

International Institute of Information Technology, Hyderabad
 (Deemed to be University)
SC3,321: Biomolecular Structure Interaction and Dynamics
Question cum Answer Booklet

End Semester Examination Monsoon 2024**Max. Time: 180 Min (3 Hrs)****Max. Marks: = 100**Roll No: 2021102033Programme: PCFDate of Exam: 28/11/24Room no: H-104 Seat No: C-6Invigilator's Signature: S. S. S. S.

Special Instructions about the exam (Example: Open book, Laptop, Calculator and etc.,)
CLOSED BOOK!

1. Answer ALL questions. Each question is for 10 marks. Also 2 BONUS Qns.
2. Answer 'within' the given space. The page behind this page is for Rough work.
3. One extra page for spill-overs. NO other EXTRA SHEETS to be used.
 Additional sheet for rough work is NOT allowed.

Marks Table (To be filled by the Examiner)

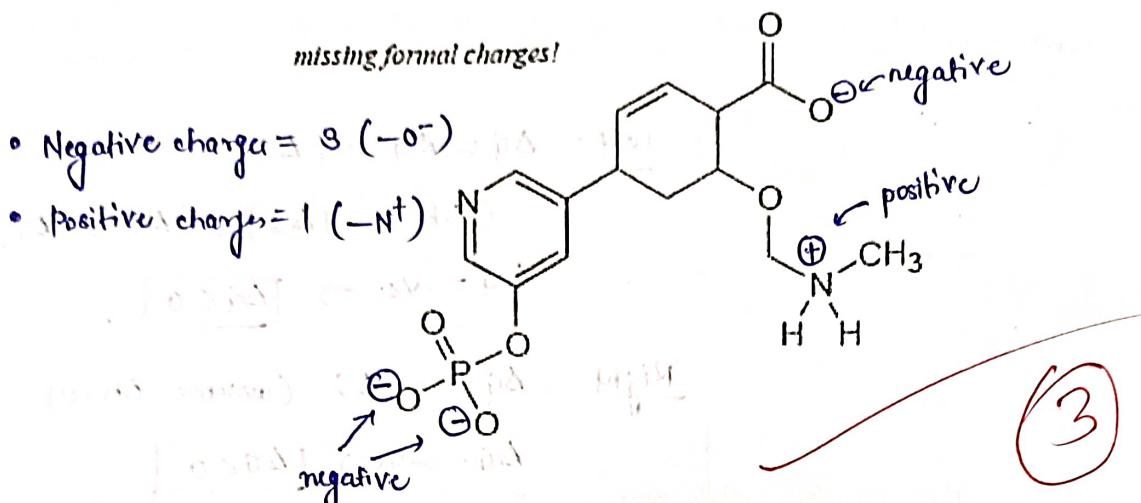
Question No / Marks	Course outcome number(s)							Name of the Examiner who marked
1	CO-1							
2	CO-1							
3	CO-3							
4	CO-2							
5	CO-1							
6	CO-3							
7	CO-4							
8	CO-1							
9	CO-2							
10	CO-3							
11	CO-4							
12	CO-1							

General Instructions to the students

1. Place your Permanent /Temporary Student ID card on the desk during the examination for verification by the Invigilator.
2. Reading material such as books (unless open book exam) are not allowed inside the examination hall.
3. Borrowing writing material or calculators from other students in the examination hall is prohibited.
4. If any student is found indulging in malpractice or copying in the examination hall, the student will be given 'F' grade for the course and may be debarred from writing other examinations.

Q1. a) Add non zero formal charges to the molecular structure drawing below:

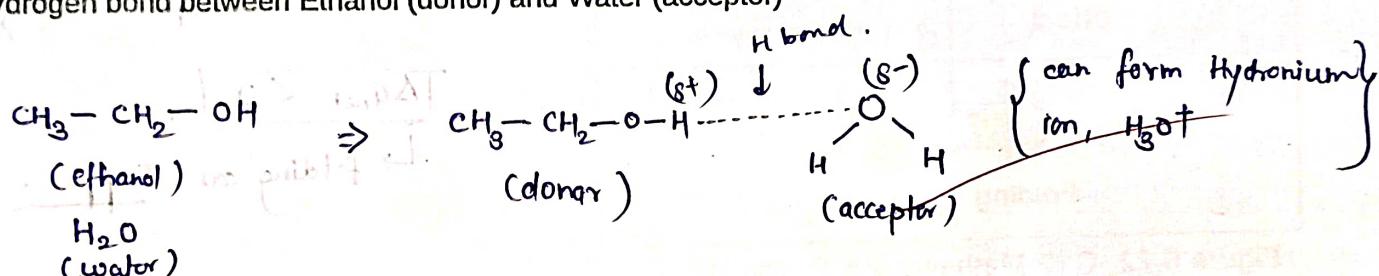
[3]



Q1 b) Draw structures that show:

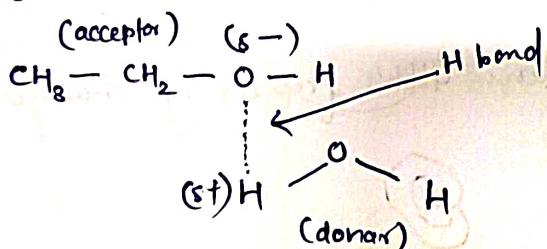
i) A hydrogen bond between Ethanol (donor) and Water (acceptor)

[1+1]



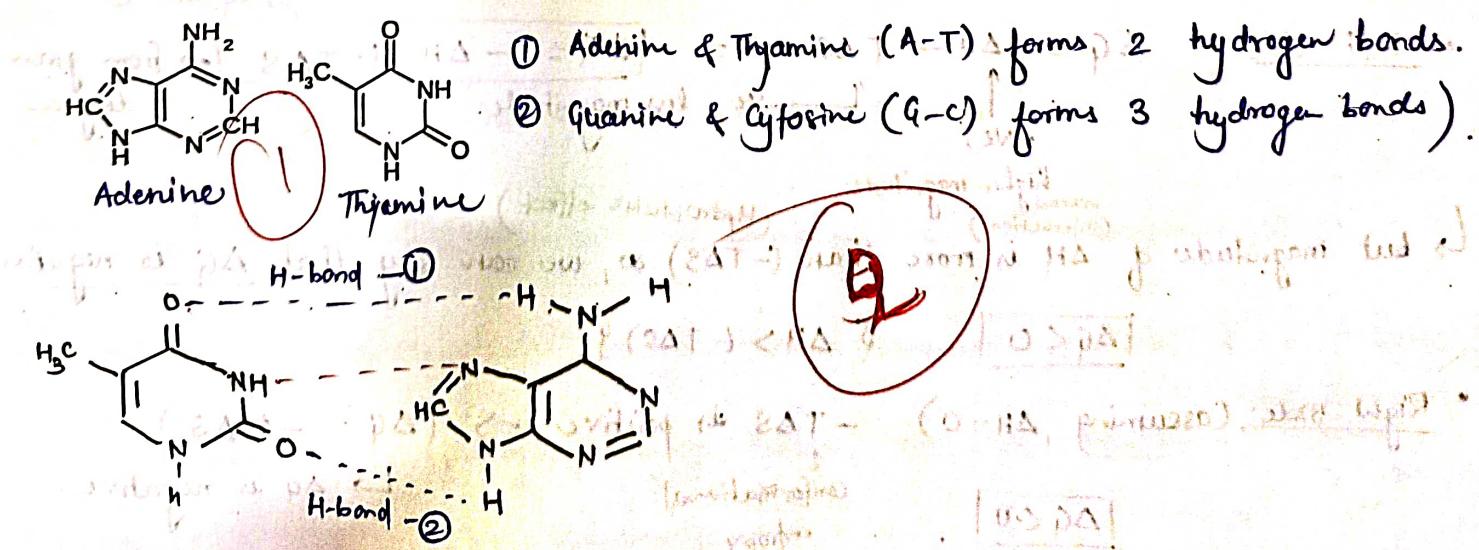
ii) A hydrogen bond between Ethanol (acceptor) and Water (donor)

(2)



iii) Name the nucleic acid bases below and draw a base-pair between them

[1+4]



Q2. See the thermodynamic view of the folding reaction $U \rightleftharpoons F$, and explain the sign and magnitude of each 'arrow' in one sentence each. [10]

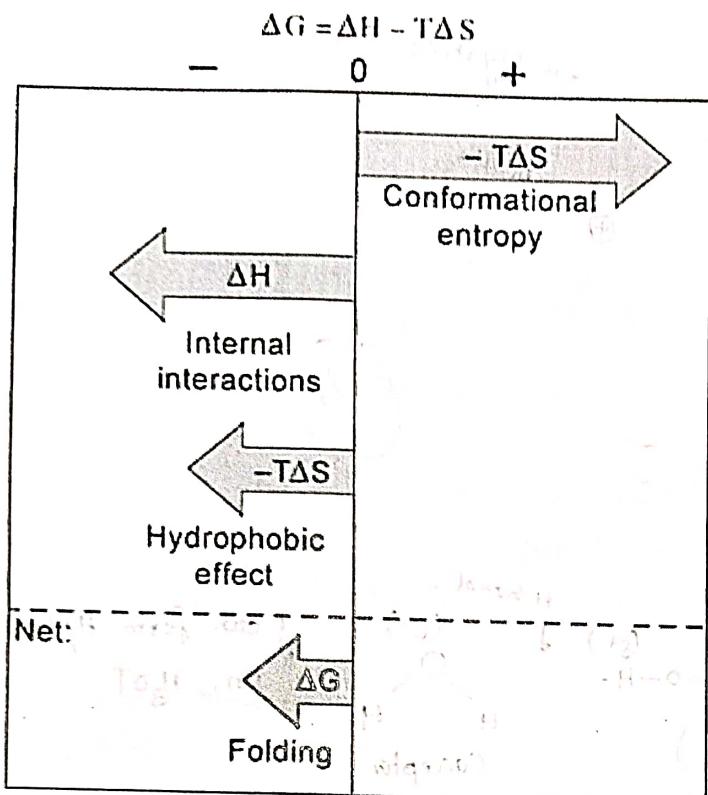
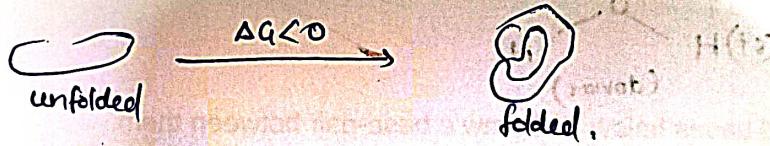


Figure 6.22, C.K. Mathews & K.E. van Holde, Biochemistry, 2nd edition (1996)

Ans: Protein folding is favourable when Gibbs free energy change i.e., ΔG is negative.



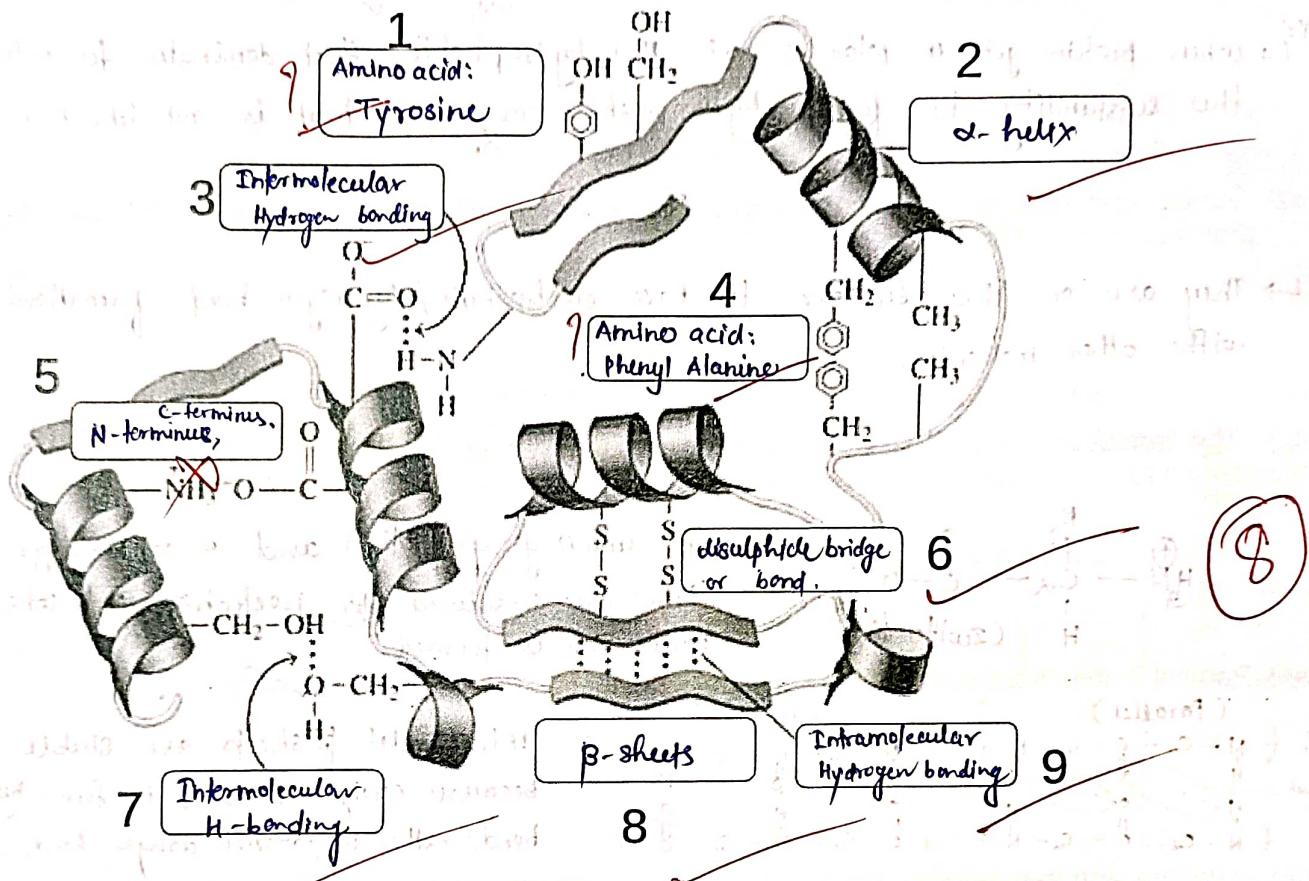
Left side: $\Delta G = \Delta H - T\Delta S \Rightarrow \boxed{\Delta G = 0 - \Delta H + T\Delta S}$ → from given diagram
 \uparrow +ve, less magnitude
 \uparrow higher magnitude (internal interaction)
 \uparrow (Hydrophobic effect)

\hookrightarrow but magnitude of ΔH is more than $(-T\Delta S)$ so, we can say that $\boxed{\Delta G < 0}$.

Right side: (assuming, $\Delta H=0$). $-T\Delta S$ is positive $\Rightarrow (\Delta G = -T\Delta S)$
 \downarrow Conformational entropy.
 $\boxed{\Delta G < 0}$
 $\hookrightarrow \Delta G$ is negative.

\therefore left side is negative & right side is negative so, net (ΔG is also negative) and protein folding is favourable.

Q 3. Study the schematic image of a protein structure below. There are several grey boxes corresponding to structure or type of interaction next to them or indicated by lines/arrows. Fill up the boxes with the appropriate names of interactions, bonds or structures. [10]
You may also write the answers below the picture if the box-space is insufficient.



- ① $-\text{CH}_2-\text{C}(\text{O})-\text{OH} \Rightarrow$ Amino acid: Tyrosine (γ)
- ② α - helix
- ③ Intramolecular Hydrogen bonding between α -helix and β -sheet (turn).
- ④ $-\text{CH}_2-\text{C}(\text{O})-$ \Rightarrow Amino acid: phenyl alanine (Γ)
- ⑤ $-\text{NH}_3^+$, $-\text{O}-\text{C}^{\text{II}}-$ \Rightarrow (N-terminus) & (C-terminus).
- ⑥ $-\text{S}-\text{S}-$ \Rightarrow disulphide bridge / bond between β -sheet & α -helix.
- ⑦ Intermolecular Hydrogen bonding between two α -helices.
- ⑧ β sheets
- ⑨ Intramolecular Hydrogen bonding between two (α -helices) β -sheets.

Q4. a) State (Tick the box) whether the following statements are true or false. If false then write down the correct statement. In either case write one sentence only. [5x1]

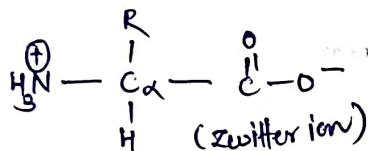
a1) The hydrophobic effect dominates the process of protein folding because when hydrophobic groups come together, a lot of heat is liberated. True False

~~False~~ when protein gets in polar solvent the hydrophobic effect dominates to reduce the instability to form hydrophobic core but heat is not liberated.

a2) Amino acid residues with charged side groups are usually more conserved in the core of proteins. True False

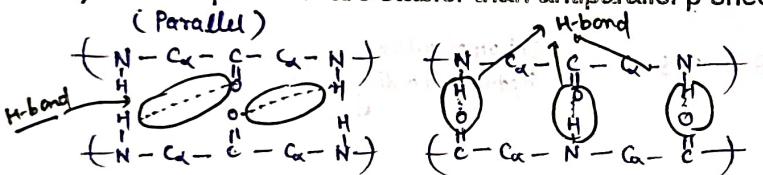
They are on the surface to have electrostatic/hydrogen bond formation with other molecules.

a3) The isoelectric point of an amino acid is always given as $(pK_1 + pK_2)/2$, where pK_1 and pK_2 correspond to the α -carboxy and the amino groups respectively. True False



→ for amino group (pK_2) and α -carboxy group (pK_1) these are considered for isoelectric point when the zwitter ion is formed.

a4) Parallel β -sheets are stabler than antiparallel β -sheets. True False



Antiparallel β -sheets are stable because straight & easier to form hydrogen bond, rather in parallel, dangle bond.

a5) Rotations and translations constitute the internal parameters of a molecule.

True False

→ Mainly 6 parameters → 3 rotational & 3 translational

3

Q4. b) Study the statements below carefully and answer each by ticking the appropriate box: [1x5]

b1) The side chains of the amino acids determine the shape and properties -- and thus the functions of proteins. True False → They define the function.

b2) Folded proteins are marginally stable. The hydrophobic effect plays a huge role in the stability of the folded protein. True False → very ~~less~~ or less stable and factor can influence and make them misfolded or unfolded.

b3) In the equation: $\Delta G = \Delta H - T\Delta S$, the value and sign of ΔG determines the state of an equilibrium reaction. What should be ΔG for the transformation Unfolded \rightleftharpoons Folded? $\Delta G = 0$; $\Delta G = \text{negative}$; $\Delta G = \text{positive}$

5

b4) Proteins do not sample every possible conformation in the time it takes them to fold, and sometimes folding must be catalyzed. True False

b5) Denaturation is often irreversible. True False → denaturation can be reversible also. { eg. Irreversible: coagulation of egg.

Reversible: Ribonuclease A if urea denaturates ribonuclease but can be renatured when urea is removed }.

Q5 a). Match the following [3]

- | | | |
|---------------|----------------------------|-------|
| a) Threonine | 1) Imidazole in side chain | [f] / |
| b) Cystine | 2) Secondary amine group | [d] / |
| c) Tryptophan | 3) Chiral side chain | [a] / |
| d) Proline | 4) Acidic amino acid | [e] / |
| e) Aspartate | 5) Disulphide bond | [b] / |
| f) Histidine | 6) Indole in side chain | [c] / |

[f] /
[d] /
[a] /
[e] /
[b] /
[c] /

(3)

Q5 b) From among the 20 naturally occurring amino acids identify the ones belonging to the following sets described using Boolean logic: [7]

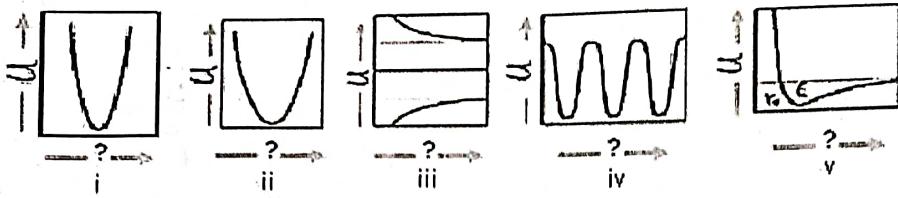
(i) Hydrophobic and small	Glycine	Alanine	Valine	
(ii) Aromatic or polar and not charged	Serine	Threonine	Tyrosine (aromatic)	
(iii) Neutral and polar	Cystine	Glutamine	Asparagine	
(iv) Polar negative and small	Glutamic acid	Aspartic acid		
(v) Surface and large	Phenylalanine	Tryptophan		
(vi) Helix breaker and helix initiator	Proline			
(vii) Small or medium	Isoleucine	Leucine	Threonine, cystine	Methionine
(viii) Large or hydrophobic	Lysine	Arginine	Histidine	
(ix) Large and polar	Tryptophan	Histidine		
(x) Side chain with chiral centre	Threonine			

$\text{G}-\text{H}$, $\text{Ala}-\text{CH}_3$
 Leu , Ile ,
 Ser , Thr , Iyr ,
 Lys , Glu , Asp ,
 Asn , Gln , Arg ,
 His , Pro , Cys ,
 Met , Tyr , Phe ,
 Val .

(7)

Q6. While estimating the potential energies of different configurations of a protein using a standard molecular mechanics force field, what are the different categories of energy contributions considered?

Given below are sketches of certain functional forms which correspond to the variations in these energy components with respect to structural changes in the protein. Correlate the energy components with the figures. In each case briefly indicate how you have made your correlation in terms of the shapes of the graphs. [10]

Ques:

- Force fields: the parameters used to calculate the potential energy.

$$\vec{m} = \nabla U(x)$$

→ Force fields can be calculated from data or quantum mechanics.

e.g. Lattice model, Off Lattice model, OPLSA, CHARMM, AMBER etc.

$$U(x) = \text{Bond stretch} + \text{Bond angle} + \text{Torsional angle} + \text{Distorted Torsion} \\ + \text{Electrostatic energy} + \text{LJ (Lennard-Jones) Interaction.}$$

$$U(x) = \sum_{\text{bonds}} \frac{1}{2} k_r (r - r_0)^2 + \sum_{\text{angles}} \frac{1}{2} k_\theta (\theta - \theta_0)^2 + \sum_{\text{torsion}} \frac{V_n}{2} (1 - \cos(\phi - \gamma)) \\ (\text{bond stretch}) \quad (\text{bond angle}) \quad (\text{torsional angle})$$

$$+ \sum V (\text{distorted torsion}) + \sum_{\text{ang}} \frac{q_i q_j}{r_{ij}} + \sum_{\text{LJ}} \left(\frac{A_{ij}}{r_{ij}^6} + \frac{B_{ij}}{r_{ij}^{12}} \right) \\ (\text{electrostatic}) \quad (\text{LJ interaction})$$

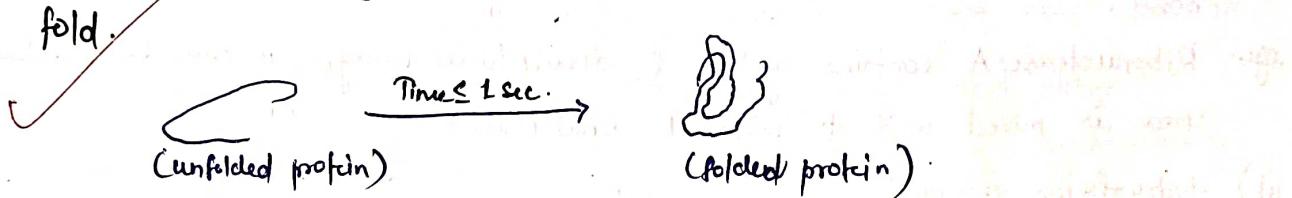
- Graphs:

- i) x-axis = bond length → using relation: $\sum_{\text{bonds}} \frac{1}{2} k_r (r - r_0)^2 \Rightarrow \{y \propto r^2\}$.
- ii) x-axis = bond angle → using relation: $\sum_{\text{angles}} \frac{1}{2} k_\theta (\theta - \theta_0)^2 \Rightarrow \{y \propto \theta^2\}$.
- iii) x-axis = electrostatic energy → asymptotes ($r=0, U \rightarrow \infty, r \rightarrow \infty, U \rightarrow 0$).
- iv) x-axis = torsion angle → using ref: $\sum_{\text{torsion}} \frac{V_n}{2} (1 - \cos(\phi - \gamma)) \Rightarrow \{y \text{ is function of shifted cosine}\}$.
- v) x-axis = radius (for Lennard-Jones interaction) → as 'r' increases the LJ terms becomes more smaller due to powers of r^6, r^{12} in denominator as we can observe the graph tending $U=0$ for greater radii & interaction increases as 'r' decreases.

Q7. Explain briefly 1) Levinthal's paradox and 2) Born-Oppenheimer approximation [5+5]

① Levinthal's paradox: A protein contains a sequence of amino acids, but when it comes to protein folding they can take huge-huge number of conformations as it can contain approx. 125 amino acids, even if it takes 10^{13} sec. to change one conformation, to get the all conformations it will take more than 10^6 years.

→ Hence, it is said that protein folding is not the random folding and for almost every protein it takes less than a second to fold.



② Born - Oppenheimer approximation: Movements of nucleus can be separated out from electrons. We can ignore the speed of nuclei w.r.t. electron as nuclei is much-much larger in size than electron.

→ Equation can be written of m' nuclei {time independent quantum eqn}.

$$\hat{H}\Psi = E(r_1, r_2, \dots, r_n) \Psi \quad \left\{ E = \text{energy}, r = \text{radii} \right.$$

Q8. a) What factors influence protein folding? [3]

Q8 b) Write briefly about the three major 'models' of protein folding: a) Frame-work model, b) Hydrophobic collapse and c) Nucleation model. [7]

(a) Protein folding happens when there is favourable conditions (e.g. $\Delta G < 0$)
 ↳ when protein get into hydrophobic solvent, the hydrophobic interaction increases or decreases, to minimize energy & increase stability protein can be folded.

• factors:

i) Temperature: breaks the Hydrogen bonds & can denature the protein.
 e.g. coagulation of egg.

ii) Detergents & reducing agents: urea, detergents etc. break the disulphide bond.

e.g. Ribonuclease A contains cysteine & disulphide bridge, it can be broken when urea is mixed with it makes it denatured.

iii) Hydrophobic interactions iv) pH.

(b)

ii) Hydrophobic collapse: it is based on the hydrophobic interaction between solvent and protein. when solvent (e.g. water) which is polar & it interact with hydrophilic amino acid, it can cause instability so, to avoid that protein gets folded with hydrophilic surface and hydrophobic core, core is densely packed so that hydrophobic interaction is minimized. The entropy is increased in this case as water was forming cage like structure before now can have better space.

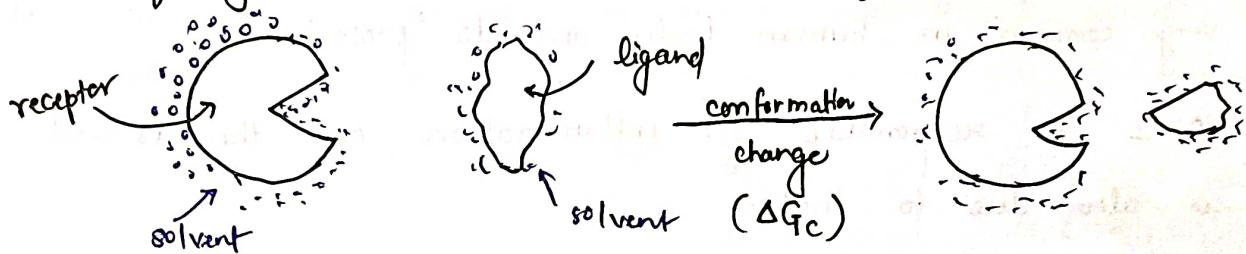
i) Framework model: it is based on predicting the protein & conformations and analysing to predict the actual conformation which is seen in protein folding. Machine learning helps in this model.

iii) Nucleation model: it is based on the stability of protein folding, generally protein folding is favourable but folded proteins can be misfolded or unfolded / denatured in influence of various factors like temperature, so, this is analyzed.

Q9 a) Explain with the help of a cartoon, the thermodynamic cycle of ligand-receptor binding. [7]

Ans: Ligand - receptor binding: (factors: Hydrophobic interaction, electrostatic interaction etc.).

Step ①: Conformation change: When ligand approaches the receptor, the conformation of ligand as well as receptor changes to favour the binding.

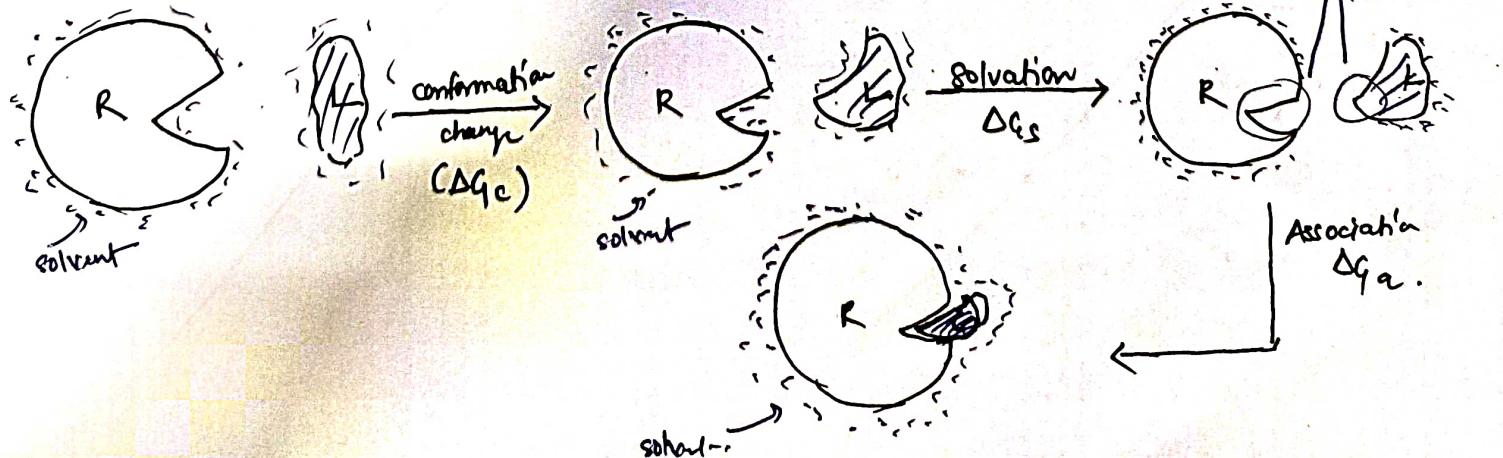


Step ②: Solvation: When conformation change happens, now next step is solvation. The bond between i) solvent (here, water) ~~breaks~~ and receptor ii) solvent and ligand, breaks leading to instability of hydrophobic interaction which is stabilized in next step.

Step ③: dissociation/ complexation: When bonds between solvents, receptors and ligands are broken, now ligand can get attached to the target site of receptor by forming Hydrogen bond or electrostatic bond, which stabilizes the hydrophobic interaction happened in previous step. (6.5)

Gibbs free energy of combination of individual free energy of conformation, solvation, association which is negative. { $\Delta G = -RT \ln K_b$ } { $\Delta G = \Delta H - T\Delta S$ }.

$$\left[\Delta G_b = \Delta G_c + \Delta G_s + \Delta G_a \right]$$



Q9 b) How is the structural difference between COX-1 and COX-2 responsible for the effectiveness of Celebrex®? [3]

Ans: COX-1 is responsible for secretion of mucus & fluids which helps stomach & intestine to protect them from the digestive juices. They mainly found in stomach & intestine lining and they are very common in human body and do protection.

COX-2 is responsible for inflammation and the arthritis pain is also due to that.

→ The drug designed NSAIDs, originally target was to cure the arthritis pain & inflammation by inhibiting COX-2 but they found side effect that it is also inhibiting COX-1 which is essential for protection, which leads to stomach ulcers.

→ COX-2 selective NSAIDs which only targets COX-2 curing arthritis pain. Histidine is the main amino acid which differs them.

Q10 Write the structure of the peptide: F-R-I-E-N-D [10]

(F) → phenylalanine

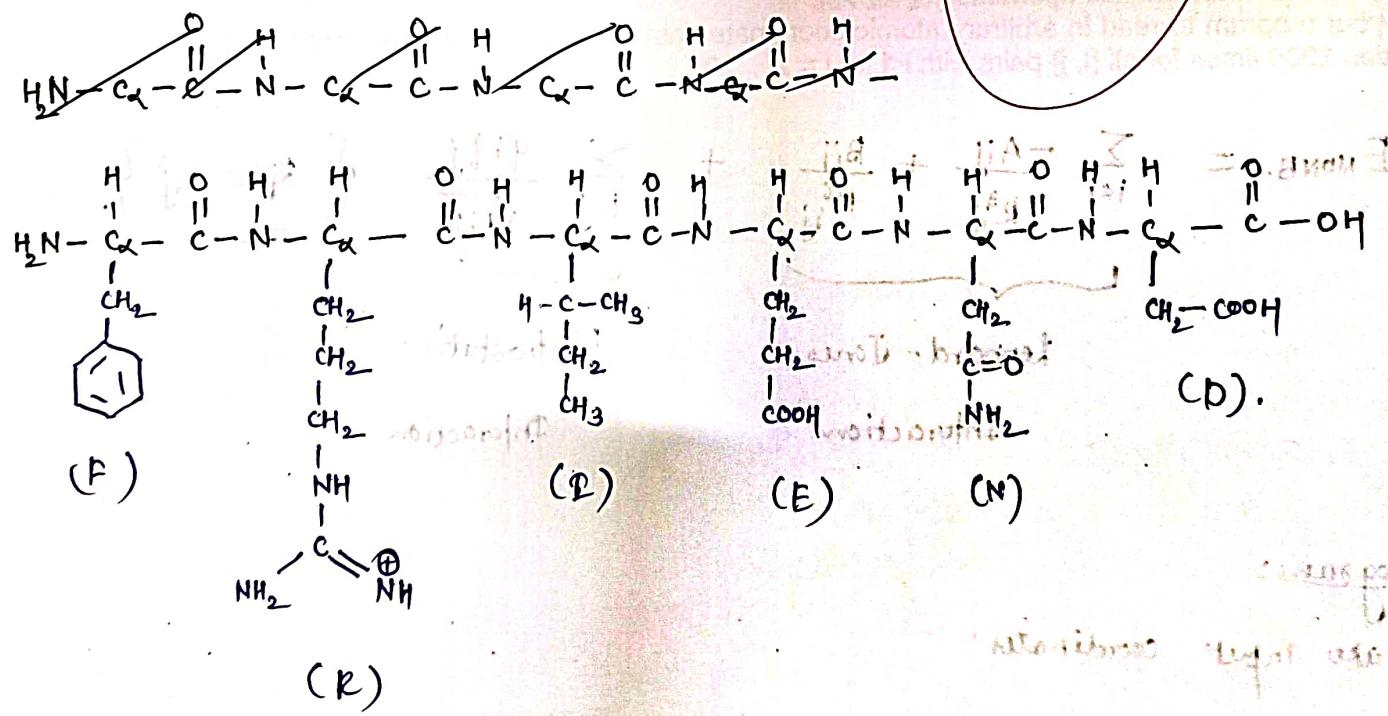
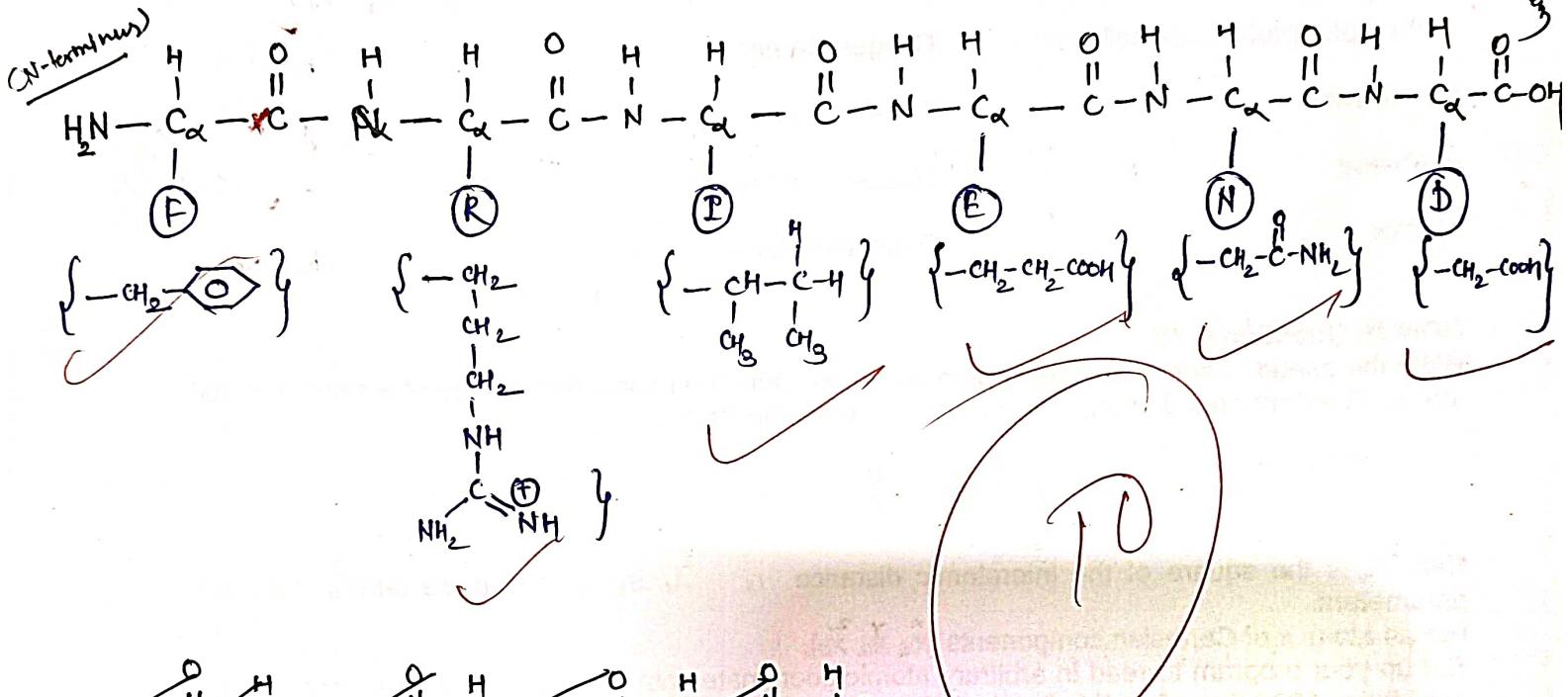
(R) → arginine

(I) - Isoleucine

(E) → Glutamic acid

(N) → Asparagine
Arginine

(D) - Aspartic acid



BONUS Question QXX

- a) α -keratin
- b) Hemoglobin
- c) Actin, Myosin
- d) Ion channel proteins
- e) Receptor proteins on cells
- f) Antibodies
- g) Kinase
- h) RNase

Match the following [4]

Signalling in and out of cells

[d] ✓

Signal transduction outside to inside cells

[e] ✓

Hair, Wool, Claws, horns

[a] ✓

Defend against foreign invaders

[f] ✓

Oxygen Carrier

[b] ✓

CB Anfinsen

[g] ✗ (3)

Muscle movement

[c] ✓

Phosphorylation

[h] ✗

BONUS Question QYY

Write the pseudo code for a simple program to compute the nonbonded energy of a system of 100 atoms. The nonbonded energy function should have the form:

$$E_{\text{NONB}} = \sum_{i < j} \left[\frac{-A_{ij}}{R_{ij}^3} + \frac{B_{ij}}{R_{ij}^6} + \frac{q_i q_j}{\sqrt{R_{ij}}} \right].$$

Here R_{ij} is the square of the interatomic distance r_{ij} . A_{ij} , B_{ij} , q_i and q_j are familiar forcefield parameters.

For an atom x_i of Cartesian components $\{x_{i1}, x_{i2}, x_{i3}\}$.

Set up your program to read in arbitrary atomic coordinate data and repeat the nonbonded energy calculation 1000 times for all $\{i, j\}$ pairs with $i < j$ for $j = 1, \dots, 100$.

$$\hookrightarrow E_{\text{NONB.}} = \underbrace{\sum_{i < j} \frac{-A_{ij}}{R_{ij}^3} + \frac{B_{ij}}{R_{ij}^6}}_{\text{Lennard-Jones Interaction}} + \underbrace{\sum_{i < j} \frac{q_i q_j}{\sqrt{R_{ij}}}}_{\text{Electrostatic Interaction}} \quad \left\{ R_{ij} = \sqrt{r_{ij}^2} \right\}.$$

Program:

// take input coordinates:

cin >> x >> y >> z >

// calculate Lennard-Jones & Electrostatic interaction

{ f(x, y, z) }

$$(R_{ij} = \sqrt{x^2 + y^2 + z^2})$$

$f(x, y, z)$

{
for ($j = 1$ to 100)

{

$$\text{Energy} = -\frac{A_{ij}}{R_{ij}} + B$$

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