CHEMISTRY

THEORY PAPER: Theoretical organic chemistry-II

(as per Model CBSGS curriculum)

M.Sc. (Prog.) Semester IV

Supramolecular chemistry

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TITLE:	**Supramolecular Chemistry**
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Suggested Readings:

- Supramolecular Chemistry; Concepts and Perspectives, J. M. Lehn, VCH.
- Crown ethers and analogous compounds, M. Hiraoka, Elsevier, 1992. 30.
- Large ring compounds, J.A.Semlyen, Wiley-VCH, 1997. 31
- Bioorganic, Bioinorganic and Supramolecular chemistry, P.S. Kalsi and J.P. Kalsi. New Age International Publishers
- Principles and Methods in Supramolecular Chemistry by Hans-Jörg Schneider & Anatoly K. Yatsimirsky
- Applications of Supramolecular Chemistry by Hans-Jörg Schneider

Web-links:

- https://youtu.be/LR1Uc_sOqmk
- https://en.wikipedia.org/wiki/Supramolecular_chemistry
- https://en.wikipedia.org/wiki/Self-assembly
- https://en.wikipedia.org/wiki/Self-organization
- https://en.wikipedia.org/wiki/Host%E2%80%93guest_chemistry

Activities:

- Tell your students to find different types of bonding.

Table of Contents

SYLLABI OF THIS MODULE:

Supramolecular Chemistry

2.1 Supramolecular Chemistry

- 2.1 Principles of molecular associations and organizations as exemplified in biological macromolecules like nucleic acids, proteins and enzymes.

Learning outcomes:

Upon completion of this course, student will be able to

- Learn about the basics of supramolecular chemistry.
- Know about non-covalent interactions.
- Understand the concepts of self-assembly and self-organization.

Introduction:

SUPRAMOLECULAR CHEMISTRY

- Jean-Marie Lehn, Nobel prize winner in 1987, together with Cram and Pedersen.
- Chemistry beyond the molecule and involve noncovalent association between different molecules.
- This branch of chemistry predominantly based on weak and reversible interaction between molecules: i.e. electrostatic interaction, Hydrogen bonding, Van der Waals interactions, π-π interactions, ion-dipole interactions, etc.
- Naturally occurring macromolecules like enzymes and membrane receptors have been a great source of inspiration in the design of supramolecular systems.

- The terms *receptor* and *substrate*, taken from natural systems which are still commonly used to indicate two different molecular units interacting by means of non-covalent interactions.
- The *receptor* is the bigger molecular unit whereas the *substrate* is the smaller one.
- It was necessary at some point to distinguish between natural and artificial supramolecular systems.
- Therefore the terms *host* and *guest* were introduced by Cram, generally used to describe the *receptor* and the *substrate* respectively.
- The *host* is the organic molecule containing convergent binding sites and the *guest* is the molecules or ions containing divergent binding sites.

Non-Covalent Interactions:

- Non-bonded interactions are susceptible to thermal fluctuations and other external factors unlike covalent linkages.
- Weak forces are able to form strong intra and intermolecular interactions only upon working together or in combination with a covalent binding.
- They are most found every where in nature and are crucial in determining the three-dimensional structures adopted by proteins and nucleic bases.
- Depending upon the origin, non-covalent interactions are divided into the following sub classes.

A) Electrostatic Interactions:

- Electrostatic or Ionic interactions are strong coulombic attractive forces between opposite charges, observed in the case of several receptors, such as cations and anions, binding effectively to the corresponding guest in place.
- This type of interaction is non-directional, whilst for the ion-dipole interactions the dipole must be suitably aligned for optimal binding efficiency. The high strength of electrostatic interactions has made them an invaluable tool amongst supramolecular chemists for achieving strong binding.
- Ionic interactions are basically of two types; the classic ionic bond which is a non-directional attractive force, for example between a positively charged metal ion and negatively charged non-metal, and the salt bridge wherein there is a balance of the electrostatic forces between three or more atoms with partial charges.
- Such strong attractive interactions stabilize the host guest complex extensively.

Hydrogen Bonding Interaction:

- Hydrogen bonding is attractive electrostatic interaction between the hydrogen atom, bearing a partial positive charge, covalently attached to an electronegative atom and another electronegative atom which has a partial negative charge developed on it.
- Hydrogen bonding is the most widely employed dipole-dipole interaction in the field of supramolecular chiral discrimination.
- Most receptors have electronegative heteroatoms such as Nitrogen, Oxygen as binding sites involved in hydrogen bonding.

(B) **π-Electronic Interactions:**

(a) **π-π Interaction :**

- π-π Interactions are rather weak bindings occurring in the face-to-face or edge-to-face or edge-to-edge manners, which play a major role in many aspects of biological, solid-state and host-guest supramolecular chemistry.
- The quadrupole–quadrupole forces are responsible for the π-π stacking of aromatic rings.
- Aromatic rings such as benzene, naphthalene, pyridine, imidazole, triazole, indole etc. are often incorporated into the chiral macrocycle for increasing the capacity for chiral recognition to a greater extent owing to the π-π stacking interaction of the host and guest systems.

(b) Cation–π Interaction:

- The interaction between a cation and delocalized π-electron cloud of the aromatic system exhibits the cation-π interaction.
- The simplest view of this non-bonding interaction is in the gas phase.
- In this case, there is no solvent and stabilization of the system is entirely dependent on the cation and π system of interest.

- The cation-π interactions between the hydrogen-bonded ammonium ion and the aromatic ring of host, exemplifies the chiral recognition of organic ammonium ions by various chiral receptors.

(C) Van der Waals Forces:

- Van der Waals forces are an attractive noncovalent type of interactions between the fixed dipole in one molecule and induced instantaneous oscillating dipole in another molecule via the corresponding distortion of electron clouds.
- These forces though underappreciated, are of immense importance to the supramolecular properties of all molecules.
- However, it is difficult to rationally design the receptors specifically, as this type of interactions is very common to most molecules.
- The binding of guest into the hydrophobic cavity of host is driven by an enthalpy stabilization. Therefore, even small molecules can make a large number of the Van der Waals contacts and each of them add in a synergistic manner.
- Additionally, there is one specific subclass in this category called the "London dispersion forces" and attributed to two induced dipoles.

(D) Hydrophobic Interactions:

- Hydrophobic interactions are a result of the nonpolar side chains (aromatic rings and hydrocarbon groups) aggregate tightly in polar solvents, especially water and exclude water molecules.
- In this case, there is no sharing of electrons between any groups, therefore it does not produce a true bond.
- The hydrophobicity of receptors can be manipulated by introducing long side chains.
- On binding of a guest, the water molecules around a polar surface of the hydrophobic cavity of the host are released into the bulk solvent, which in turn leads to enhancement of its hydrogen bonding capabilities simultaneously increasing the entropy of the system.
- The hydrophobic interactions are comparatively stronger than Van der Waals forces or Hydrogen bonding. For example, cyclophanes and cyclodextrins being macrocyclic itself possess inbuilt hydrophobicity contributing to the host-guest affinity and are well-designed to encapsulate guest molecules from an aqueous solution.

Nucleic Acids

- DNA and RNA have great chemical similarities.
- In their *primary structures* both are linear polymers (multiple chemical units) composed of monomers (single chemical units), called nucleotides.
- Two major classes of nucleic acids; (1) deoxyribonucleic acid (DNA): carrier of genetic information; (2) ribonucleic acid (RNA): an

intermediate in the expression of genetic information and other diverse roles.

- Cellular RNAs range in length from less than one hundred to many thousands of nucleotides.
- Cellular DNA molecules can be as long as several hundred million nucleotides.

Structure of Nucleic Acid:

- The monomeric units for nucleic acids are nucleotides. Nucleotides are made up of three structural subunits

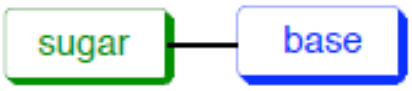
1. Sugar: ribose in RNA, 2-deoxyribose in DNA

2. Heterocyclic base

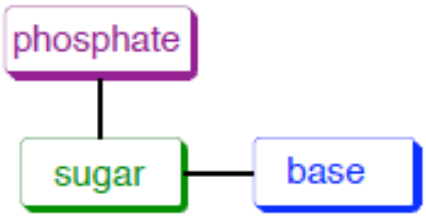
3. Phosphate

- Nucleoside, nucleotides and nucleic acids

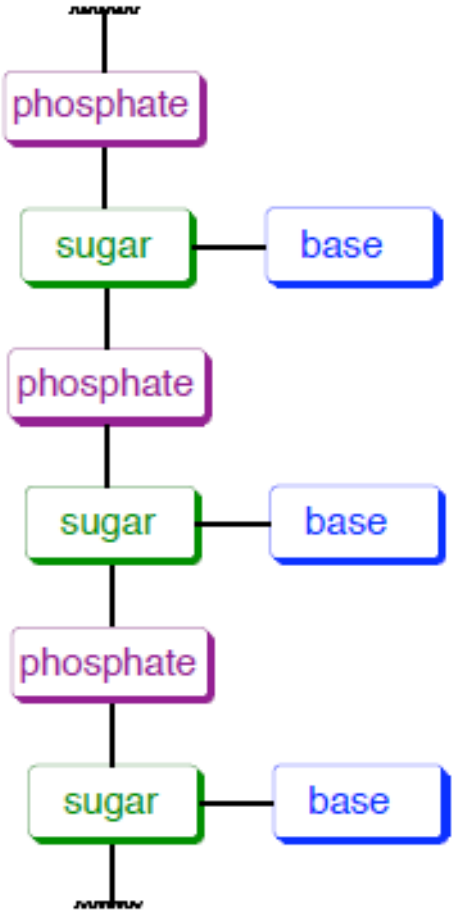
Nucleoside



Nucleotides

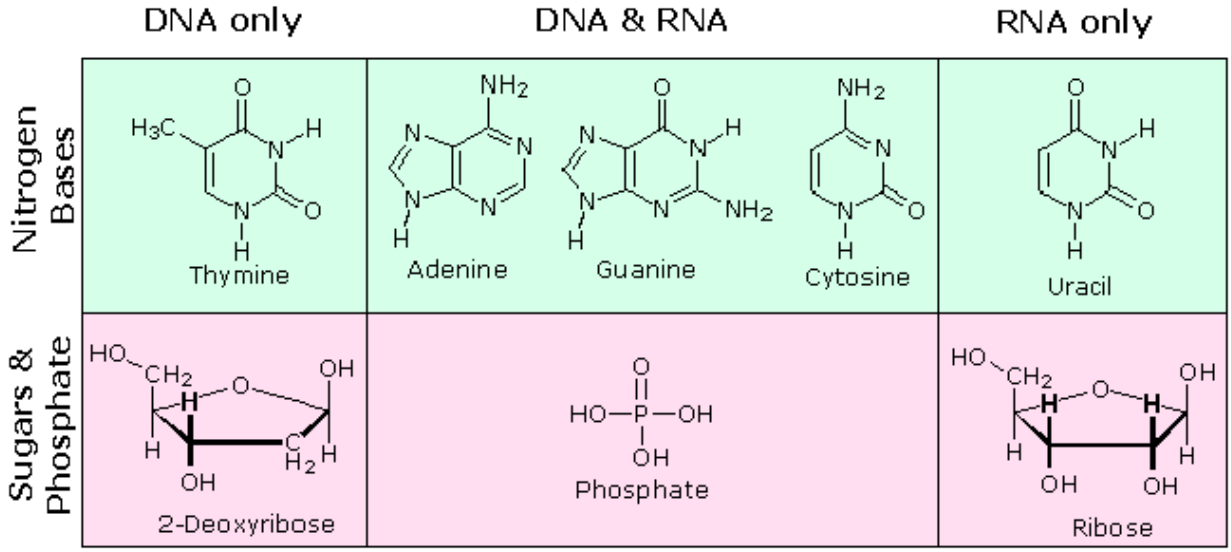


Nucleic acids

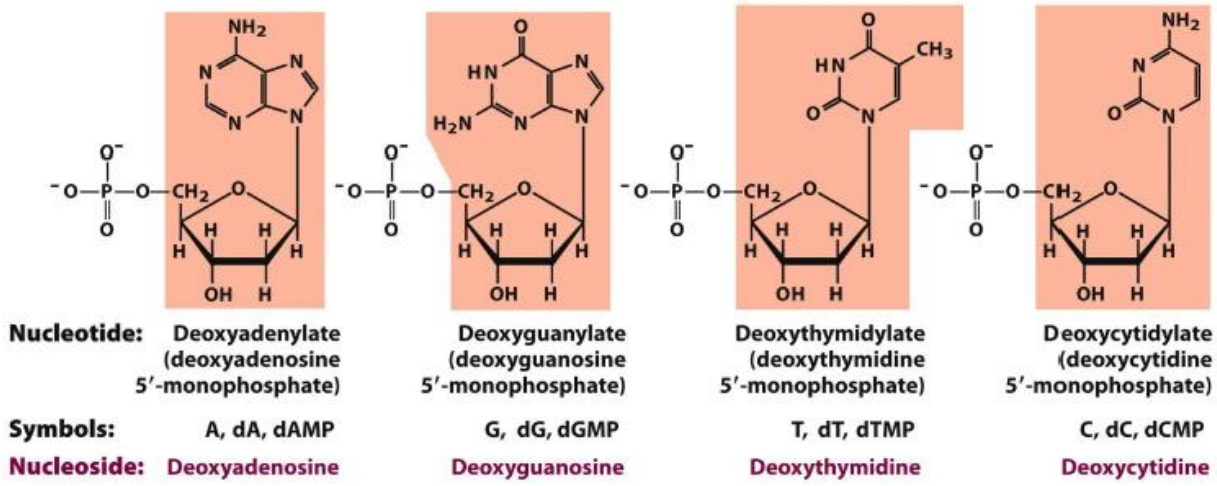


- The chemical linkage between monomer units in nucleic acids is a phosphodiester

Components of Nucleic Acid

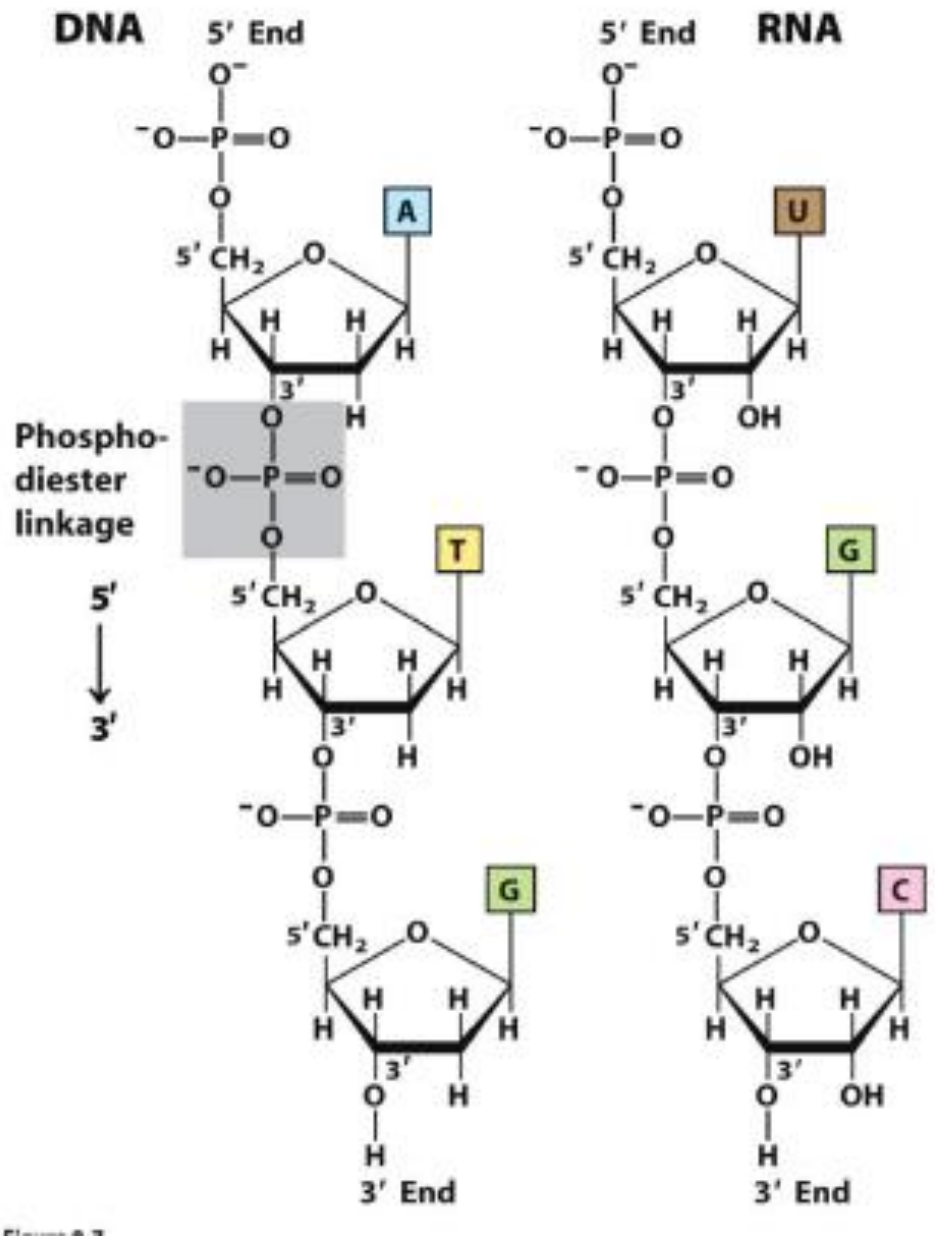


Nomenclature: Deoxyribonucleotides



Deoxyribonucleotides

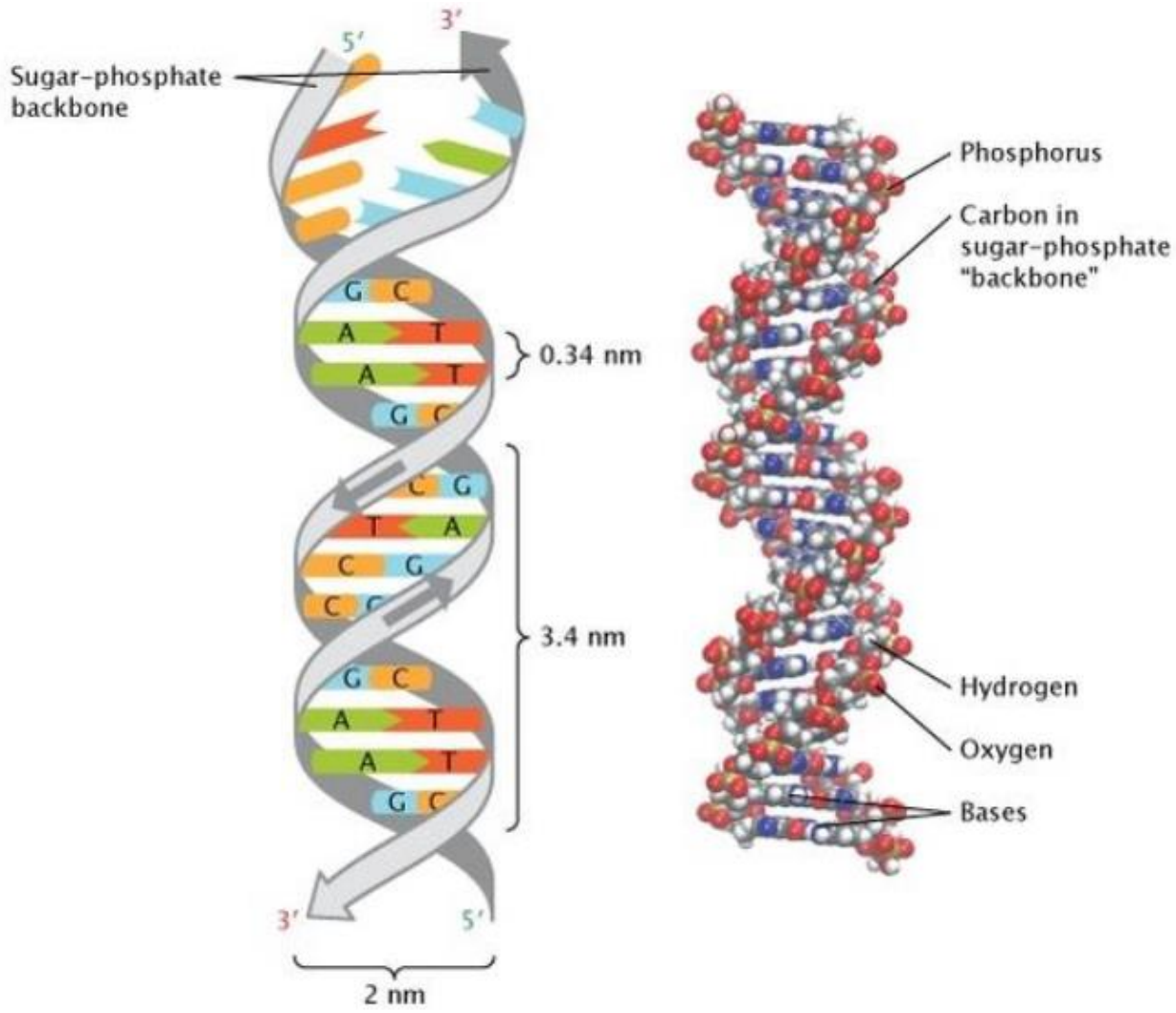
- Polymerization of nucleotides takes place by esterification of 3'-OH group of one nucleotide with 5'-phosphoryl group of another giving rise to phosphate bridges and nucleic acid.
- The strand has two terminals, one ending with a phosphate group at C-5' (5'-end) and the other ending with a free –OH group at C-3' (3'-end).

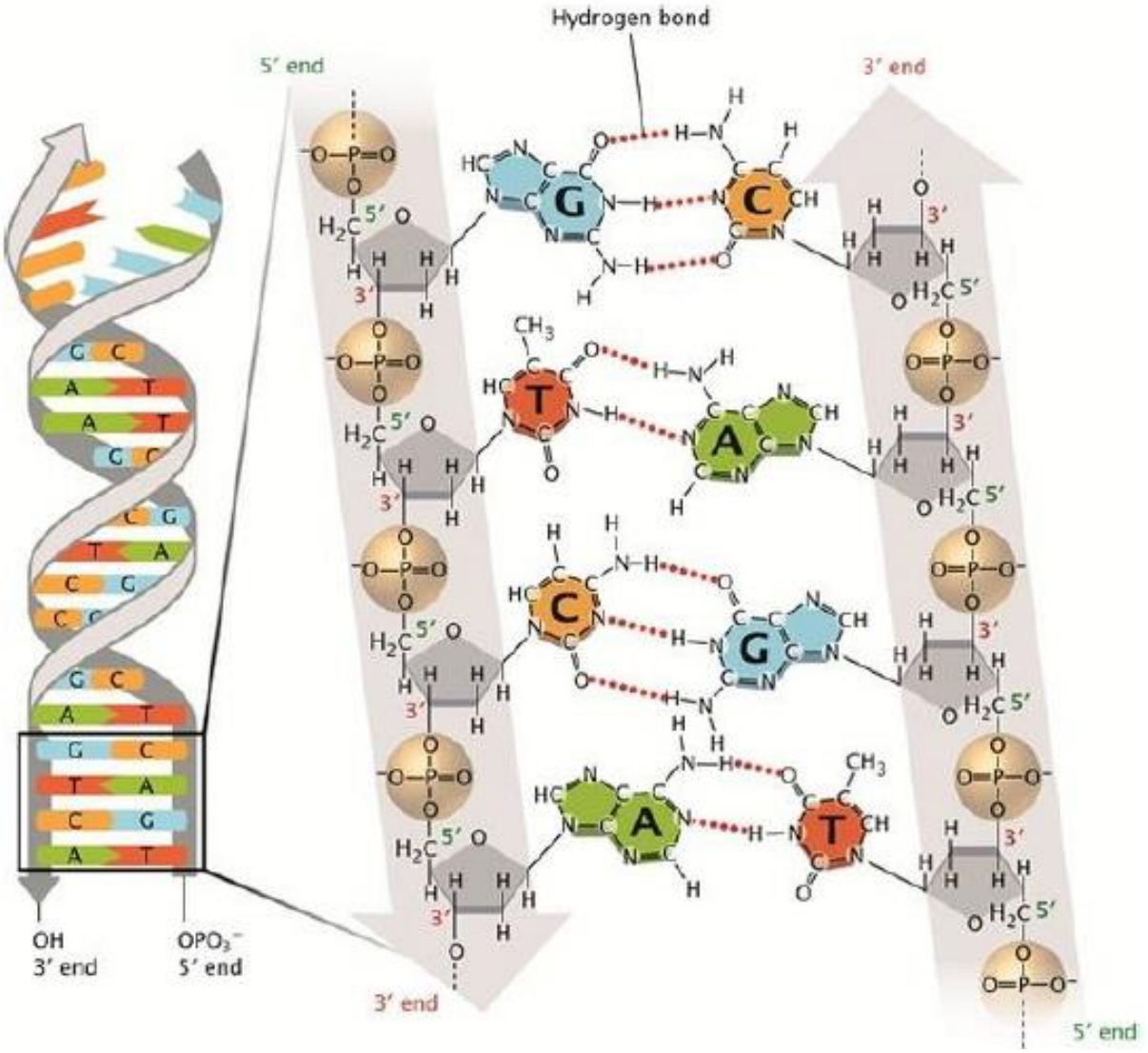


Formation of double helix:

- The detailed structure of DNA has been worked out by Watson and Crick (1953) who established that a pair of DNA strands coil around a common axis to form a right handed double helix, often called a duplex.
- The two strands in the duplex run in opposite directions i.e. their 3' and 5' ends are oppositely directed as shown in figure.
- The geometry of duplex is determined by the shape of pentose ring, the disposition of the bases along the strand, and the conformation of the phosphate linkage.
- The helix is 2.0 nm in diameter and complete turn is 3.4 nm in length containing ten nucleotide units.

- The two strands are complementary to each other and molecular recognition is established through (i) hydrogen bonding (edge to edge) between specific base pairs situated in opposite strands and (ii) The stacking interactions between the hydrophobic heterocyclic bases.





- The covalent backbone of the DNA strands with alternating deoxyribose and negatively charged phosphate groups are hydrophilic and so directed outwards facing the surrounding water while the bases are stacked inside the double helix away from water with their planes perpendicular to axis of the helix.
- The hydrophobic character common to them makes a major contribution to the stability of the double helix in aqueous medium.
- The distance between the planes of two adjacent bases in the same strand is 0.34 nm.
- The two antiparallel DNA strands in a duplex are not identical either in composition or in the base sequence but they are complementary to each other in the sense that adenine (A) in one strands faces thmine (T) in the other and so does guanine (G) in one with cytosine (C) in the other separated by distances which permit formation of two and three hydrogen bonds respectively without any steric constraint.

- The spacing between two strands also leaves two grooves, one major and another minor.

Replication of DNA:

- Reproduction is fundamental to all living systems
- Regardless of the reproductive mechanism a method must exist to transfer genetic material from one generation to the next.
- DNA must copied (replicated) in a manner that minimizes mistakes.
- Damage to DNA must be repaired to prevent that damage from being transferred to the next generation.
- Watson & Crick (1953) - proposed DNA structure & suggested how it might "self duplicate“
- *Possible copying mechanism for the genetic material*

(A) Suggested that replication occurred by gradual double helix strand separation via successive breakage of H bonds, much like the separation of the two halves of a zipper.

(B) Since each strand is complementary to the other, each has the information needed to construct the other; once separated, each strand can serve as template to direct the formation of the other strand.

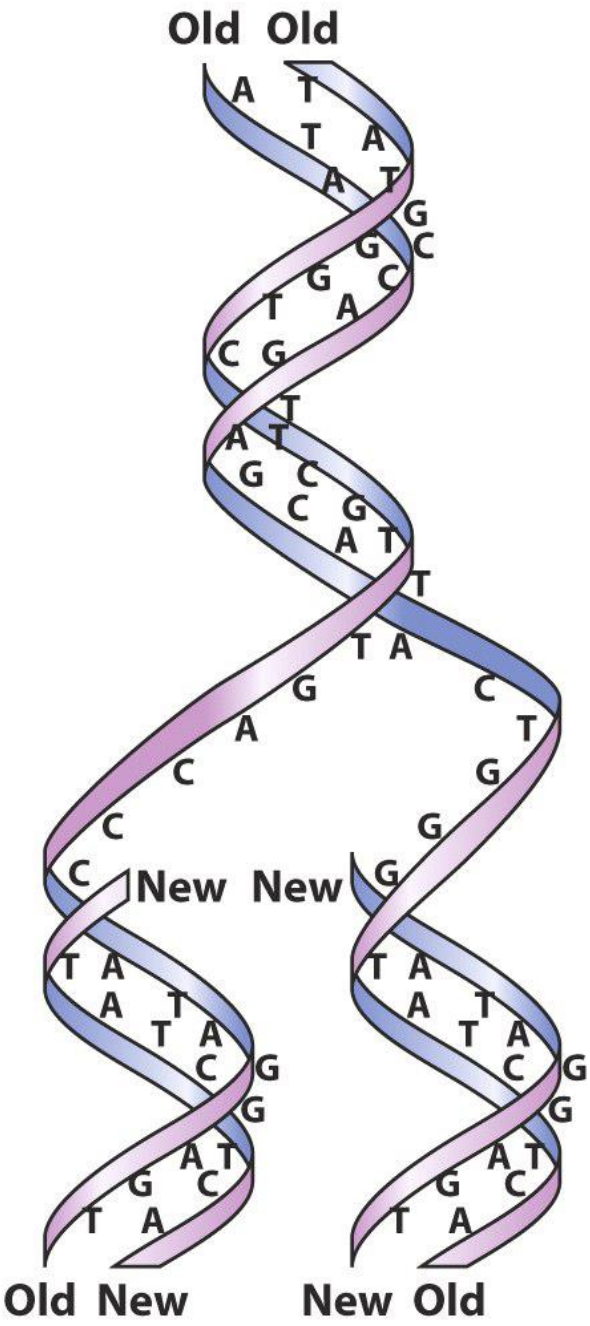


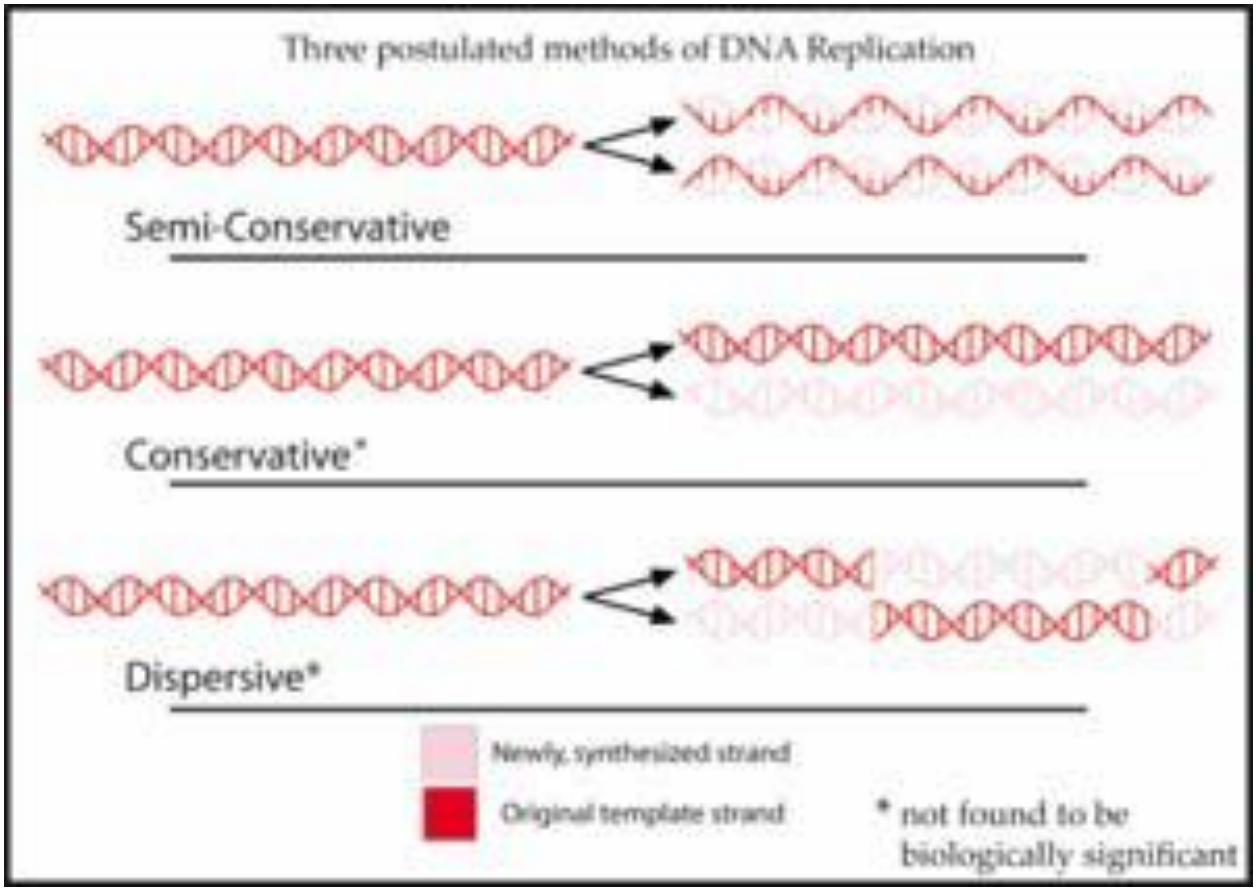
Figure 13-1 Cell and Molecular Biology, 4/e (© 2005 Jo

Possible types of DNA replication

1. Semiconservative – daughter duplex made of one parental & one newly synthesized strand

– 2. Conservative - 2 original strands stay together after serving as templates for 2 new strands that also stay together; *one contains only "old" DNA, the other only "new" DNA*

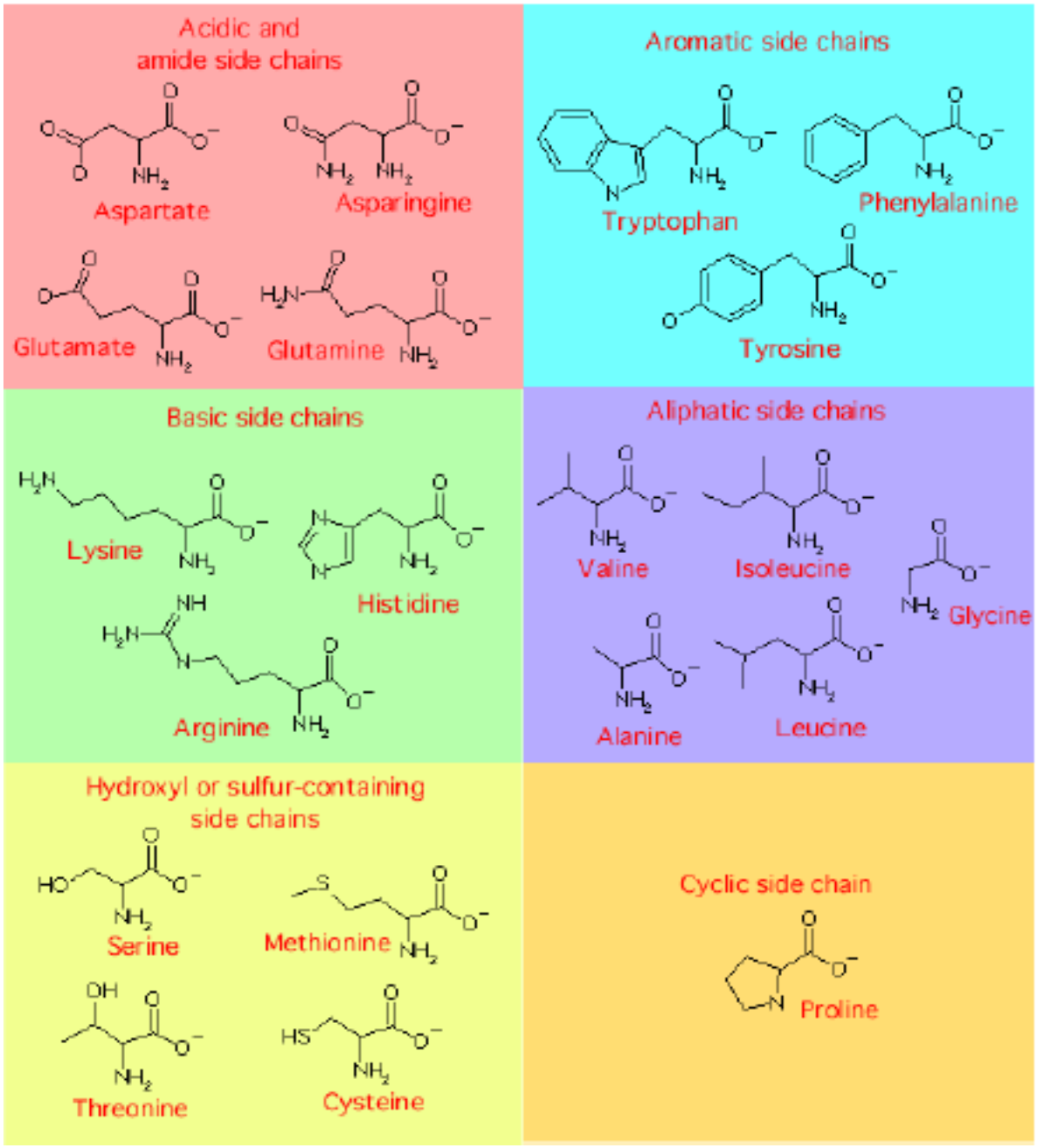
– 3. Dispersive – integrity of both parental strands disrupted; new duplex strands made of old & new DNA; *neither the parental strands nor the parental duplex is preserve.*



Proteins and Enzymes

- Proteins are the most abundant macromolecules present in cells by which genetic information is expressed.
- There are thousands of different kinds of proteins each designed to carry out a specific function.
- In spite of their diversity of functions, the proteins are built from the same twenty alpha amino acids joined through peptide linkage forming long peptide chain which is the primary structure of all proteins.

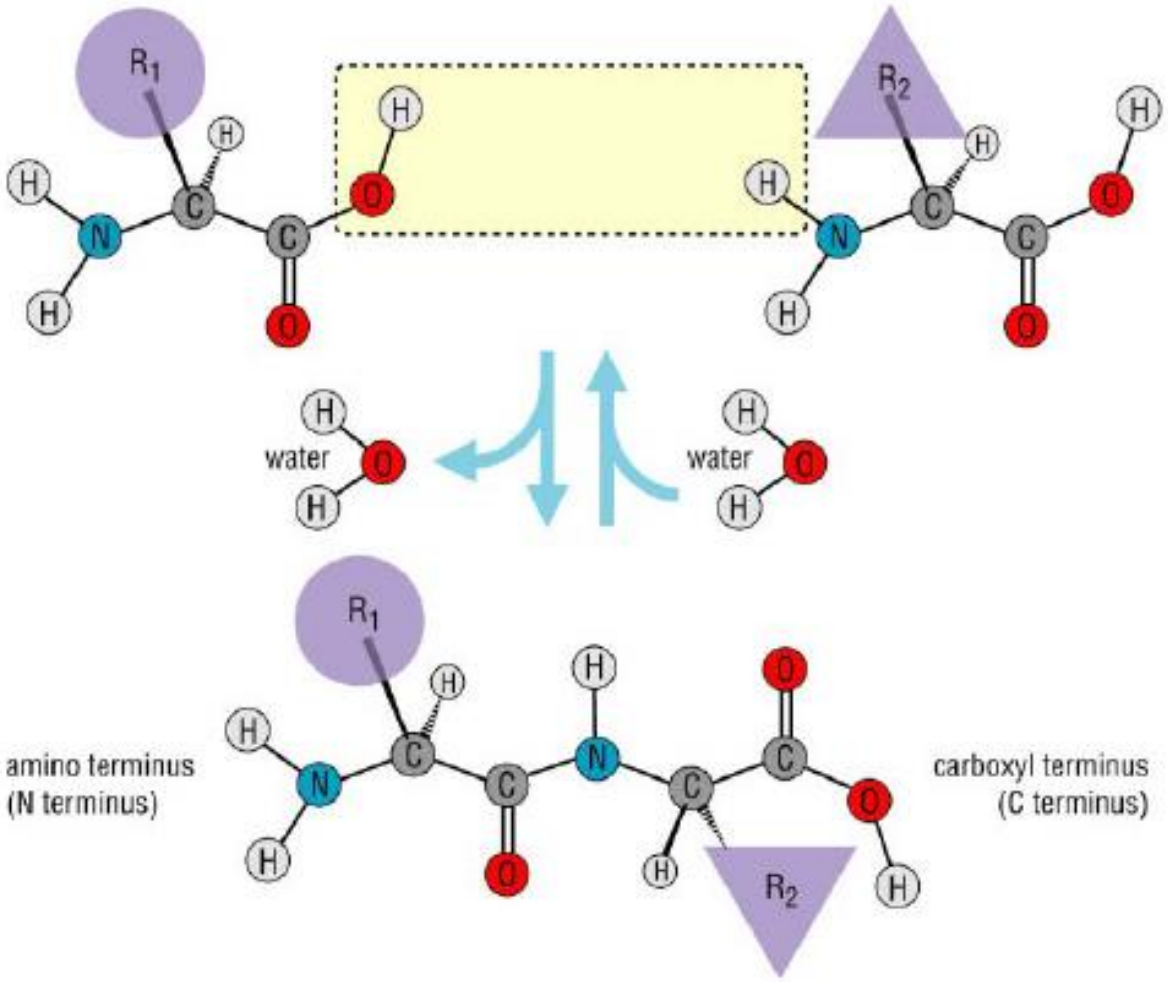
Their specific properties and functions are determined by the amino acid sequences in the chain as well as by the secondary, tertiary, and quaternary structures stabilised by noncovalent forces.



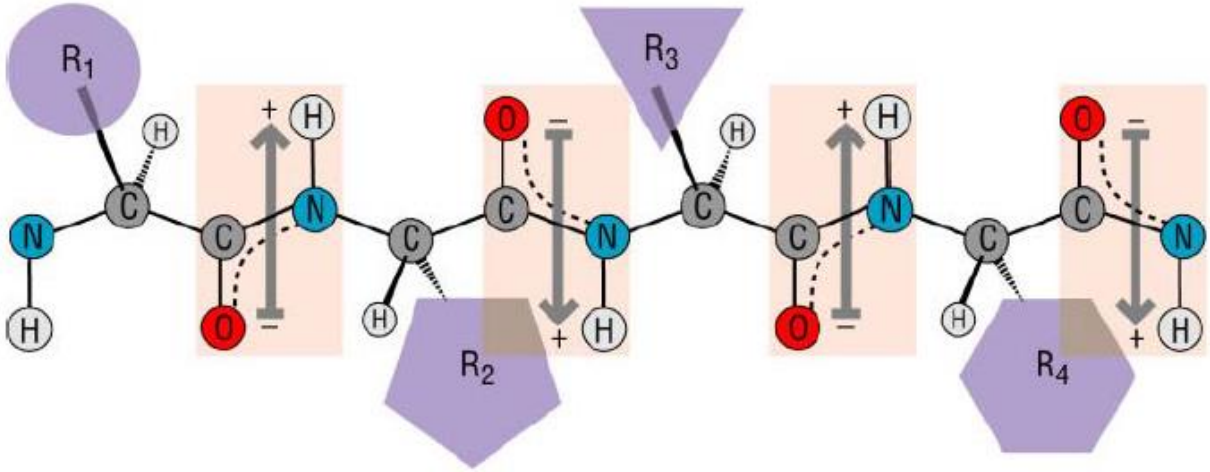
Structure of Protein:

The Peptide Bond:

To make a protein, these amino acids are joined together in a polypeptide chain through the formation of a peptide bond.



Primary Structure

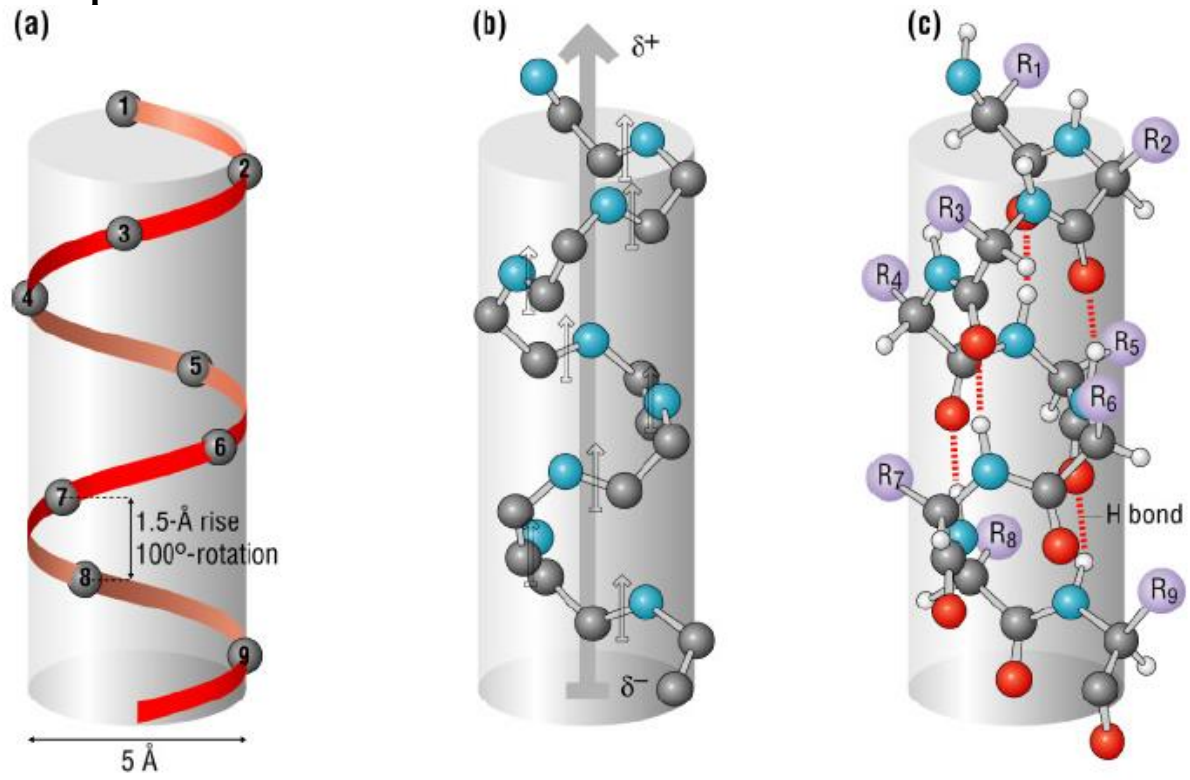


Characteristics of the extended polypeptide chain are as,

- It consist only of L-alpha amino acids and the polymer chain is therefore, isotatctic.
- Due to partial double bond character of the amide C-N bond, the peptide moiety is planar and rigid with C=O and N-H bonds oriented in opposite directions (trans).

- The substituents R (the side chains) introduce steric and electro-static interactions which may not be compatible with the extended planar conformation beyond certain length.
- Finally, the C=O and N-H are capable of forming intra and interchain hydrogen bonds which stabilise only a few selected conformations. One such conformation is known as alpha helix which is formed by coiling the polypeptide chain around an axis to give a rodlike structure with the R groups projecting outwards.
- The helix is mostly righthanded. Each coil of the helix is 0.54 nm in length and contains 3.6 amino acid residue.
- The helical shape is maintained primarily by intrachain hydrogen bonds, each of approximately 20kJ mol-1 of energy, formed between amide C=O and N-H groups 3.6 units away making 13-membered ring.

The alpha helix



- Other interactions are hydrogen bondings between side chains, S-S cross –links, and ionic bonds between RCO2- and RNH3+ in the side chains.
- In addition of the alpha helix, there exists a second conformation known as beta sheet or pleated sheet in which polypeptide chains are arranged side by side, antiparallel to each other, and held together by interchain hydrogen bonds, as in silk fibroin.
- Further, folding of alpha helix upon itself gives globular proteins with spherical shape known as tertiary structure in which the polar hydrophilic side chains project outwards to increase of solubility in

water while the nonpolar hydrophobic side chain lie within the sphere forming hydrophobic packets.

- The surfaces of a globular protein can thus recognise their complementary molecules.
- In oligoproteins containing two or more different polypeptide chains, there exists yet another level of confprmation, known as quaternary structure in which the subunit interact with one another.

Enzymes and Catalytic Activity

- ***Enzymes*** are proteins with molecular weights of 12000-100000 daltons or even more and are the most remarkable catalysts enhancing the reaction rates by a factor 10^{8}-10^{20} and exhibiting almost total substrate and product selectivity.
- An enzyme (E) first forms a complex (ES) with the substrate (S) in a first and reversible step followed by a relatively slow step in which the ES complex breaks down into the product (P) and enzyme is set free.
- In every enzyme, there is an active site where the actual reaction takes place either through general acid-base catalysis (R groups in proteins may be acidic or basic) or with the help of prosthetic group called cofactors.
- Many enzymes are conjugated proteins that require nonprotein portions known as ***cofactors***.
- Some cofactors are metal ions, others are nonprotein organic molecules, bound loosely or covalently to the enzymes called ***coenzymes***.
- Organic cofactors such as vitamins are called coenzyme.
- Recognition between an enzyme and a substrate to form the ES complex is established by noncovalent forces.
- More often, an enzyme is folded into a conformation to generate a pocket or pockets in which the complementary substrate or its subunit fits in and the susceptical bond in the substrate is brought into close proximity and right orientation to the active site and the reaction goes easily.
- In many cases, the enzyme or the substrate or both have to distort their relaxed conformations in order to be complementary to each other.
- E.g. dehydrogenation of succinic acid into fumaric acid by succinate dehydrogenase provides an example in which the active site consists of coenzyme, flavin adenine dinucleotide (FAD) covalently bonded to the enzyme.
- Two electrophilic pockets as shown schematically in figure are created in the enzyme which are so spaced that not only the two CO2- groups of succinic acid fit in there but the CH2-CH2 chain comes into juxtaposition with the reactive group of the coenzyme.

- FAD here acts as an oxidising agent and abstract two hydrogens from adjacent carbon atoms stereoselectivity to give fumaric acid and FADH2 without a trace of maleic acid.
- A similar oxidation-reduction process carried out by yeast alcohol dehydrogenase with NAD-NADH acting as the coenzyme system.

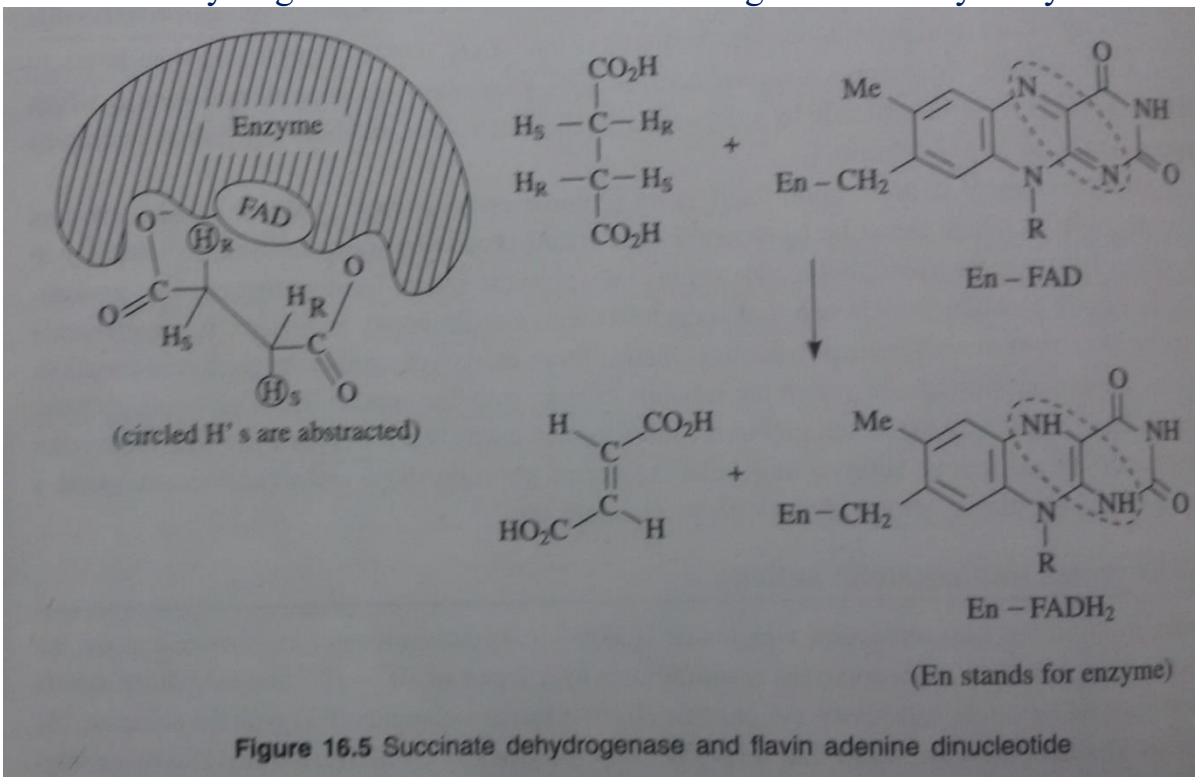


Figure 16.5 Succinate dehydrogenase and flavin adenine dinucleotide

- In the enzymic dehydrogenation, if other dicarboxylic acids of approxiamately the same size such as malonic acid and oxalic acid are added, the reaction is inhibited.
- These inhibitors compete with succinic acid in the formation of complex with the enzyme but themselves are not hydrogenated.
- Enzyme inhibition works on the principle of molecular recognition and very often the nature of the inhibitors gives valuable information regarding the active site of an enzyme.

Summary:

- Supramolecular chemistry deals with the organized chemical species of greater complexity than molecules themselves, which are held together and organized by means of intermolecular (non-covalent) binding interactions.
- The supramolecular chemistry generally concerns non-covalent bonding interactions such as ion-ion interactions, ion-dipole interactions, dipole-dipole interactions, hydrogen bonding, cation-π interactions, anion-π interactions, π-π interactions, closed shell interactions, Van der Waals forces and crystal close packing.
- In general, supramolecular chemistry involve the self-assemble and host-guest systems using a variety of interactions, some of which are clearly non-covalent (e.g. hydrogen bonds) and some of which possess a significant covalent component (e.g. metal–ligand interactions).
- Self-assembling systems do not involve hosts and guests but rather selfcomplementary molecules or complementary partners (tectons).
- In host-guest compounds a host component with convergent binding sites and a guest component with divergent binding sites are involved.