Exercise 11 2024

Question 1

During cellular respiration, a glucose molecule is gradually broken down into carbondioxide and water. Below you have a reaction:

$$C_6H_{12}O_6(\text{glucose}) + 6\,O_2(\text{gas}) \rightarrow 6\,CO_2(\text{gas}) + 6\,H_2O(\text{liquid})$$

Using a table from the lecture:

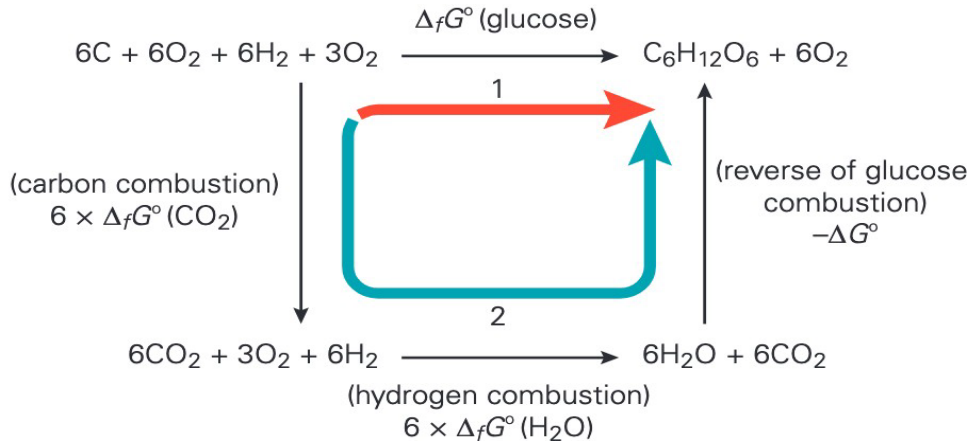
Compound	$\Delta G^{\circ\prime}$ (kJ•mol^{-1})
acetate$^-$	−369.2
CO_2 (gas)	−394.4
CO_2 (aqueous solution)	−386.2
carbonate ion	−587.1
ethanol	−181.5
fructose	−915.4
fructose-6-phosphate^{2-}	−1758.3
α-D-glucose	−917.2
glucose-6-phosphate^{2-}	−1760.2
H^+ (aqueous solution)	0.0
H_2 (gas)	0.0
H_2O (liquid)	−237.2
isocitrate^{3-}	−1160.0
lactate$^-$	−516.6
OH^-	−157.3
pyruvate$^-$	−474.5
succinate^{2-}	−690.2

a) Calculate the standard Gibbs free energy change (ΔG) for the reaction

b) Interpret the result: Is the reaction thermodynamicallyfavorable under standard conditions?

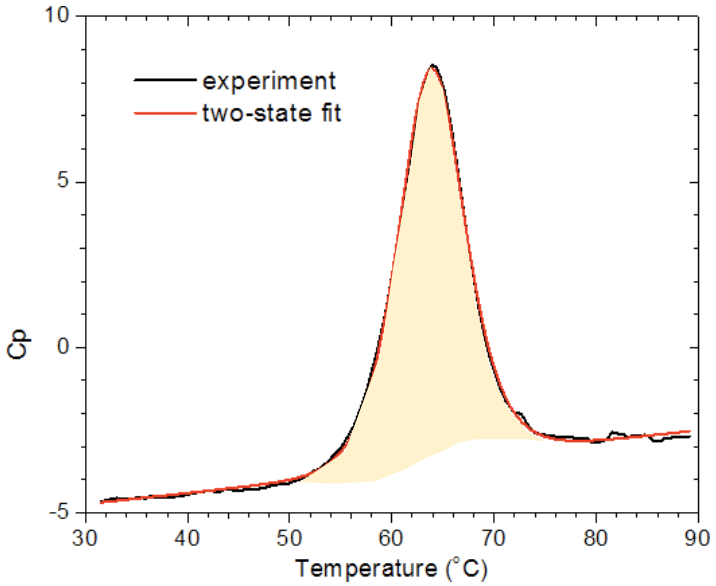
Question 2

In the lecture you had 2 pathways (1) and (2) on the picture below.Check what would be the Gibbs energy for both. What you can say?



Question 3

You have a protein sample that was subjected to a technique that produces the piece of data shown below. The area under the curve of the peak between 55 and 75 ºC (yellow) is 200 kJ/mol and the difference of C_p at low and high temperature (ΔC_p) is 3.5 kJ/K mol.



a) Which technique can produce these data?

b) Which type of biochemical reaction is the protein undergoing?

c) Using the data available calculate the entropy contribution for the reaction at the temperature at the maximum of the curve and at 35 ºC.

Question 4

Which of the following statements are TRUE, and which are FALSE?

a. The binding affinity of a molecule increases as the dissociation constant (K_d) decreases.

b. Enthalpy (ΔH) is the sole determinant of binding specificity in molecular recognition.

c. Hydrophobic interactions play a major role in molecular recognition by reducing the entropy loss upon ligand binding.

d. The Gibbs free energy (ΔG) of binding is independent of temperature.

e. The binding of a ligand to a receptor often involves an enthalpy-entropy trade-off.

f. The equilibrium constant (K_a) is inversely proportional to the dissociation constant (K_d).

g. Specificity in molecular recognition is always determined by the strongest non-covalent interaction.

h. Hydrogen bonds in molecular recognition are stronger in a non-polar environment than in a polar environment.

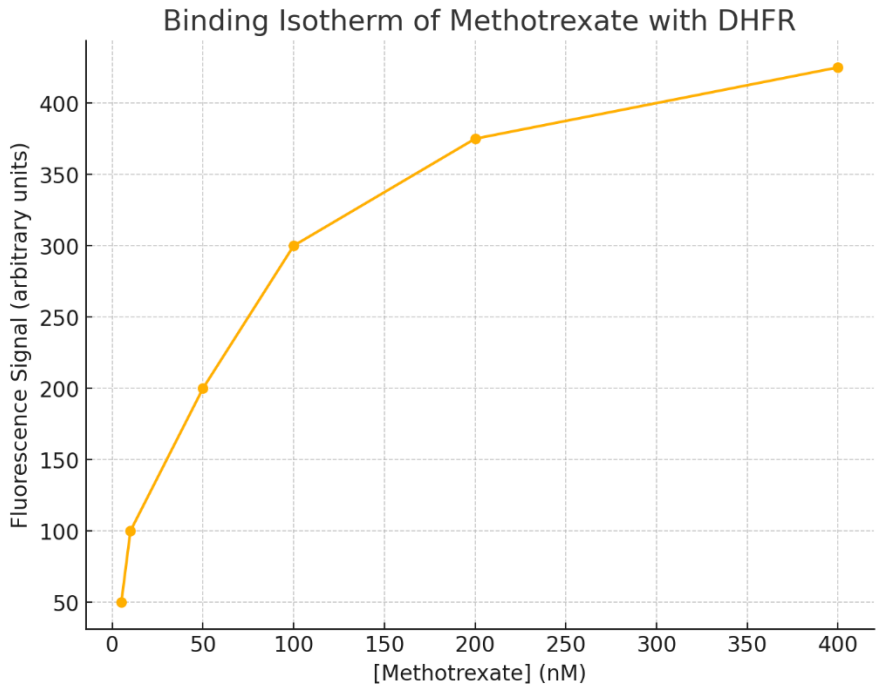
i. The entropy (ΔS) of binding is always positive for favorable binding interactions.

j. Allosteric binding refers to the binding of a ligand at a site other than the active site of the receptor, affecting the receptor's activity.

Question 5

Methotrexate is a potent inhibitor of dihydrofolate reductase (DHFR), binding to the active site and preventing the reduction of dihydrofolate to tetrahydrofolate. Below is a binding isotherm showing the interaction between DHFR and methotrexate. The fluorescence signal (arbitrary units) is measured as a proxy for binding. At the highest concentration of methotrexate tested (500 nM), the fluorescence signal saturates at 425 units.

a) Estimate the dissociation constant (K_D) for methotrexate from the binding curve.



b) Calculate the ΔG_{bind}° at 298 K for methotrexate's interaction with DHFR.

Question 6

The binding between the drug Ritonavir and the protein HIV-1 protease is measured, giving a binding free energy of −45 kJ/mol at human body temperature. What is the value of K_d?

Question 7

At 298 K, the enzyme lysozyme binds to a specific polysaccharide substrate with a dissociation constant of 20 µM. What are the values of association constant and ΔG_{bind}°?

Question 8

The drug jafrasitor (MW = 540 Da) binds the histone deacetylase enzyme Sir2 with a dissociation constant of 0.1 nM. What mass of jafrasitor should be administered to a patient with a blood volume of 5.5 L such that Sir2 is at least 91% inhibited?

Question 9

Using your knowledge about calculating protonation states and the energy of charge-charge interactions, answer the following questions:

a) Consider a protein with a surface-exposed histidine residue in a pH **5.5** solution. What is the fraction of protein molecules in which this histidine residue is charged? (Assume that the pKa is 6.0.)
b) For a protein with a surface-exposed aspartic acid, at what pH will this residue be charged in 60% of the protein molecules? (Assume that the pKa is 3.65)
c) Consider an electrostatic interaction between the histidine and the aspartic acid at a distance of 5.0 A˚. What is the energy of interaction if the residues are on the protein surface (ε=70) at the pH is 5.0? Define the charge of these amino acids by checking the pKa values below.

TABLE 3–1 Properties and Conventions Associated with the Common Amino Acids Found in Proteins

Amino acid	Abbreviation/ symbol	M_r	pK_a values: pK_1 (—COOH)	pK_2 ($—NH_3^+$)	pK_R (R group)	pI	Hydropathy index*	Occurrence in proteins (%)†
Nonpolar, aliphatic R groups								
Glycine	Gly G	75	2.34	9.60		5.97	−0.4	7.2
Alanine	Ala A	89	2.34	9.69		6.01	1.8	7.8
Proline	Pro P	115	1.99	10.96		6.48	1.6	5.2
Valine	Val V	117	2.32	9.62		5.97	4.2	6.6
Leucine	Leu L	131	2.36	9.60		5.98	3.8	9.1
Isoleucine	Ile I	131	2.36	9.68		6.02	4.5	5.3
Methionine	Met M	149	2.28	9.21		5.74	1.9	2.3
Aromatic R groups								
Phenylalanine	Phe F	165	1.83	9.13		5.48	2.8	3.9
Tyrosine	Tyr Y	181	2.20	9.11	10.07	5.66	−1.3	3.2
Tryptophan	Trp W	204	2.38	9.39		5.89	−0.9	1.4
Polar, uncharged R groups								
Serine	Ser S	105	2.21	9.15		5.68	−0.8	6.8
Threonine	Thr T	119	2.11	9.62		5.87	−0.7	5.9
Cysteine	Cys C	121	1.96	10.28	8.18	5.07	2.5	1.9
Asparagine	Asn N	132	2.02	8.80		5.41	−3.5	4.3
Glutamine	Gln Q	146	2.17	9.13		5.65	−3.5	4.2
Positively charged R groups								
Lysine	Lys K	146	2.18	8.95	10.53	9.74	−3.9	5.9
Histidine	His H	155	1.82	9.17	6.00	7.59	−3.2	2.3
Arginine	Arg R	174	2.17	9.04	12.48	10.76	−4.5	5.1
Negatively charged R groups								
Aspartate	Asp D	133	1.88	9.60	3.65	2.77	−3.5	5.3
Glutamate	Glu E	147	2.19	9.67	4.25	3.22	−3.5	6.3

Question 10

A histidine is involved in an interaction with a glutamic acid that stabilizes the charged form of the histidine, such that the value of ΔGo for deprotonation is 15 kJ•mol–1 at pH 7.0 and 293 K (calculated using the biochemical standard state). What is the pKa of this histidine?