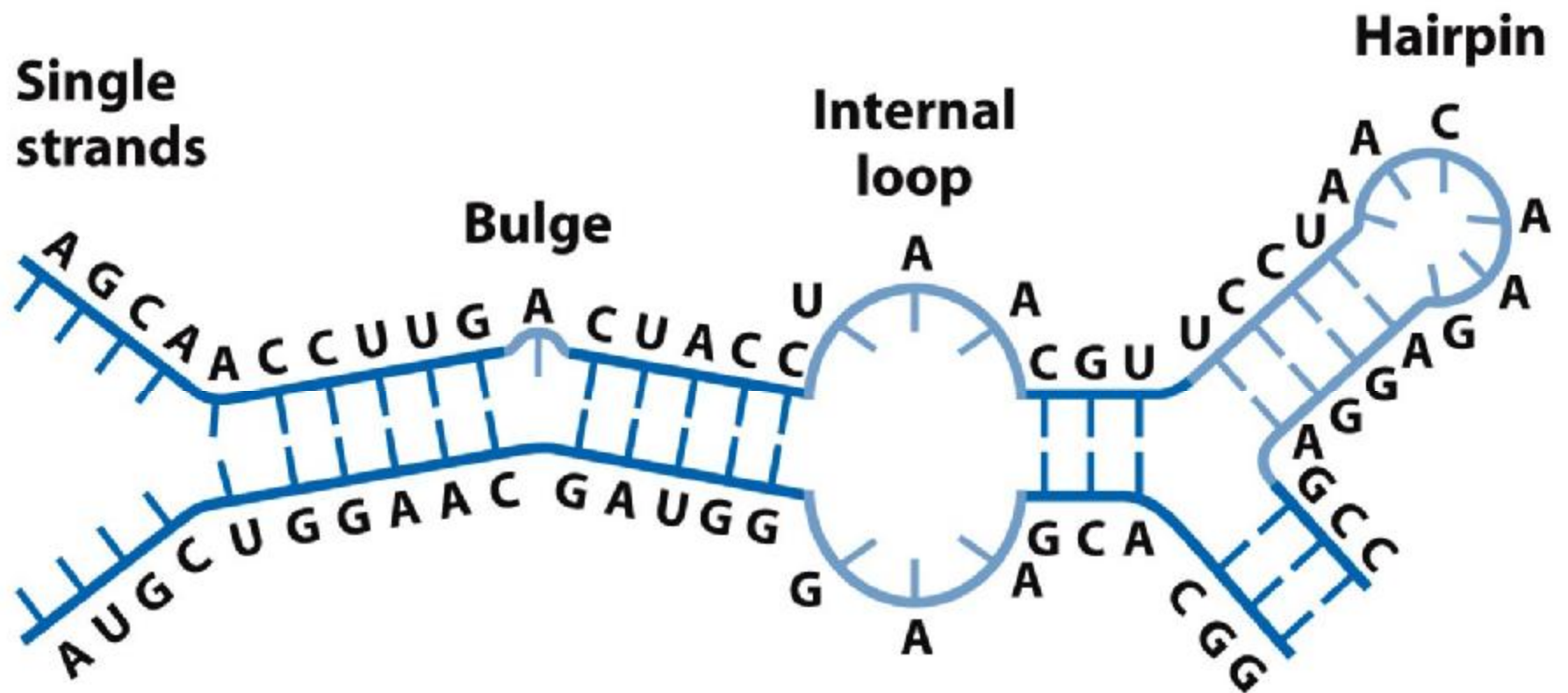
**Figure 8-21**

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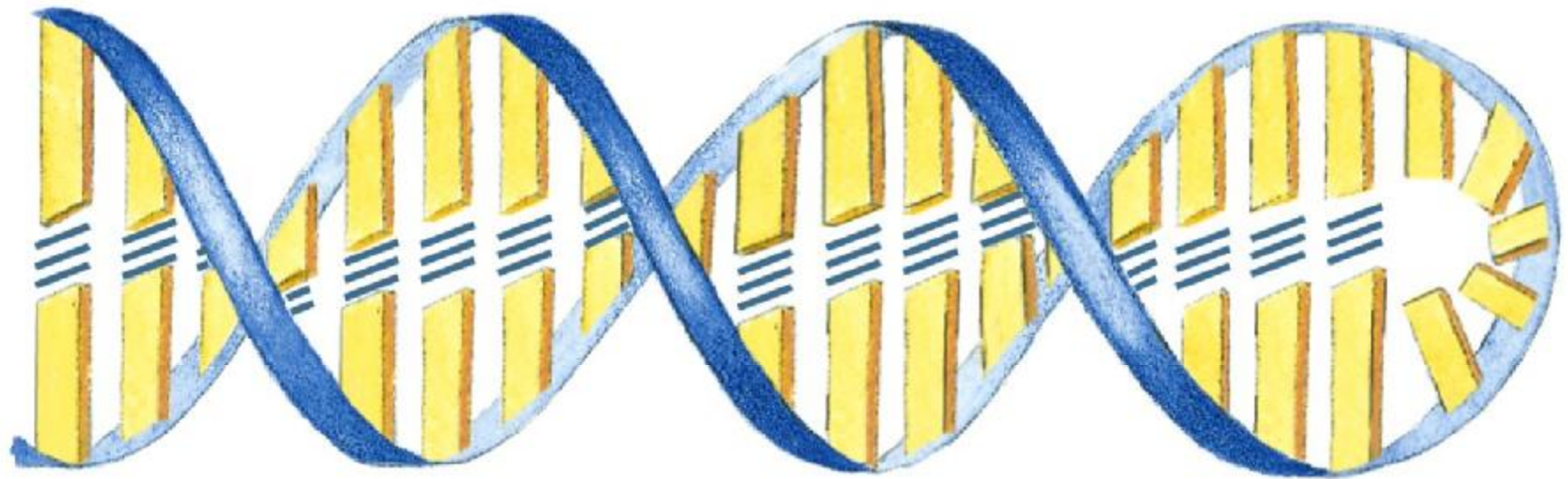
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**Figure 8-23a**

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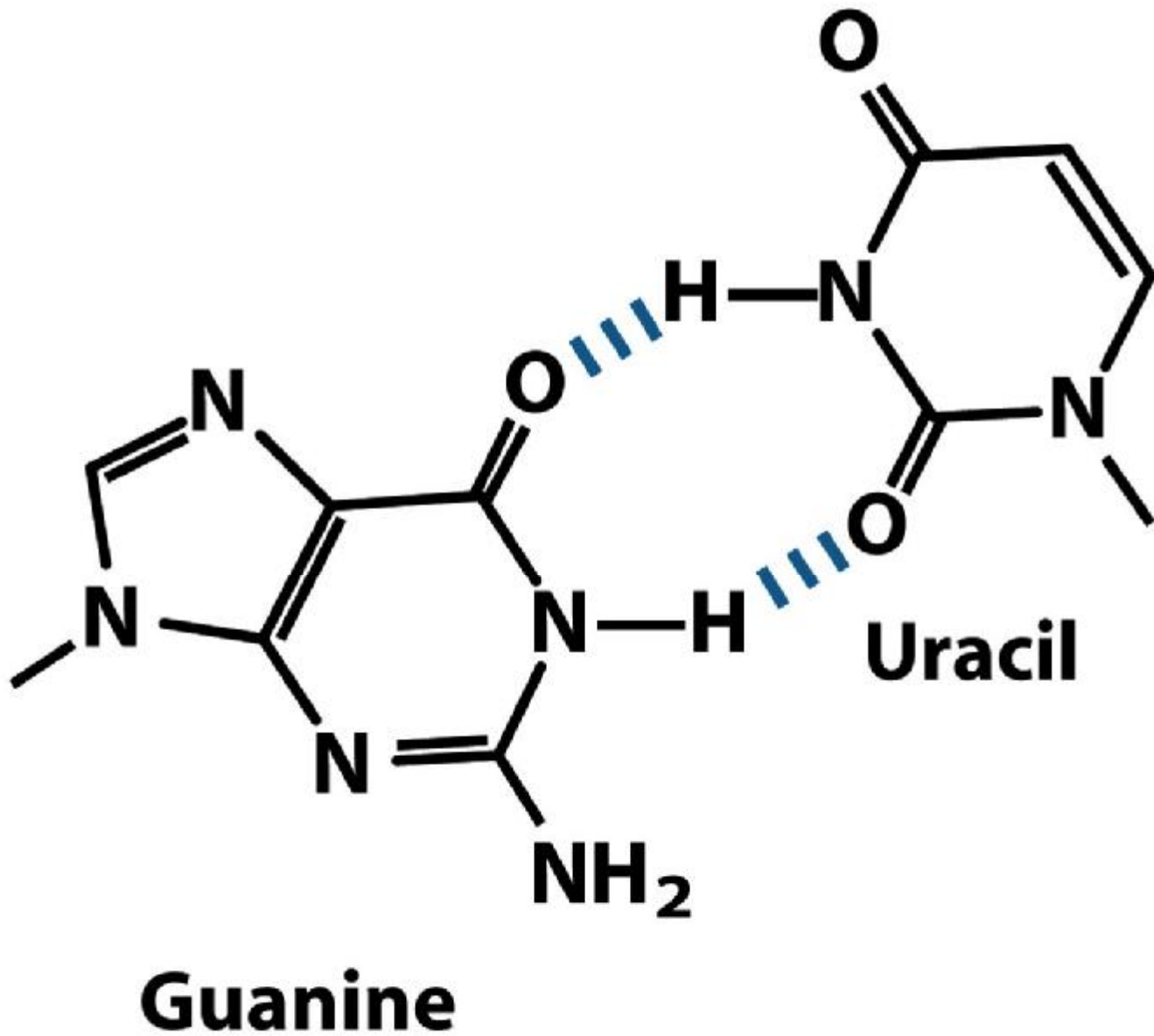


## Hairpin double helix

**Figure 8-23b**

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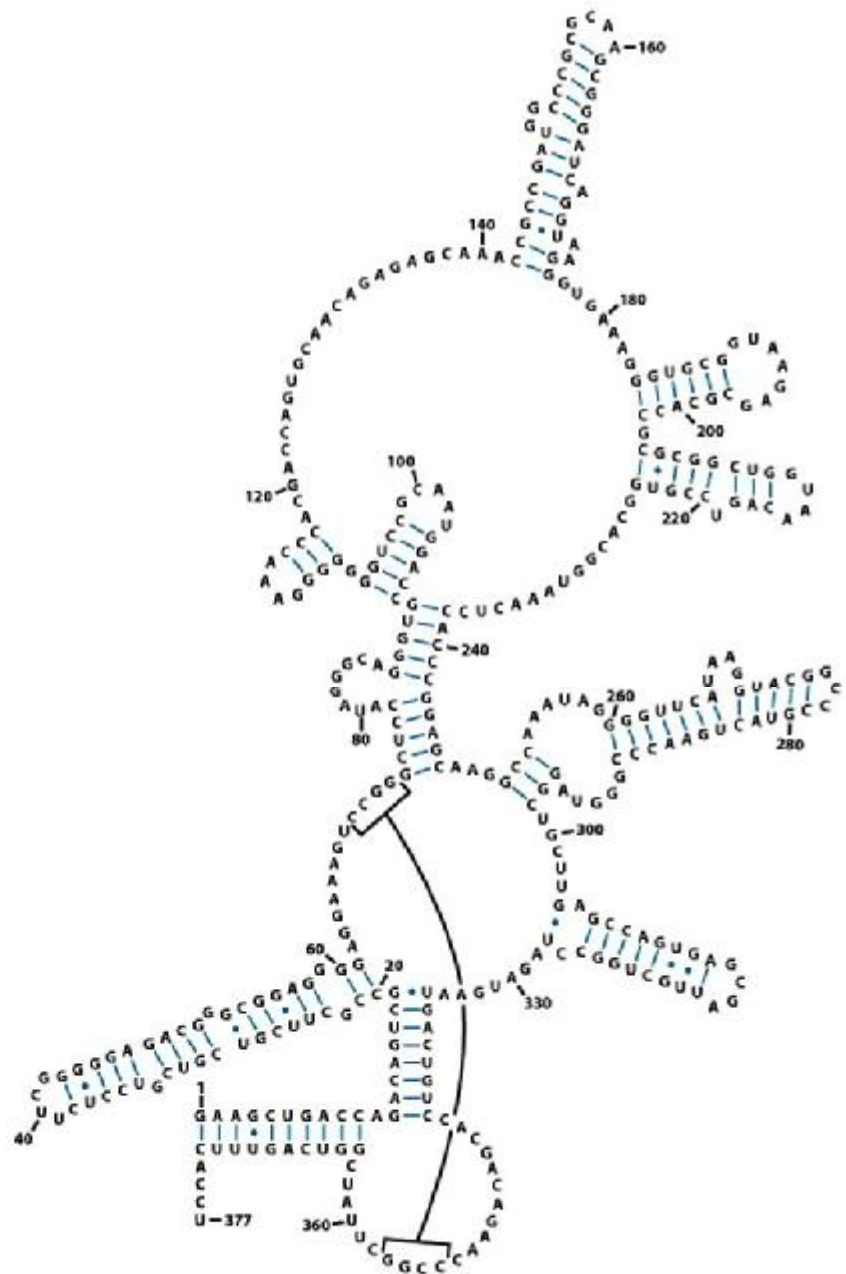
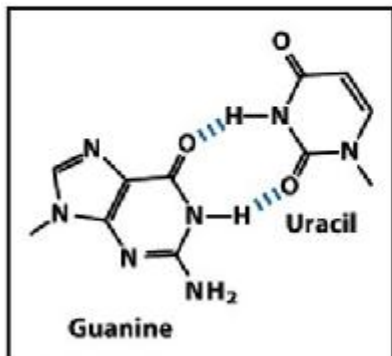
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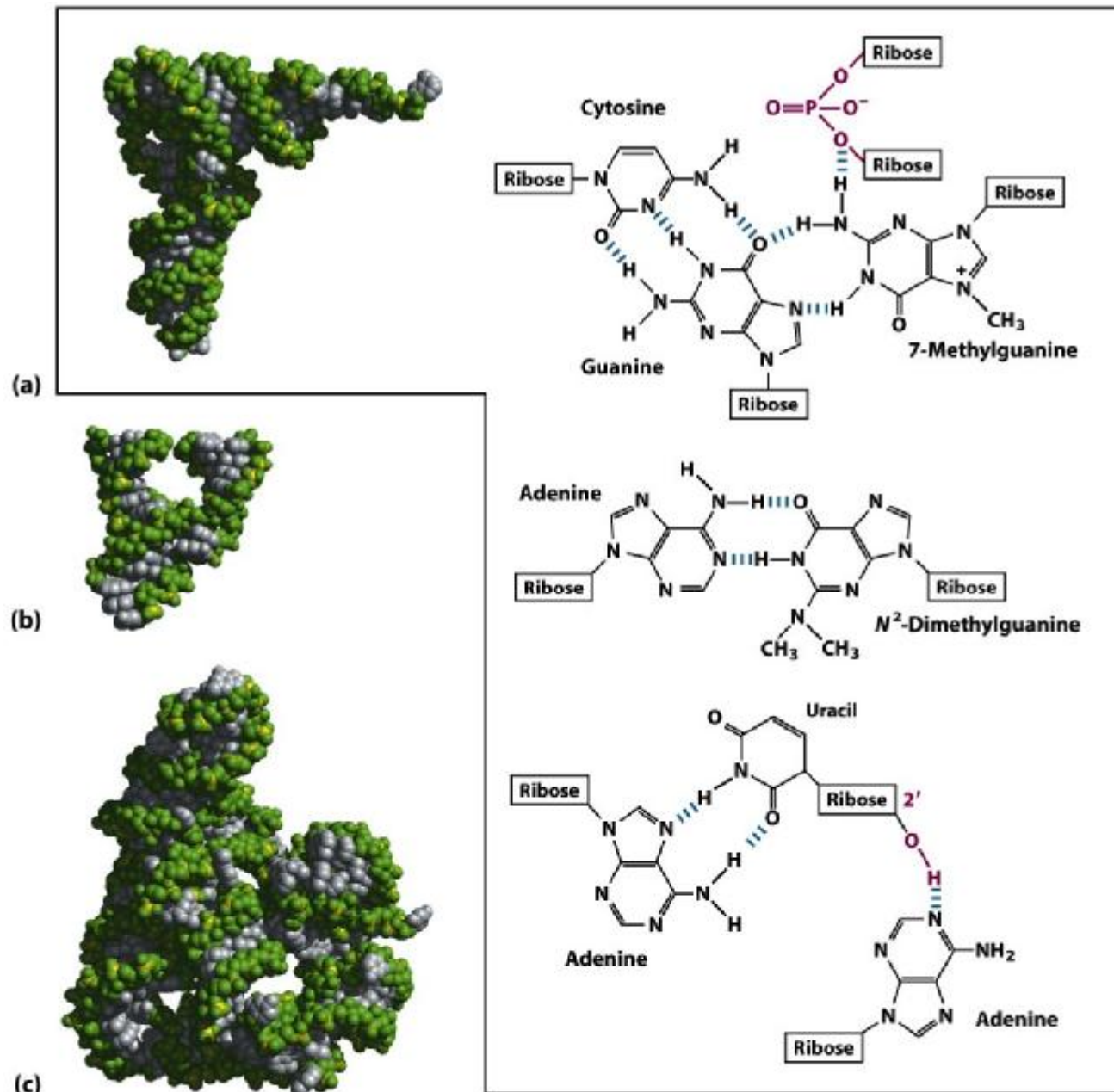
**Figure 8-24 part 1**

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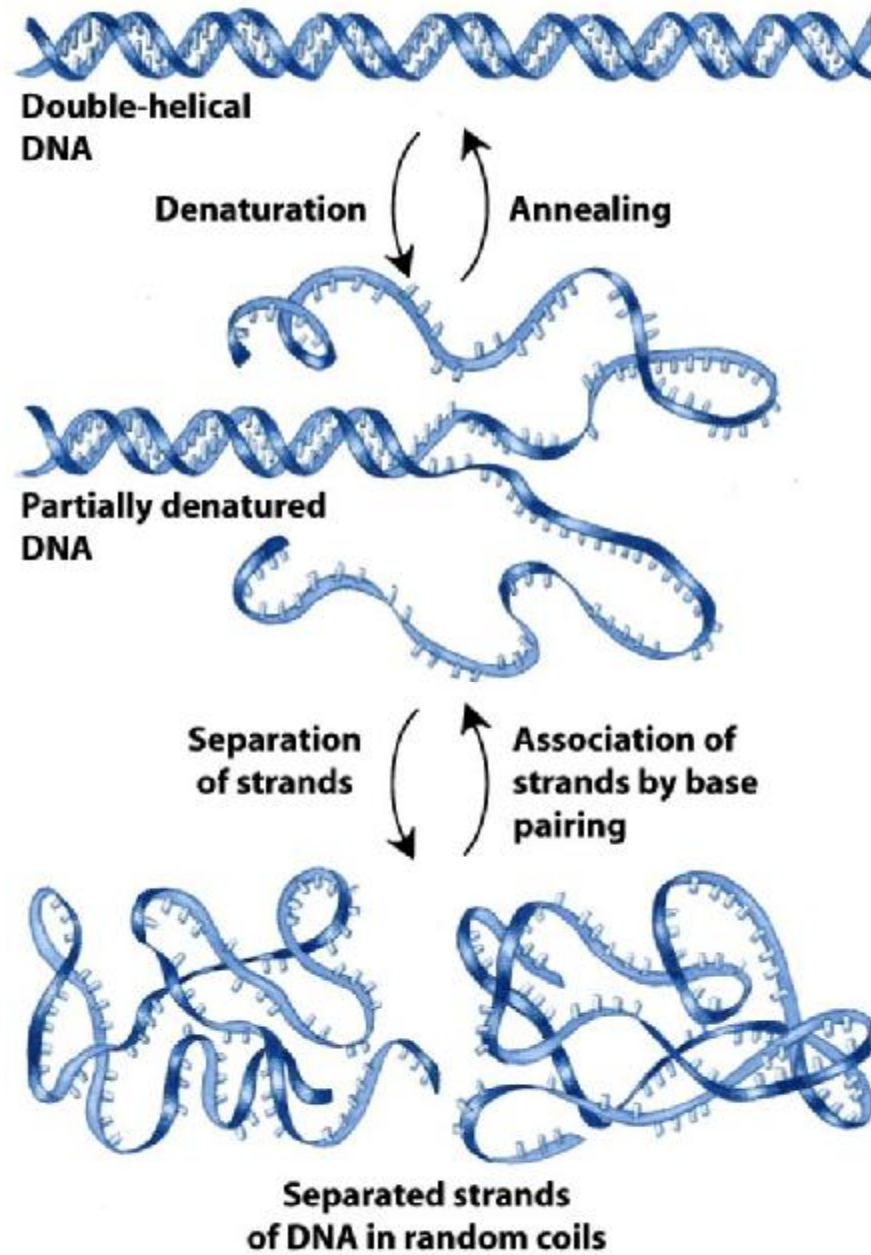
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**Figure 8-25**

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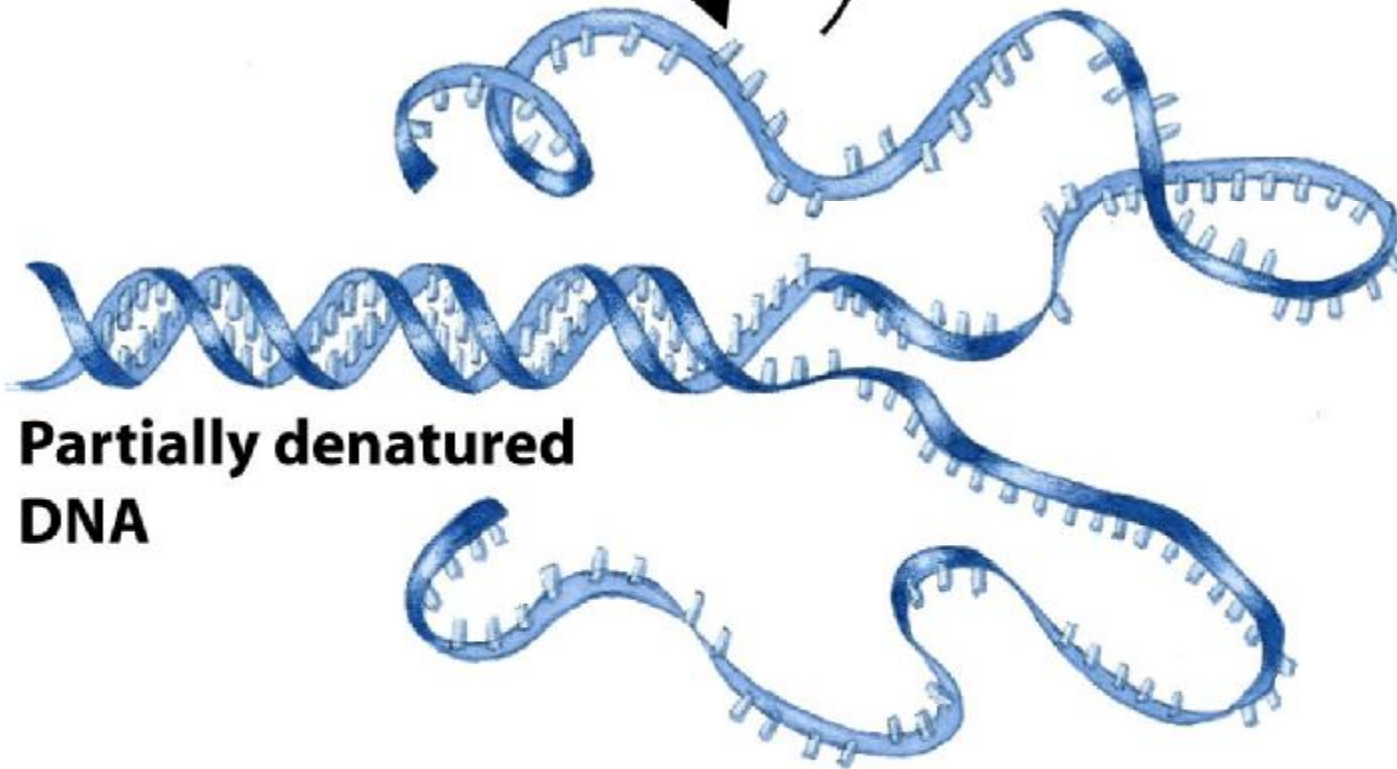
**Figure 8-26**  
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**Double-helical  
DNA**

**Denaturation**

**Annealing**

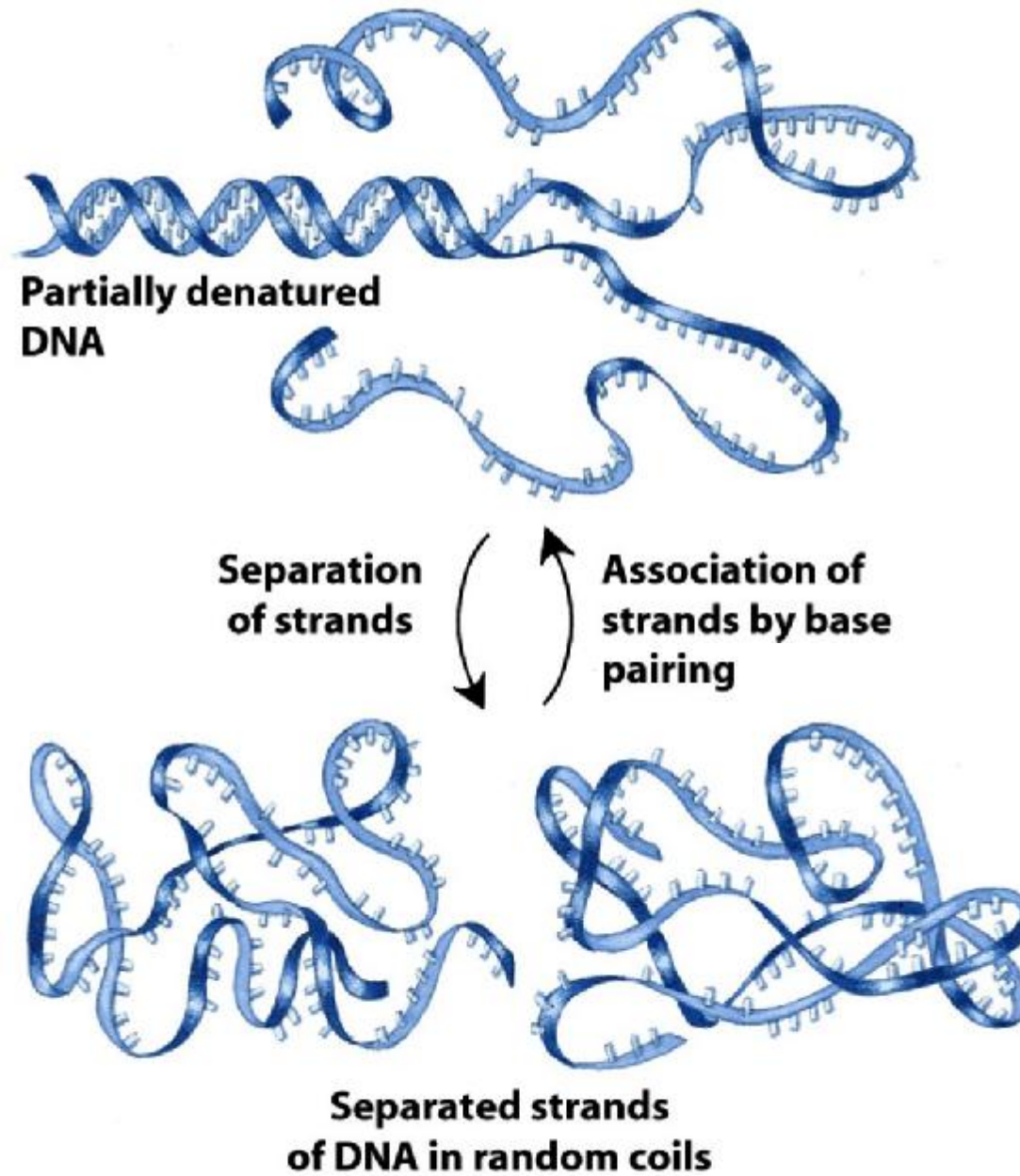


**Partially denatured  
DNA**

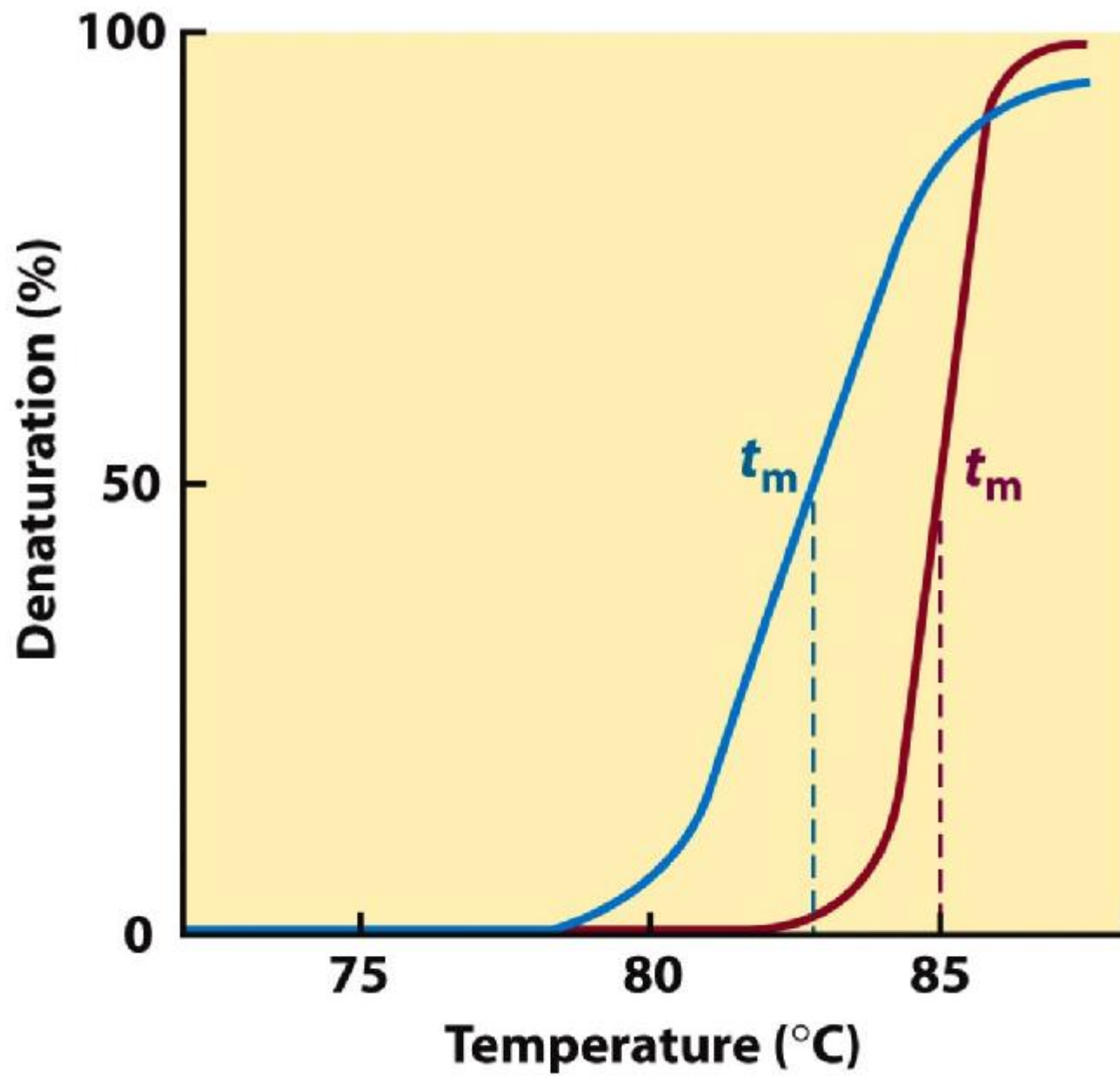
**Figure 8-26 part 1**

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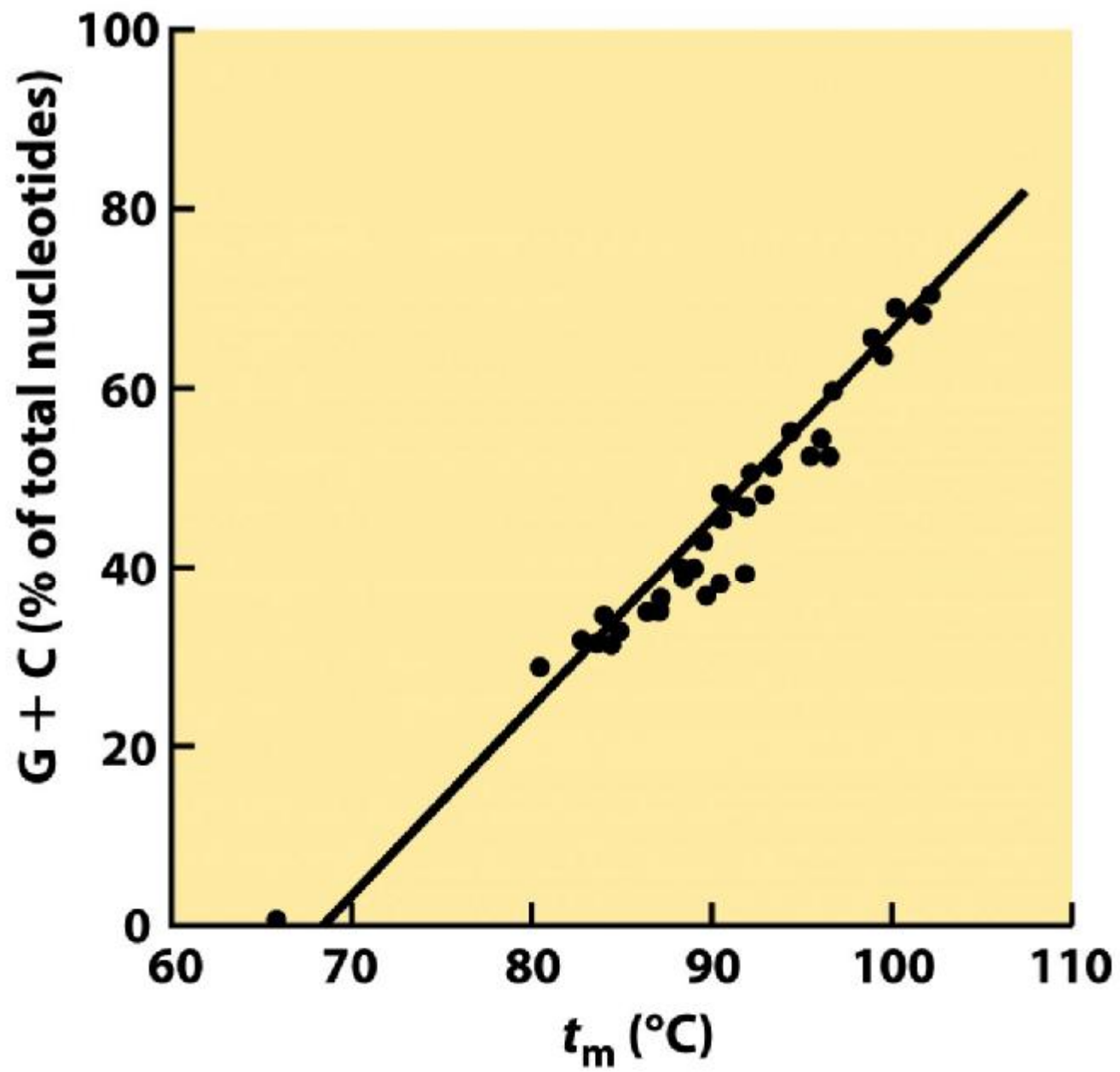
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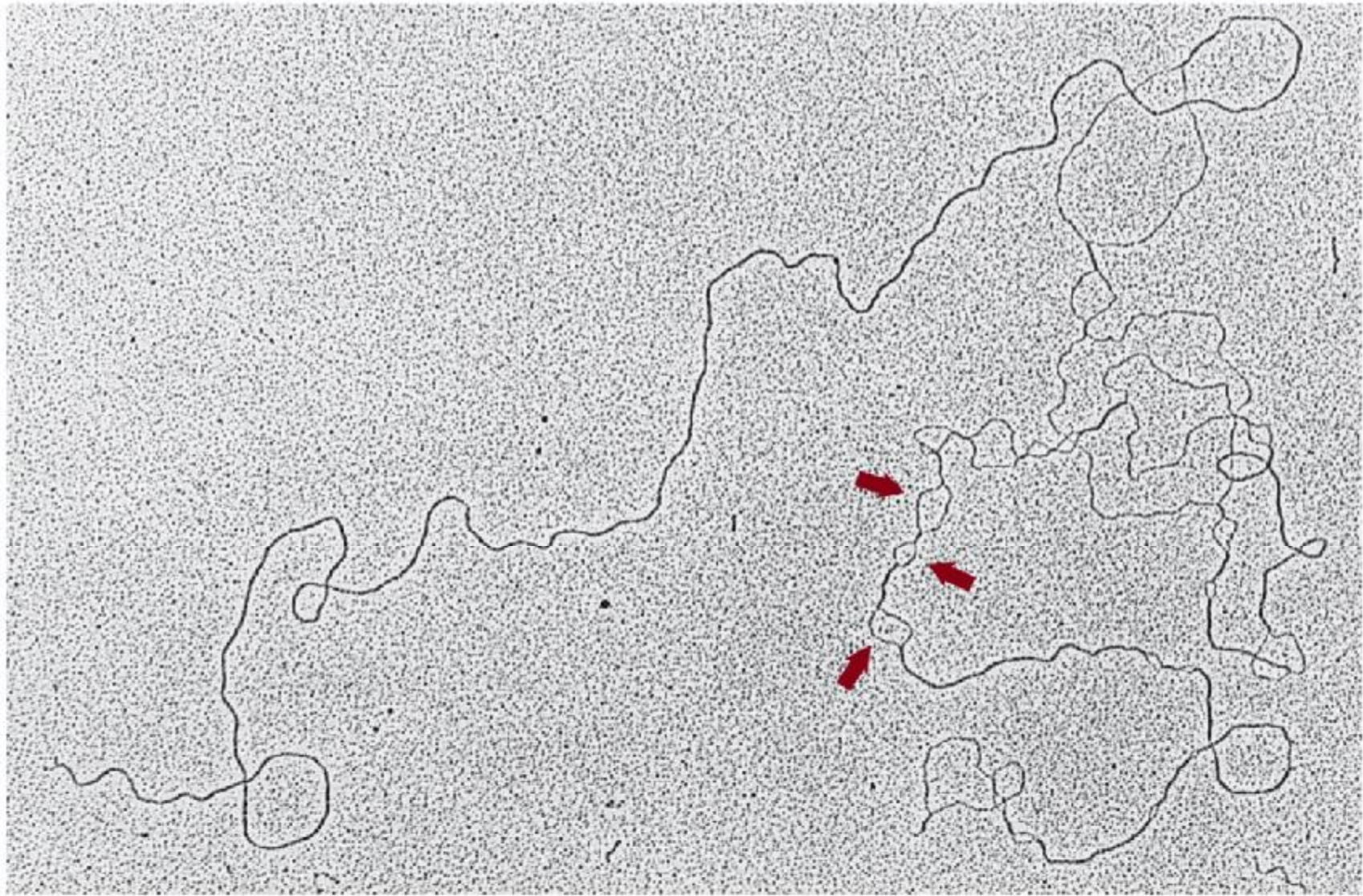
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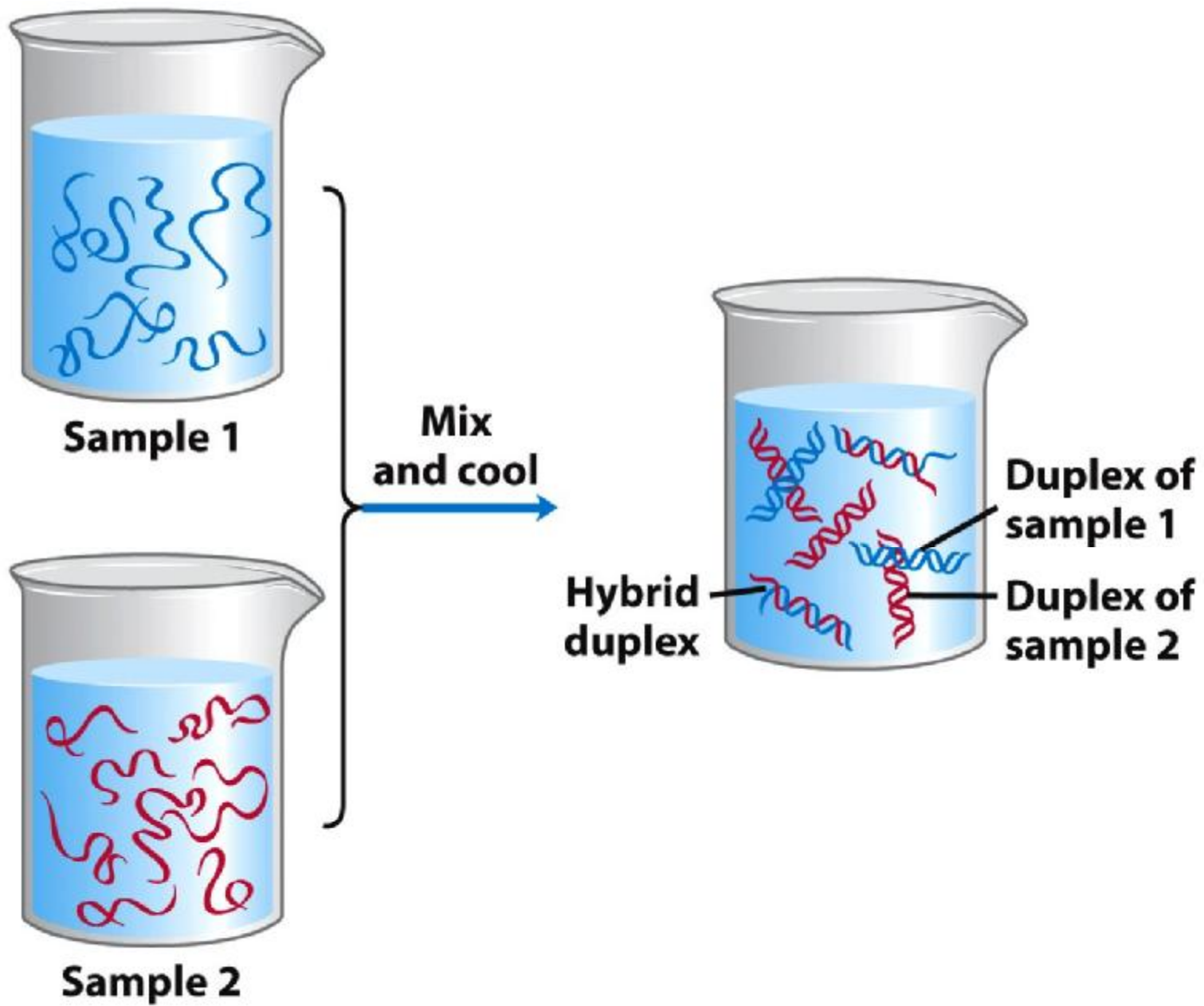


3  $\mu$ m

**Figure 8-28**

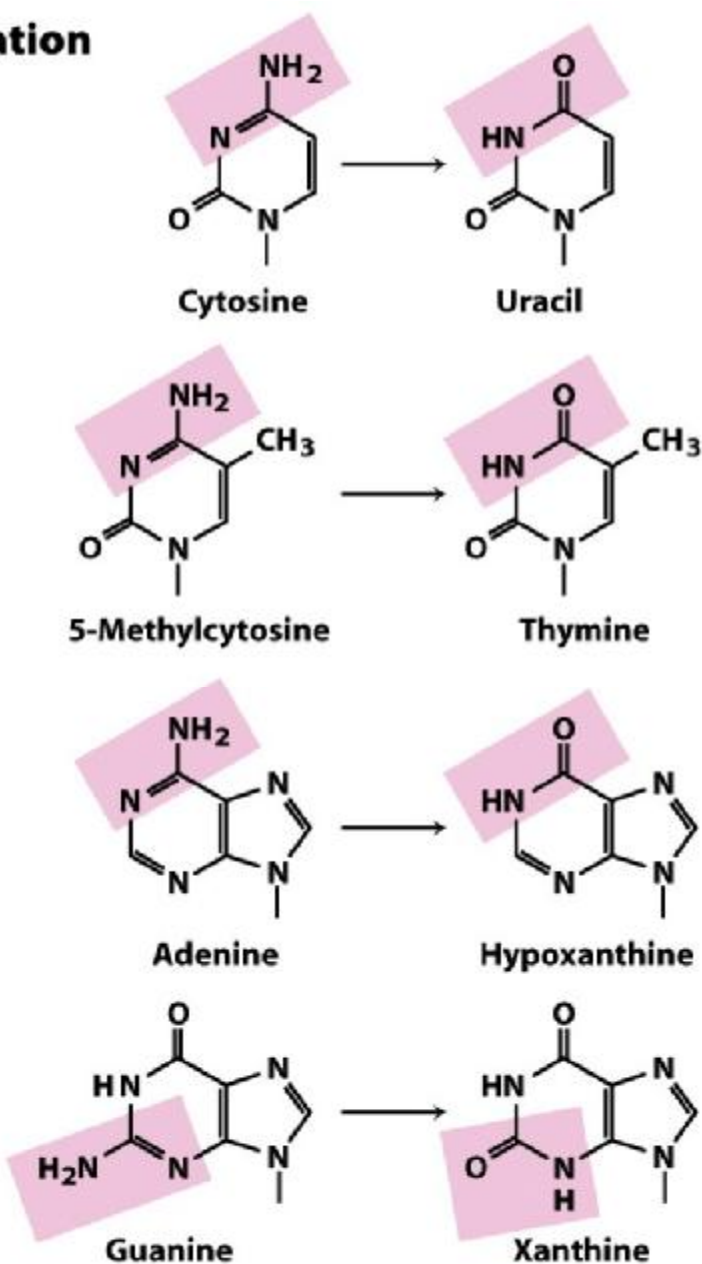
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## Deamination

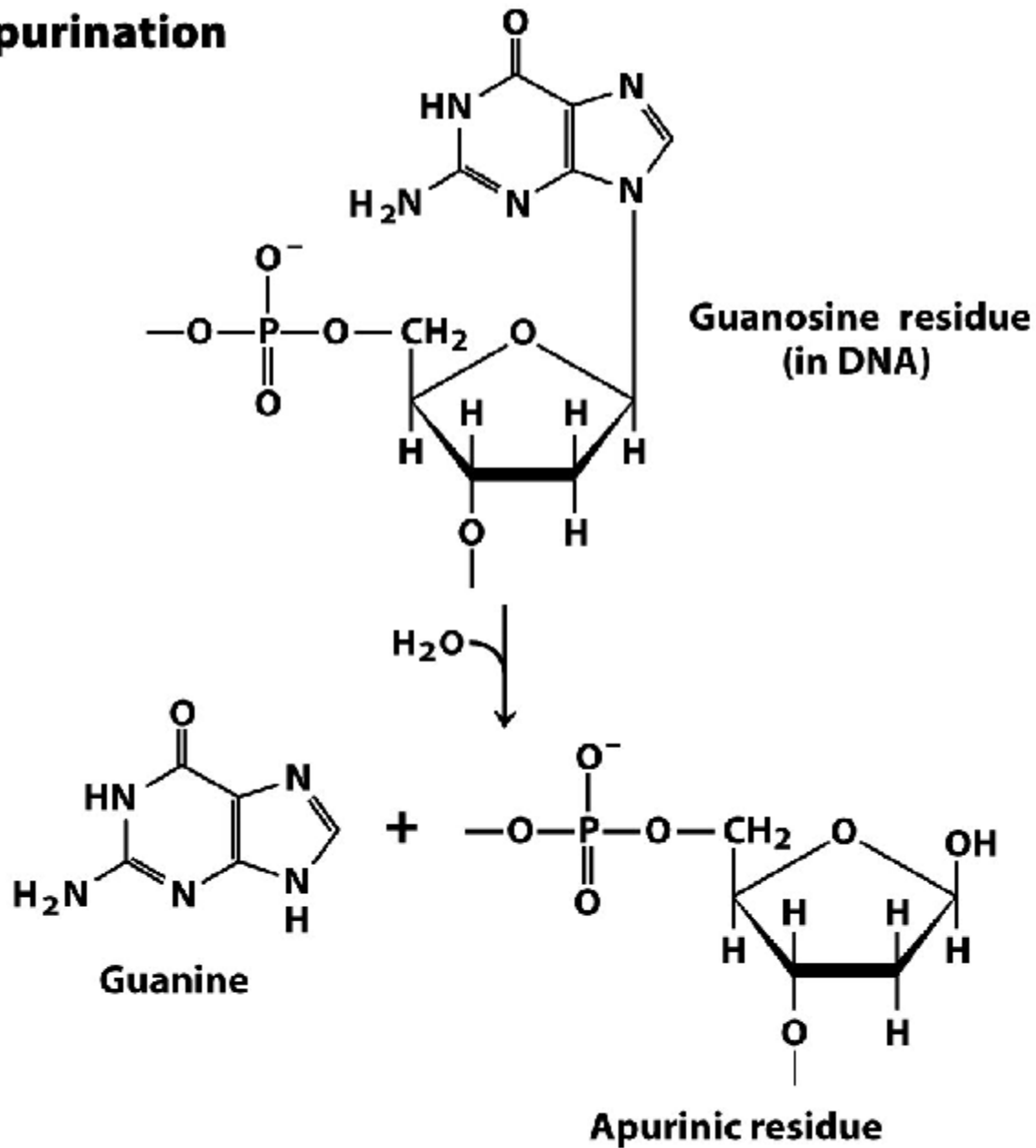


**Figure 8-30a**

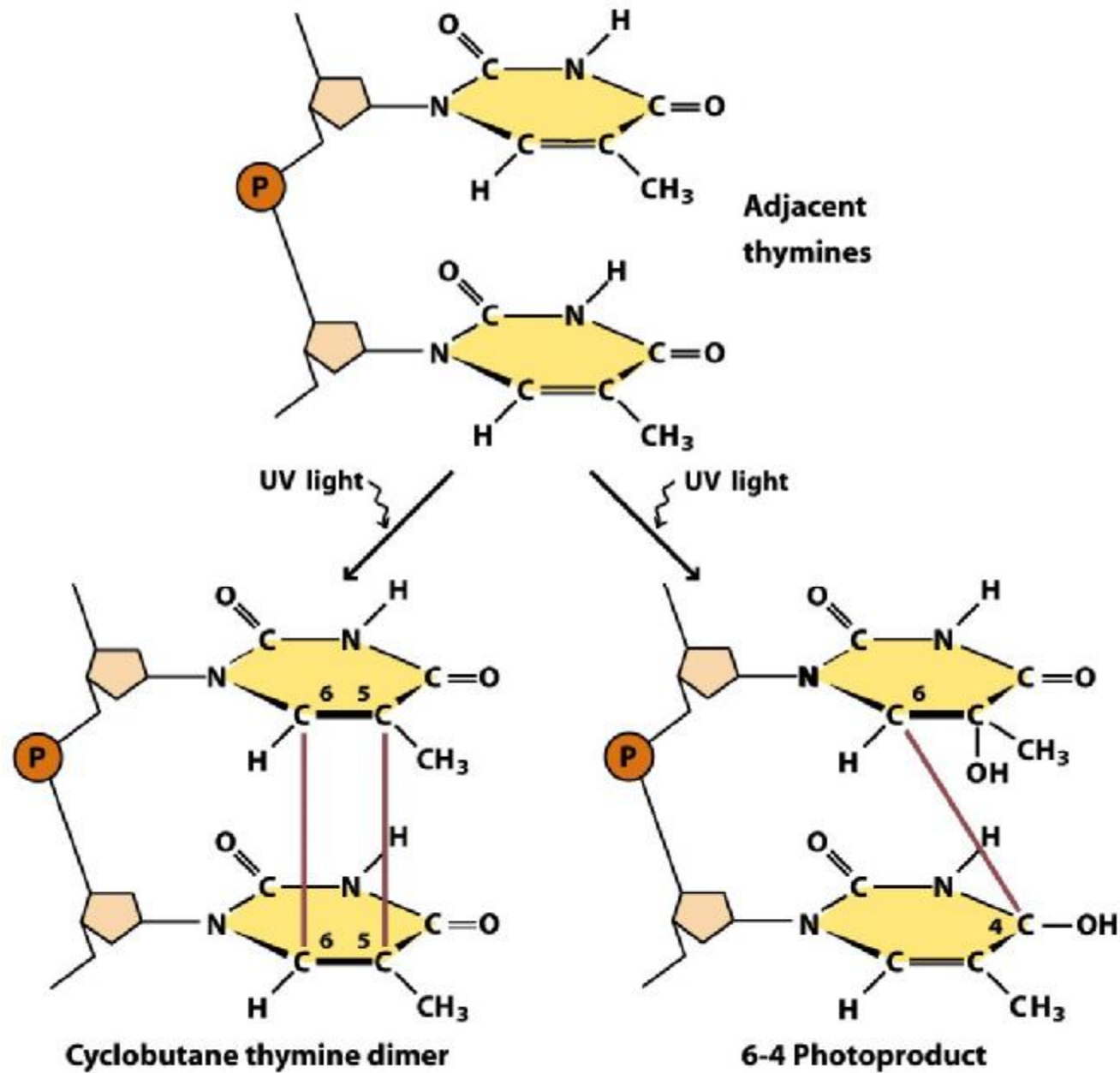
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## Depurination

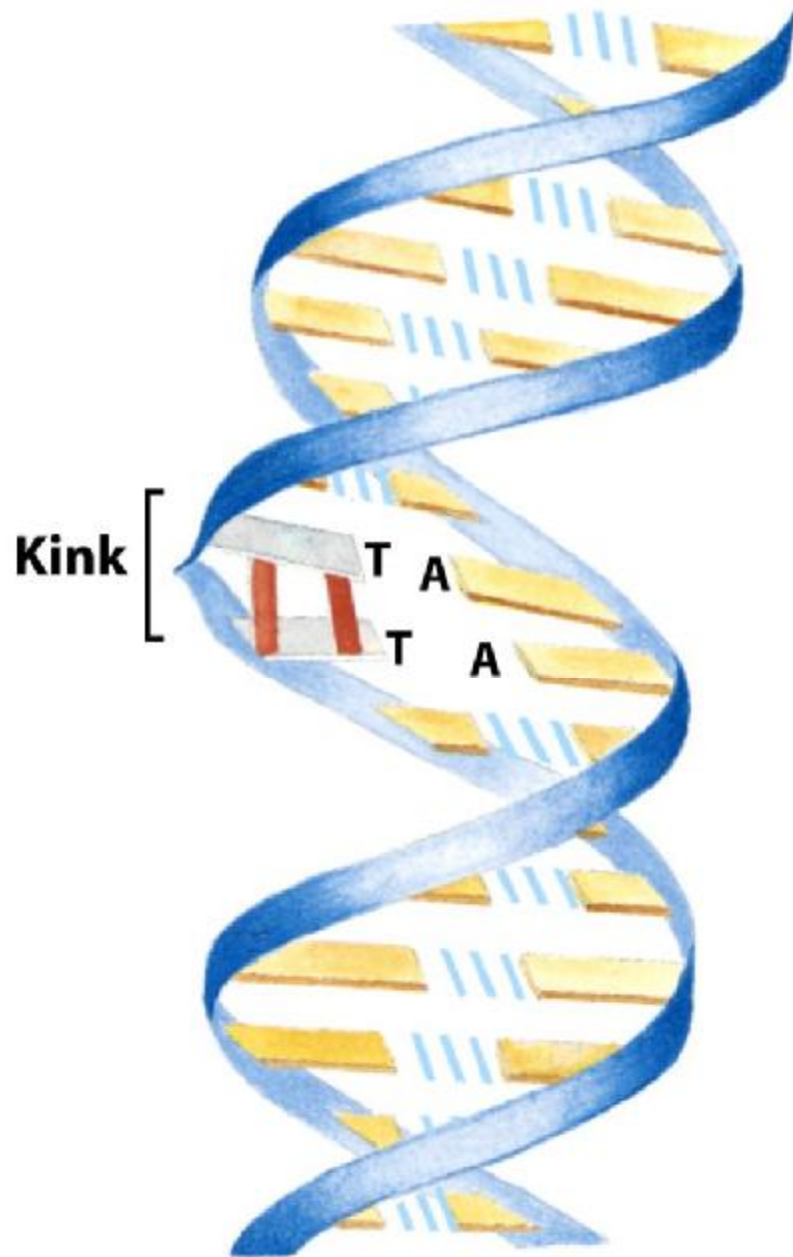


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**Figure 8-31a**

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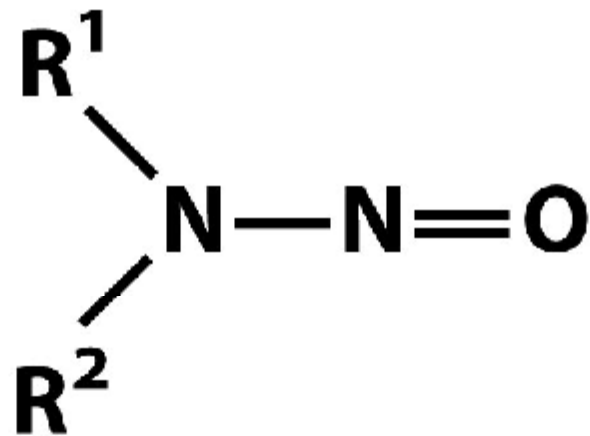
**Figure 8-31b**  
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**Sodium nitrite**



**Sodium nitrate**



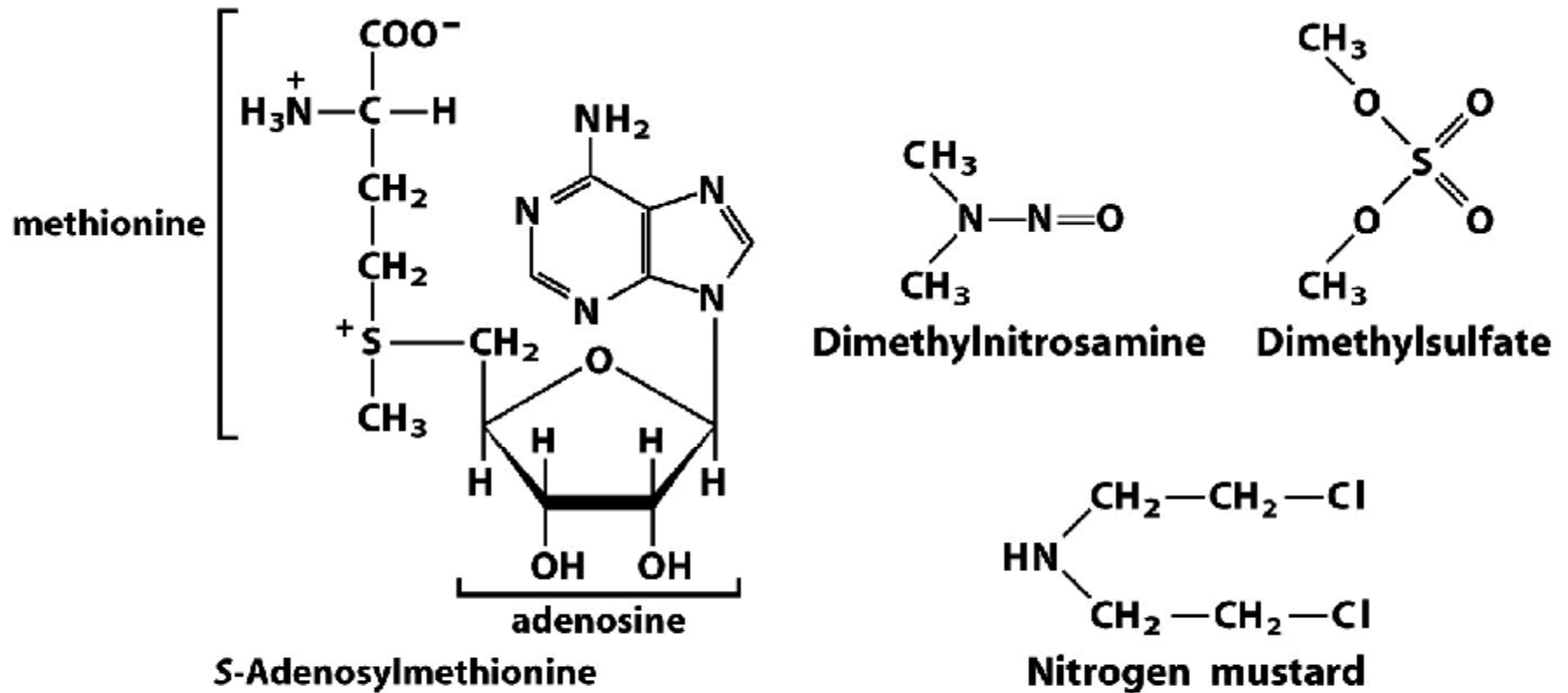
**Nitrosamine**

## **Nitrous acid precursors**

**Figure 8-32a**

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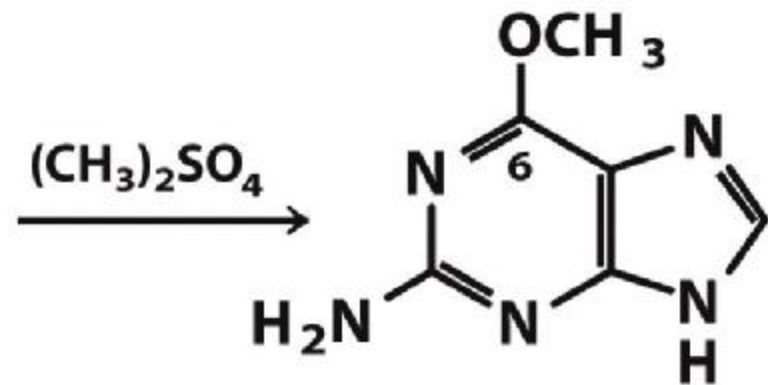
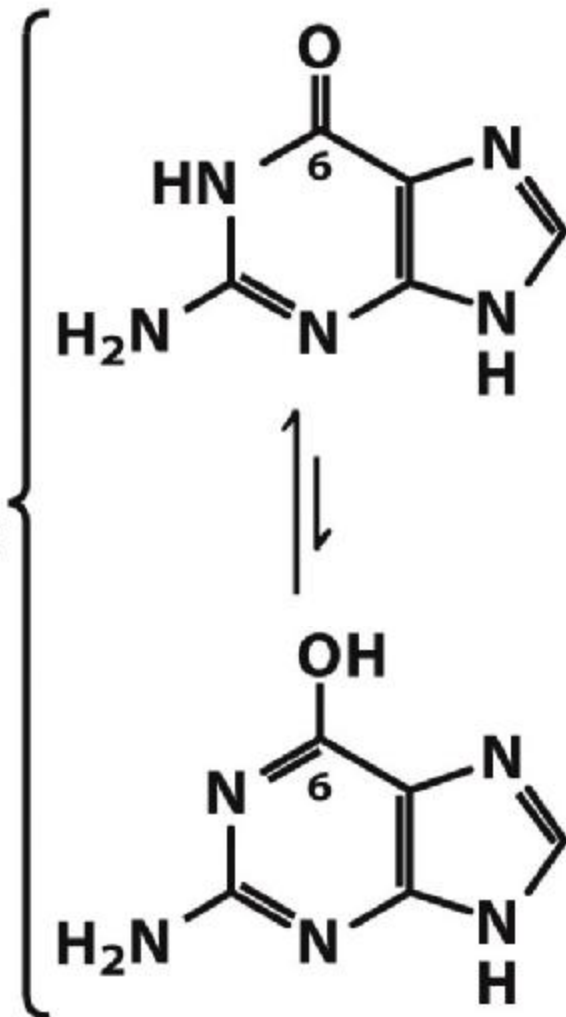


## Alkylating agents

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**Guanine  
tautomers**

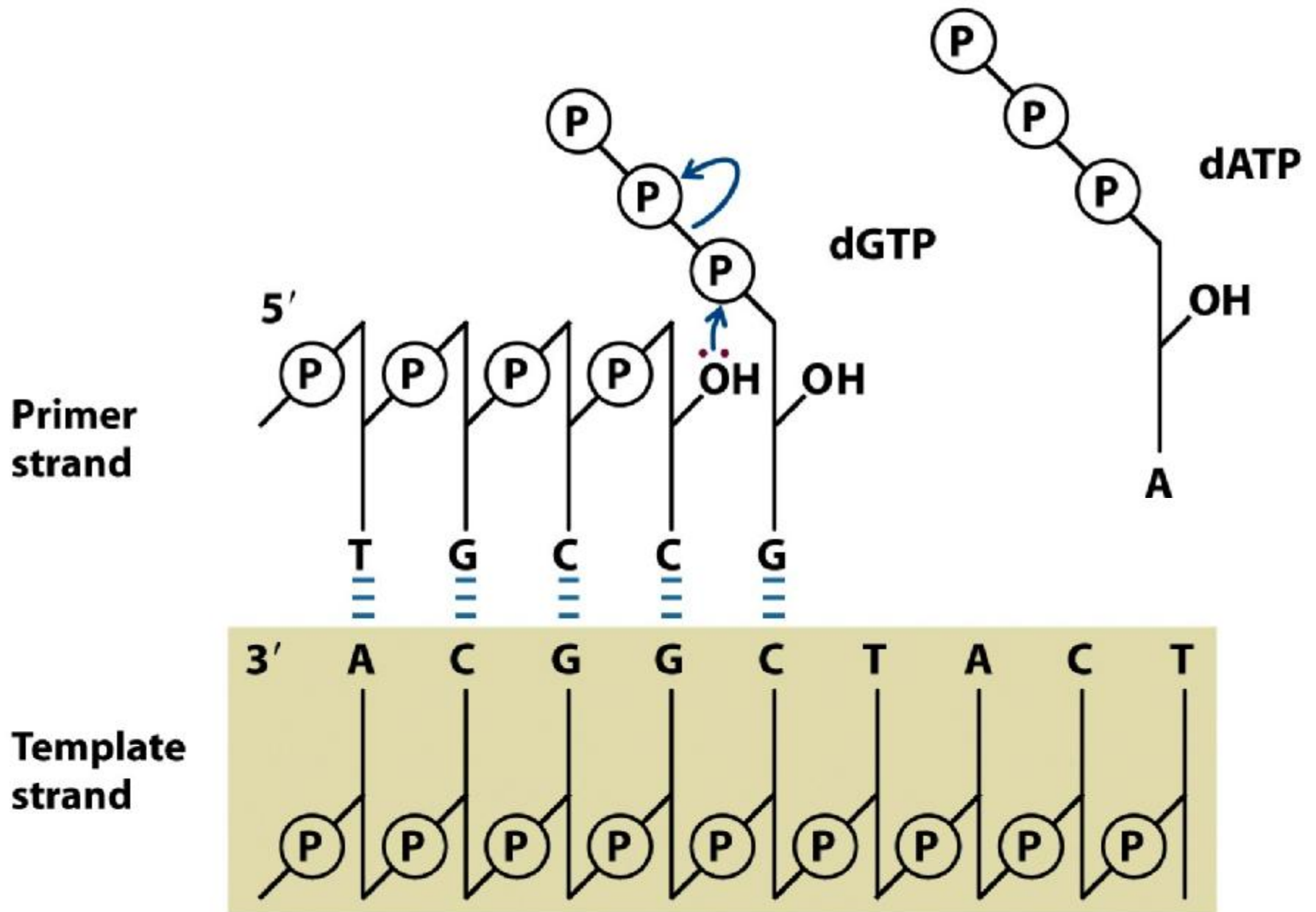


**$\text{O}^6$ -Methylguanine**

Unnumbered 8 p292

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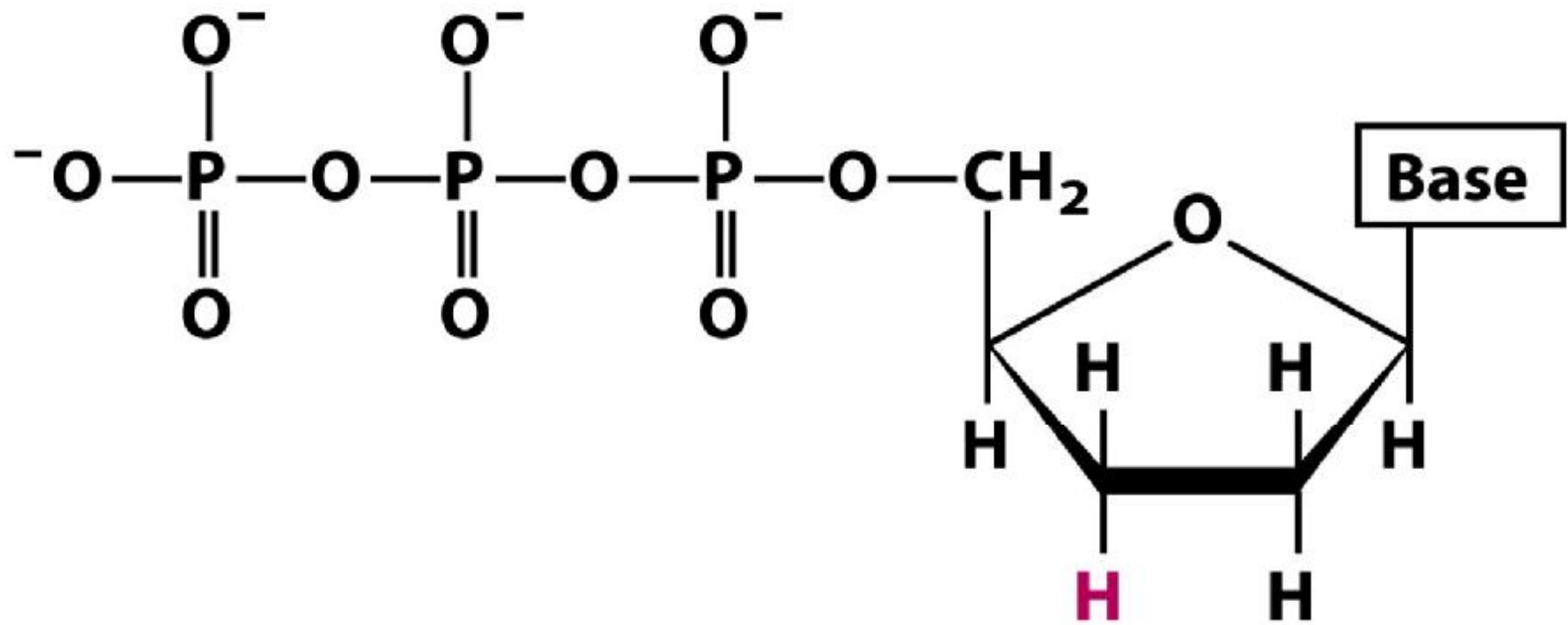
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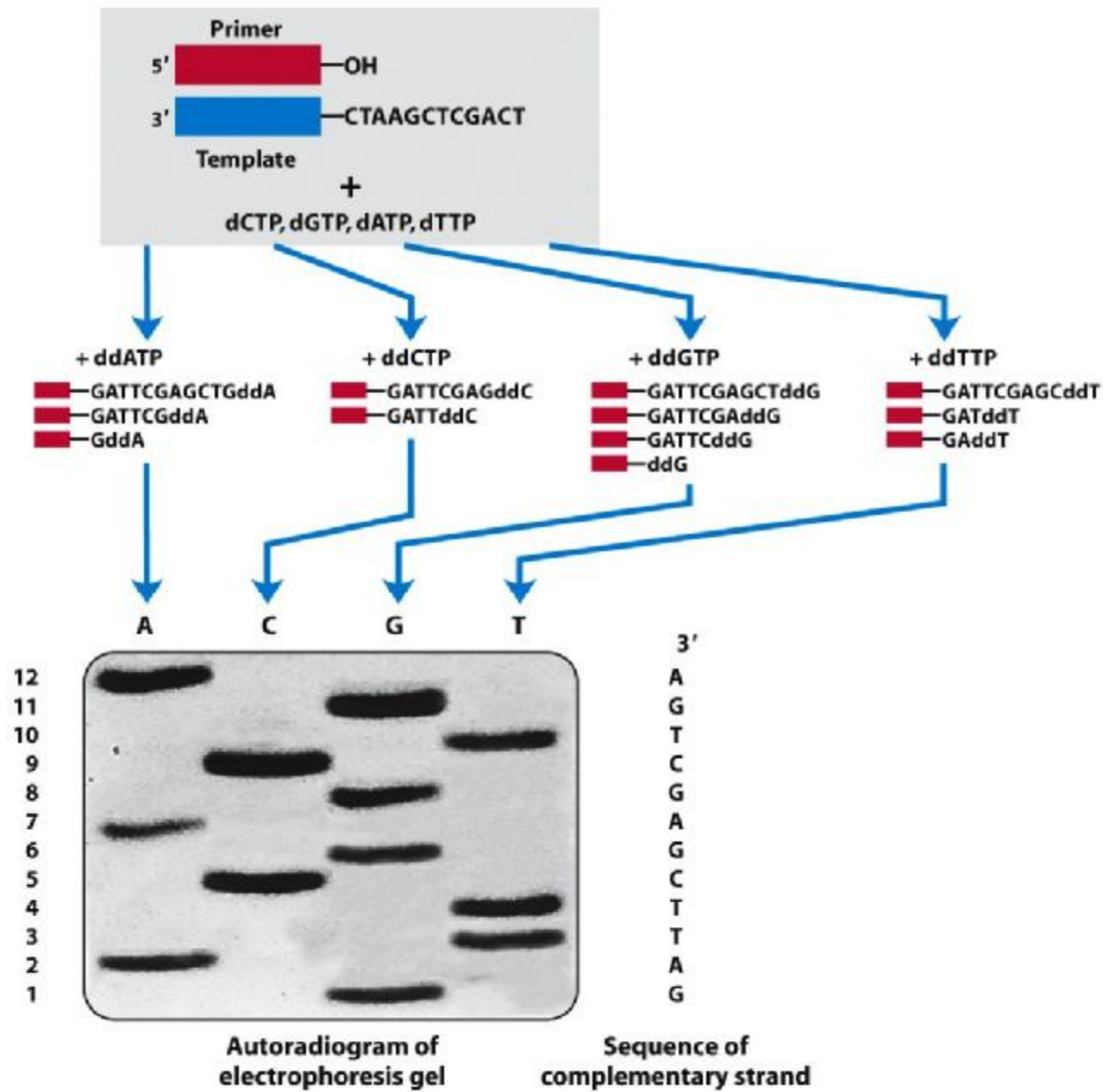
## ddNTP analog

Figure 8-33b

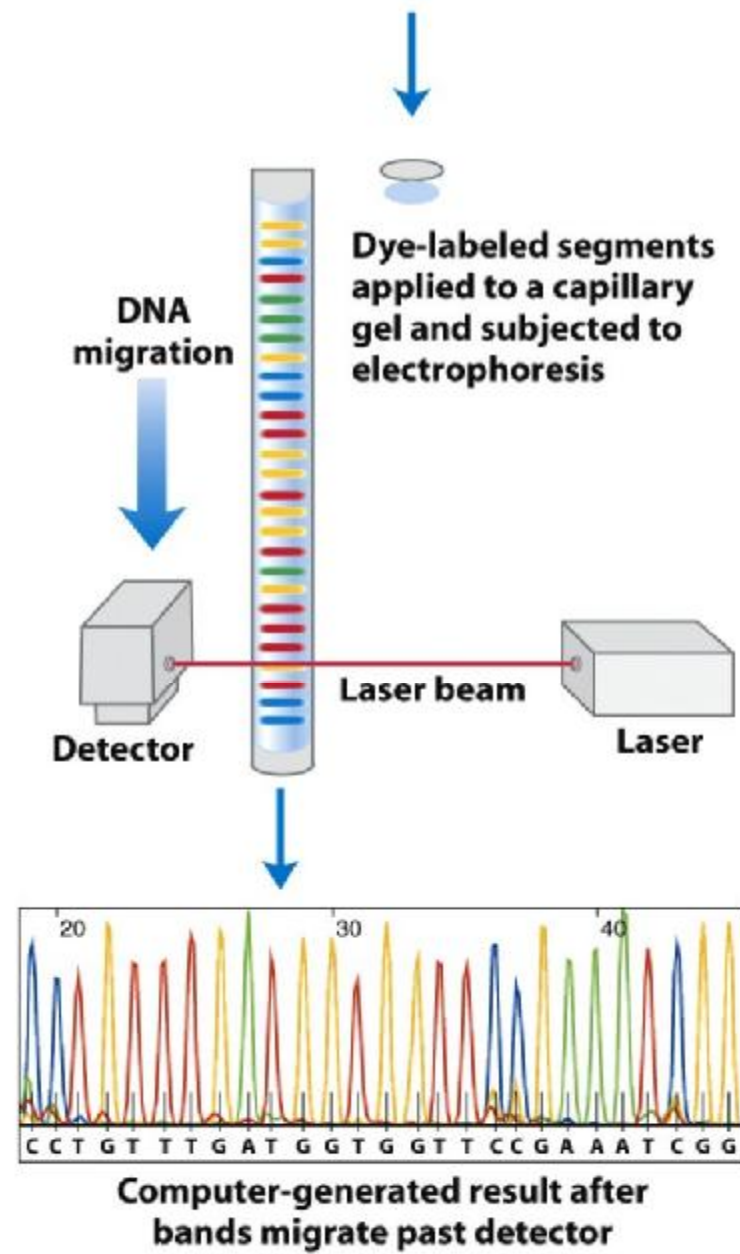
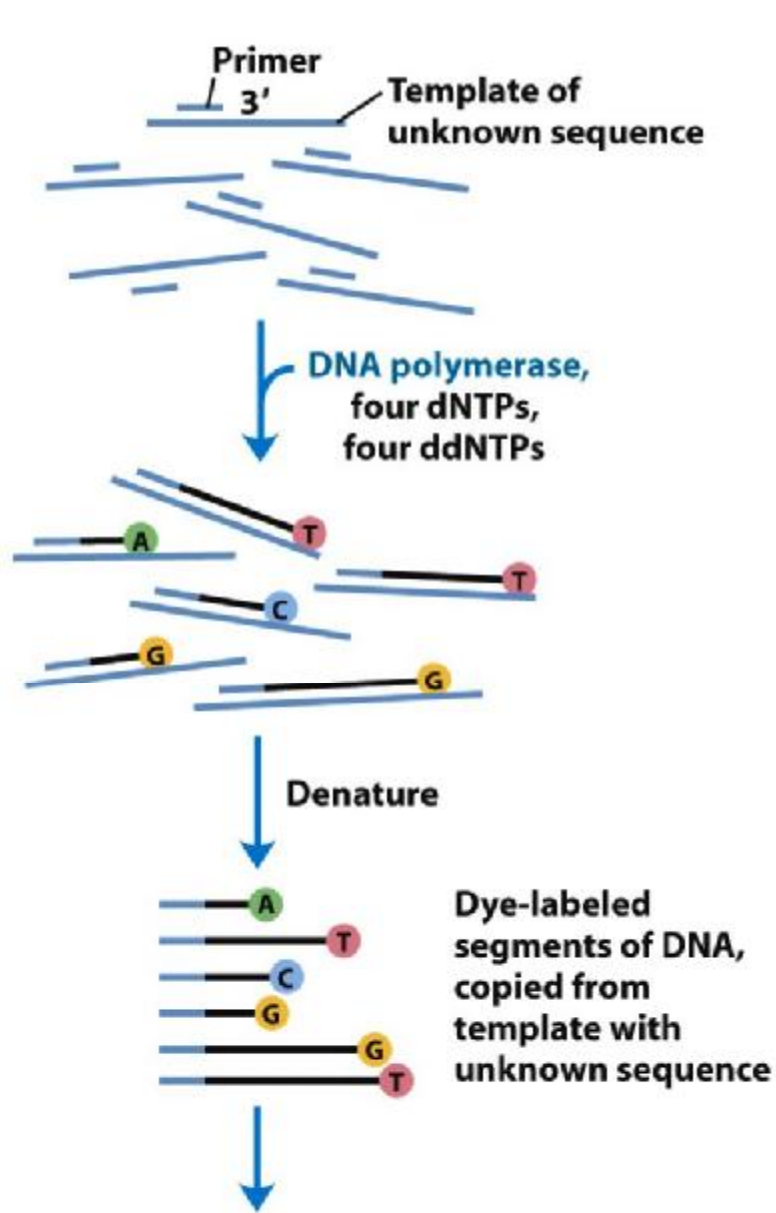
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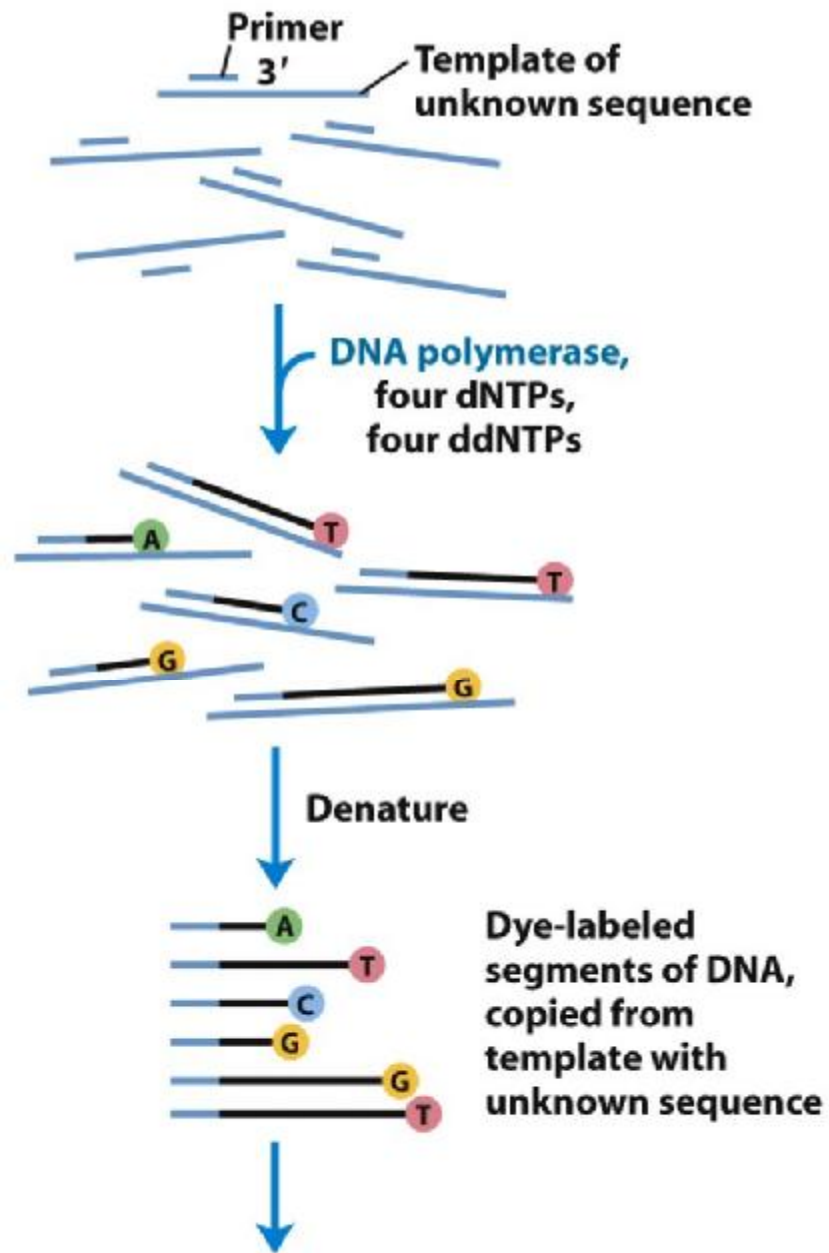




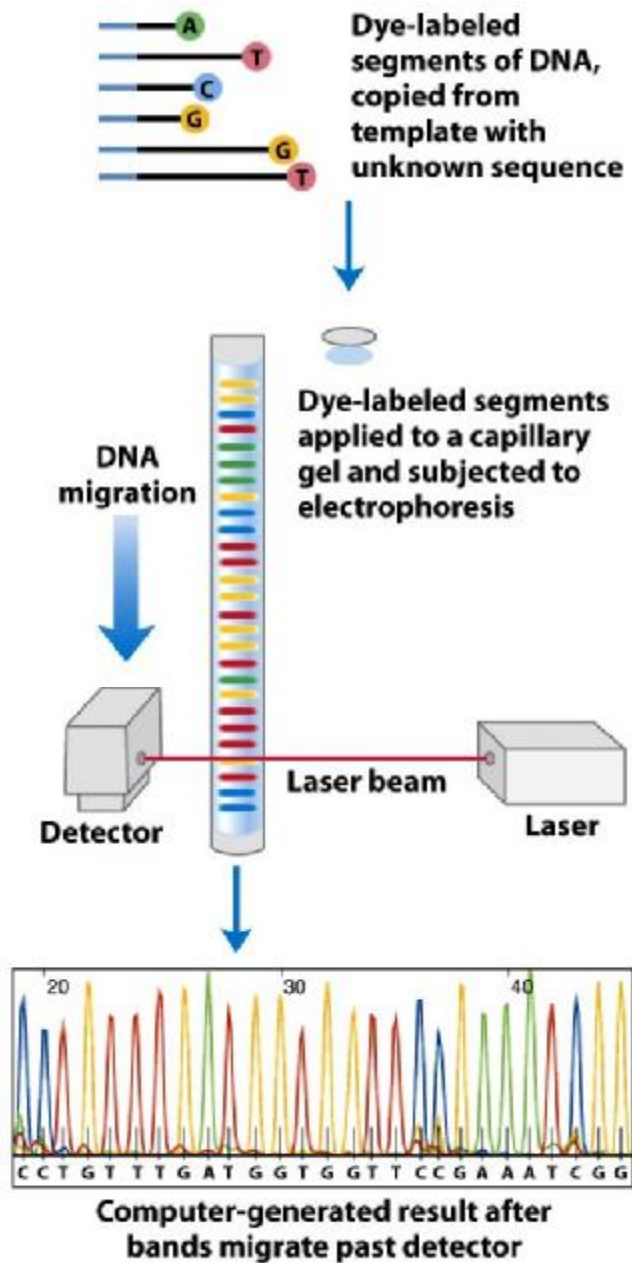
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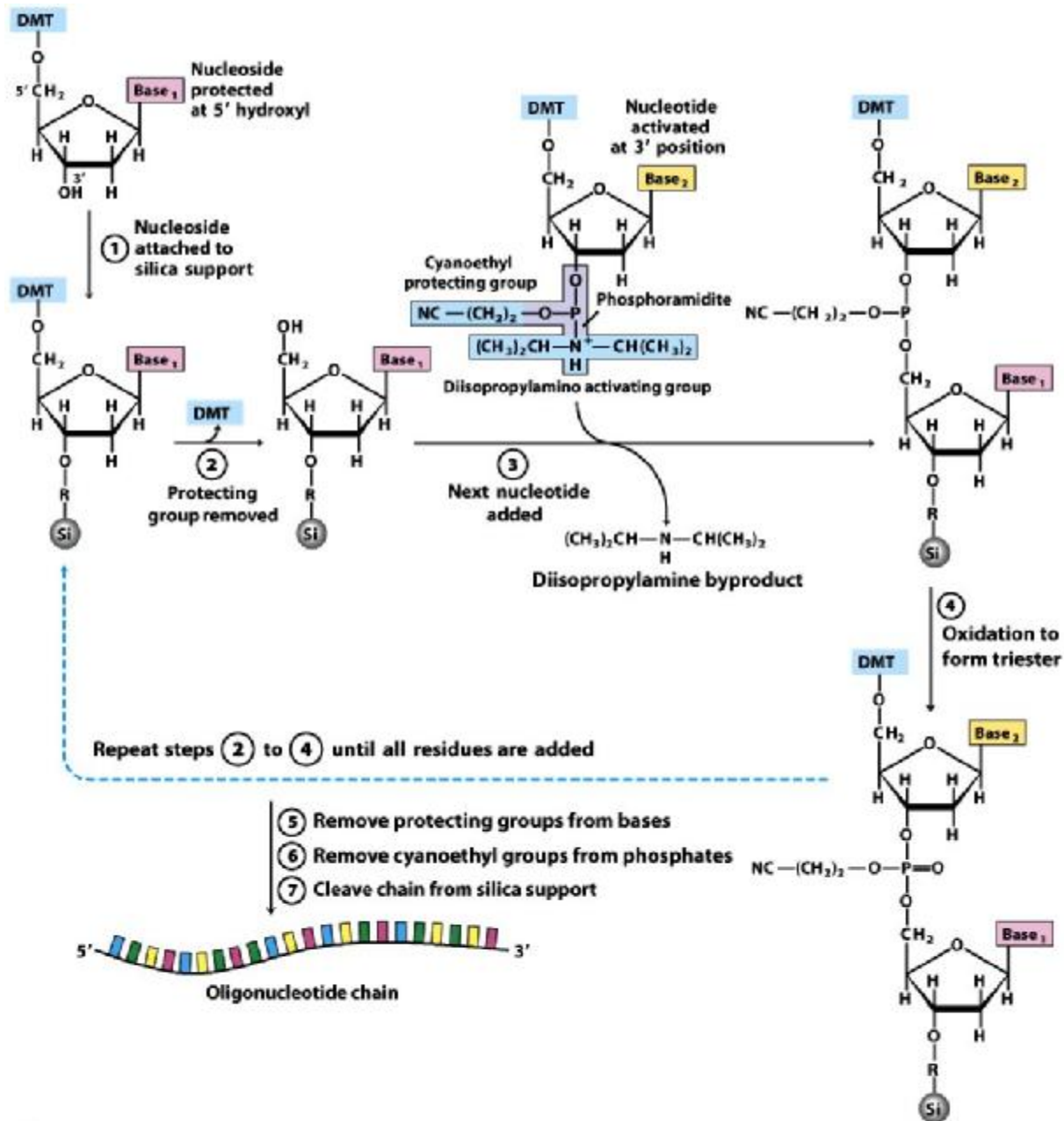


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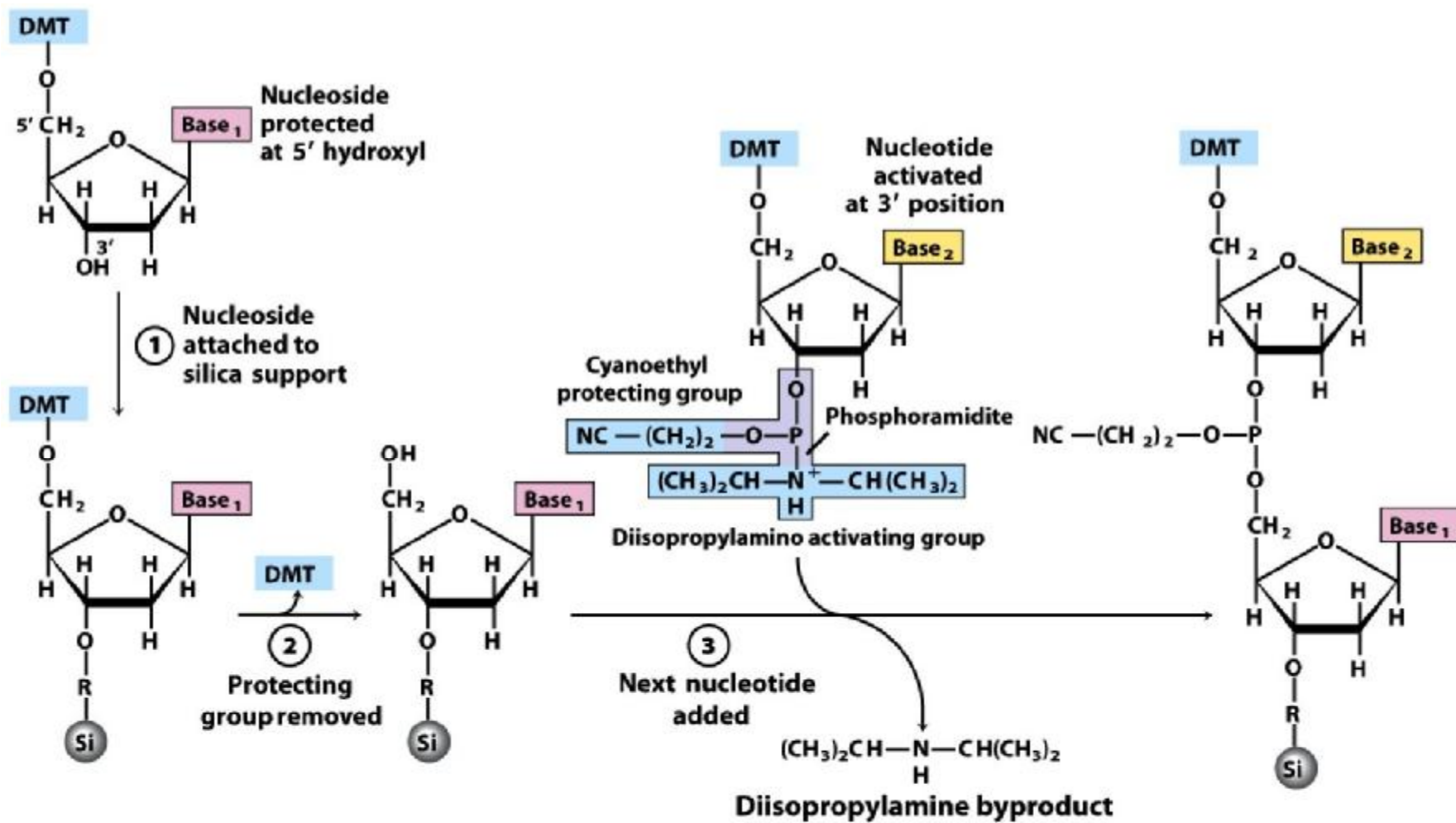
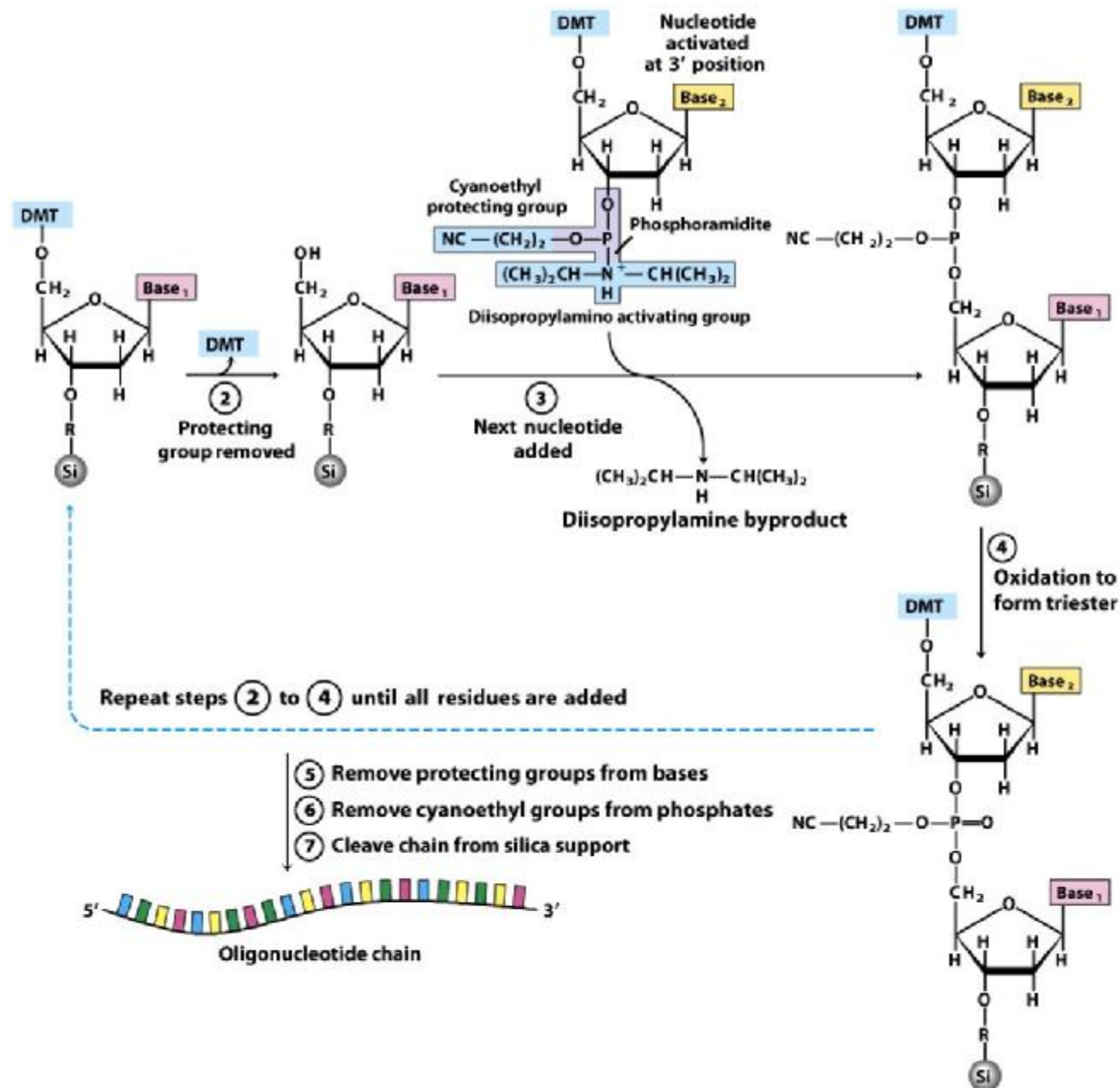


Figure 8-35 part 1

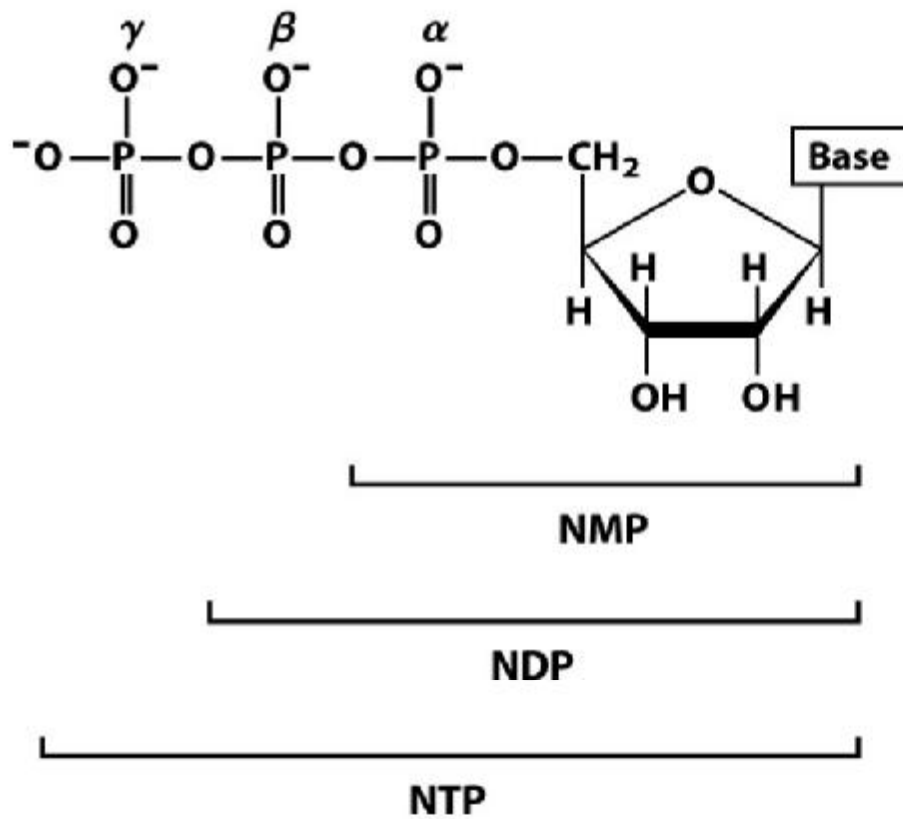
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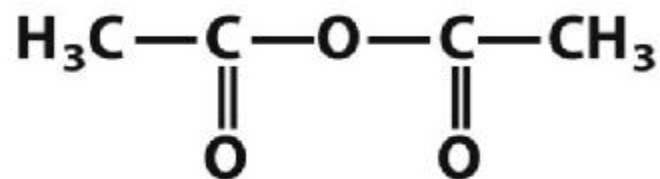
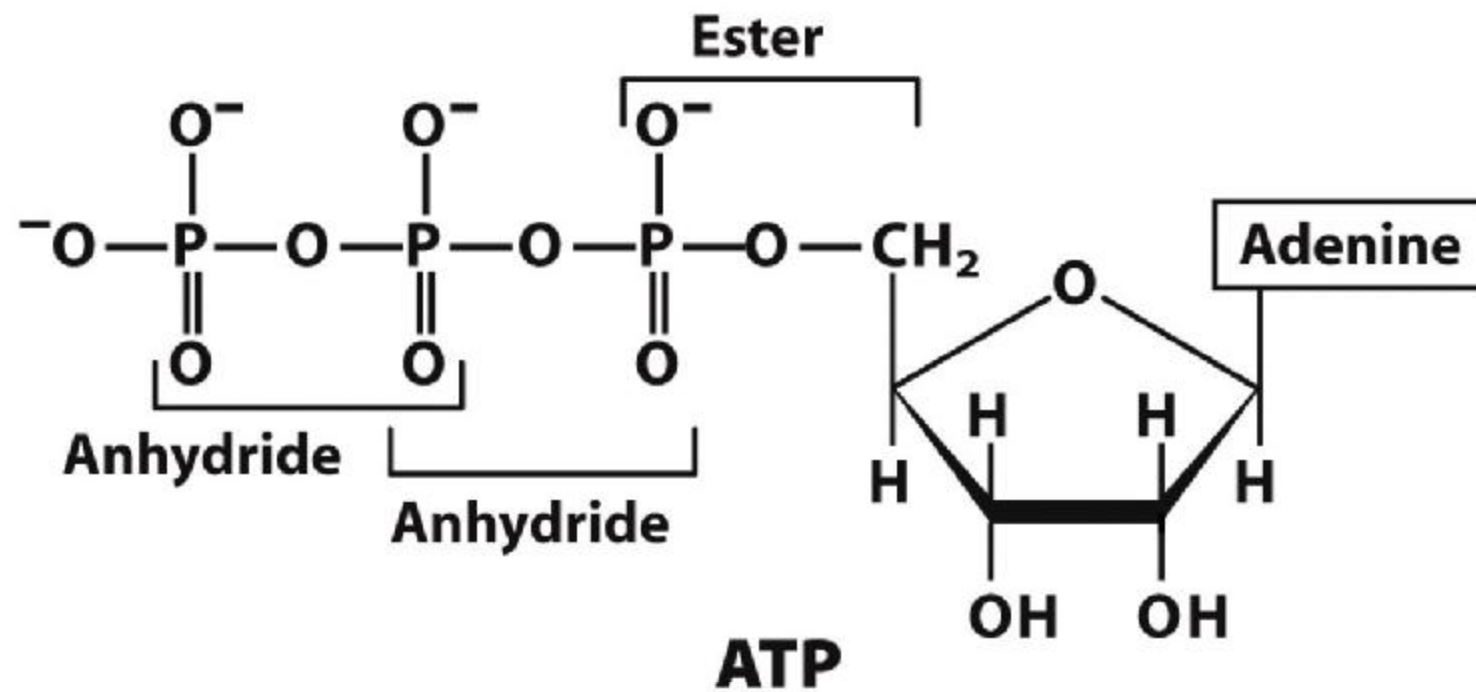
Abbreviations of ribonucleoside 5'-phosphates			
Base	Mono-	Di-	Tri-
Adenine	AMP	ADP	ATP
Guanine	GMP	GDP	GTP
Cytosine	CMP	CDP	CTP
Uracil	UMP	UDP	UTP

Abbreviations of deoxyribonucleoside 5'-phosphates			
Base	Mono-	Di-	Tri-
Adenine	dAMP	dADP	dATP
Guanine	dGMP	dGDP	dGTP
Cytosine	dCMP	dCDP	dCTP
Thymine	dTMP	dTDP	dTTP

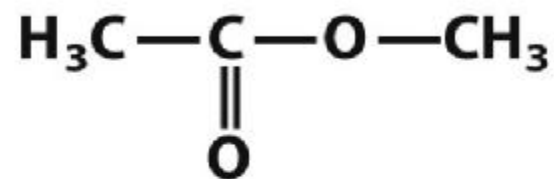
**Figure 8-36**

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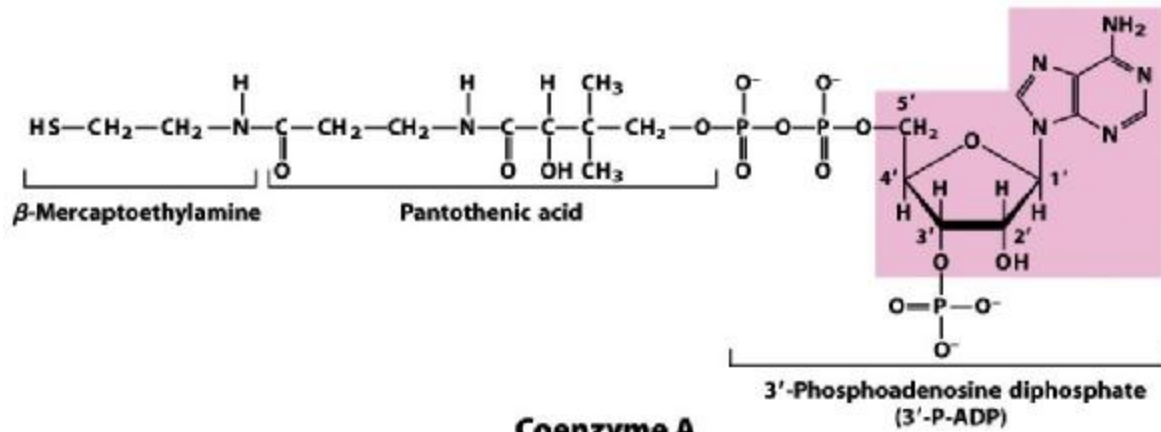




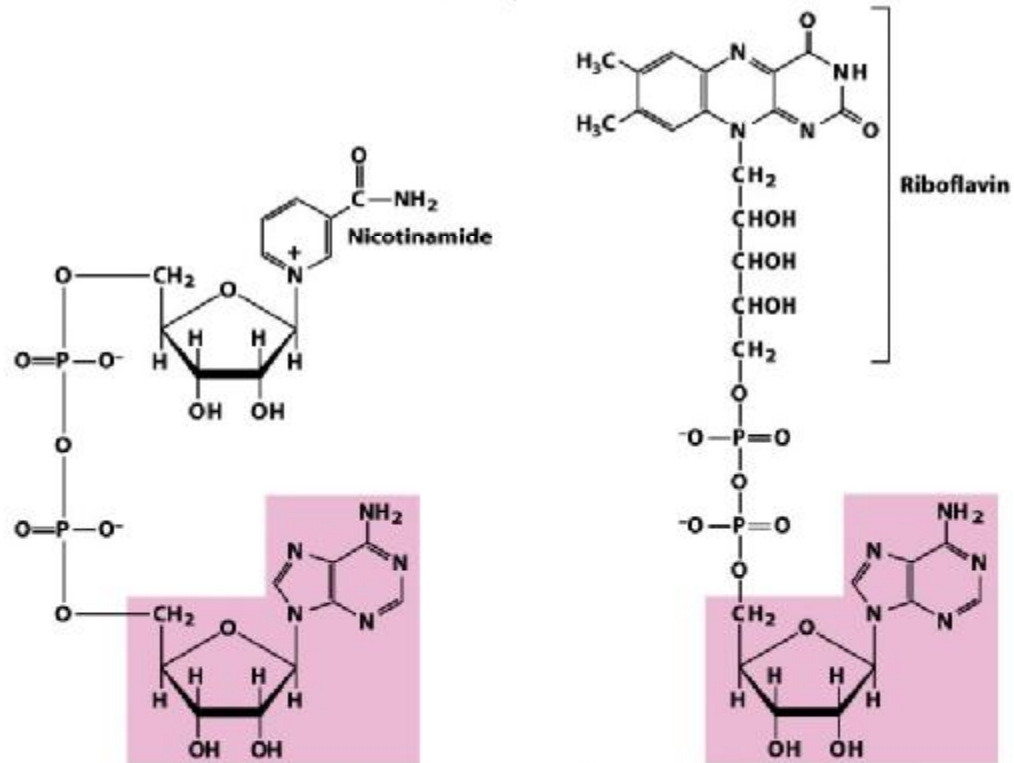
**Acetic anhydride,  
a carboxylic acid  
anhydride**



**Methyl acetate,  
a carboxylic acid  
ester**



### Coenzyme A



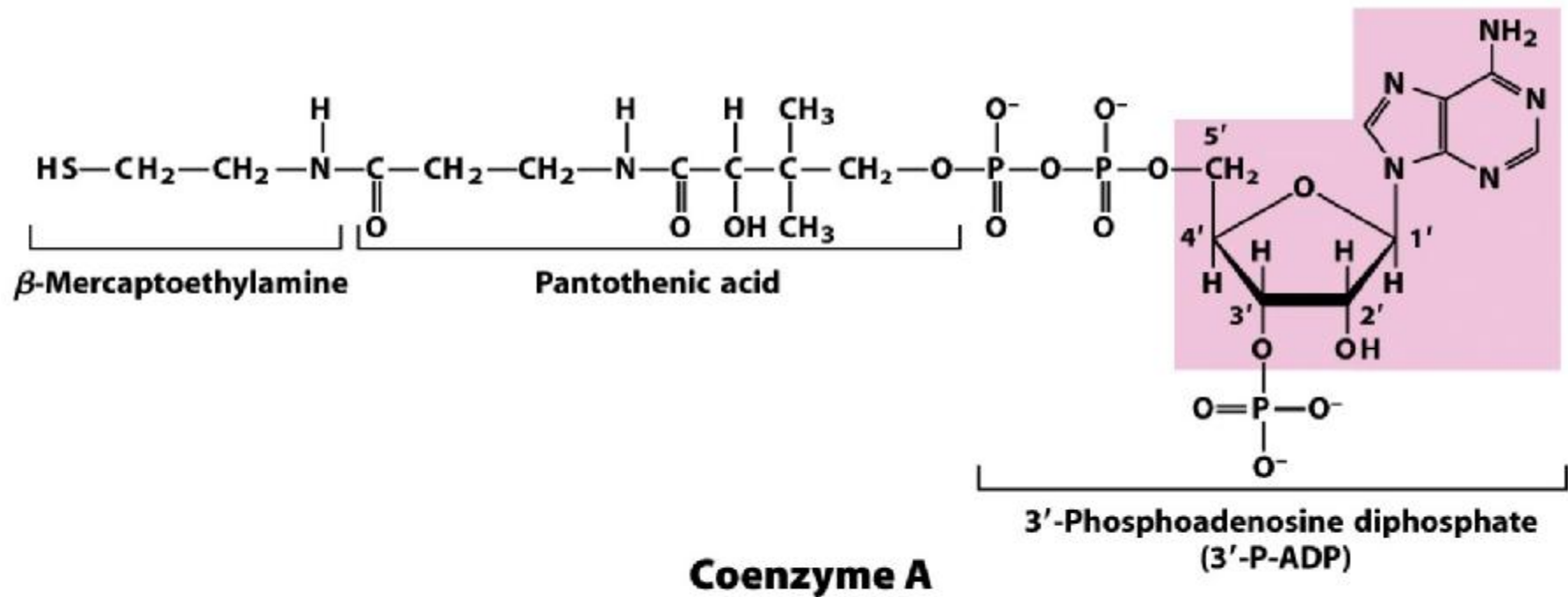
### Nicotinamide adenine dinucleotide (NAD<sup>+</sup>)

### Flavin adenine dinucleotide

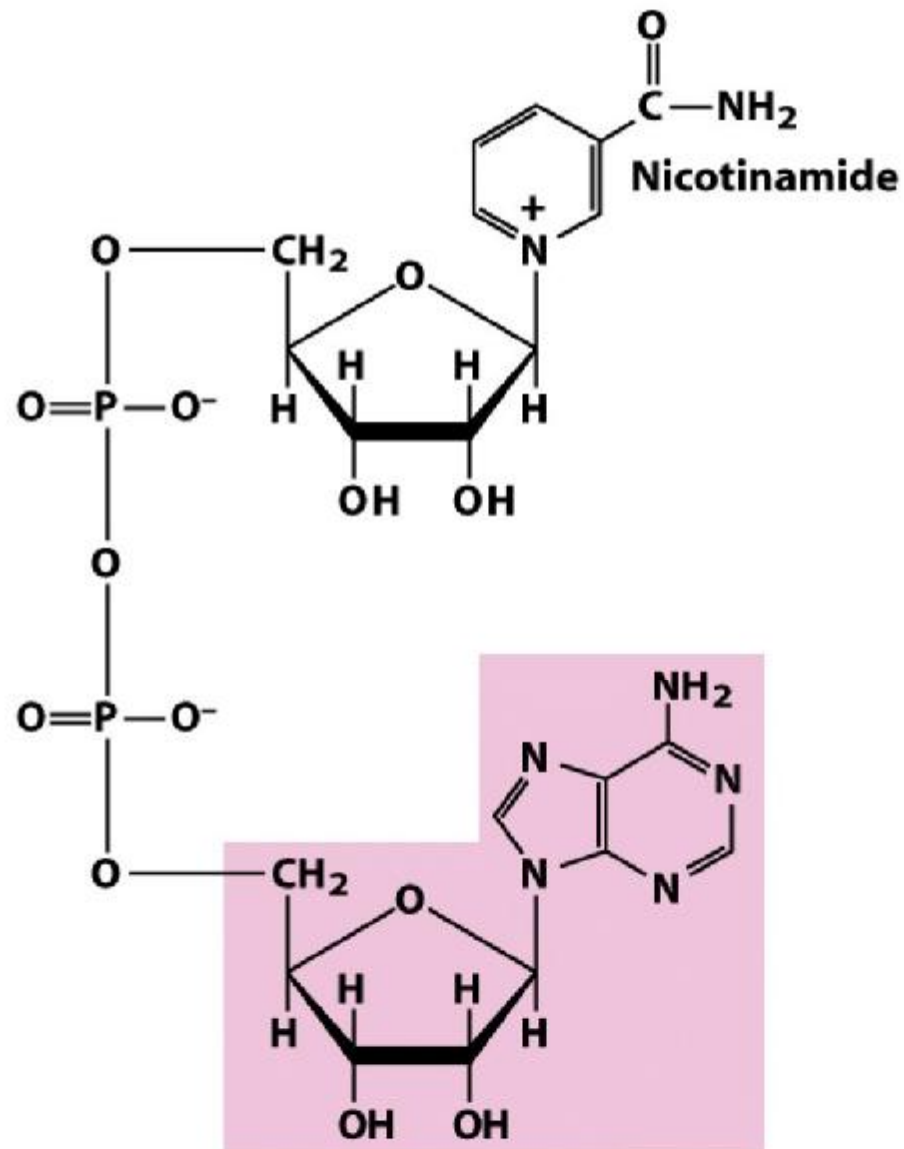
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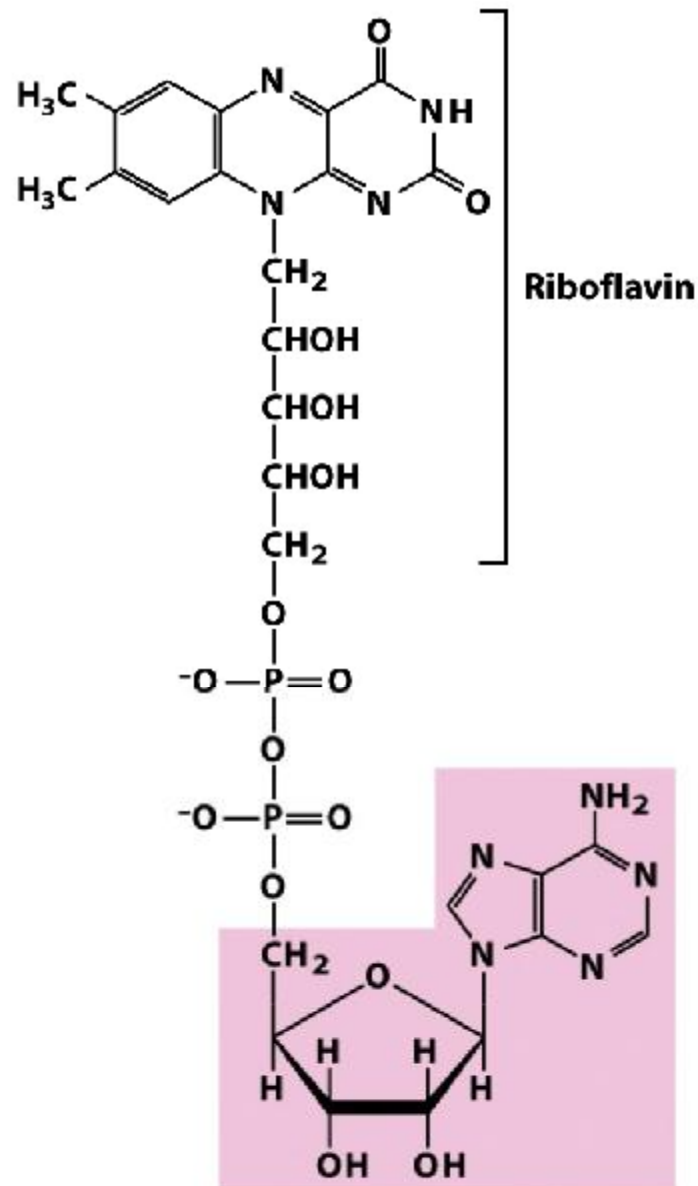


## Nicotinamide adenine dinucleotide (NAD<sup>+</sup>)

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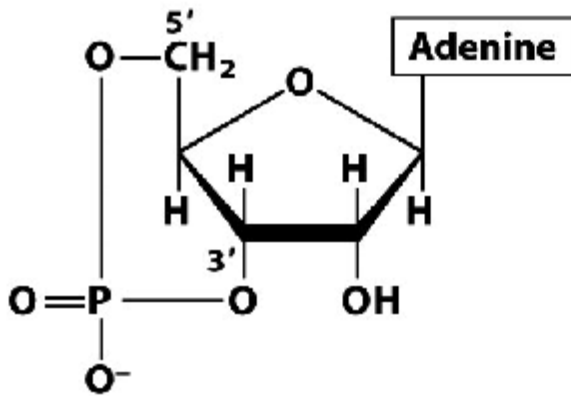


## Flavin adenine dinucleotide (FAD)

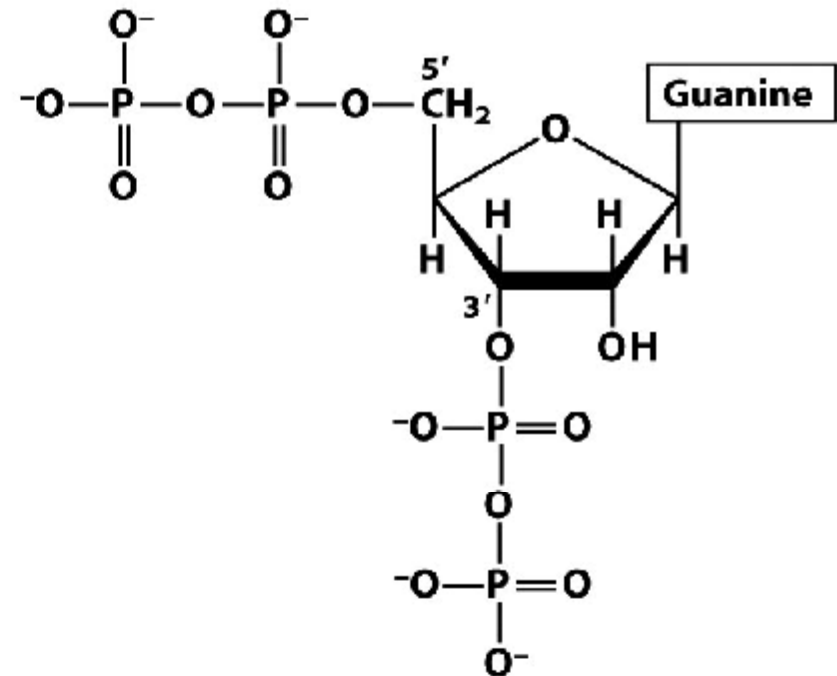
Figure 8-38 part 3

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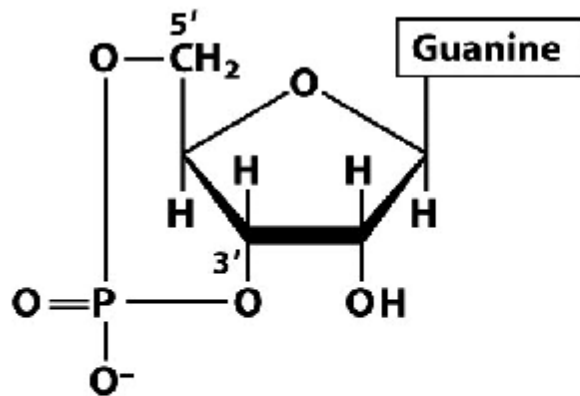
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**Adenosine 3',5'-cyclic monophosphate  
(cyclic AMP; cAMP)**



**Guanosine 5'-diphosphate, 3'-diphosphate  
(guanosine tetraphosphate)  
(ppGpp)**



**Guanosine 3',5'-cyclic monophosphate  
(cyclic GMP; cGMP)**

**Figure 8-39**

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