Biological Macromolecules

Introduction for Chem 493

Chemistry of Biological Macromolecules

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Biological Macromolecules

Biological macromolecules are the molecules of life

- allow for organization
- serve a functional purpose
- structural complementarity allows for chemical interactions

Biological macromolecules are carbon based compounds

- consist of building blocks
- many are polymeric with repeating subunits
- sequence of the subunits determines structure and function

Biological Macromolecules

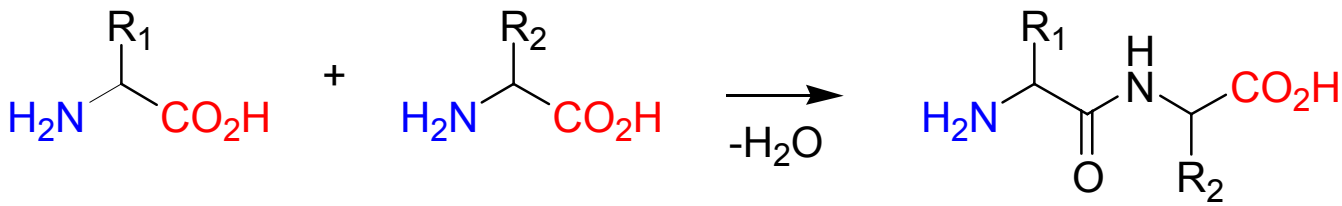
Summary of biological macromolecules relevant to Chem 493

Amino Acids	Monosaccharides	Nucleotides
↓	↓	↓
Peptide/Protein	Polysaccharide	Nucleic Acid
• enzymes • hormones • receptors • membrane channels • cell structure	• energy storage • structure	• DNA, storage of information • RNA, protein synthesis

Biological Macromolecules

Properties of biomolecules:

1. Have a directionality
    - Structural polarity
    - Consists of a head and tail, direction to structure



N-terminus ⇨ C-terminus

Biological Macromolecules

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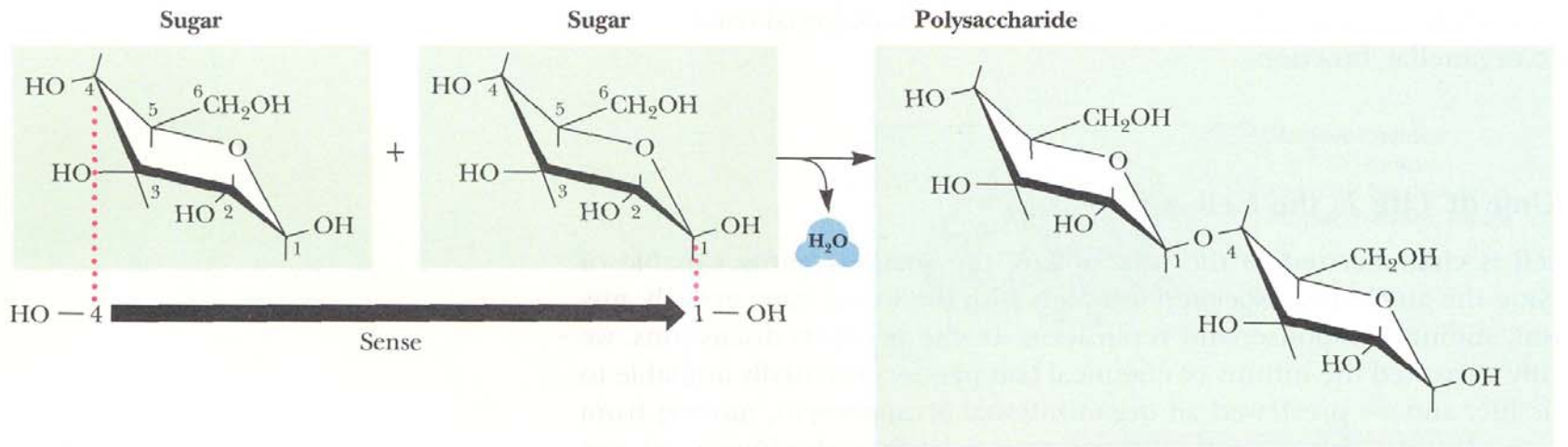

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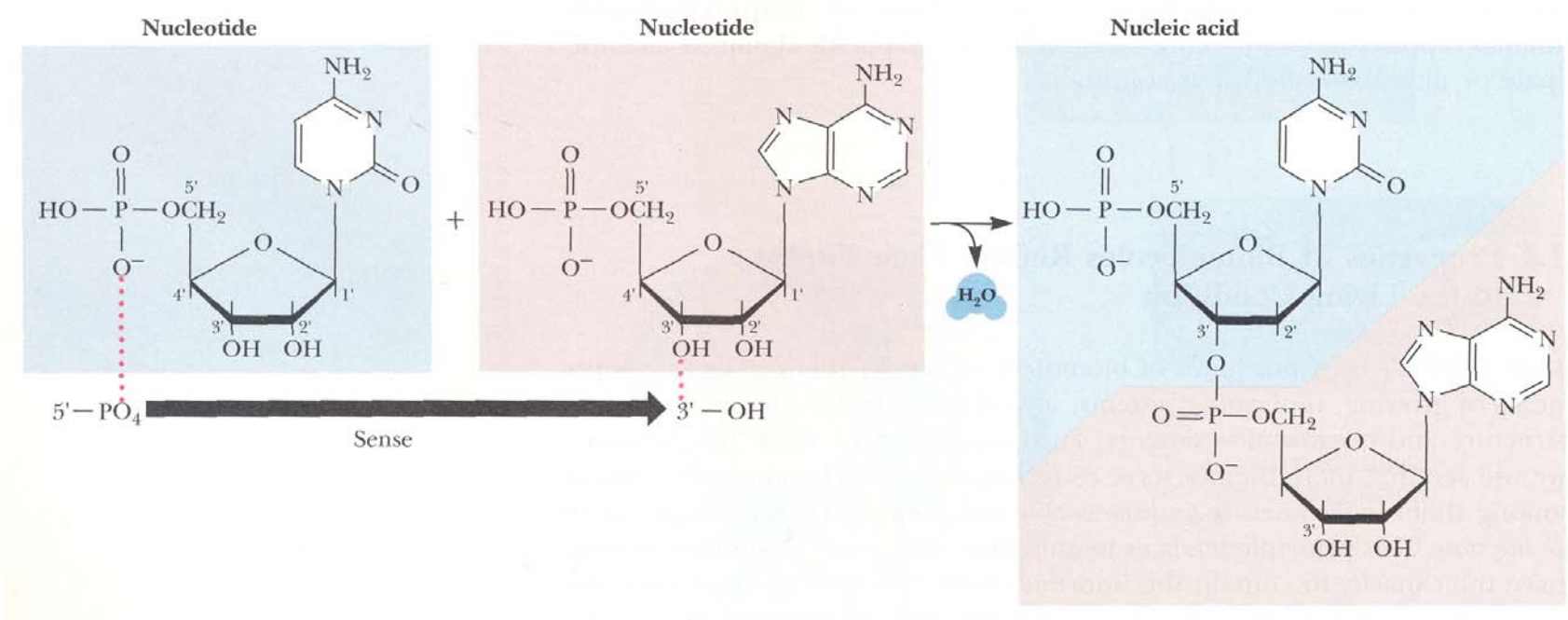


Biological Macromolecules

Properties of biomolecules:

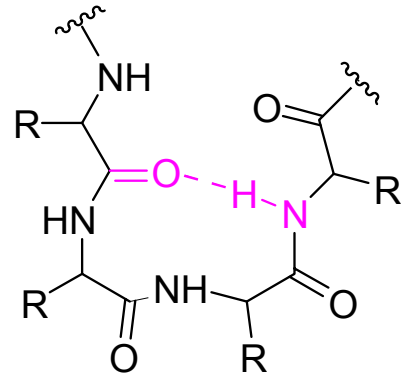
2. Contains information
    - Sequence of monomers contains information
    - Especially for peptides and nucleic acids
    - Side-chain functional groups give unique properties

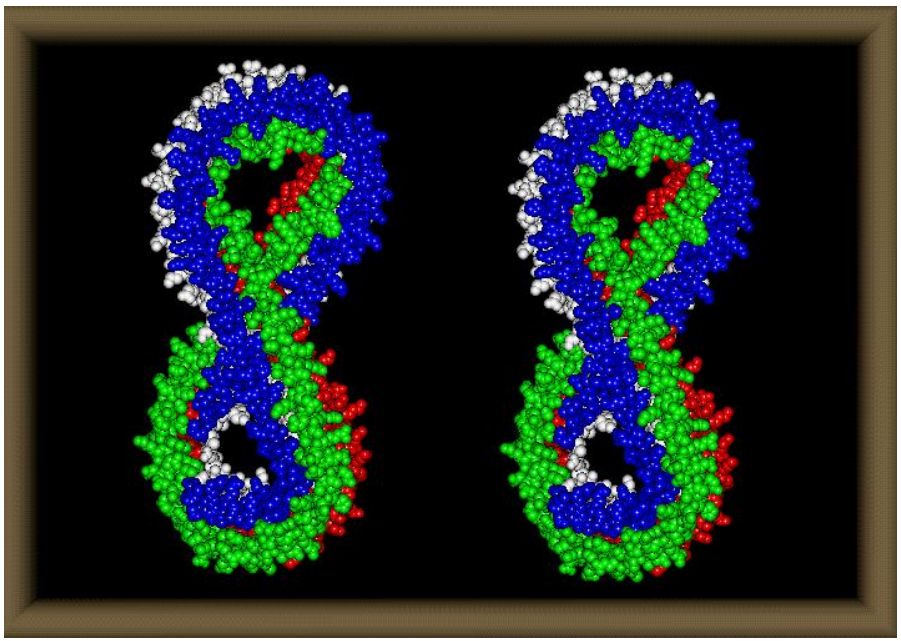
Unique Sequence = Unique Recognition

Biological Macromolecules

Properties of biomolecules:

3. Consist of a 3-dimensional architecture
    - Linear sequences, but can turn, fold, coil
    - Adapt unique 3-dimensional structures





Number ’88’

CRYSTAL STRUCTURE OF HUMAN APOLIPOPROTEIN A-I (PDB code: 1av1)

www.pdb.org

Biological Macromolecules

Structure of Peptides and Proteins

Primary Structure:

- amino acid sequence
- protein of n residues = possibility of 20^n sequences

Neuromedin B

Gly-Asn-Leu-Trp-Ala-Thr-Gly-His-Phe-Met-NH_2

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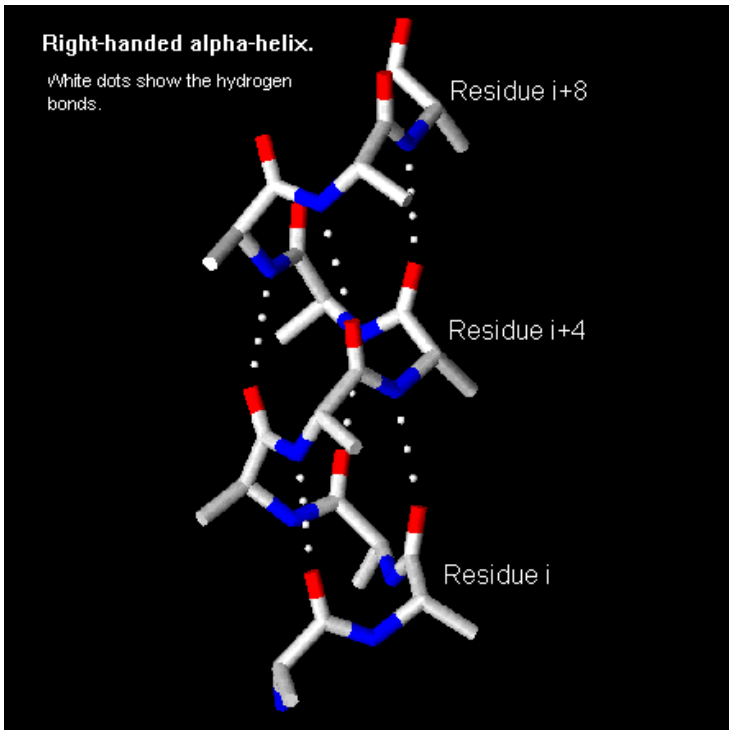
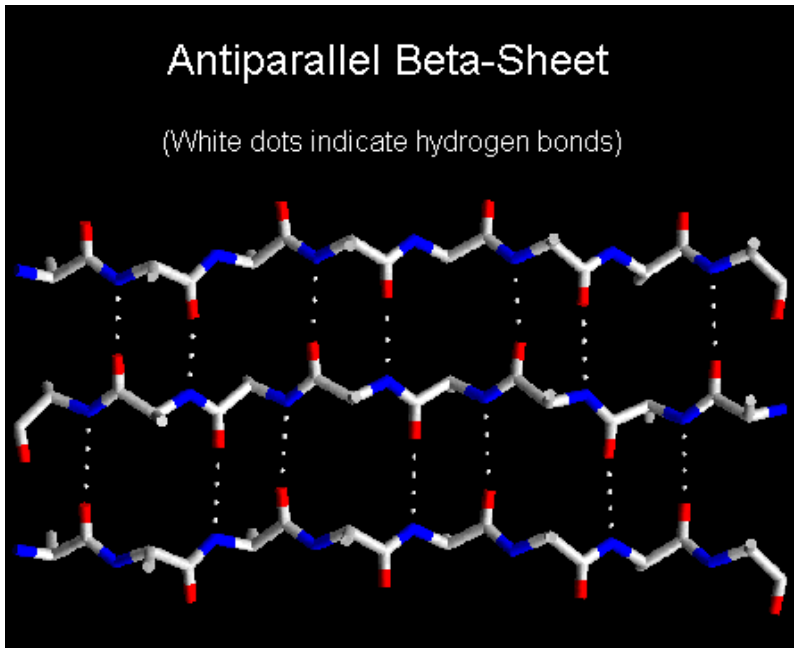
Secondary Structure:

- spatial arrangement of peptide backbone
- α-helix, β-sheet, random coil, reverse turns





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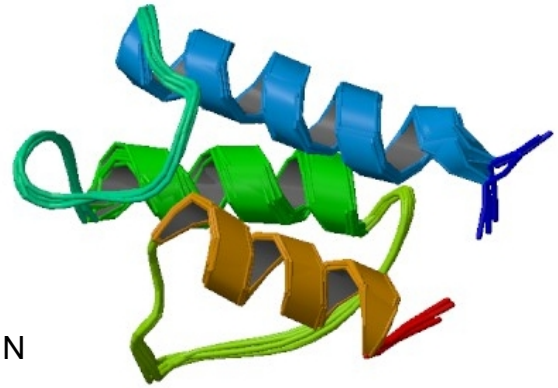
Tertiary structure:

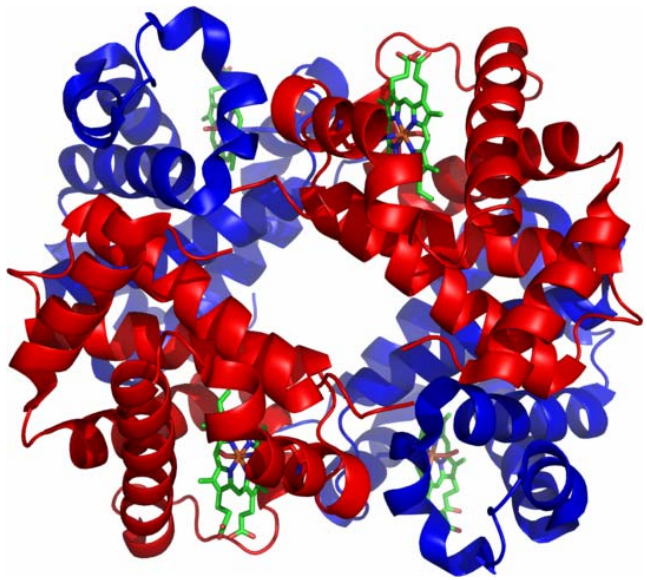
• folding of secondary structures to create the three dimensional structure of a single polypeptide chain



TERTIARY STRUCTURE OF APO-D-ALANYL CARRIER PROTEIN

Quaternary structure:

• the arrangement of subunits where more than one peptide chain creates the protein



Crystal structure of hemoglobin

4 subunits = tetramer

Biological Macromolecules

Properties of biomolecules:

4. Interact through structural complementarity
    - Biological function of a biomolecule is achieved through structural complementarity
    - Weak chemical interactions
        - Ionic bonds, ion/dipole, dipole/dipole
        - Hydrogen bonding
        - Hydrophobic interactions
        - Van der waals interactions

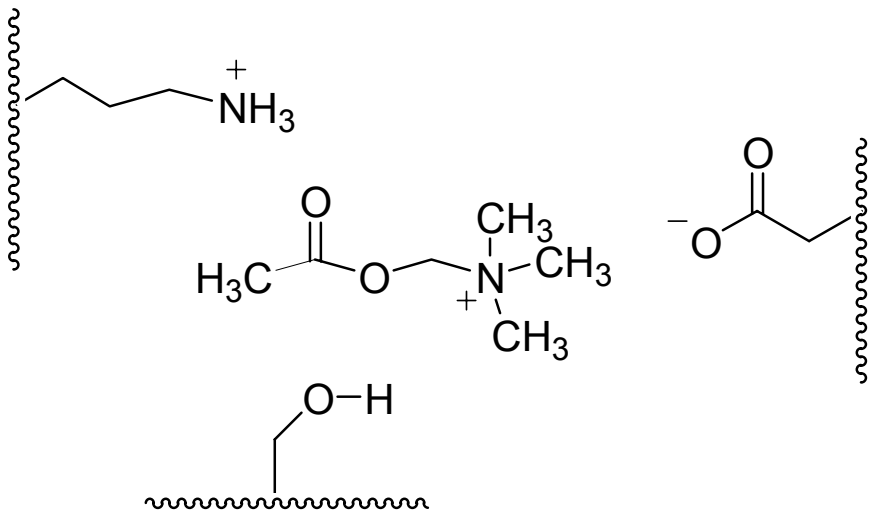
Biological Macromolecules

Properties of biomolecules:

4. Interact through structural complementarity

- Weak chemical interactions
  - Ionic bonds 5-10 kcal/mol
    - attractive forces between oppositely charged polar functions
  - Ion/dipole 2-8 kcal/mol, dipole/dipole 1-3 kcal/mol

Eg. Acetylcholine interaction with muscarinic receptor

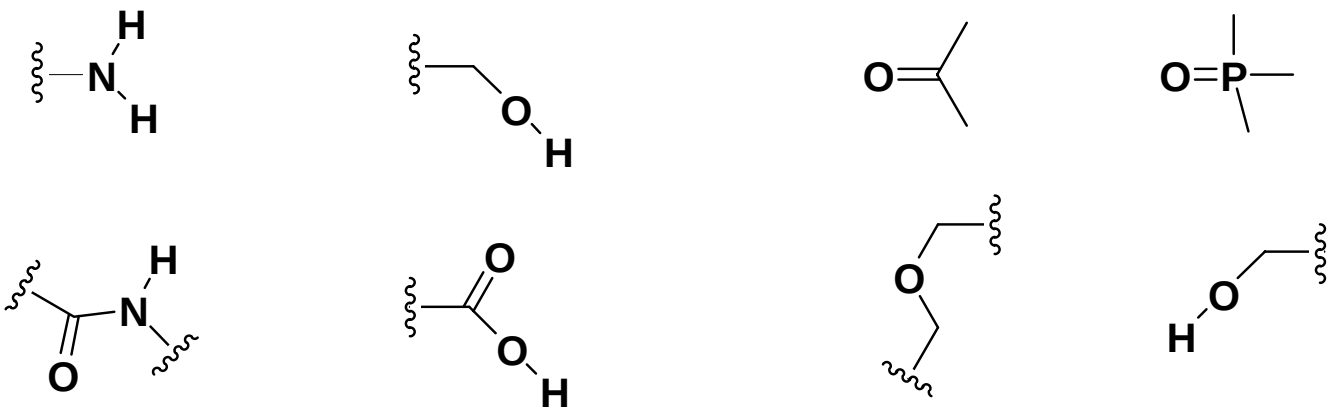


Properties of biomolecules:

4. Interact through structural complementarity

- Weak chemical interactions
  - Hydrogen bonding 2-5 kcal/mol
    - between a hydrogen atom (covalently bonded to N, O, S) and a second electronegative atom (H bond acceptor)

Donors **Acceptors**



Biological Macromolecules

Properties of biomolecules:

4. Interact through structural complementarity

- Weak chemical interactions
  - Hydrophobic interactions, very weak 0.5-1 kcal/mol
    - between nonpolar molecules in close proximity
    - this minimizes the hydrophobic surfaces available to water

  - Van der waals interactions, very weak 0.5 kcal/mol
    - induced dipole interactions between closely approaching atoms/molecules

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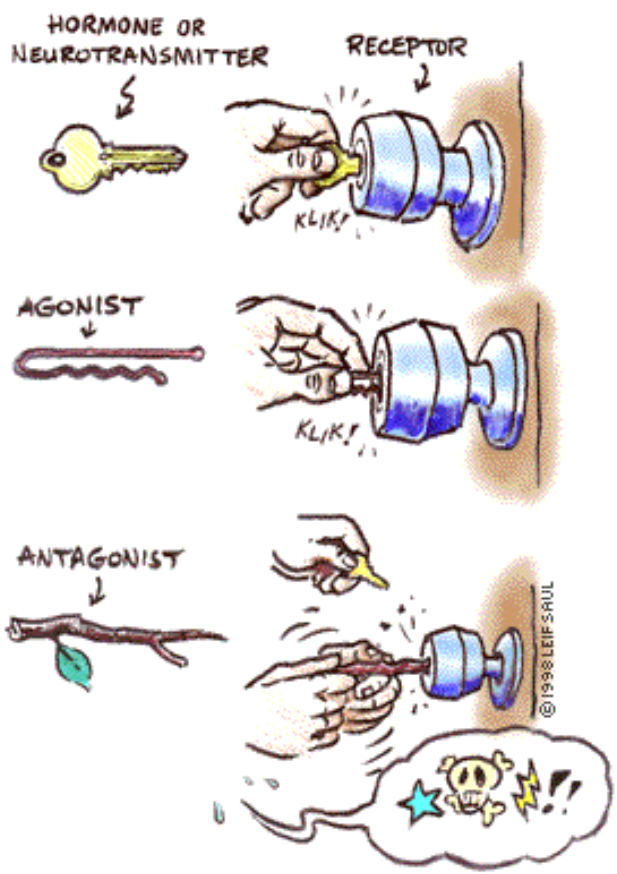
Properties of biomolecules:

4. Interact through structural complementarity
    - Lock and Key

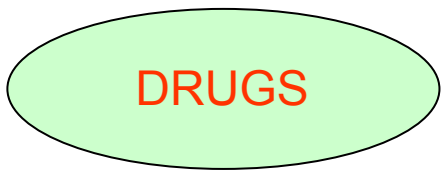


Chemistry of… Biological Macromolecules

As organic chemists, we want to synthesize and modify biological macromolecules.

Purposes for doing this?

- structural elucidation
- chemical synthesis of biologics
- modifying the properties of biomolecules
  - prevent enzymatic degradation
  - improve bioavailability, pharmacokinetics, potency
  - conjugate to dyes, radionuclides, cytotoxic agents



Chemistry of… Biological Macromolecules

As organic chemists, we want to synthesize
and modify biological macromolecules.

This course will demonstrate:

- protecting groups required for biomolecule synthesis and derivatization
- solid-phase (polymer supported) synthesis and automation
- preparation and reactivity of monomers (amino acids, monosaccahrides, nucleotides)
- synthesis of polymeric biomolecules (peptides, oligosaccharides, nucleic acids)
- approaches used to design drugs from biological macromolecule leads
- recent literature for applications

Examples of biomolecules – peptide hormones and analogues

Gonadotropin-releasing hormone (GnRH) agonists

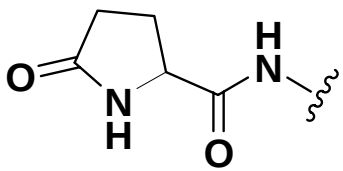
H–Glu–His–Trp–Ser–Tyr–Gly–Leu–Arg–Pro–Gly–NH_2

- gonadorelin acetate (Lutrepulse) used to treat infertility
- pump delivers peptide via IV every 90 min

pGlu–His–Trp–Ser–Tyr–Gly–Leu–Arg–Pro–Gly–NH_2

- Leuprolide acetate
- 15X potency, daily injection or implant

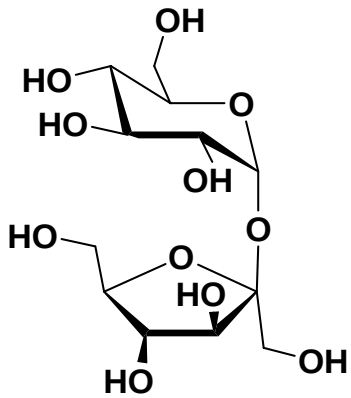
pGlu–His–Trp–Ser–Tyr–Gly–DLeu–Arg–Pro–NH—



pGlu = pyroglutamate = 5-oxoproline

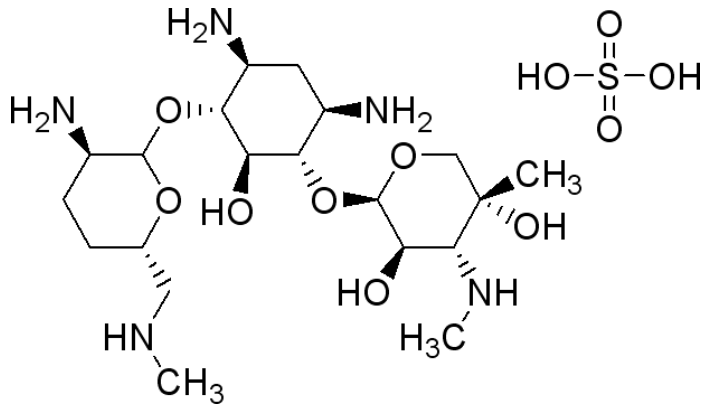
Examples of biomolecules – oligosaccharides

Disaccharides - sucrose



Gentamicin

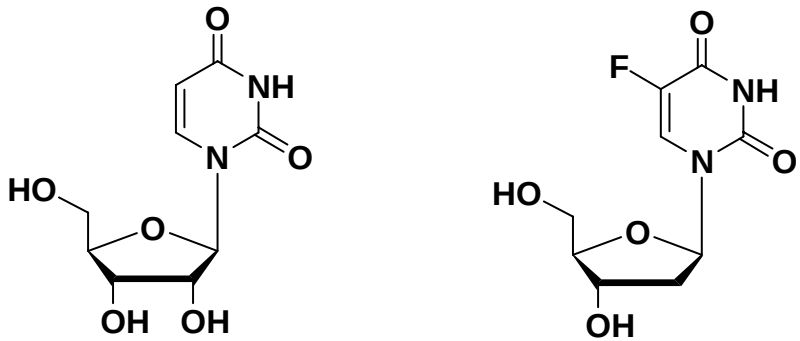
- antibiotic



Examples of biomolecules – nucleoside analogues

5-Fluorodeoxyuridine (Floxuridine)

- A pyrimidine based antimetabolite



SUMMARY

Properties of biomolecules:

1. Have a directionality
2. Contains information
3. Consist of a 3-dimensional architecture
4. Interact through structural complementarity

As organic chemists, we want to synthesize and modify biological macromolecules.