SOLUTIONS MANUAL FOR INTRODUCTION TO PROTEINS

STRUCTURE, FUNCTION, AND MOTION

by

AMIT KESSEL • NIR BEN-TAL

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Solutions to sample exercises

Chapter 1

3. The number of possible unique sequences constructing a protein with *n* amino acid is 20^n. Thus, a 60 amino-acid protein may be formed by 20^{60} unique sequences.

5. The attraction between the two groups is mediated by the following interactions:

a. van der Waals interactions, which exists between any atoms close enough to each other.

b. Electrostatic interactions between the charged amino group and the partially charged carbonyl dipole.

c. Nonpolar interactions, which exist between any three-dimensional physico-chemical entities possessing.

7. Although the hydrophobic effect induces attraction between two atoms, it is not based on classical interatomic interactions, because it does not involve a direct attraction between the atoms, but rather an indirect effect resulting from entropy changes in the solvent molecules around them.

8. Molecular transfer experiments have provided the following dependency of the nonpolar interaction energy on the change in surface area (Equation 1.6):

$$\Delta G_{np} \sim -0.025 \Delta SA$$

Thus, a 200 $Å^2$ decrease in the interactions surface area is likely to involve a drop of ~0.025 (kcal/(mol×$Å^{-2}$)) × 200 $Å^2$ = **5 kcal/mol** in the nonpolar interaction energy.

11. There are two main differences:

a. Ionic interactions occur between fully charged chemical species, where hydrogen bonds occur between electric dipoles.

b. Hydrogen bonds, but not ionic interactions, are geometry-dependent.

Chapter 2

5. A. The free energy of the electrostatic interaction between the two residues can be estimated by calculating their pairwise potential energy, using Coulomb's law (equation 1.2):

$$U_{Coul} = 332\frac{q_i q_j}{\varepsilon r_{ij}}$$

To solve the equation analytically we approximate the two residues as point charges. Then, the pairwise electrostatic energy can be calculated as follows:

$$U_{Coul} = 332\frac{(+1)\times(+1)}{(80)\times(2)} = \mathbf{2.1\ kcal/mol}$$

Again, this is only an estimate of the total electrostatic interaction energy. First, the two residues are not point charges but rather two 3D entities, on which the electric charge is distributed. Secondly, the pairwise energy is only one component of the complete interaction energy. The other component, which is missing here, is the polarization energy, which describes the interaction of each residue with the surrounding water. In principle, the polarization potential energy can be calculated as the pairwise (Coulomb) interactions between all solute and all solvent charges. Finally, both pairwise and polarization energies, when calculated in a static system, represent only one component

of the total (free energy), i.e. the potential energy. To calculate the free energy, one must describe the interactions in all possible configurations of the system, or use the Poisson-Boltzmann equation instead of the Coulomb equation.

B. The side-chain pKa values of lysine and arginine in isolation are 10.5 and 12.5, respectively. This means that when put in pure water (pH=7), each will tend to acquire a positive charge by protonation. However, when the two residues are put in proximity to each other, their unfavorable Coulomb interaction encourages them to remain in an electrically neutral state. The extent of this effect can be calculated using equation 2.1:

$$\Delta E_{Coul} = -2.3RT \times \Delta pKa$$

Substitution yields:

$$2.1 = -2.3 \times (0.6) \times \Delta pKa$$

and therefore:

$$\Delta pKa = \mathbf{-1.52\ kcal/mol}$$

C. This change lowers lysine's and arginine's pKa to ~9 and ~11, respectively, which is not enough to drive their de-protonation into an electrically neutral state. This is the result of the water's strong screening effect on the two charged residues. Thus, to make ΔpKa large enough to de-protonate the residues, the dielectric constant of the residue's environment must be low enough to reduce their pKa beyond 7. For lysine, this means ΔpKa > -3.5, and for arginine, ΔpKa > 5.5. The change in dielectric can be calculated using equations 1-2 and 2-1, as follows:

For lysine:
$$E_{Coul} = 332\frac{(+1)\times(+1)}{(\varepsilon)\times(2)} > -2.3\times(0.6)\times 3.5$$

$$\varepsilon < \mathbf{34.4}$$

For arginine: $$E_{Coul} = 332\frac{(+1)\times(+1)}{(\varepsilon)\times(2)} > -2.3\times(0.6)\times 5.5$$

$$\varepsilon < \mathbf{21.9}$$

8. Indeed, certain chemical derivatives of the 20 'natural' amino acids can be found in proteins. Two mechanisms are responsible. The first, which is commonest of the two, involves post-translational modification of a natural amino acid. The second involves incorporation of the 'non-natural' amino acid inside the sequence of the protein during translation. This mechanism, which is known to involve only two amino acids (selenocysteine and pyrrolysine), relies on specific tRNA species that carries the amino acid and is identified by the translation machinery thanks to its unique structure.

11. The function of backbone hydrogen bonds in α-helices is to reduce the energy penalty paid for the burial of polar backbone groups inside the nonpolar core of the protein. The role of nonpolar interactions is to stabilize the helix form with respect to the unfolded chain.

12. The change in electrostatic (potential) energy accompanying the transfer of an ion from water to a low-dielectric medium, such as the protein core, can be approximated by the Born model of solvation, which determines the change in Coulomb's energy (equation 2.2):

$$\Delta U = 166\left(\frac{q^2}{r}\right)\left(\frac{1}{\varepsilon_{np}} - \frac{1}{\varepsilon_w}\right)$$

Thus, the transfer of Zn^{2+} from a water-like medium (ε=80) to the protein core (ε=2) involves the following change in Coulomb's energy: $\Delta U = 166(\frac{4}{1.4})(\frac{1}{2} - \frac{1}{80}) =$ **231.2 kcal/mol**

13. The sequence given in the question is predicted to acquire an α-helical conformation, for two reasons. First, it is rich in residues, which according to Figure 2-19 have a strong helical preference (Ala, Glu, Arg, Leu). Secondly, it contains polar/nonpolar residues every three or four position, which is a periodicity found in amphipathic helices. Specifically, the four-positions spacing between Arg, Glu and Lys in the sequence places them on the same face of the helix, thus allowing them to electrostatically stabilize each other.

17. Three main post-translational modifications have been implicated in cancer development. These are:

I. Phosphorylation: a popular activity switch in many signal transduction processes. Uncontrolled phosphorylation of signal transduction proteins (e.g. growth factor receptors) has been implicated in the cancerous transformation of cells.

II. Glycosylation: reduction in the number of glycosyl moieties on the surface of cancer cells, compared to normal ones, allows the former to metastise and avoid detection by the immune system.

III. Ubiquitinylation: reduced tagging of p53 with the 'death protein' ubiquitin allows cells in danger of becoming cancerous to arrest their cycles and prevent this occurrence from happening.

19. Fibrous proteins differ from globular proteins in the following features:

- The single protein molecule has a repetitive, super-secondary structure, which creates an elongated shape.
- The single protein molecules tend to self-assemble into fiber-like ultra-structures.
- Their surfaces are often hydrophobic.
- They tend to have structural and organizational roles in the cytoskeleton and extracellular matrix.

21. Structural proteins may be fibrous, but not necessarily. That is, some globular proteins (e.g. actin) also self-assemble into fibers that fulfill structural roles in cells.

23. Soft and hard keratins differ in the number of disulfide bonds fortifying their structure. The more disulfide bonds, the harder is the keratin molecule.

24. Scurvy results from vitamin C deficiency, which prevents the body from hydroxylating pro-collagen, and therefore from building strong connective tissues. Thus, the treatment for scurvy, beyond the supportive care to the symptoms, is replenishment of the vitamin.