CHEM-E4245 Natural Product Chemistry
Lecture 5 - Nucleosides, Nucleotides And Nucleic Acids

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Building blocks

**Nucleobases**

- adenine (A)
- guanine (G)
- cytosine (C)
- thymine (T)
- uracil (U)

**Sugars**

- deoxyribose (DNA)
- ribose (RNA)

**Nucleoside**

- deoxyadenosine (dA)

**Nucleotide**

- deoxyadenosine monophosphate (dAMP)

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Structure of RNA

- Adenine
- Cytosine
- Guanine
- Uracil

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Structure of DNA

Adenine

Cytosine

Guanine

Thymine
Base Pairing

Watson-Crick  Hoogstein
Forces stabilizing DNA double helix

1. Hydrogen bonding
   • (2-3 kcal/mol per base pair)

2. Stacking (hydrophobic) interactions
   • (4-15 kcal/mol per base pair)

3. Electrostatic forces
**B-DNA**

right handed helix

- helical axis passes through base pairs
- planes of bases are nearly perpendicular to the helix axis.
- 3.4 Å rise between base pairs

Wide and deep

Narrow and deep

23.7 Å

- Sugars in 2’ endo conformation.
- Bases in *anti* conformation.
- Bases have a helical twist of 36° (10.4 bases per helix turn)
- Helical pitch = 34 Å
B-type duplex not possible for RNA

steric “clash”
**A-form helix: DNA; RNA-DNA hybrids**

Right handed helix

- Planes of bases are tilted 20° relative the helix axis.
- 2.3 Å rise between base pairs
- Sugars in 3’ endo conformation.
- Bases in *anti* conformation.
- 11 bases per helix turn
- Helical pitch = 25.3 Å
Z-form double helix: polynucleotides of alternating purines and pyrimidines (GCGCGCGC) at high salt

Left handed helix

- planes of the bases are tilted $9^\circ$ relative the helix axis.
- 3.8 Å rise between base pairs
- Flat major groove
- Narrow and deep minor groove

- Backbone zig-zags because sugar puckers alternate between 2’ endo pyrimidines and 3’ endo (purines)
- Bases alternate between anti (pyrimidines) and syn conformation (purines).
- 12 bases per helix turn
- Helical pitch $= 45.6$ Å
Groove binding drugs and proteins

Leucine zipper proteins bind DNA major groove

5’-ATT-3’

Drug DAPI bound at the minor groove

(4,6-diamidino-2-phenylindole)
Minor groove binders


Binding of an antitumor drug to DNA, Netropsin and C-G-C-G-A-A-T-T-BrC-G-C-G.

Kopka ML, Yoon C, Goodsell D, Pjura P, Dickerson RE

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Mitomycin

Organization of chromosomal DNA

- Chromosomal DNA is organized in loops (no free ends)
- It is negatively supercoiled: 1 (-) supercoil per 200 nucleotides
Adenosine derivatives

- ATP
- ADP
- AMP
- cAMP
- NADH
- cAMP
- Pantothenic acid
- Coenzyme A
Nucleoside antibiotics

8-aza-adenosine

araA

AZT

puromycin

doxyfluridine
Natural Nucleoside Antibiotics

- Sinefungin
- Polyoxin J
- Hikizimycin
- Nikkomycin B
Sinefungin

Sinefungin

Sinefungin

Two-directional synthesis

• One-directional

linear synthesis

\[ A \rightarrow A \rightarrow A \rightarrow A \rightarrow A \quad B \]

convergent synthesis

\[ A \rightarrow A \rightarrow A \rightarrow A \quad B \]

\[ B \rightarrow A \quad B \rightarrow A \quad B \]

• Two-directional

sequential homologation

\[ * * \rightarrow A * * \rightarrow A * * \rightarrow A * * \quad B \]

simultaneous homologation

\[ * * \rightarrow * * \rightarrow * * \rightarrow A * * \quad B \]
Terminus Differentiation

meso chain + 1 eq achiral reagent \[\rightarrow\] racemic mixture

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
+ \quad \text{Mel} & \quad \rightarrow \\
\text{MeO} & \quad \text{OH} \\
\quad & \quad 1:1 \\
\text{HO} & \quad \text{OMe}
\end{align*}
\]

meso chain + 1 eq chiral reagent \[\rightarrow\] high ee, esp. after extended rxn time

meso chain + 1 eq chiral reagent \[\rightarrow\] usually high ee
  e.g. first rxn gives 10:1 (R:S) and second is also 10:1 (R:S)
  Overall rxn gives 100:10:10:1 (RR:RS:SR:SS), i.e. 100:1 ee, but 101:20 de

chiral chain + 1 eq achiral reagent \[\rightarrow\] chiral product; statistical distribution of products
  (both termini, one terminus and no reaction)
Substrate Controlled Reaction

Asymmetric Induction followed by Kinetic Resolution

\[
\begin{align*}
X_1 + X_3 &= \text{enantiomers!} \\
\text{de} &= \frac{X_1 + X_3}{X_2 + X_4}
\end{align*}
\]

\[\text{Ti(OiPr)_4, (+)-DIPT, tBuOOH} \]

\[
\begin{array}{c|c|c}
\text{time} & \%\text{ee} & \%\text{de} \\
3 \text{h} & 84 & 92 \\
24 \text{h} & 93 & 99.7 \\
140 \text{h} & 97 & >99.7 \\
\end{array}
\]
Simultaneous homologation

\[
\text{O} \quad \xrightarrow{\text{Me}_2\text{CO}, \text{CuSO}_4} \quad \xrightarrow{\text{Na}^+} \quad \text{O} \quad \xrightarrow{n-\text{BuLi}} \quad 14\% \\
\text{OH} \quad \xrightarrow{\text{SAE} \, (+)-\text{DIPT}} \quad \text{meso} \\
\text{72\%; very high ee} \\
\text{OH} \quad \xrightarrow{\text{SAE} \, (-)-\text{DIPT}}
\]

Two-directional Chain Synthesis

Two-directional Synthesis

Two-directional Synthesis: Mycoticin

Hikizimycin

DNA Topoisomerases control supercoiling

Change the number of times a strand of DNA is wound by concerted breakage and re-joining of DNA strands

Topoisomerase enzymes

Topoisomerases I
Relax DNA supercoiling by increments of 1 (cleave one strand)

Topoisomerases II
Change DNA supercoiling by increments of 2 (break both strands)
Usually introduce negative supercoiling
Drugs that inhibit DNA Topoisomerase I

- Camptothecin, topotecan and analogs
- Antitumor activity correlates with interference with topoisomerase activity
- Stabilizes topoisomerase I-DNA intermediate, preventing DNA strand re-ligation
- Used in treatment of colorectal, ovarian, and small cell lung tumors
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Drugs that inhibit bacterial Topo II (DNA gyrase)

Interfere with breakage and rejoining DNA ends:

- Nalidixic acid
- Ciprofloxacin

Inhibit ATP binding:

- Novobiocin