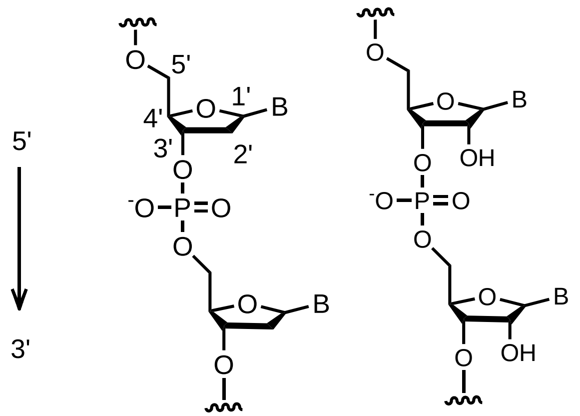
Lecture 1- Nucleic Acid Structure

Book recommendation:
Principles of Nucleic Acid Structure
Saenger, 1984

DNA structure RNA structure



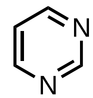
Properties of Bases

1. Pyrimidine and purines are aromotic planar systems

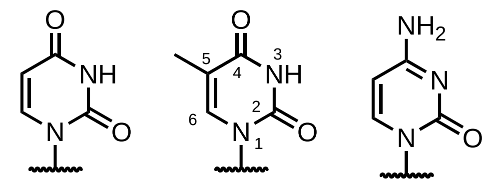
2. Altered bond lengths

C−NH_2	1.34 Å - DNA exocyclic amine
C−NH_2	1.47 Å -Alkyl amine bond length
H_3C-CH_3	1.54 Å
C−H	1.09 Å - Alkyl C-H
C=O	1.22 Å - in DNA
HN C=O	1.23 Å - Amide
C−O	1.43 Å - Alkyl C-O

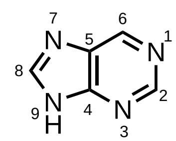
Bases



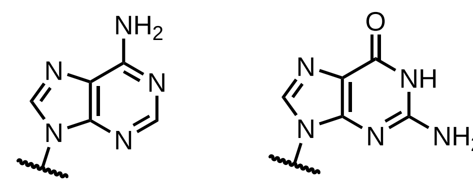
Pyrimidines



Base	Uracil	Thymine	Cytosine
Nucleoside	Uridine	Deoxythimine	Cytidine
Location	RNA only	DNA only	RNA/DNA

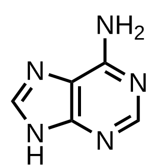


Purines

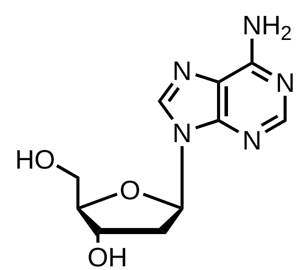


Base	Adenine	Guanine
Nucleoside	Adenosine	Guanosine
Location	RNA/DNA	RNA/DNA

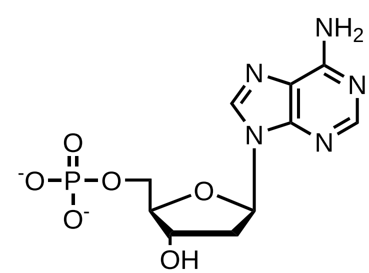
Base	**Nucleoside**	**Nucleotide**



Adenine

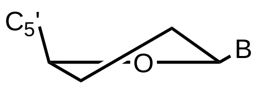


Adenosine

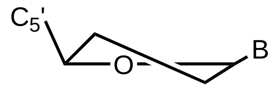


Adenosine monophosphate

Sugar puckering determines helical structure



C2' endo

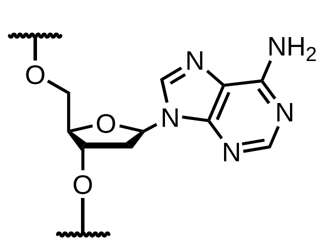


C3' endo

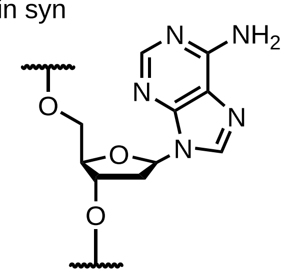
-Electronegative atoms prefer to be in the axial position
-RNA preferably in C3' endo due to presence of 2' OH
-DNA C2' endo in B form while C3' in A form

Syn/Anti conformations

1. Purines normally half syn and half anti in nucleosides
2. Substitution at 8 position can bias the confromation to syn
3. Purines in DNA prefer to be in anti (B/A form DNA)
4. Z form DNA contains purines in syn

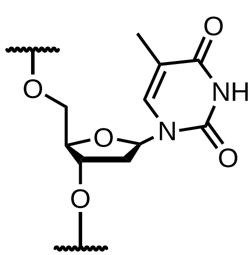


Anti

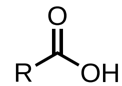
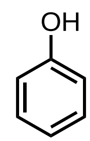
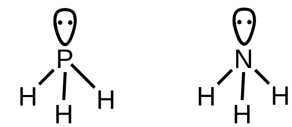
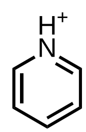
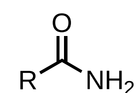
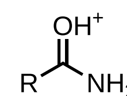
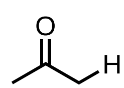
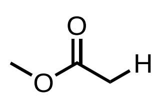
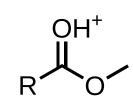


Syn

Pyrimidines rarely in syn form.



Relevant pKa values

Structure	pKa	Structure	pKa
	4-5	$R-NH_3^+$	9-12 *
$R-NH_3^+$	9-12	$R-PH_3^+$	-15
	9-10	*  P-H bond is longer and contains higher p character; less orbital overlap with H	
	4-5	$H_3PO_4 \rightarrow H_2PO_4^-$	2
		$H_2PO_4^- \rightarrow HPO_4^{2-}$	6-7
$R-OH$	15-17		15
$R-SH$	9-10		-1
	19-20		
	24		-6

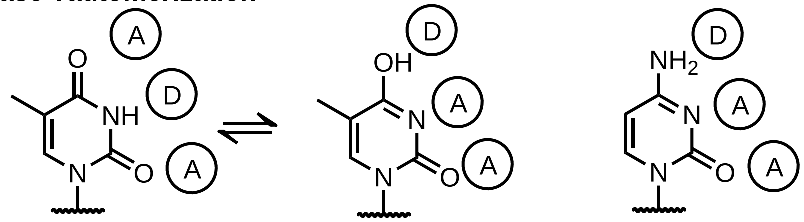
Lecture 1- Nucleic Acid Structure (cont)

pKa values continued

Structure	pKa
	10.6
$H_2N-NH_3^+$	8.12
$HO-NH_3^+$	6

pKa values decrease with the addition of EWD substituents

Base Tautomerization

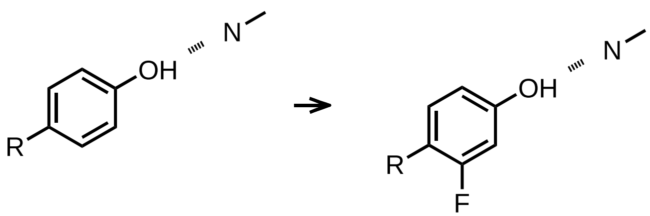


-Tautomerization of Thymine leads to H-Bond donor/ acceptor switch to resemble Cytosine
-Tautomerization of T can lead to DNA mutagenesis
-Base tautomerization most important with pyrimidine bases

(A) H Bond acceptor
(D) H Bond donor

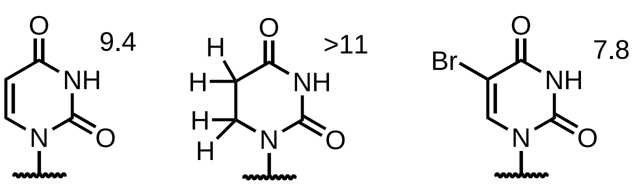
Modulation of H-Bond Strength

Example: How to increase H-Bond strength in drug X



Increasing acidity of OH group via the addition of EWD group on the aryl group increases H-bond stength

Example: Changing the acidity of H-bond donor in uracil



100	30	240

K_A (M^{-1})

In general, H-Bond strength is greater with more acidic H-Bond donors and more basic H-Bond acceptors

Forces stabilizing DNA

Hydrogen Bonding

-Hydrogen bonding is largely an electrostatic interaction

$$A\text{-}H + B \rightleftharpoons \left[\overset{\delta^-}{A} \cdots H \cdots \overset{\delta^+}{B} \right]^{\ddagger} \rightleftharpoons A^- + H\text{-}B$$

-Must consider the equilibrium

$$H_2O \cdot B + HA \cdot H_2O \rightleftharpoons B \cdot HA + H_2O \cdot H_2O$$

-Directionality important to H-bond strength

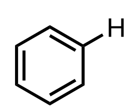
-Strict distance for H-bonding

OH ⋯⋯ O 2.8 - 3.2 Å

-H-Bonding dependent on solvent

To generate an H-bond between two molecules, the H-bonding interaction between the two molecules must be stronger than potential H-bonding with solvent. It is therefore easier to design H-bonding pairs in solvents other than water (e.g. $CHCl_3$).

Bond Strengths

OH ⋯⋯ O	3-6 kcal/mol (H-Bond in water)	HO-H	111 kcal/mol
C−C	84 kcal/mol (C-C bond 1.54Å)		110 kcal/mol
C−H	98 kcal/mol (C-C bond 1.09Å)		

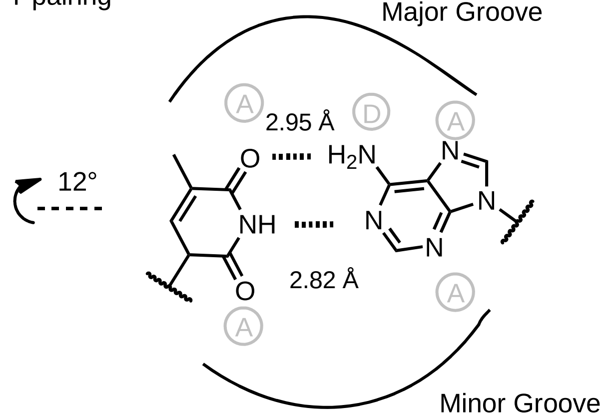
Common H-Bond Pairs

OH ⋯⋯ O
NH ⋯⋯ N
NH ⋯⋯ O
OH ⋯⋯ N

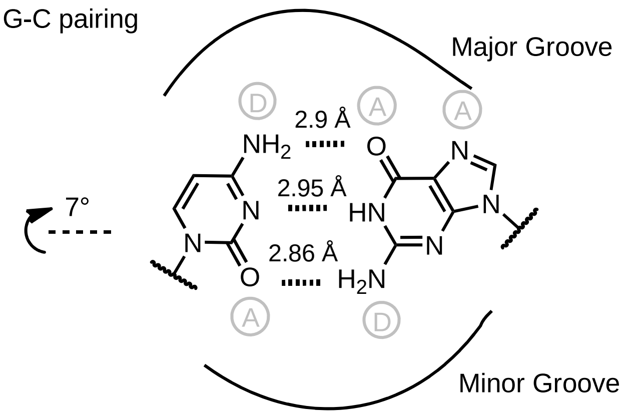
Lecture 1- Nucleic Acid Structure (cont)

DNA base pairing

A-T pairing

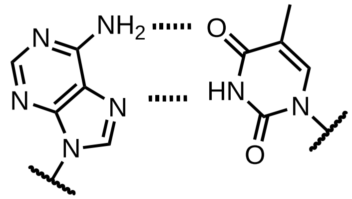


G-C pairing



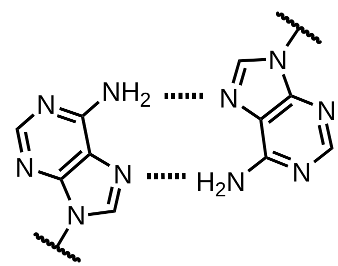
Hoogsteen Base Pairing

A-T hoogsteen pair

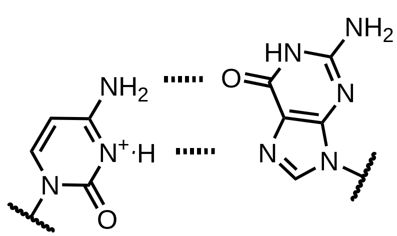


Alternative Base Pairing

Atypical A-A pairing



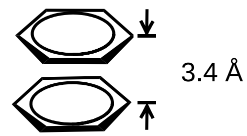
Protonated C-G Base pair



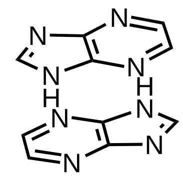
Protonation occurs at ~pH 6

Forces stabilizing DNA

Base Stacking



Stacking distance in DNA



Stacking of purine pairs results in a larger energetic contribution to DNA stability due to increased surface area

	$-\Delta H$ (kcal/mol)	$-\Delta S$ (kcal/mol*K)	
dA/dA	6.5	18	(in H_2O)
dU/dU	2.7	10	

Pur-Pur > Pyr Pur > Pyr Pyr

Stability of DNA therefore depends not only on absolute G-C content (increased H-bonding) but also the specific sequence of DNA.