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Biophysics. Degree in Bioinformatics

3 Dec 2018

1. (2 points) Thermodynamics

a) In a four-level system at T= 100°C the population of the four levels is: 50%, 30%, 15% and 5%. Calculate the population of these four levels at T= -200ºC. Comment if there is any temperature at which the population of the last two levels could be the same.

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b) Calculate the entropy of a system of 7500 particles distributed as indicated with the following configuration {4000, 2000, 1000, 500}.

If the particles were uniformly distributed among the four levels, calculate also the entropy associated with this new configuration. Comment the observed differences.

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2. (1 point) Chemical Kinetics.

The reaction of decomposition of cyclo-butane $C_4H_8(g) \rightarrow 2\ C_2H_4(g)$ follows a first order reaction with reaction constants of $k_{20°C} = 1.2 \cdot 10^{-31} s^{-1}$ and $k_{500°C} = 9.0 \cdot 10^{-3} s^{-1}$ at 20°C and 500°C respectively. Calculate at which temperature the half-live of this first order reaction will be 2 hours.

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3. (1.5 point) Answer in the spaces provided.

molecule	measured context at 25ºC	diffusion coeficient ($\mu m^2/s$)
protein (30 kDa)	water	100
protein (30 kDa)	*E. coli* cytoplasm	7
protein (100 kDa)	*E. coli* cytoplasm	0.8

a) Explain the tendency of measured diffusion coefficients in the cases indicated in the table.

b) Calculate the time required for the proteins indicated in the table to traverse a distance of 20 µm. Which effect it could be observed if the measurements were performed at 40°C?

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c) Estimate the viscosity of the cytoplasm of *E. coli* considering that the viscosity of water is 10^{-3} N s m^{-2}. Estimate de radius of the protein of 30 kDa.

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5) (2 points) Indicate whether the following sentences are **true or false**. Justify briefly the answer.

a) Solvation energy in water cannot be calculated using classical forcefields

b) Flexible residues like Gly decrease protein stability

c) Statistical potentials are needed to identify properly folded structures

d) Protein folding is driven by entropic contributions

e) Monte Carlo simulations are limited to the conformational space between energy barriers

f) NVT ensembles can be obtained by molecular dynamics simulations at constant volume

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g) Hydrogen bonds do not contribute to the overall stability in nucleic acid double helices

h) Calculation of binding energies requires only the calculation of interaction energies between interacting molecules.

i) When analyzing reaction rates, the concentration of substrate known as K_M corresponds to a fully saturated protein

j) Chaperones accelerate protein folding “in vivo” by catalyzing the formation of disulfide bonds.

6) (1 point) Identify related terms in the two columns

a. Solvent entropy	A. Morse equation
b. Bond length	B. Poisson-boltzmann equation
c. Van der Waals energy	C. Hydrophobic effect
d. Electrostatic solvation energy	D. Quantum mechanics calculation
e. Bond breaking energy barrier	E. 12-6 Potential

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8) (1 point) Bond stretching energy can be evaluated using both Morse and Hooke equations. The energy profile of a C-C single bond can be estimated (Morse law) using D_M =520 kcal mol^{-1} $Å^{-2}$, b_0 = 1.52 Å, and a = 0.55.
Evaluate the error that implies using Hooke's law instead, for the following C-C distances:
a) 1.0 Å, b) 1.5 Å, c) 2 Å, and d) 5 Å

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7) (1.5 points) A series of drugs (A100-A102) have been designed to bind to an internal cavity of a given protease. Drugs act as competitive inhibitors with the following inhibition constants:

Compound	K_I (μM)
S (K_M)	2100
A100	156.8
A101	4.82
A102	353.3

The compounds have a common chemical group analogous to an Arg side chain, mimicking the natural ligand (S), and variable hydrophobic groups.

All compounds retain the original Arg-like positive charge and bind to the protein at the same site and conformation. In these conditions it can be assumed that the differences in binding are due only to differences in solvation.

Substrate (S) binding is in equilibrium; hence K_M corresponds to a true dissociation constant. Consider T=298 K

a) Order the drugs regarding their inhibitory power
b) Determine the degree of inhibition (see Equations) caused by 5 μM of the drug at a concentration of S of 1 mM
c) Evaluate the difference of hydrophobic solvation energy between S and the inhibitors

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Annex. Equations

$$D = \frac{k_B T}{6\pi\eta a}$$

Free energy related to equilibrium constants

$$\Delta G = -RT \ln K_{eq}$$

ΔG: Process free energy (units: energy/mol, depending on the R value used). R (gas constant), T: Temperature (K); K_{eq}: Equilibrium constant (Concentrations in M)

Degree of inhibition for a competitive inhibitor (I)

$$i(I) = \frac{v(I=0) - v(I)}{v(I=0)} = \frac{K_M \, {}^{I}/_{K_I}}{K_M \left(1 + {}^{I}/_{K_I}\right) + S}$$

I: inhibition degree (no units); S: Substrate concentration; I: Inhibitor concentration; K_M: Michaelis constant; K_I: Inhibition constant. Units to match: S and K_M, I and K_I

Morse law for bond stretching energy

$$E_{pot} = D_M \left(1 - e^{-a(b-b_0)}\right)^2$$

D_M: Well depth (kcal mol^{-1}), b_0: bond length at energy minimum (Å); a: well width parameter ($Å^{-2}$); b: bond length (Å)

Hooke law for bond stretching energy (as used in the Amber parm99 forcefield)

$$E_{pot} = \frac{K_B}{2} (b - b_0)^2$$

K_b: Force constant (kcal mol^{-1} $Å^{-2}$), b_0: equilibrium bond length (Å); b: bond length (Å)

Constants:

$k_B = 1.3806488 \cdot 10^{-23}$ J/K

R=8.314 J K^{-1} mol^{-1}

R=0.082 atm L K^{-1} mol^{-1}

$N_A = 6.022 \cdot 10^{23}$ mol^{-1}